UNIVERSITY OF BELGRADE SCHOOL OF MEDICINE

CLINICAL CENTRE OF SERBIA

UGOSCGRS

18th INTERNATIONAL CONGRESS

ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS OF SERBIA, MONTENEGRO AND REPUBLIC OF SRPSKA

HOTEL CROWNE PLAZA, BELGRADE
19–21 OCTOBER 2023

BOOK OF ABSTRACTS

УОФОС SSFPO
УДРУЖЕЊЕ ЗА ОЧУВАЊЕ ФЕРТИЛИТЕТА И ОНКОФЕРТИЛИТЕТ СРБИЈЕ
SERBIAN SOCIETY FOR FERTILITY PRESERVATION AND ONCOFERTILITY

including
The Second International Symposium of the Serbian Society for Fertility Preservation and Oncofertility

GAS SLD

100th Anniversary of the Clinic for Gynecology and Obstetrics UCCS

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Dear Colleagues,

It is with exquisite pleasure to welcome you to 18th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska (UGOSCGRS) which will be held on October 19-21st, 2023, in Belgrade (Serbia). In addition to the great importance for keeping and improving connections between colleagues from our region, this year's annual meeting of UGOSCGRS is truly special because it is dedicated to the celebration of the 100th anniversary of the foundation of Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia. Being alma mater for the generations of Ob&Gyn specialists who founded majority of relevant gynecological institutions in Serbia and in the region, the Clinic for Gynecology and Obstetrics (University Clinical Center of Serbia) has been essential for the development of our profession in this part of Europe. Being a place of Ob&Gyn specialization since its foundation in 1923, the Clinic for Gynecology and Obstetrics (University Clinical Center of Serbia) has been pivotal for women health care on all levels of health system. We hope that we will celebrate this important anniversary properly.

As every year so far, participation in the congress will be taken by some of the most important experts from the world and the region, as well as representatives of relevant international associations. The congress program will cover interesting topics in gynecology, gynecological oncology, obstetrics, perinatology, minimally invasive surgery, assisted reproductive technologies and reproductive endocrinology.

Appreciating the importance of fertility preservation, both at the individual and the level of society, in partnership with the Serbian Society for Fertility Preservation and Oncofertility, within the congress, we will host the 2nd International Symposium of the Serbian Society for Fertility Preservation and Oncofertility, where leading experts will share with us novelties from this particular field of reproductive medicine.

We hope that this year's congress will meet the expectations of all participants and that we will celebrate the centenary of the Clinic for Gynecology and Obstetrics (University Clinical Center of Serbia).

With best wishes,
President of Association of Gynecologists and Obstetricians
of Serbia, Montenegro and Republic of Srpska
Prof. Aleksandar Stefanović

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ACCREDITATION:

Congress is accredited by the decision of the Health Council of the Republic of Serbia No. A-1-1873/23 as International Congress with 15 points for invited lecturers, 13 points for free communications and 10 points for listeners.

Thursday, 19th of October, 2023

08.00 – 09.00	**Registration**

Hall Pacific

SESSION	**100th anniversary of the KGA UKCS**
	Chair: A. Stefanović
09.00 – 09.15	**Aleksandar Stefanović (Serbia)** Introduction
09.15 – 09.30	**Paja Momčilov (Serbia)** 100 years of obstetrics at the Clinic for Gynecology and Obstetrics in Belgrade
09.30 – 09.45	**Ivan Tulić (Serbia)** Treatment of infertility and Artificial Reproductive Technologies at the Clinic for Gynecology and Obstetrics (UKCS)
09.45 – 10.00	**Vesna Kesić (Serbia)** Gynecological surgery and oncology at the Clinic for Gynecology and Obstetrics (UKCS)
10.00 – 10.15	**Tatjana Nikolić (Serbia)** Neonatology at the Clinic for Gynecology and Obstetrics (UKCS)
SESSION	**Key Note 1**
	Chairs: A. Stefanović, M. Gojnić Dugalić, Ž. Miković, T. Vejnović
10.15 – 10.30	**Gian Carlo di Renzo (Italy)** Miscarriage and preterm birth, similar risk factors: there are clues for prevention?
10.30 – 10.45	**Coffee break**
SESSION	**Panel – HPV in cervical cancer**
	Chairs: A. Stefanović, V. Ećim Zlojutro, V. Čolaković Popović
10.45 – 11.00	**Verica Jovanović (Serbia)** Human Papillomavirus and HPV immunization in Serbia
11.00 – 11.15	**Goran Dimitrov (North Macedonia)** Ablative versus excisional procedures in the treatment of cervical intraepithelial neoplasia - efficacy, acceptability and safety
11.15 – 11.30	**Radomir Živadinović (Serbia)** HPV infection and CIN in pregnancy: clinical significance and management
11.30 – 11.45	**Aleksandar Stefanović (Serbia)** UGOSCGRS recommendations for HPV immunisation
11.45 – 12.00	**Disscusion**
	Commercial lecture: Roche Diagnostics
12.00 – 12.30	**Katarina Stefanović (Serbia) / Verica Jovanović (Serbia)** Transforming cervical cancer screening – The power of HPV DNA testing
	Commercial lecture: San Pharma
12.30 – 12.45	**Saša Kadija (Serbia)** HPV infection and effective therapy of LGT lesions: Two ways of applying molecularly activated Glycyrrhizic Acid

12.45 – 13.45	**Lunch**

SESSION	**Fertility Sparing and Oncofertility 1**
	Chairs: K. Stefanović, V. Kesić, B. Kobal, S. Crnogorac, A. Stefanović
13.45 – 13.50	**Katarina Stefanović (Serbia)** Introduction
13.50 – 14.05	**Vesna Kesić (Serbia)** Oncofertility – an emerging discipline: our experiences
14.05 – 14.20	**Philippe Morice (France)** Fertility sparing in management of border-line ovarian tumors
14.20 – 14.35	**Iztok Takač (Slovenia)** New approaches to fertility sparing management in cervical cancer
14.35 – 14.50	**Basil Tarlatzis (Greece)** New trends in ovarian stimulation for IVF
14.50 – 15.05	**Borut Kobal (Slovenia)** Cervical cancer in pregnancy
15.05 – 15.20	**Miroslav Đorđević (Serbia)** Genital organs transplantation – step forward
15.20 – 15.35	**Snežana Crnogorac (Montenegro)** Pregnancies following malignancies: possibilities and challenges
15.35 – 15.50	**Darko Antić (Serbia)** Fertility Preservation in hematological malignancies in young patients
15.50 – 16.05	**Disscusion**

Hall Mediterranean/Adriatic

SESSION	**Minimally Invasive Gynecological Surgery**
	Chairs: M. Kopijar, M. Dokić, Đ. Ilić
13.45 – 14.00	**Miroslav Kopjar (Croatia)** The role of technique in laparoscopic pelvic lymphadenectomy
14.00 – 14.15	**Đorđe Ilić (Serbia)** The latest opinions on endometriosis
14.15 – 14.30	**Milan Dokić (Serbia)** MIGS and Acute Gynaecological Emergencies
14.30 – 14.45	**Rastko Maglić (Serbia)** Hysteroscopic management of ectopic pregnancy in Cesarean Section niche
14.45 – 15.00	**Rajko Fureš (Croatia)** Endometrial cancer – the role of hysteroscopy
15.00 – 15.15	**Tatjana Ilić Mostić (Serbia)** Preoperative evaluation and anesthesia for gynecological laparoscopy
15.15 – 15.30	**Disscusion**

Friday, 20th of October, 2023

Hall Pacific

SESSION	Obstetrics 1
	Chairs: V. Miketić, T. Vejnović, P. Momčilov, G. Relić
08.30 – 08.45	**Vojislav Miketić (Montenegro)** Education and psychological preparation for delivery
08.45 – 09.00	**Tihomir Vejnović (Serbia)** Uterus after Cesarean Section
09.00 – 09.15	**Slađana Mihajlović (Serbia)** Treatment of postpartum bleeding
09.15 – 09.30	**Vladimir Čančar (Republic of Srpska)** Transfusion in obstetrics
09.30 – 09.45	**Danko Natalić (Montenegro)** Prostaglandin E1 for the pregnancy termination after the first trimester: experiences from KCCG
09.45 – 10.00	**Disscusion**

SESSION	Key Note 2
	Chairs: A. Stefanović, M. Gojnić Dugalić, V. Ećim Zlojutro, Ž. Miković
10.00 – 10.15	**Wolfgang Holzgreve (Germany)** Non-invasive prenatal diagnosis - what have we learnt so far after millions of cases worldwide
	Commercial lecture: Innotech
10.15 – 10.30	**Aleksandar Stefanović (Serbia)** Current trends in the management of vaginal infections with Polygynax treatment
	Commercial lecture: Pharma Swiss
10.30 – 10.45	**Miloš Radojević (Serbia)** It's time for Lomexin – an effective solution for vaginal candidiasis
10.45 – 11.00	**Coffee break**

SESSION	Perinatology 1
	Chairs: V. Ećim Zlojutro, M. Gojnić Dugalić, Ž. Miković, V. Miketić, P. Momčilov
11.00 – 11.15	**Vesna Ećim Zlojutro (Republic of Srpska)** Polypragmasia in pregnancy
11.15 – 11.30	**Miroslava Gojnić Dugalić (Serbia)** Raising quality of natality in Serbia
11.30 – 11.45	**Željko Miković (Serbia)** Hereditary thrombophilia – therapeutic dilemmas in women with unsuccessful pregnancy
11.45 – 12.00	**Olivera Kontić Vučinić (Serbia)** Clinical implication of new insight about the first trimester screening and diagnostics
12.00 – 12.15	**Snežana Plešinac (Serbia)** Obesity – an obstetrical challenge

12.15 – 12.30	**Gordana Vukčević (Montenegro)** Obstetrics in Montenegro: past and present
12.30 – 12.45	**Disscusion**
	Commercial lecture: Merck
12.45 – 13.05	**Aleksandra Jotić (Serbia)** Glucophage XR – therapy of prediabetes in the periconceptional period: achievements and challenges
	Commercial lecture: Roche Diagnostics
13.05 – 13.20	**Kateryna Vashutina** Innovation in the assessment of preeclampsia - management of suspected preeclampsia with sFlt-1 and PLGF tests
	Commercial lecture: Biessen Pharma
	Chair: A. Stefanovic
13.20 – 13.50	**Snežana Plešinac (Serbia)** Significance of Lactobacillus rhamnosusa Lcr35 in female reproductive health
13.50 – 14.45	**Lunch**
	Commercial lecture: Magna Pharmacia
14.45 – 15.00	**Goran Dimitrov (North Macedonia)** New Era in Cervical Cancer Screening
	Commercial lecture: Astra Zeneca
15.00 – 15.15	**Katarina Stefanović (Serbia)** What is coming new in the treatment of advanced Ovarian Cancer
SESSION	**Oncology 1**
	Chairs: A. Stefanović, S. Kadija, V. Čolaković Popović, V. Kesić
15.15 – 15.30	**Saša Kadija (Serbia)** PSTT, ETT and APSN: a whole new challenge
15.30 – 15.45	**Ivana Likić Lađević (Serbia)** MRI in cervical cancer: an update
15.45 – 16.00	**Jelena Jeremić (Serbia)** VY sliding fasciocutaneous flap in the reconstruction of vulvo-perineal defects
16.00 – 16.15	**Aleksandra Dimitrijević (Serbia)** Recent advances in endometrial cancer management
16.15 – 16.30	**Aljoša Mandić (Serbia)** Place of immunotherapy in cervical cancer. New horizons
16.30 – 16.45	**Disscusion**
16.45 – 17.00	**Coffee break**
SESSION	**Oncology 2**
	Chairs: A. Stefanović, S. Kadija, V. Čolaković Popović, V. Kesić
17.00 – 17.15	**Lazar Nejković (Serbia)** Endometrial Cancer: clinical aspect of treatment
17.15 – 17.30	**Vesna Čolaković Popović (Montenegro)** SLN in Gynecological Oncology

17.30 – 17.45	**Admir Agić (Germany)** SLN with ICG in gynecological cancer
17.45 – 18.00	**Svetlana Rogovskaya (Russia)** Novel screening technologies for cervical cancer
18.00 – 18.15	**Disscusion**

Hall Mediterranean/Adriatic

SESSION	**Gynecology**
	Chairs: S. Raičević, K. Sedlecki, G. Relić, S. Kadija, I. Likić Lađević, G. Plemić Gubić
08.30 – 08.45	**Saša Raičević (Montenegro)** Fibrothecoma in Adolescence
08.45 – 09.00	**Katarina Sedlecki (Serbia)** Should we treat bacteriology reports or vulvar infection in girls?
09.00 – 09.15	**Goran Relić (Serbia)** Reproductive health in youth population in the North of Kosovo and Metohija in emergency situation
09.15 – 09.30	**Zoran Stanković (Serbia)** FIGIJ educational center of pediatric and juvenile gynecology in Belgrade
09.30 – 09.45	**Svetlana Spremović Rađenović (Serbia)** Hormones and aging – what are the connections with metabolic changes in menopause
09.45 – 10.00	**Disscusion**

SESSION	**Fertility Sparing and Oncofertility 2**
	Chairs: K. Stefanović, V. Kesić, I. Takač
11.00 – 11.15	**Jelena Stojnić (Serbia)** Efficacy and safety of different protocols of controlled ovarian stimulation (COD) for fertility preservation in women with breast cancer
11.15 – 11.30	**Jure Knez (Slovenia)** Fertility sparing management of endometrial cancer in the era of molecular classification
11.30 – 11.45	**Svetlana Milenković (Serbia)** Limitations of Pathological Diagnostics in Oncofertility Treatments
11.45 – 12.00	**Zoran Vilendečić (Serbia)** Adnexal mass in reproductive-aged woman – diagnostic and therapeutic considerations
12.00 – 12.15	**Igor Pilić (Serbia)** Fertility preservations in gynecological cancers
12.15 – 12.30	**Miloš Radojević (Serbia)** Fertility preservation in the GTN treatment
12.30 – 12.45	**Disscusion**

SESSION	**IVF and Infertility 1**
	Chairs: S. Spremović Rađenović, J. Stojnić, O. Džatić Smiljković
15.15 – 15.30	**Jelena Stojnić / Lela Šurlan (Serbia)** Donation programme in Serbia

15.30 – 15.45	**Olivera Džatić-Smiljković (Serbia)** Intrauterine inseminations in GAK N. Front
15.45 – 16.00	**Nebojša Zečević (Serbia)** Metalom - a new aspect in understanding male infertility
16.00 – 16.15	**Radomir Aničić (Serbia)** Uterine-ovarian hemodynamic following laparoscopic treatment of infertility caused with moderate and severe endometriosis
16.15 – 16.30	**Aleksandar Jurišić (Serbia)** Classification and non-invasive diagnostics of congenital uterine anomalies
16.30 – 16.45	**Disscusion**

SESSION	**IVF and Infertility 2**
	Chairs: S. Spremović Rađenović, J. Stojnić, O. Džatić Smiljković
17.00 – 17.15	**Vesna Mandić Marković (Serbia)** Pregnancies after IVF procedures – outcome and delivery
17.15 – 17.30	**Angela Ćorić (Montenegro)** Premature ovarian failure – hormone substitution therapy in prevention of comorbidities
17.30 – 17.45	**Snežana Rakić (Serbia)** Different ways of conception: impact on perinatal outcome of IVF pregnancies
17.45 – 18.00	**Disscusion**

Saturday, 21th of October, 2023

Hall Pacific

SESSION	**Perinatology 2**
	Chairs: O. Kontić Vučinić, M. Gojnić Dugalić, M. Petronijević, D. Filimonović, V. Mandić Marković
09.00 – 09.15	**Miloš Petronijević (Serbia)** New understanding of functional changes of GIT in pregnancy
09.15 – 09.30	**Svetlana Vrzić Petronijević (Serbia)** The potential role of artificial intelligence in prenatal diagnosis of fetal heart anomalies
09.30 – 09.45	**Bojana Petrović (Serbia)** Significance of exome sequencing for prenatal diagnosis
09.45 – 10.00	**Srboljub Milićević (Serbia)** Detection of the first trimester anomalies: thorax and abdomen
10.00 – 10.15	**Nataša Karadžov-Orlić (Serbia)** Prenatal Diagnosis, Management, and Treatment of Fetal Cardiac Disease
10.15 – 10.30	**Dejan Filimonović (Serbia)** Laser photocoagulation of anastomoses in TTT Syndrome: seven year of experience
10.30 – 10.45	**Disscusion**

SESSION	**Key Note 3**
	Chairs: A. Stefanović, M. Gojnić Dugalić, V. Ećim Zlojutro, V. Miketić
10.45 – 11.00	**Sabaratnam Arulkumaran (United Kingdom)** Landmark papers on PPH and preterm labour

	Commercial lecture: Vivogen
11.00 – 11.20	**Bojana Petrović (Serbia) / Monique Olima (United Kingdom)** Benefits of Microarray Testings in Reproductive Diagnostics
	Commercial lecture: NIC Pharmaceutical
11.20 – 11.35	**Marina Obućina (Serbia)** Cerviray AI – artificial intelligence based screening system
	Commercial lecture: Herba Svet
11.35 – 11.50	**Nemanja Milinčić (Serbia)** Phytotherapy in the treatment of dysmenorrhea and irregular menstrual cycles
11.50 – 12.15	**Coffee break**
SESSION	**Perinatology 3**
	Chairs: S. Plešinac, O. Kontić Vučinić, I. Hudić, S. Vrzić Petronijević, F. Skokić
12.15 – 12.30	**Igor Hudić (Bosnia and Herzegovina)** Immunological aspects of pregnancy
12.30 – 12.45	**Tatjana Nikolić (Serbia)** Neonatal dysbiosis – the significance and the risk factors
12.45 – 13.00	**Selma Đurbuzović Ramović (Montenegro)** Prenatal ultrasound assessment of fetal lung maturation
13.00 – 13.15	**Saša Grbović (Montenegro)** Intrahepatic cholestasis in pregnancy
13.15 – 13.30	**Fahrija Skokić (Bosnia and Herzegovina)** Preventive procedures in neonatology
13.30 – 13.45	**Višnja Stamatović (Serbia)** The significance of RSV infection in neonatal age
13.45 – 14.00	**Disscusion**
SESSION	**Obstetrics 2**
	Chairs: A. Šahmnović, S. Vrzić Petronijević, N. Karadžov Orlić
14.00 – 14.15	**Aida Šahmanović (Montenegro)** Scientific base for partogram development: from Friedman curve to “Labor care guide”
14.15 – 14.30	**Bojan Vučetić (Montenegro)** Treatment and mode of delivery in PPROM
14.30 – 14.45	**Dragan Rakanović (Republic of Srpska)** Management of complicated epidural analgesia in obstetrics
14.45 – 15.00	**Emira Kalamperović Pelinković (Montenegro)** Outcomes of pregnancy complicated with preeclampsia
15.00 – 15.15	**Disscusion**
SESSION	**Free Communications**
	Chairs: S. Pantović, V. Mandić Marković, S. Mihajlović
15.15 – 15.20	**Bojana Petrović (Serbia)** Genetic alterations of tumor suppressor genes and proto-oncogenes in sporadic epithelial ovarian cancers
15.20 – 15.25	**Milana Radovanović (Serbia)** Case report: Ectopic pregnancy of unconvincing clinical presentation

15.25 – 15.30	**Dejan Mihajlović (Serbia)** Vitamin-mineral supplementation as a new therapeutic approach to Polycystic ovary syndrome (PCOS) and metabolic syndrome – a case report
15.30 – 15.35	**Dejan Pavlović (Serbia)** Evaluation of perioperative complications in patients after myomectomy
15.35 – 15.40	**Maja Sebez (Republic of Srpska)** Breast cancer diagnosed in third trimester of pregnancy: a case report
15.40 – 15.45	**Ivan Hristov (Serbia)** Differential diagnostic dilemmas and management of perimenopausal bleeding: a case report
15.45 – 15.50	**Tijana Veličković (Serbia)** Congenital afibrinogenemia – anesthesiology perspective and pregnancy outcome: a case report
15.50 – 15.55	**Ljiljana Zdelar Stojanović (Serbia)** Determination of IgG subclass in risk assessment for the development of Hemolytic disease of newborn: a case report
15.55 – 16.00	**Zvjezdana Ritan Mičić (Republic of Srpska)** Management and pregnancy outcome in newly diagnosed tuberculosis in the second trimester: a case report
16.00 – 16.05	**Dejan Pavlović (Serbia)** Perinatal outcome in preterm growth restricted fetuses with brain sparing effect based on venous blood flow
16.05 – 16.10	**Aleksandar Panić (Republic of Srpska)** Methotrexate in treatment of ectopic pregnancy: our experiences
16.10 – 16.15	**Jana Dabović (Serbia)** Elevated creatinine in pregnancy and its role in diagnosis of rare syndrome: a case report
16.15 – 16.20	**Dejan Pavlović (Serbia)** Values of serum estradiol on the fifth day of the stimulated cycle in the prediction of IVF success in poor responder
16.20 – 16.25	**Tamara Bezbradica (Republic of Srpska)** Terminal stage of cervical cancer in puerperium: a case report

Hall Mediterranean/Adriatic

SESSION	**Urogynecology**
	Chairs: S. Pantović, D. Plemić Gubić, R. Fureš
09.00 – 09.15	**Danica Plemić Gubić (Republic of Srpska)** Vaginal hysterectomy in 10 steps: our experiences
09.15 – 09.30	**Sveto Pantović (Serbia)** Complications of vaginal hysterectomy
09.30 – 09.45	**Snežana Buzadžić (Serbia)** Ten years of experience in suburethral sling application: tertiary center experience
09.45 – 10.00	**Svetlana Janković (Serbia)** Vaginal pessaries: past and present
10.00 – 10.15	**Disscusion**

SESSION	**Short Communications 1**
	Chairs: I. Likić Lađević, Z. Vilendečić, M. Radojević

12.15 – 12.25	**Dragana Maglić –** Prediction of neonatal outcome in preterm birth
12.25 – 12.35	**Petar Cabunac –** The application of FMF algorithm in prediction of preeclampsia
12.35 – 12.45	**Branislav Milošević –** Treatment of malignancies in pregnancy
12.45 – 12.55	**Milena Perišić Mitrović –** Strategies for cervical cancer screening
12.55 – 13.05	**Bojana Ivić –** Human biomonitoring of essential, nonessential, rare earth and noble elements in placental tissues
13.05 – 13.15	**Stefan Dugalić –** Contemporary Perinatology - Preventing Gestational Diabetes in both women and newborn
13.15 – 13.25	**Slavica Akšam –** Delivery of the low birth weight singleton fetus with cephalic presentation
13.25 – 13.35	**Dušica Kocijančić Belović –** Fetal surveillance in pregnancies with asymmetric growth restriction
13.35 – 13.45	**Marko Stanković –** Longitudinal changes in HDL metabolism in high-risk pregnancies
13.45 – 13.55	**Danka Mostić –** Acute appendicitis in pregnancy – an overview of literature and case report
SESSION	**Short Communications 2**
	Chairs: J. Bila, I. Pilić, M. Radojević
14.00 – 14.10	**Dejan Dimitrijević –** Basic principles of electrosurgery in ginecological endoscopy
14.10 – 14.20	**Aleksandar Ristić –** Malignancy index in differential diagnosis of benign and malignant ovarian tumors
14.20 – 14.30	**Tijana Janjić –** Atypical presentations of dermoid cysts
14.30 – 14.40	**Aleksandar Rakić –** Bioinformatic analysis of biomarkers and signal pathways in diagnosis and prognosis of uterine leiomyosarcoma
14.40 – 14.50	**Aleksandar Dmitrović –** Ultrasound classification and diagnostics of breast lesions
14.50 – 15.00	**Jovana Ćosić –** Follicular fluid biomarkers as an indicator of oocyte quality in the process of ART
15.00 – 15.10	**Ivana Vuković –** AIN vs. CIN. Cause or Consequence
15.10 – 15.20	**Jovana Ćupić –** Persistent low level of elevated hCG
15.20 – 15.30	**Željka Vuković –** Isthmocele diagnosis and management: review of literature with case report
15.30 – 15.40	**Luka Andrić –** Molecular features and histology impacting new FIGO staging of endometrial cancer
15.40 – 15.50	**Jelena Štulić –** Oncology outcomes in cervical stages Ib1-Ib2 following radical hysterectomy without adjuvant treatment
15.50 – 16.00	**Olga Mihaljević –** Awareness, network and advocacy in oncofertility
16.00 – 16.10	**Aleksandra Beleslin –** Oncofertility unlocked: conservative treatment of early stage endometrial cancer – Case reports
16.10 – 16.20	**Jelena Mitrović –** Immunological factor as a cause of recurrent implantation failure and habitual abortions
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HPV IN CERVICAL CANCER

ABLATIVE VERSUS EXCISIONAL PROCEDURES IN THE TRETMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA – EFFICACY, ACCEPTABILITY AND SAFETY

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History of CIN

Development of histopathology began in the 19-th century and its pioneer was Johannes Muller [1] in 1930.

First histological classification of tissues was introduced by Jacob Henle from Zurich and Rudolf Virchow from Heidelberg [2] who are thought to be the founders of cellular pathology. They were the first who followed the growth of a cervical carcinoma with palpation, and not as before just with observation.

Sir John Willian [3] in 1886 and Cullen in 1900 have described the lesion that is known as a carcinoma in situ (CIS).

In 1908 Schauenstein developed his assumption that the cervical cancer is preceded by an intraepithelial growth stage.

The terms preinvasive carcinoma [4] and carcinoma superficialis [5] were replaced by a new term - carcinoma in situ [6, 7].

In 1946 George Papanicolaou [8] described a group of vaginal smears that were difficult to classify and according to him “they constantly contain atypical cells that didn’t have malignant characteristics, but they were so similar to malignant cells, so I examined it several times for a certain period of time and I asked myself: Is it possible that these are initial malignant changes?”. Later on, these cells were described as “atypical epithelium” or hyperactivity of basal cells, anaplasia, precancerous metaplasia and atypical metaplasia, hyperplasia atypica epithelialis, and even some authors were using the term leukohyperkeratosis.

Concept of CIN

The normal tissue is marked as an euplastic versus anaplastic that is characterized with loss of maturation and differentiation which lead to a new atypical or malignant tissue through uncertain period of time. Dysplasia occurs with losing the harmony of the processes of maturation and differentiation of the tissue. The very well know term dysplasia was introduced by Regan 1953 [9] and it is used by many authors until present time. The origin of the term comes from Greek words DYS that means abnormal and PLASIA that means development.

On the First International Congress of exfoliative cytology In Wien in 1961 a cytological definition was used for the first time. Wied [10] defined it as a “condition when all the squamous epithelium that is located on the surface or in the glands shows changes in differentiation (without invasion)” addressing to the term carcinoma in situ (CIS). These kinds of changes differ in stadium and they are being graded as low, medium and severe.

WHO (World Health Organization) defines the dysplasia as “lesion in which part of the stratified squamous epithelium is being replaced with epithelium with different stage of atypia”.

In the same time with the classical concept of two terms (dysplasia and CIS) another unified theory was introduced by Richart [11] where cervical preneoplastic lesions were labeled as cervical intraepithelial neoplasia (CIN).

According to the intensity of the changes of the epithelium there are three stages of CIN.

- CIN – 1: Mild dysplasia where the lesions affect only the lower third of the thickness of the epithelium.
- CIN – 2: Moderate dysplasia where the lesions affect two thirds of the thickness of the epithelium.
- CIN – 3: Severe dysplasia and carcinoma in situ where the changes affect the whole thickness of the epithelium.

This terminology was debatable by many cytologists and pathologists with many controversies. [12, 13].

With the numerous studies that showed huge impact of human papilloma virus (HPV) in the etiology of the squamous cervical cancer in 1988 [14] National Cancer Institute (NCI – USA) introduced the so called "BETHESDA" system of cytological classification. This classification was later revised three times. The first time was in 1991 [15] and in 2001 [16, 17].

The latest revision has been done in 2014 with the help of an appointed task force. This group of renowned cytopathologists conducted an internet-based open comments survey with participation from the international cytopathologist community. The feedback was compiled, reviewed, and resulted in the 2014 edition of The Bethesda System and its accompanying atlas [18].

In 1990, Richrat [19], offered new classification that was accepted by Nacional Cancer Institute (NCI - USA), in which the term neoplasm was roll out and the cytological and histological classifications became very close and similar. According to this classification the changes were divided in two categories:

1. Squamous intraepithelial lesion of low grade (LGSIL) in which CIN – 1 is included so as the changes provoked by human papilloma virus that gives a lesion with unpredicted evolution.
2. Squamous intraepithelial lesion of high grade (HGSIL) which reflects to CIN – 2, CIN – 3 and carcinoma in situ, including high risk HPV and are believed to be the precursors of invasive cervical cancer.

Modalities of treatment of CIN

There are several different modalities of treatment for women that are diagnosed with the cervical intraepithelial neoplasm. For women that are diagnosed with CIN – 1 there is a possibility to be followed and not treated at the moment when the diagnose is made. Follow up is advised only for patients that can be fully followed in a certain period of time. Choosing the right treatment includes many factors so as the wish of the patient, but also the experience of the doctor. When a treatment should be chosen there are a few important perspectives. The age of the patient and her wish to preserve the fertility. Every patient should know that none of the treatments has 100% effectiveness so as that every kind of treatment has potential risk to her health and wellbeing.

In some patients who have small fully visualized lesion, that lesion can be entirely removed with a biopsy forceps by a skilled colposcopist. On the other hand, many authors agree that the whole transformational zone should be destroyed or removed, so that the risk of progression can be minimalized.

In general consideration there are two groups of modalities of treatment: ablative and excisional procedures. These procedures have different mechanisms, efficacy rates, acceptability among patients and also different safety profiles.

Ablative procedures (include cryotherapy, CO2 laser vaporization, thermal ablation (cold coagulation), and diathermy):

1. Mechanism: Ablative procedures, such as laser therapy and cryotherapy destroy the abnormal tissue of the cervix. Laser uses a focused beam of light to vaporize the cervical tissue, while the cryotherapy freezes the involved tissue.
2. Efficacy: Ablative technics are in general effective for treating low grade CIN (CIN - 1). In some cases high grade CIN (CIN 2). They have lower success rates for treatment of CIN – 3 (severe dysplasia).
3. Acceptability: These procedures are well-tolerated by patients because they are less invasive and with less discomfort compared to excisional procedures.
4. Safety: Ablative procedures are in general safe, less prone to bleeding and infection. Also, there is a risk of incomplete treatment and in need of up-close follow up.

Excisional procedures (cold knife conization; loop electrosurgical excision procedure [LEEP], also called large loop excision of the transformation zone [LLETZ]; laser conization):

1. Mechanism: Excisional procedures, such as cold knife conization and loop electrosurgical excision (LEEP) also called large loop excision of the transformation zone (LLETZ); laser conization, remove a cone-shaped part of the tissue of the uterine cervix that is abnormal. With this kind of procedures, a tissue sample is obtained for histopathological examination.
2. Efficacy: These procedures are highly effective for treating CIN-2, CIN -3 and CIS, because they provide a more accurate diagnosis of the severity of the lesion.
3. Acceptability: They are related with higher discomfort for the patient, longer hospital stay, longer recovery time.
4. Safety: Although these procedures are in general safe, they carry a higher risk of post OP bleeding and infection. Also, there is a slightly concern in incompetence of the cervix in pregnancies later on.

Discussion and Conclusion

The choice between ablative or excisional procedures depends on the severity of the CIN, preferences of the patient, availability of the resources and surely the expertise of the physician.

In cases of low-grade CIN and in cases when preserving the fertility is highly important, ablative procedures should be the first choice of preference.

Ablative techniques do not obtain a tissue specimen for histopathological examination as the tissue is being destroyed during the procedure. Therefore, these procedures are not of diagnostic value. They are appropriate for selected group of patients with well-characterized lesion that are histologically proven and colposcopic observed in which invasive cancer has been excluded. [20].

For higher grades of CIN or CIS or in cases when a definitive diagnosis is needed, excisional procedures are far more recommended.

Treatment of CIN has been associated with subsequent cervical stenosis, second-trimester pregnancy loss, and preterm birth. These risks are higher with excisional compared with ablative procedures and increase with increasing weight and volume of tissue removed.

Postoperative surveillance and close follow-up of the patients are essential to monitor the recurrence or residual disease.

There are 3 versions of Cochrane Database Reviews so far (1999 and 2010) with a title - Surgery for cervical intraepithelial neoplasia, of which the third one from 2013 [21] compares: laser ablation, laser conization, large loop excision of the transformation zone (LLETZ), knife conization or cryotherapy treatments for cervical intraepithelial neoplasia. Twenty-nine trials were included. Several surgical techniques were tested in various comparisons. No significant differences in treatment failures were demonstrated in terms of persistent disease after treatment. Large loop excision of the transformation zone appeared to provide the most reliable specimens for histology with the least morbidity. Morbidity was lower than with laser conization, although the trials did not provide data for every outcome measure. In this meta-analysis there was not enough data to assess the effect on morbidity when compared with laser ablation.

In our "big" study from 2014 [22] (3169 patients) we have concluded that there is no statistical correlation to persistence, recurrence and progression of CIN with the type of treatment performed (cold knife conization, ultracision, laser vaporization and laser conization) The variables that show a correlation with statistical significance are: smoking, the histological grade of the lesion (grade of CIN), the involvement of the surgical margins, the parity as well as the strongest is the post-treatment detected HPV infection (with a high-risk type of HPV). After persistence or reinfection with HPV after treatment with a high-risk type (which is the strongest variable as a factor in this analysis) a group of variables appears that includes the histological grade of the lesion (grade of CIN at first treatment), tobacco smoking, involvement of surgical margins as well as parity.

The newest systematic review by Zhang et al. in 2023 [23] the comparison of ablative and excisional techniques to treat CIN 2/3 was done head-to-head and not like in the previous reviews. The included studies in this analysis were directly comparing efficacy and safety of excisional and ablative treatments on histologically confirmed CIN2/3. Eligibility criteria for the women treated with ablation had to be same as those treated with excision. The risk of persistence/recurrence following ablation was significantly higher than that following excision (overall: RR: 1.65, 95%CI: 1.25, 2.19; at 6-month follow-up: RR: 1.94, 95%CI: 1.29, 2.91; at 12-month follow-up: RR: 1.78, 95%CI: 1.27, 2.51; at 24-month follow-up: RR: 1.57, 95% CI:1.11, 2.23). The findings remained similar among WLHIV (women living with HIV). Both procedures were equally safe. And the final conclusion was that: excisional treatment was more effective than ablative treatment with both procedures having similar safety profiles.

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HPV INFEKCIJA I CERVIKALNA INTRAEPITELNA NEOPLAZIJA U TRUDNOĆI – KLINIČKI ZNAČAJ I DALJI POSTUPAK

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Zbog godina života, visoke HPV pozitivnosti i specifičnih fizioloških, endokrinih i imunoloških promena - karcinom grlića materice je najčešći od svih ginekoloških maligniteta koji se detektuju u trudnoći. Incidenca ovog karcinoma koja se pominje u literaturi se kreće od 0,02 do 0,9 % (1). Incidenca CIN a je oko 0,1 na 100000 trudnoća i najveća je kod trudnica izmedju 25 i 35 godine života (2). Treća dekada života predstavlja i inače pik incidence za CIN.

HPV infekcija i cervikalne intraepitelne neoplazije u trudnoći zahtevaju specifičan pristup vezan za bezbednost majke i ploda. Mnoga pitanja vezana za ovu patologiju ostaju i dalje otvorena a podaci iz literature kontradikatorni.

HPV infekcija i trudnoća

Fiziološke promene u trudnoći vezane za hormonalne promene i promene u imunološkom sistemu u smislu imnotolerancije na fetus (kao semialogeni antigenu), olakšavaju perzistenciju HPV infekcije, pogotovo u prvom i drugom trimstru trudnoće (3).

Poznato je da smanjenje NK (natural kiler) ćelija u sklopu blage imunosupresije na početku trudnoće, povećava osteljivost trudnica na sve pa i virusne infekcije (4).

Sa druge strane kod trudnica sa povećanom imunloškom aktivnošću u sklopu rekurentnih pobačaja je zapažen statistički značajno manji procenat dokazane HPV pozitivnsoti (5).

Mnoge studije iznose podatke o većoj HPV prevalenci kod trudnih u odnosu na kontrolnu grupu žena (istog godišta) koje nisu trudne. Liu i saradnici iznose 16 , 82 % : 12 , 25 % , Luo 24,2 : 14,8 % u korist trudnica (6).

Sem imunitolerancije perzistenciji virusa doprinosi i glikokortikoidni response element GRE koji se nalazi u HPV regulatornom region koji reguliše promociju transkripcije viralnog genoma i replikaciju virusa a koji stimuliše povećanje steroidnih hormona koje se javlja u trudnoći (7).

Anti-HPV IgA antitela se povećavaju u trudnoći ali je njihova lokalna koncetracija u prvom trimestru trudnoće suprimirana faktorima lokalanog imunološkog odgovora (8).

Zbog svih pomenutih mehanizama na koje trudnoća deluje na HPV opisuje se ne samo veća pozitivnsot već i sporija eliminacija HPV. Tako jedna od studija pokazuje negativizaciju HPV kod žena koje niu trudne od 36 , 9 % dok je kod trudnica ona iznosla 26, 7 % (9).

Negativizacija HPV tokom trudnoće je u vezi i sa postpartalnom regresijom CIN a. Tako je kod trudnica kod koih je CIN regredirao pole porodjaja u 36,4 % došlo do klirifikacije HPV(10).

Iako se u radovima opsiuje nešto veća negativizacija na HPV kod žena koje nisu trudne u zadnjem trimestru trudnoće i u pospartalnom periodu dolazi do povećenja imunološke reakcije i ubrzanja HPV klirensa. Tako sumirano gledano posle jedne godine praćenja je klirens HPV kod trudnica

isti kao u žena koje nisu trudne (11). Nedostatak ovih studija je što ne uzimaju u obzir posebno tip virusa i viral loud.

Jedna skorija Švedska studija koja analizira klirifikaciju HPV u trudnoći, navodi pušenje kao nezavisni faktor koji ako je prisutan u trudnica dovodi do teže eliminacije HPV i češću detekciju HSIL promena (12).

Zbog svih navdenih mehanizama relativno teže eliminacije HPV u trudnoći, ispitivan je njen uticaj na: PPROM, abortus, prevremeni porodjaj i IUGR.

Pre svega treba naglasiti da postoje jasni dokazi o mogućnosti vertikalne transmisije HPV infekcije sa intaktnim plodovim ovokima. HPV DNA je tako detktovana i u plodovoj vodi, placenti, plodovim ovojima i pupčaniku (13).

Sve veći broj radova ispituje moguće uticaje HPV infekcije na izhod trudnoće.

HPV infekcija u trudnoći dovodi do modifikacije vaginalnih mikrobiota koja dovodi do imuno-inflamatornog odgovora koji može uticati na trudnoću i pokrenuti produkciju prostaglandina a samim tim i kontrakcija (14).

Što se tiče uticaja HPV na trofoblast, dokazano je da humani trofoblast poseduje receptore za HPV i olakšava njegovu replikaciju (15).

Sa druge strane E6 i E7 fragmet HPV virusa inhibišu sposbnost trofoblasta da se atherira za endometrijalne ćelije. Ovi delovi virusa smanjuju koncetraciju E cadherina, molekula koji je esencijalan za ćelijsku adheziju (16).

E5 fragment virusa ima toksični efekat kao viroporin koji doodi do kreiranja hidrofilnih pora na ćelijskoj membrani trofoblasta izazivajući osmotski stress i apoptozu (17).

Zbog ovakovog uticaja HPV infekcije na trudnoću sve veći broj radova ispituje mogući uticaj HPV infekcije na ishod trudnoće PPROM i prevremeni porodjaj.

Podaci iz literature su kontradiktorni. Većina studija koje ne dokazuju povezanot HPV infekcije sa prevremenim porodjajem, su malog uzorka metodološki nerigorozni sa različitim varijablama (18).

Ipak studije koje su dobro kontrolisane na velikom uzorku pokazuju direktnu povezanost PPROM a i perzistentne HPV infekcije.

Wiik et al u jednoj većoj studiji iz 2021godine, na 400.583 trudnica opisuju direktnu vezu pozitivnosti na onkogene HPV i PPROMa (19).

Značaj PPROM a i HPV infekcije za početak pobačaja i prevremenog porođaja posebno ističu Cotton i Cabaleo koji su na 2153 trudnica dokazali da HPV dovodi do prevremenog porođaja isključivo zbog povećane incidience PPROMa (20).

Slične podatke iznsoi Cho 27 , 3 % : 14,2 % PPROMa u korist HPV pozitivnih trudnica (21).

Neki autori posebno izdvajaju HPV infekciju udruženu sa CINom kao veći rizik za pojavu PP (prevremnog porodjaja) nego samo pozitivnost na HPV (22).

Drugi autori insistiraju na perzistenciji i dolaze do zaključka da samo perzsitentna HPV tokom trudnoće dovodi do PPROMa.

Kako god uzimnje uzorka iz tkiva posteljice kod normalne trudnoće i prevremenog porođaja pokazuje veći procenat detektovane HPV kod pobačaja i PP (24 , 9 : 8,3 %) (23).

Posle svih radova neki autori u svojim revijalnim radovima koji sumiraju veliki broj radova iz literature ističu da HPV infekcija dovodi do placentnog distresa, pa su trudnice koje su HPV pozitivne u dva puta većem riziku od pojave prevremenog porođaja u odnosu na žene koje su HPV negativne (24).

Sem prevremenog porođaja i pobačaja horioamnionitis izazvan HPV infekcijom koji dovodi do citolize i difunkcije posteljice može da dovede i do fetalnog inflamtornog response sindroma koji rezultira pojavom IUGR. Ford u jednoj većoj studiji na 31 827 trudnica ukazuje na direktnu povezanost HPV unfekcije sa intrauterinim zastojem rasta (IUGR) (25).

Još uvek mali broj radova na ovu temu zahteva pre donošenja konačnog zaključka jednu veću multicentričnu meta analizu.

HPV infekcija u trudnoći se može manifestovati kao:

- latentna (samo pozotivan HPV test),
- subklinička (detektuje se mikroskopom i kolposkopom), i
- klinički manifestna, koja može biti : benigna proliferativna (Kondilomata acuminata) i deregulisana neproliferativna sa integracijom virusa u DNK domaćina pokretanjem karcinogeneze CIN a i invazivnog karcinoma.

Što se tiće benignih manifestacije HPV infekcije u trudnoći, pre sveg se misli na Kondilome ž. U litraturi se navodi njihova retka udruženost sa CINom od nekih 2 % (26).

Problem kondiloma u trudnoći je njihova povezanost sa juvenilnom respiratornom papilomatozom (JORP). Jedna velika Danska studija na preko 10000 porođaja je pokazala statistički značajnu povezanost ove bolesti novorođenčadi sa dokazanim kondilomima. Ipak u ukupnom broju dokazanih slučajeva JORP taj rizik je mali i iznosu jedan slučaj na 140 porođaja majki sa istorijom Kondiloma (27).

Uklanjanje kondiloma tokom trudnoće nije pokazalo nikakav efekat u prevenciji JORP. S obzirom na vertikalnu transmisiju HPV i dokazanu HPV infekciju u plodovoj vodi i posteljici, elektivni carski rez ne smanjuje rizik od JORP (27).

Ako se odluči da se kondilomi tretiraju tokom trudnoće najbolje je to uraditi u zadnjem trimestru kada je rekurenca manja u odnosu na prva dva trimestra (28).

U slučaju oblitertivnih kondiloma koji vrše obstrukciju porodjajnog puta savetuje se porođaja Carskim rezom (29).

CIN trudnoća i porođaj

Fiziološke promene u trudnoći uzrokovane endokrinim faktorom, dovode do everzije cilindričnog epitela i prostranim najbržim procesom metaplazije koja se ne sreće ni u jednom periodu života. Ovakva brza metaplazija uz visoku HPV pozitivnsot i imunotoleranciju dovodi u početku trudnoće do većeg rizik za pojavu CINa.

Na sreću podaci iz litarture pokazuju da je cervikalni karcinom ipak redak u trudnoći (0,05 %) i da se oko 3 % prekanceroza dijagnoistikovanih u trudnoći u toku 1 godine potpartum komplikuje sa invazivnim karcinomom (30).

Prirodna evolucija i patogenza CINa tokom trudnoće se ne razlikuje u odnosu na period pre trudnoće. Ipak šansa za progresiju i detekciju invazivnog karcinoma u grupi trudnica sa CINom je veća u odnosu na opštu populaciju te je neophodan veći oprez i praćenje ovih trudnica od strane eksperta na svakih 8 do 12 nedelja u zavisnosti od nalaza i starosti trudnoće (31).

Dijagnostika premalignih promena u trudnoći se bazira na citologiji. Problem citologije u trudnoći je neadekvatnost uzoraka iz endocervikalnog kanala (uzorkovanje stapicem sa vatom), citoliza (uzrokovana endokrinim progesteronskim uticajem), prisustvo decidualnih ćelija u razmazu (zbog hiperhromazije ovih ćelija veći procenat lažno pozitivnih nalaza) (32).

Procenat patoloških citoloških nalaza u trudnoći se kreće od 2 – 7 % i sličan je sa procentom kod negravidnih žena (33).

Uzorkovanje štapićem sa vatom daje oko 29, 2 % nezadovoljavajućih citoloških nalaza. Sa druge strane uzorkovanje četkicom u trudnoći dovodi često do obilnih krvarenja i uklanjanja cervikalnog sluznog čepa (34).

Sa druge strane kolposkopija kao metoda koja treba da daje dijagnostičke smernice i eventualnu odluku o ciljanoj biopsiji, u trudnoći takođe pokazuje neka ograničenja. Hormonske promene u trudnoći dovode do hiperemije grlića materice, zadebljanje epitela (over ekspresija nalaza), hiperplazije endocervikalnih žlezdi, preteranu produkciju mukusa, prostrana polja imaturne metaplazije (slika nežnog mozaika), decidualizacija strome (neoangiogneza sa iregulkarnim krvnim sudovima), kontaktno krvarenje i prolaps vaginalnih zidova (35).

Kombinacija kolposkopije u citologiji u trudnoći daje senzitivnost u detekciji CINa od 85 – 93 % (36).

Ako kolposkopska impresija pokazuje sumnju na CIN III + lezije neophodna je histološka evaluacija. Jedino lezije koj su sumnjive na invaziju se tretiraju u trudnoći. Nažalost u trudnoći zbog straha od krvarenja i poštedne intervencije se najčešće uzima jedan uzorak koji je često i neadekvatan. Tako neki autori navode da je biopija u trudnoći u skoro 70 % neadekvcatna (37).

Ekscizione procedure se rade u trudnoći kod HSIL lezija za koje sumnjamo da su težeg invazivnog gradusa. U slučaju odluke za ekscizionu dijagnostičko terapijsku procedure u trudnoći, treba imati u vidu da su češće prisutne neadkvatne pozitivne posebno endocervikalne ivice i da su zbog izražene vaskularizacije, često prisutna obilna krvarenja koja u oko 10 % slučajeva zahtrevaju transfuziju (38).

Takođe je statistički značajno veći broj pobačaja i prevrenenih porođaja kod trudnica kod kojih se radi eksciziona terapija CINa u trudnoći (39).

Pojedini autori (Lantsman) sa druge strane, negiraju povećani broj komplikacija ekscizionih procedura na grliću materice u trudnoći (40).

Upravo iz ovih razloga kao i činjenice da intrapitlne neoplazije u trudnoći kao i van trudnoće imaju sporo evolucije u svim ostalim slučajevima kada postoje HSIL promene koje nisu sumnjive na invaziju, savetuje se princip - prati i čekaj. Interval praćenja je na 8 do 12 nedelja. U slučaju da se primeti pogoršanje nalaza savetuje se ponovn biopsija.

Svakako sve pacijentkinje sa dijagnostikovanim HSIL promenema u trudnoći zahtevaju postpartalnu evaluaciju, ali ne pre 8 nedelje od porođaja.

Što se tiče prirodne evolucije dijagnostikavnih CIN promena u trudnoći radovi iz literature su kontradiktorni. Uglavnom svi autori ističu da određeni procenat CINova pogotovo nižeg gradusa u velikom procentu regrediraju nakon trudnoće i porođaja. Tako jedan od novijih radova na velikom broju slučajeva izdvojenih HSIL promena u trudnoći opisuje regresiju kod 20 % trudnica, perzistenciju kod 76,1 % a samo u 3, 2 % progresiju bolesti. U istom radu se naglasšva da je procenat regresije veći kod vaginalnog porođaja u odnosu na carski rez (27 :15 ,2 %) a da je i progresija bila dva puta veća kod porodjaja carskim rezom (6,5 : 2, 7 %) 41 .

Što se tiče podataka o progresiji CINa u invazivni karcinom opet postoje kontradiktorni podaci. Dok Origoni sa sardanicima navodi ekstermno retku progrsiju u invazivni karcinom (IK) od 0,4% , Cappolilio sa saradnicima prati samo teže CIN III promene i navodi nešto veću progresiju u trudnoći od 13 % od toga je bilo 20 % MIK (42.43).

Kaplan u svom radu ističe da su promene niskog gradusa samo u 6 % slučajeva postpartalno progredilo i to u CIN višeg gradusa, dok su CIN promene najtežeg gradusa (CIN III) u 11 % progredile u IK (41).

Prosečno zbirni procenat regresije koji se navodi u radovima se kreće od 16 – 69, 5 % CIN II – III promena (43).

Mehanizam regresije je još uvek nepoznat predpostavlja se da je u pitanju prestanak hormonskog uticaja i modulacije imunog sistema (44).

Još jedna veća studija pokazuje da kod 69,3 % trudnica dolazi do regresije, a kod 3.9 % progresije CIN 2/ 3 promnba u trudnoći (45).

Način završavanja porođaja i regresija CIN je još jedna od kotradiktornih podataka iz literature. Ipak najveći broj radova ističe da je procenat regresije CINa i procenat pogresije manji kod vaginalnog porođaja.

Dok Shuster ne nalazi razliku u regresiji u odnosu na način završavanja, Chung nalazi visoku statističku značajnost od 21% progresije CINa kod porođaja carskim rezom, a 14 % kod vaginalnog porođaja (44,46).

Ukupan procenat invazivnog karcinoma grlića materice gledano u periodu trudnoće i posle porođaja u prvoj godini iznosi od 1 – 3 % (47).

Kakvi god bili procenti evolucije CIN a u radovima, činjenica je da trudnice kod kojih je dijagnostikovan CIN visokog gradusa u trudnoći imaju veći rizik u dijagnozi invazivne bolesti i zahtevaju pažljivi postpartalni monitoring.

Mehanizam koji kod vaginalnog porođaja dovodi do češće regresije CIN je takodje nepoznat. Predostavlja se da jedan razlog cerviklna trauma tokom porođaja i pokretanje reparornih remodulirajućih inflamatornih odgovara. Drugi mogući razlog je ishemija koju grlić trpi tokom porodjaja pritiska glavice i gubitak displastiučnih ćelija tokom prolaska glavice (42).

Takođe jedno od mogućih objašnjena veće progresije CINa kod porođaja koji su završeni carskim rezom je da je odluka za carski rez bila češća kod trudnica koje su imale kolposkopsku sliku težeg izgleda od epitelne (sumnjivu na invazivnu bolest), pa se u cilju prevencije komplikacija i krvarenja u porođaju češće donosila odluk za carski rez (42).

Umesto zaključka

Nakon svega postavlja se pitanje “Imamo li smernice u praćenju tretmanu i planiranju porođaja kod trudnica sa HPV infekcijom i CINom?”.

Postoje preporuke ASCCP koje su revidirane tokom 2021. godine. Trudne žene imaju isti stepen rizika od progresije CINa kao i žene koje nisu trudne. Ekscizioni tretman u trudnoći se preporučuje samo u slučaju kolposkopske sumnje na invazivnu bolest odnosno ako je kolposkpski stepen rizika za CIN 3 + promene > od 60 % (48).

Pored svih preporuka ono o čemu treba stalno da mislimo je da su trudnice specifična populacija kod koje se pre donošenja odluke o tretmanu treba imati u vidu rizik po fetus ali i potencijalna

mogućnost nedetktovane maligne bolesti majke. Onkološke smernice će se menjati sa razvojem neonatologije i mogućnostima neonatologa da bezbedno zbrinu prevremeno rođenu decu.

Intreval pregleda u trudnoći treba da bude na 12 do 24 nedelje u zavisnosti od starosti trudnoće, imunološkog stanja trudnice, težine lezije i iskustva kolposkopičara. Svakako mora imati individualni pristup i u težim diferencijalno dijagnostičkim slučajevima konsultovati eksperta iz oblasti dijagnostike patologije cerviksa.

Najranije 4 nedelje nakon porodjaja po završtku remodulacije i formiranja grlića treba uraditi dijagnostičku reevaluaciju od koje će zavisti odluka o daljim dijagnostičkim i terapijskim procedurama.

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FERTILITY SPARING AND ONCOFERTILITY

ONCOFERTILITY: A BRIDGE BETWEEN ONCOLOGY AND REPRODUCTIVE MEDICINE

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The age of women in the reproductive period who are childless is increasing in most countries [1]. Many of these women are deciding to postpone pregnancy for later in life, mostly in the desire to finish school and start a career. However, many of them are still wishing to give birth [2]. Delayed motherhood is associated with more frequent multiple pregnancies, higher demands for IVF, a higher rate of complications during pregnancy, a higher frequency of cesarean sections and, most importantly, a higher frequency of cancer.

On the other hand, cancer is more often diagnosed in the early stages, when treatment with conservative methods is successful, even in gynecological cancer. Thanks to advances in therapy over the past 25 years, the outcome of young cancer patients has improved significantly, with an overall 5-year survival rate of over 80% [3]. Most young women diagnosed with malignancy can expect to live decades after treatment, making many life issues such as future fertility more important.

- **The importance of fertility care in cancer patients**

In the initial stages of treatment, the concern about future fertility is usually secondary to the concern for survival. A woman diagnosed with cancer must process complex treatment information. The decision-making process for accepting the proposed therapeutic modalities has long been recognized as lengthy and particularly difficult for women [4]. And while the problem of fertility may not be in the first place at the time of diagnosis, over time it becomes more important.

The turmoil experienced by women who are simultaneously diagnosed with cancer and possible infertility leaves emotional consequences, which are described as “adding the insult to injury” or “double trauma”, especially if the localization of the disease is such that it directly affects the reproductive organs [4].

For some women, infertility may be unexpected because they have not been able to process or remember the information about the treatment side effects which oncologist presents to them during the conversation about treatment.

Research has shown that infertility, as an unique health problem, has a level of suffering comparable to that of coping with a life-threatening illness such as cancer [5]. Infertility itself is associated with significant psychological distress, with levels of depression being twice as high as in women without this problem, while quality of life is reduced in the areas of emotional well-being, relations with others and sexuality [6].

Clinicians, researchers and societies of cancer survivers are beginning to recognize infertility as a late effect of cancer treatment, which negatively affects the quality of life of young cancer patients, as well as the importance that building a family has for these women. Realizing the importance of this problem, the American Society of Clinical Oncology (ASCO) has published recommendations on preserving fertility in patients being treated for cancer [7]. These guidelines

instruct oncologists to discuss with patients the risk of infertility after treatment for malignancy. They should be prepared to discuss various fertility options or to refer the patient to a reproductive medicine specialist.

Despite the fact that ASCO published these recommendations back in 2006 and has supplemented them twice since then [8], research among America's most eminent oncologists has shown that less than 50% of them refer patients to reproductive medicine specialists [9]. In a similar study conducted in France, only 46% of all surveyed doctors stated that they discussed infertility risks in patients of reproductive age, and even fewer (22%) referred them to a fertility center before starting treatment [10]. Only 14% of docotrs were considered themselves versed in fertility preservation techniques, and ovarian transposition was the most frequently mentioned technique during consultations. Doctors believe that they lack the knowledge and tools that would enable them to provide patients with appropriate information.

- **Oncofertility**

Understanding these problems, Dr. Teresa K. Woodruff from the Department of Obstetrics and Gynecology at the Northwestern University in Chicago, introduced the term "oncofertility" in 2006 to refer to a new field of medicine that links oncology to reproductive health [11]. Oncofertility includes all procedures for the treatment of malignant disease with the aim of preserving fertility, but without compromising the oncological outcome.

During the reproductive period, breast cancer is the most common malignancy with the increasing incidence in young women. Hematologic malignancies, melanomas and thyroid cancer also have a high incidence in the younger population. Out of the total number of women diagnosed with malignancy in Europe, 5.42% are under the age of 40 [12]. The largest share of young women in the number of all patients is seen in cervical cancer, accounting more than 22%. This percentage is even higher in some less common malignancies, such as CNS tumors (38%) or bone and joint cartilage tumors (36%) [12].

Treatment of gynecological cancer, as a rule, is associated with permanent loss of function of the reproductive organs, either due to surgical removal, or as a result of radio or chemotherapy. Chemotherapy used in breast cancer and hematological malignancies during the pre-menopause often reduces fertility or leads to permanent ovarian failure. For example, after adjuvant chemotherapy for breast cancer with existing regimens, only 10% to 20% of women under the age of 35 develop permanent amenorrhea. The risk of ovarian insufficiency increases tenfold for women treated in their late thirties, so that up to 90% of women over the age of 40 remain with permanent ovarian failure [13].

However, even in those cases, preservation of fertility is possible. Today, fertility preservation techniques are available before starting cancer treatment. New reproductive technologies are becoming more widely available and more successful and can give hope to those who have no other pregnancy options.

- **Options for preserving fertility in cancer patients**

Traditional treatment of gynecological malignancies with radical surgery, pelvic radiotherapy, and/or chemotherapy leads to infertility. With the growth of knowledge about the biological behavior of tumors, in modern oncology, the approach to surgical treatment has shifted from radical procedures to less radical procedures. Today, under strictly controlled conditions, the treatment can be adjusted to the extent of the disease.

It has been confirmed that the oncological outcome after fertility sparing surgery in early cervical cancer is equal to that after a radical approach. Surgical treatment options to preserve fertility in these patients include excision procedures (loop excision, conization) and radical vaginal or abdominal trachelectomy [14].

Hormone therapy has emerged as an option for young patients with early-stage well-differentiated endometrioid endometrial cancer. High remission rates have been described after applying hormone therapy to preserve fertility. This approach is based on the use of progesterone, which acts as a protective factor for estrogen-induced growth and proliferation of the endometrium. This typically occurs in young women with a history of infertility, obesity and polycystic ovary syndrome, all conditions associated with prolonged and unopposed estrogen exposure [15].

In young patients with ovarian cancer, unilateral salpingo-oophorectomy with appropriate staging of the disease, gives the possibility of preserving fertility, if the tumor is limited to one ovary and has favorable characteristics that place it in the category of low risk [16].

When other malignancies requiring chemotherapy are concerned, temporary ovarian suppression with gonadotropin-releasing hormone (GnRHa) analogues during chemotherapy to protect ovarian function and fertility is a widespread option that has been shown to be effective in preserving ovarian function and possible fertility in young women with cancer, especially those with breast cancer [17]. It is important to know, however, that temporary ovarian suppression with GnRH during chemotherapy is not considered as an alternative to embryo/oocyte cryopreservation, which remains the first options to be discussed with cancer patients interested in preserving fertility. This option should be considered valid only for those who have failed previous cryopreservation procedures or when surgical procedures are contraindicated.

When it comes to the possibilities brought by reproductive medicine, today, techniques for preserving fertility before starting the treatment of malignant disease are already widely developed. Most women can delay treatment for a few days until the ovarian tissue is surgically removed, or for up to two to three weeks in order to achieve a cycle of ovarian stimulation and collect oocytes. These oocytes can be preserved in the unfertilized state by cryopreservation or can be used to create an embryo which is then stored by cryopreservation. In addition, it is necessary to provide information on modern options for assisted fertilization, including reproduction with the help of a third party. Patient-independent reproduction includes oocyte donation and surrogate mother. New reproductive technologies are becoming more widely available and successful and can give hope to those who have no other options for pregnancy [18].

- **Requirements for fertility preservation**

Fertility preserving treatment can only be applied if the tumor is in the initial stage and has favorable prognostic features clinically and pathologically, with clear indications and under strictly controlled conditions. A decision on this can only be made by a multidisciplinary team.

A multidisciplinary team that includes a gynecologist-oncologist, a reproductive medicine specialist, a medical oncologist, a pathologist, as well as specialists from all other fields involved in treatment, especially psychologists and social workers, should take care of the patient and her family, provide them with the right information and guide them through the decision-making process. Such a strategy must be tailored to each case individually and must respect the patient's wishes. It must be tailored to each case individually, and the final decision should be the product of understanding treatment options, medical advice, recognition of the patient's personal values and beliefs, and awareness of available options for the entire process.

Helping patients to accept treatment requires absolute honesty, the most accurate medical information and detailed advice. Effective communication, which includes active listening, expressing empathy, discovering and reacting to emotional signs and sensitivity to the experience of the disease, in a patient with cancer leads to improved psychological adjustment, respect for the treatment plan and satisfaction with care. And acceptance of a certain treatment option and careful monitoring are the basic requirements for successful treatment.

Patient counseling regarding future fertility should include a discussion not only about the side effects of the treatment on fertility, but also about the course of the future pregnancy and the potential risks for the child. Psychosocial outcome studies in women after treatment for malignancy revealed that women had long-standing fears about their ability to carry a normal pregnancy, but were also concerned that pregnancy would increase the risk of disease recurrence. If they remain pregnant, women additionally struggle with worrying about the health risks of pregnancy and the risk of possible genetic problems in children.

Doctors treating young patients for malignancies should be aware of the negative effects of cancer treatment on fertility and ways to minimize these effects. If the toxic effects of treatment on the gonads cannot be avoided, they should have knowledge about the possibilities of preserving fertility. Although many doctors who treat cancer in young people are sensitive to these issues, oncologists have traditionally focused on providing the most effective treatment, and less on the quality of life after treatment. Therefore, they must know to whom to refer patients who want to preserve fertility. On the other hand, specialists in reproductive medicine must be aware that the fact that someone has been diagnosed with cancer or that she has survived the acute or prolonged phase of dealing with cancer, distinguishes a patient with cancer from other patients with infertility. They must cooperate with the oncologist, because there are numerous differences in the type of tumor and the method of treatment, which requires that the treatment strategy be adjusted to each individual case.

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NEW APPROACHES TO FERTILITY-SPARING MANAGEMENT IN CERVICAL CANCER

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Primary treatment of early or localized cervical cancer is based on surgical treatment. Advances in our understanding of disease mechanisms lead to changes of also surgical approaches to improve patient outcomes. Herein some recent advances and future challenges in cervical cancer surgery in patients wishing to retain fertility are presented.

The first challenge in early cervical cancer is the decision on the surgical approach. Through mainstreaming the use of minimally invasive surgical approaches, laparoscopic techniques were also commonly introduced into the treatment of cancers. Prospective trials and meta-analyses have shown that laparoscopic treatment is feasible in most women with endometrial cancer, but has shown inferior outcomes in cervical cancer. The LACC trial has reset open surgery again to the current golden standard of surgical treatment. Studies are currently addressing the mechanisms underlying these findings.

The second challenge is the decision on when to escalate and de-escalate the treatment of lymph nodes in cervical cancer. In recent years, studies such as SENTIX and similar designs have shown the feasibility of using sentinel-lymph node biopsies instead of lymph node dissections as treatment options. The question is how to best select patients deemed as high or low risk for lymph node dissections or sentinel-node biopsies. Understanding different risk-to-recurrence profiles has enabled us to develop trials currently running on the understanding of using the risk profiles in deciding surgical treatment in the future.

Cervical cancer is the fourth most common cancer among women worldwide and affects women at a significantly younger age than most other malignancies. Approximately 42% of the women diagnosed with cervical cancer are ≤45 years old. Combined with a trend towards delayed childbearing, many of these women may desire to preserve their fertility at the time of cancer diagnosis. Recent studies on the effects of treatment-associated infertility among young cancer survivors have quantified the impact of treatment-induced infertility which results in long-lasting emotional and physical distress (1).

In Slovenia, among 104 patients diagnosed with cervical cancer in 2019, there were 50 patients (48.1%) younger than 50 years, 37 (35.6%) younger than 45 years, and 29 (27.9%) patients younger than 40 years (2).

Although radical hysterectomy, with or without neoadjuvant chemotherapy or pelvic radiation, remains the treatment of choice for more advanced diseases, women with stage IB1 or lower may consider fertility-sparing surgery.

Fertility-sparing surgery (FSS) is a term that includes both radical trachelectomy (RT) (including vaginal, abdominal, and minimally invasive approaches) and conization or simple trachelectomy. RT involves almost complete resection of the cervix, upper vagina, and surrounding tissue.

Although the risk of cancer recurrence remains low, there are significant risks of infertility and perinatal complications for women who do conceive.

Prior studies have reported highly variable pregnancy rates after FSS, making it very difficult to counsel women who want to know what their chances of pregnancy are if they choose this approach. Vaginal and minimally invasive RT approaches may have more favorable reproductive outcomes, with similar risks of recurrence. However, the reported pregnancy rates vary considerably, ranging from 5% to 88% for vaginal RT and from 13% to 67% for abdominal RT. Reported live birth rates among these pregnancies have also been highly variable, with rates of 27% to 80% for vaginal RT and 16% to 100% for abdominal RT (with 50% of births very preterm). One of the major limitations of many studies has been that it is not clear how many of these women were actively trying to conceive or had access to reproductive care, so there remains considerable heterogeneity among women who undergo FSS (3).

Less radical fertility-sparing surgery with SLN is safe in cervical cancers < g2 cm at the largest diameter and infiltrating less than half of the cervical stroma (4).

The guidelines recognize various approaches, depending on the tumor stage and other risk factors such as histotype and lymphovascular positivity. Much more debate has centered around the boundary within which these treatments should be considered. Indeed, these are methods to be reserved for early-stage cervical carcinoma (ECC), but tumor size may represent the most significant limitation. In particular, there is no consensus on the strategy to be adopted in the case of ECC ≥ 2 cm.5, of the five possible principal FSSs (conization, vaginal trachelectomy, minimally invasive trachelectomy, abdominal trachelectomy, and neoadjuvant chemotherapy combined with conization or trachelectomy), there is evidence of the inadequacy of the vaginal trachelectomy approach described by Dargent. The minimally invasive and abdominal approaches should also be set aside in parallel with the valid evidence for traditional radical hysterectomy surgery. Conversely, there is no consensus on the gold standard between radical abdominal approaches and neoadjuvant chemotherapy (NACT). Many referral centers use opposing strategies, making this field an open debate. In addition, more confusion is related to the fact that tumors ≥ 2 cm in size are at higher risk of recurrence regardless of FST. FST should be considered a non-routine approach for the management of ECC ≥ 2 cm and deserves further investigation (5).

In women with early-stage cervical cancer (ECC), fertility-sparing surgery techniques include laparoscopic, abdominal, or vaginal radical trachelectomy (RT) and cold knife conization (CKC) with or without pelvic lymph node dissection. Currently, RT is proposed as FSS, an alternative to radical hysterectomy, in patients with ECC staged IA1-IB1, as by the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification. According to a recent meta-analysis, RT and CKC present similar oncologic outcomes in terms of recurrence rates, but CKC presents better obstetrical outcomes in terms of pregnancy rate (36% for CKC vs. 20% for RT). The National Cancer Comprehensive Network (NCCN) guidelines suggested RT as an alternative to radical hysterectomy (RH) in young women desiring to preserve fertility with disease limited to cervix, tumor size < 2 cm (or < 2.5 cm if exophytic lesion), absence of parametrial extension, an estimated distance of ≥ 1 cm from the proximal aspect of the tumor to the internal os, absence of lymphadenopathies or metastatic disease. Some authors have proposed neoadjuvant chemotherapy (NACT) followed by CKC as a safe and effective approach in ECC. MRI is reported to be very accurate in selecting patients eligible for FSS in tumor size evaluation and deep stromal invasion assessment. In the evaluation of parametrial invasion, the specificity and negative predictive value of MRI were 97%

and 100%, respectively. Furthermore, MRI has demonstrated very high sensitivity and specificity in the assessment of internal os involvement, 90% and 98%, respectively (6).

Options for Fertility-Sparing Treatment

- Radical Trachelectomy

Radical trachelectomy, which entails en bloc removal of the cervix, upper vagina, and parametria, while leaving the uterine body and fundus in situ, has been a widely accepted fertility-sparing procedure since its development in 1987 by French surgeon Daniel Dargent. It is the current standard of care for women with early-stage cervical cancer desiring fertility preservation. Different surgical approaches have been used including the classic Dargent radical vaginal trachelectomy with laparoscopic pelvic lymphadenectomy, abdominal trachelectomy, and total laparoscopic or robotic-assisted laparoscopic routes. The ideal candidate for radical trachelectomy should be of reproductive age, have low-risk histology (squamous, adenocarcinoma, adenosquamous), have negative lymph nodes on imaging, and have a small lesion (≤ 2 cm). Pelvic MRI is recommended to rule out upper endocervical involvement. While radical trachelectomy has been associated with a low rate of recurrence, it is associated with similar risks to radical hysterectomy including bladder dysfunction, lymphocele, hematoma, and lymphedema.

- Cervical Conization and Simple Trachelectomy

A cone biopsy, which is defined as the excision of a cone or wedge-shaped piece of the uterine cervix including the transformation zone, is accepted as treatment for stage IA1 disease without evidence of LVSI in women who desire fertility preservation provided there are negative margins. Outside of this cohort, the NCCN recommends pelvic lymph node assessment with lymphadenectomy in addition to the fertility-sparing procedure. Although systematic lymphadenectomy is the standard of care at many treatment centers, it has been shown that the rate of lymph node metastases is 2.9% in patients with early-stage disease and no LVSI, and 0% in patients with either stage IA2 disease or stage IB disease with grade 1 tumors.

Simple trachelectomy is the removal of the uterine cervix without parametrial resection (thus, the difference from cervical conization is a matter of degree of excision), and is usually done in association with pelvic lymphadenectomy.

- Neoadjuvant chemotherapy followed by surgical resection

Many women desiring fertility preservation have cervical tumors that do not meet the existing criteria for a fertility-sparing approach. Neoadjuvant chemotherapy has been used in this setting to reduce tumor size to facilitate surgical resection. This has been studied previously in women with larger tumors > 2 cm who desired future fertility and was shown to reduce nodal metastases, parametrial invasion, and tumor size.

In 2011, Fokom Domgue et al. performed a literature review of 47 cases of stages IBI–IIA cervical cancer and calculated a crude recurrence rate of 8.5% and a crude mortality rate of 2.1% using this approach. The authors then reviewed obstetrical outcomes from these studies and concluded that the live birth rate was 78.6% (7).

While neoadjuvant chemotherapy is accepted as a treatment option for tumor sizes between 2 and 4 cm, there is less data regarding its role in tumors < 2 cm (8, 9).

In 2021 a review of 29 studies on cervical cancer, involving 2432 patients, LLETZ, conization, or simple trachelectomy with or without pelvic lymphadenectomy was performed. In total, 28

(3.6%) patients had recurrent disease and 6 (0.8%) died of disease during a median follow-up of 53 months (range 9–131 months). More detailed information was available on 23 recurrences. Significantly more recurrences occurred in patients with FIGO stage IB1 (3.1%) and IB2 (5.6%) disease than in patients with FIGO stage IA1 (0.2%) and IA2 (0.7%) disease. SCC recurred in 0.7% of patients, adenocarcinomas in 1.1%, and adenosquamous cell carcinomas in 4%. The differences between these histological subtypes are statistically not significant (10).

From the above, it becomes clear that counseling by experts is required to help patients make the life-changing decision whether or not to undergo FSS. However, it is difficult to become an expert, as the situation is rare. According to the WHO, a disease is rare if the number of affected people is less than 5 per 10,000. The care for patients with rare diseases is challenged by the small number of patients, lack of validated treatment options, scattering of patients across the country, and limited clinical expertise. Although cervical cancer does not meet the official criteria of a rare disease, the care for adolescents and young adults with gynecological cancer and a wish to preserve fertility is a unique situation encountering the same problems described for rare diseases. Tailor-made medicine in oncological care is a rapidly growing approach where, based on malignancy-specific characteristics, individualized treatment is given. Patient-specific characteristics are equally important to consider for a specific treatment. Adolescents and young adults have their unique social situations, personal beliefs, and preferences. The outcome of a process of shared decision-making is important for tailor-made care. Fertility decisions are not only difficult for the patient but also for the treating gynecologist. Therefore, management of these patients should involve a (experienced) multidisciplinary team. It is generally accepted that exposure of a medical specialist to a rare health problem or situation is related to knowledge and quality of care. Participation in clinical trials or registration studies is indispensable, as this is the only way to evaluate and improve the quality of care. International collaboration will facilitate achieving larger patient numbers and the development of guidelines (10).

In conclusion, fertility-sparing therapy (FST) is an oncologically valid alternative to radical hysterectomy for young patients with cervical cancer < 2 cm (squamous cell carcinoma and HPV-related adenocarcinoma) who want to preserve the option to have children. Before initiating fertility-sparing therapy, consultation at an onco-fertility center and discussion in a multidisciplinary tumor board is recommended. Counseling of eligible patients should encompass the oncologic and obstetric risks related to this type of management as well as the risk of FST abandonment if there are positive resection margins or LN involvement. FST should be performed exclusively in gynecological-oncological centers with comprehensive expertise in all types of these surgical procedures (11).

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CERVICAL CANCER IN PREGNANCY

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Cervical cancer (CC) detected in pregnancy is extremely rare and is usually detected in the early stages; IA-IB1 according to the FIGO classification and pregnancy itself should not affect survival with standard oncological treatment. The discovery of CC in pregnancy requires a multidisciplinary approach with the aim of curing the pregnant woman and, in the event of continued pregnancy, providing the best outcome for the fetus.

Recently, joint recommendations of the European Society of Gynecological Oncology, the European Society of Radiotherapy, and the European Society of Pathology were published, which also include the basic instructions and procedures required for the treatment of cervical cancer in pregnancy and are presented in this lecture.

Since the incidence of CC in Slovenia is continuously declining, we have only isolated cases of CC in pregnant women. Nevertheless, few cases are presented, and the decisions for treatment discussed

Introduction

Cervical cancer (CC) detected in pregnancy is extremely rare, according to some estimates, the rough incidence is 4/100,000 pregnancies, or the proportion of CC in pregnancy is supposed to be 1-3/1000 of all CCs. In most pregnant women, CC is detected in the early stages; IA-IB1 according to the FIGO classification and pregnancy itself should not affect survival with standard oncological treatment.

The discovery of CC in pregnancy requires a multidisciplinary approach, involving a gynecological oncologist, an oncologist, and a perinatologist, to cure the pregnant woman and, in the event of continued pregnancy, provide the best outcome for the fetus. The pregnant woman must receive all the necessary information regarding the risks for the outcome of oncological treatment and possible perinatology complications. Factors that influence decisions related to the treatment of a pregnant woman with CC are: gestational age at diagnosis, histological type and stage, and wishes to preserve reproductive capacity or pregnancy.

- Treatment recommendations

Recently, joint recommendations of the European Society of Gynecological Oncology, the European Society of Radiotherapy, and the European Society of Pathology were published, which also include the basic instructions and procedures required for the treatment of cervical cancer in pregnancy.

- *Stage IA*

For stage IA, conization or trachelectomy is recommended in early pregnancy, and if detected after the first trimester, the procedure is postponed until the end of pregnancy.

- *Stage IB1*

When CC is detected within the first trimester, most women decide to terminate the pregnancy and undergo oncological treatment. A similar decision can be made even before the end of the second trimester. For young patients who wish to preserve fertility, we can decide on a radical

trachelectomy and pelvic lymphadenectomy, if the criteria for procedure are met. When CC is detected in the third trimester, the pregnancy is usually terminated by cesarean section, if possible after >32 weeks of pregnancy, and in the same act, we proceed with radical hysterectomy and pelvic/bi-aortic lymphadenectomy. Radical surgical treatment can also be performed after cesarean section and partial involution of the uterus.

- Postponement of oncological treatment

For pregnant women who want to keep the pregnancy, we have to decide on postponing oncological treatment in the last two trimesters. Cases of radical vaginal and abdominal trachelectomy with successful preservation of pregnancy are described in the literature. Postponing oncological treatment at the end of the second or beginning of the third trimester should be relatively acceptable for small tumors. In stage IB1, the delay in oncological treatment should not be longer than 12 weeks. The risk of relapse due to delay in oncological treatment is around 5%, i.e. similar to non-pregnant patients. Treatment with neoadjuvant chemotherapy with cisplatin is considered if >14 weeks of pregnancy have passed, and treatment is continued until >32 weeks of pregnancy when labor should be induced and radical hysterectomy with pelvic/bi-aortic lymphadenectomy performed simultaneously.

- Stage IB2 to IVA

Termination of pregnancy and initiation of standard oncological treatment is the most common choice when CC is detected in advanced stages at the beginning of pregnancy. A prerequisite for postponing oncological treatment is the absence of metastatic disease. Even with negative lymph nodes, treatment should not be delayed for longer than 6 weeks in stage IB2; in the case of a longer delay in oncological treatment, neoadjuvant chemotherapy with cisplatin is recommended until the 32nd week, when delivery by cesarean section and continuation of radiation treatment should be initiated - chemotherapy.

- Completion of labor with delayed CC treatment

Bleeding and the possibility of spreading cancer during vaginal delivery are just two of the reasons against vaginal delivery. The cesarean section thus represents the first choice for completion of childbirth.

- Survival or recurrence of the disease when standard oncological treatment is postponed

Numerous individual cases have been published in the literature, in which survival, depending on the stage, did not differ significantly from non-pregnant patients with CC. In the only larger series, Kohler reported an overall survival of 95.7% at a follow-up time of 7 to 88 months in 21 pregnant women in whom treatment was delayed with neoadjuvant chemotherapy.

Our data

Because of the active screening program (ZORA) in Slovenia, the discovery of invasive CC in pregnancy is extremely low. In the last 20 years, only 6 pregnant women with invasive CC were detected. In three cases cancer was diagnosed in the first trimester. All three had a termination of pregnancy and radical trachelectomy with pelvic lymphadenectomy. Two conceived again and delivered near term. Unfortunately, one of those two recurred one year after delivery.

Two had CC diagnosed at the beginning or the end of the third trimester. One had a radical hysterectomy immediately after a cesarean section and the other postponed a radical

hysterectomy. The last one had HGSIL diagnosed in the first trimester and stage IIB at the end of the pregnancy.

Conclusion

The discovery of CC in pregnancy does not change standard oncological treatment procedures, in case of postponing it at the expense of continuing the pregnancy, one of the possible choices is neoadjuvant chemotherapy. Each pregnant woman must be treated individually, multidisciplinaryly, and with extensive informed consent.

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EFIKASNOST I BEZBEDNOST RAZLIČITIH PROTOKOLA KONTROLISANE OVARIJALNE STIMULACIJE U PREZERVACIJI FERTILITETA KOD ŽENA SA KANCEROM DOJKE

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Najčešći malignitet kod žena u reproduktivnoj dobi je karcinom dojke [1]. Incidenca karcinoma dojke se povećava sa starenjem, dijagnoza se najčešće postavlja u reproduktivnom dobu, sa 10.5% novih slučajeva godišnje, u grupi ispod 45 godina [2].

Zahvaljujući sve ranijoj detekciji, uspešnijoj terapiji i podizanju opšte svesti o ovom kanceru, i preživljavanje je sve veće. Naime, 88% žena sa dijagnozom karcinoma dojke pre 45 godine, preživeće minimum petogodišnji period [3].

Međutim, stope trudnoća kod pacijetkinja preživelih od kancera dojke su oko 70% niže od očekivanih u odgovarajućoj reproduktivnoj populaciji [4,5]. Nasuprot tome, oko 50% žena sa karcinomom dojke, želi da se ostvari u ulozi majke kasnije u životu ili nije u potpunosti završilo svoje želje u pogledu reprodukcije [6] .

Uz opšti globalni trend za odlaganjem reprodukcije, uz zahteve za emancipaciju žena, obrazovanje i finansijsku sigurnost, u obzir treba uzeti i opadanje fertilne sposobnosti i ovarijalne rezerve posle 35 godine. Ove tendencije se odražavaju i na žene sa karcinomom dojke, što rezultuje povećanim brojem zahteva za prezervacijom fertiliteta.

Uzroci koji mogu objasniti nisku stopu spontanih trudnoća kod žena sa lečenim kancerom dojke, su sledeći [7]:

- Toksičnim efektima hemioterapije na ovarijum
- Dugom endokrinološkom terapijom
- Preventivnom ovarijektomijom
- Strahom i uverenjem da će trudnoća dovesti do relapsa bolesti

Mlađe žene, sa često agresivnijim formama tumora, zahtevaju gonadotoksičnu terapiju uz posledičnu endokrinu terapiju (sa pozitivnim hormon receptorima karcinom dojke), koje mogu ozbiljno ugroziti fertilitet.

Prema podacima, u vreme dijagnoze karcinoma dojke, 50% pacijetkinja održava zabrinutost zbog mogućeg infertiliteta nakon tretmana, ali svega oko 10% se opredeli da iskoristi neku od strategija za prezervaciju fertiliteta [8].

Prezervacija fertiliteta i posedovanje osigurača u vidu krioprezerviranog materijala je veoma bitna kod žena preživelih od ca dojke, i čini jednu od glavnih stavki njihovog doživljaja i vrednovanja kvaliteta života.

Žene, koje su u sklopu terapije primile adjuvantnu sistemsku terapiju imaju 14% šanse za trudnoću, u okviru 40% niže stope šanse za ostvarivanje trudnoće u odnosu na opštu reproduktivnu populaciju.

Sve pacijentkinje u reproduktivnom dobu sa dijagnozom karcinoma dojke, moraju dobiti informaciju pre započinjanja lečenja o mogućim negativnim efektima onkološke terapije na fertilitet i koje su opcije prezervacije fertiliteta na raspolaganju.

Do sada dostupni podaci i rezultati istraživanja, ukazuju da trudnoća kod preživelih nakon terapije Ca dojke, ne dovodi do povećanog rizika za recidiv bolesti, bez obzira na hormonski status, pa je svaka indikacija za prekid trudnoće iz terapijskih indikacija neopravdana [9,10] . Optimalno vreme za trudnoću, nakon terapije karcinoma dojke, još uvek nije jasno određeno i definisano, ali se preporučuje period od najmanje dve godine, kada je najviši rizik recidiva [11] .

Studija POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive BC, Clinical Trials), istražuje uticaj prekida upotrebe endokrinološke terapije za mlade pacijetkinje sa hormon receptor pozitivnim tumorima, koje žele trudnoću, na povećanje rizika za recidiv karcinoma dojke, kao i ishode trudnoće i stanja deteta [12].

Kontrolisana ovarijalna stimulacija

Kontrolisana ovarijlna stimulacija (KOS) je tretman u cilju dobijanja zrelih oocita (MII) uz povećanje niove serumskog stradiola (prosečno 2000 pg/ml) do nekoliko puta u odnosu na fiziološke u okviru faze menstruacionog ciklusa (oko 250 pg/ml). Ovo su nalazi klasičnih protokola stimulacije u okviru IVF (in vitro fertilizacija), ali su za krioprezervaciju u onkofertilitetu neprihvatljivi i nepoželjni. Izloženost ovakvim koncentracijama estradiola nije preporučljiva kod žena sa kancerom dojke, pogotovu onim sa pozitivnim hormonskim receptorima. Pojavu OHSS (ovarijalni hiperstimulacioni sindrom) ne bi trebalo uopšte dozvoliti, odnosno treba ga preventivno izbegavati po svaku cenu. Stoga se postupci stimulacije ovulacije moraju prilagoditi i promeniti u postupcima prezervacije fertiliteta kod maligniteta. Naime, sa jedne strane moramo težiti da dobijemo optimalni broj oocita (8 do 9 oocita) u postupku stimulacije ovulacije, pri tome često imamo priliku za samo jedan pokušaj, a sa druge strane ne smemo dozvoliti pojavu komplikacija odnosno OHSS. Sa stanovišta reproduktivne medicine, na osnovu procene ovarijalne rezerve, treba selektovati kandidate za postupak KOS.

Prema trenutnim propisima u Srbiji, adekvatna ovarijalna rezerva kod žena mlađih od 40 godina, bez živorođene dece, bez sistemskih infekcija i sa prisustvom nemetastatske bolesti, uz saglasnost odrinarajućeg onkologa, su uslovi da RFZO finansira proces krioprezervacije. Na taj način je omogućen jednak pristup i mogućnost svim ženama sa ca dojke, već u momentu postavljanja dijagnoze.

Za postupak stimulacije ovulacije nam je često na raspolaganju ograničen vremenski period pre započinjanja sistemske adjuvantne terapije, ili pre operacije, obično maksimalno do 3 do 4 nedelje, stoga se stimulacija ovulacije započinje brzo, u bilo kojoj fazi ciklusa, ne čekavši pojavu mesntruacionog krvarenja.

Slučajna (random) stimulacija

Slučajan (random) početak stimulacije u odnosu na konvencionalni, donosi približno iste nalaze u pogledu dobijenog broja ćelija, kao i broja krioprezerviranih oocita i embriona. Slučajan početak stimulacije obično zahteva nešto veće doze gonadotropina ili nešto duže trajanje stimulacije za postizanje adekvatnog učinka. Češće je zastupljena stimulacija sa početkom u lutealnoj fazi u odnosu na kasnu folikularnu.

Istraživanja navode oprečne rezultate o uspehu slučajne stimulacije, npr. dobijen nešto veći procenat M II oocita u slučaju lutealne faze [13]. Postupci i protokoli KOS kod pacijentkinja sa

karcinomom dojke su se vremenom menjali i transformisali, na osnovu stečenog iskustva. Preživljavanje pacijetkinja nakon terapije karcinoma dojke, onih koje su podvrgnute KOS radi krioprezervacije i onih bez toga, se ne razlikuje tokom 5 godišnjeg perioda [13].

Slučajni početak KOS omogućava početak stimulacije u bilo kojoj fazi ciklusa, bez potrebe za odlaganjem primene hemioterapije i eventualnim kompromitovanjem onkološkog lečenja. Različite efekte slučajnog početka KOS su prijavile do sada mnogobrojne studije, ali uz ogradu da su u pitanju manji uzorci, retrospektivne prirode. Stoga, ne čudi što su prijavljeni efekti često kontradiktorni.

Većina studija se prezervacijom fertiliteta prijavljuje komparabilan broj zrelih oocita i krioprezerviranih embriona u odnosu na konvencionalni početak stimulacije [14]. Danis i saradnici navode kraće trajanje KOS u odnosu na konvencionalne protokole [15] . Neke studije navode da KOS započet random u lutealnoj fazi ili kasnoj folikularnoj, traje duže od onih konvencionalno započetih [16,17].

Sonmezer i saradnici su opisali populaciju pacijetkinja sa karcinomom dojke i početkom stimulacije 11., 14. i 17. dana ciklusa, koja je rezultovala prihvatljivim i zadovoljavajućem brojem oocita i embriona za krioprezervaciju.

Gubruz i saradnici su poredeći konvencionalni početak stimulacije u odnosu na slučajni, konstatovali duži period trajanja stimulacije uz veće doze gonadotropina kod random početka. Ali, takođe su ukazali i na značajno niže koncentracije serumskog estradiola kod slučajnog početka stimulacije [18].

Protokoli sa inhibitorima aromataze

Od protokola KOS samo sa upotrebom inhibitora aromataza (Letrozol), posebno kod hormon pozitivih receptora tumora dojke, došli smo do protokola sa gonadotropinima uz konkomitantnu upotrebu Letrozola, kao danas dominantnih. To su protoli uz gonadotropine, GnRh antagoniste (gonadotrophin releasing hormone) i primenu HCG (humani horionski gonadotropin) kao okidača. Protokli sa GnRh agonistima su nepraktični, dugo traju, skupi, nekomformi za pacijenta, sa mnogo većim procentom komplikacija u vidu OHSS, i sa povećanom konzumcijom gonadotropina, i danas su veoma zastupljeni u klasičnom IVF, a kod krioprezervacije u onkofertilitetu se ne koriste uopšte. U slučaju rizika od OHSS, kao način snižavanja koncentracije estradiola, istovremena upotreba letrozola dok traje stimulacije se preporučuje, a može se i nastaviti nakon TVAO (transvaginalna aspiracija oocita) do pada koncentracije estradiola ispod 20 pg/ml.

Međutim, neki Centri insistiraju, kod žena sa ca dojke i estrogen pozitivnim receptorima, na single agent stimulaciju letrozolom uz GnRh antagoniste i HCG, gde je obično rezultat stimulacije jedan folikul, ređe do 3 folikula, što ga sa stanovišta reproduktivne medicine čini slabo efikasnim, i treba ga ponoviti više puta, za šta nemamo dovoljno vremena na raspolaganju. Dodatak male količine gonadotropina letrozolu, ne dovodi do bitnije korekcije rezultata (maksimalno do 4 folikula).

Protokol uz upotrebu gonadotopina i inhibitora aromataze kao kočničara rasta estradiola, ali bez ugrožavanja rasta folikula, rezultuje pojavom sličnog broja folikula, krioprezerviranih oocita i embriona u odnosu na konvencionalne KOS protokole.

Međutim, uglavnom su studije pokazale nekonzistentne rezultate tj. da dodatak inhibitora aromataze gonadotropinima u KOS dovodi do:

- Nema efekta na broj dobijenih oocita [19,20]
- Povećava broj oocita [21]

- Smanjuje broj oocita na raspolaganju za krioprezervaciju [22]

Možemo konstatovati da dodatak inhibitora aromataze, uglavnom letrozola kao osigurača gonadotropinima u KOS ne smanjuje broj ukupno dobijenih oocita [23,24,13]. Protokoli stimulacije single agensom inhibitorom aromataze, u našem slučaju letrozolom, terapijom, proizvode mali broj oocita (maksimalno do 3), obično samo jedan folikul-jedan oocit, ne proizvodi visoke nivoe estradiola i najbezbedniji je za pacijetkinje sa ca dojke, ali zahteva veći broj ciklusa radi dobijanja većeg broja ćelija. Ovo ih čini sigurnim i bezbednim za stimulaciju, posebno kod onih sa hormon pozitivnim receptorima, ali ne preterano efikasnim sa reproduktivnog stanovišta. Obično ne zahteva dodatak GnRh antagonista, a primena hCG je komforna. Procenat zrelih M II oocita se ne razlikuje u odnosu na druge načine stimulacije u odnosu na ukupan broj dobijenih oocita.

Protokoli KOS sa tamofixenom kao jedinim agensom stimulacije su slabo zastupljeni u Evropi, i mnogo manje uspešni od protokola sa letrozolom. Čest neželjeni efekat su neočekivano visoke koncentracije estradiola u ovim protokolima, posebno uz dodatak gonadotropina. Poželjna opcija za KOS u ciklusima prezervacije fertiliteta, posebno sa hormon receptor zavisnim karcinomima dojke je protokol sa gonadotropinima uz konkomitantni letrozol, jer su bezbedniji, sa dobijenih više zrelih oocita u odnosu na paralelu sa tamoxifenom.

Bitna stavka u protokolima za krioprezervaciju oocita je upotreba GnRh agonista kao okidača, u cilju prevencije OHSS. Čitav niz studija o KOS sa gonadotropinima i letrozolom kao kočničarom rasta estradiola uz primenu GnRh agonista kao okidača, navode veći broj dobijenih zrelih oocita M II [24,25,26], kao i embriona [26].

Prevencija komplikacija kontrolisane ovarijalne stimulacije

Moramo imati u vidu potencijalne neželjene efekte i komplikacije postupla KOS, uključujući i prekid stimulacije zbog izostanka odgovora odnosno neadekvatnog odgovora, OHSS (sindrom ovarijalne hiperstimulacije), komplikacije postupka TVAO (transvaginalna aspiracija oocita) u vidu krvarenja, infekcije, perforacije visceralnih organa, ili ciklusi bez dobijenih oocita ili embriona za krioprezervaciju.

Najčešća komplikacija postupka stimulacije ovulacije je sindrom ovarijalne hiperstimulacije (OHSS), koji se javlja sa učestalošću od 0.6 do 5% i može zahtevati produženu hospitalizaciju i odlaganje terapije kancera. Smatra se da KOS protokoli sa upotrebom GnRh antagonista, uz istovremenu upotrebu letrozola uz gonadotropine, uz okidanje GnRh agonistima kao okidačom, može smanjiti rizik od OHSS za 80% [27]. Pitanje okidanja sa GnRh agonistima se ne svodi samo na smanjenje rizika od OHSS, već i na problem rizika od pojave „empty“ folikula i zato se moraju odrediti parametri za okidanje GnRh aginistima umesto hCG. Naša iskustva podrazumevaju primenu GnRh agonista kao okidača ako imamo više od 15 folikula većih od 14 do 15 mm i vrednosti estradiola viših od 3000 pg/ml.

Reproduktivni ishod nakon krioprezervacije reproduktivnog materijala

Žene sa dijagnozom karcinoma dojke imaju velike nade za oporavak i očekivanje potencijalne reprodukcije nakon onkološkog lečenja. Prema novijim shvatanjima, sama trudnoća ne remeti i ne pogoršava prognozu nakon uspešnog tretmana ca dojke [28,7].

Mada, iskustva sa upotrebom krioprezerviranih oocita i embriona, radi prezervacije fertiliteta su još uvek dosta ograničena. Postavljaju se dva ključna pitanja:

1. Koje je pravo vreme za upotrebu zamrznutog materijala odnosno koliko vremena treba da prođe nakon uspešne terapije ca dojke tj maligne bolesti?

2. Zašto se mali broj žena odlučuje na vraćanje zamrznutog materijala uprkos uspešnoj onkološkoj terapiji?

Podaci o reproduktivnom ishodu sa krioprezerviranim oocitima ili embrionima kod prezervacije fertiliteta sa kancerom dojke su ograničeni, usled malog broja pacijetkinja sa vraćenim materijalom, kratkog vremena praćenja i uglavnom retrospektivne prirode.

Druckenmiller i saradnici 2016. godine su naveli stopu od 6% vraćenih uzoraka sa 44% stope živorođenja kod 176 žena sa ca dojke, tokom 9 godišnjeg perioda praćenja [29] . Oktay i saradnici navode 131 ženu sa ca dojke sa krioprezervacijom nakon KOS sa gonadotropinima uz konkomitantni letrozol, njih 25% se vratilo da upotrebi embrione sa stopom 45% i 5.25 godina kao prosečno vreme do upotrebe [30] . Moravek i saradnici su 2018. godine naveli 10.3% od 204 pacijentkinje sa hemioterapijom kod Ca dojke, koje su upotrebile uzorke sa 57.1% živorođenja [31] U svim navedenim studijama, pacijetkinje su koristile gestacijaki surogat, koji u našoj zemlje nije dozvoljen [29,30,31] .

Marklund i sar.adnici 2020. godine prijavljuju oko 7% (34/468) sa onkološkim tretmanom ca dojke, vratilo da iskoristi krioprezervirani materijal, i od tog broja 32% (11/34) je postiglo bar jednu trudnoću [13].

Rodriquez-Wallberg i saradnici su 2019. godine sa podacima o ženama sa svim vrstama karcinoma, uključujući i dojku, na uzorku od 852 žene, zabeležili stopu živorođenja od 21% sa prosečnim periodom praćenja od 3.9 godina [32] .

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FERTILITY-SPARING MANAGEMENT OF ENDOMETRIAL CANCER IN THE ERA OF MOLECULAR CLASSIFICATION

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Endometrial cancer is the most common gynecological malignancy in developed countries today. It is most commonly a disease of postmenopausal women, but the incidence in younger women of reproductive age is also increasing. Women younger than 40 years represent up to 5% of endometrial cancer cases and around 20% of cases are diagnosed before menopause (1). This is partly related to increasing global epidemics of obesity, and this trend of increasing disease occurrence in young women is expected to further increase. In younger women, the development of atypical endometrial hyperplasia or endometrial cancer is often associated with obesity and anovulation (2). Further risk factors include a history of oligomenorrhea, chronic anovulation and polycystic ovary syndrome (PCOS), infertility, nulliparity, and diseases related to excessive production of estrogens. In these cases, the balance between estrogens and progesterone is disturbed and relatively higher levels of estrogens lead to excessive proliferation of endometrial tissue, development of endometrial hyperplasia, and endometrial cancer.

The diagnosis of cancer is traumatizing for any woman, but the prognosis in terms of survival in young women undergoing standard surgical management is in most cases excellent. As endometrial cancer causes symptoms of irregular bleeding, most young women are diagnosed with early-stage adenocarcinoma which is most commonly low-grade and rarely grows invasively into the myometrium (3,4). In these cases, standard surgical management results in 5-year survival that exceeds 90%.

The loss of reproductive function and ovarian hormone production is a serious and frustrating consequence of standard oncological management. Young patients who desire fertility preservation and have good expected oncological outcomes may prefer more conservative approaches. In these cases, it is of utmost importance to carefully select the women for whom fertility-sparing treatment is ontologically safe and tailor the treatment according to their needs. Undertreatment of women with endometrial cancer to preserve fertility may translate to excessive oncological risk and progression of the disease. On the other hand, overtreatment may cause loss of fertility, lifelong side-effects, such as increased risk of cardiovascular events, or even result in secondary malignancies. Today, this decision still relies on standard histopathological assessment of endometrial biopsy and imaging methods to assess the stage of the disease (most commonly expert ultrasound or magnetic resonance imaging) (5). Witnessing the developments in the techniques of endometrial biopsy assessment in the last decade, there is a possibility of a more precise characterization of the disease and the risk it poses to women. In this chapter, we will describe current approaches to the selection of candidates for fertility-sparing management of endometrial cancer. We will discuss the potential changes in risk stratification that molecular characterization of tumors could contribute to the management of young women with endometrial cancer.

Current approaches to candidate selection based on tumor grade and stage

According to the very recently updated European Society of Gynaecological Oncology (ESGO) / European Society for Human Reproduction and Embryology (ESHRE) / European Society for Gynaecological Endoscopy (ESGE) guidelines, only women with grade 1 endometrial cancer without evidence of myometrial invasion can be offered the possibility of fertility-sparing management options (6). It is suggested that grade 2 tumors without myometrial invasion should only be counseled about fertility-sparing treatment in highly experienced centers, as current evidence of safety in this setting is sparse. Since evidence in these cases is limited, it is suggested that fertility-sparing treatment should be discussed on a case-by-case basis. Although based on low-quality evidence, according to recent guidelines, hysteroscopic biopsy is preferred over blind biopsy to reliably confirm the diagnosis of endometrial cancer. For exclusion of pelvic and paraaortic lymph node involvement or distant metastasis, an MRI or CT scan is recommended.

Incorporating tumor biology into risk assessment

The most common classical risk factor for endometrial cancer is estrogen excess. In the last decade, we have witnessed a growing interest in the identification of other risk factors and stratification of women based on the biology of the disease. A retrospective study focusing on younger women with endometrial cancer (under 50 years of age) has shown that based on the causes and the interconnected biology, women with endometrial cancer can be classified into three groups. These are (I) “the high estrogen” group (57.7% cases), (II) the “Lynch” group (8.3% cases), and (III) the “neither” group (34.2% cases) (7). This is especially important in patients with progestin therapy failure, as in these patients, there can be a higher influence of other, progestin-independent signaling pathways (8).

The presence of Lynch syndrome in young women with endometrial cancer is higher compared to the general population (9). Inherited genetic mutations predisposing women for endometrial cancer account in the general population for 3–5% of cases. The most prevalent genetic mutation predisposing women to endometrial cancer among inherited genetic mutations is Lynch syndrome (present in 2–3% of all patients) (10). Prospective trials testing women with endometrial cancer under the age of 50, however, show that in this population, Lynch syndrome was present in 9% of cases. Currently, there is no unified consensus on guiding testing for Lynch syndrome in women opting for fertility-sparing management. Undergoing fertility-sparing management may limit the detection of this mutation that predisposes women to an increased risk of colorectal, endometrial, and ovarian cancer. Young women with endometrial cancer should therefore always be carefully consulted about the need for Lynch syndrome testing. The possibility of conservative management in the presence of Lynch syndrome is questionable and extensive counseling is needed in these cases.

Histopathological examination of endometrial biopsy is associated with significant inter- and intra-observer variability and is unreliable in predicting the risk of disease recurrence. Thus, novel molecular classifications to improve the risk stratification of patients are being investigated today. Four distinct molecular subtypes of endometrial cancer have been identified from the Cancer Genome Atlas (TCGA), leading to several studies assessing the impact of endometrial cancer molecular classification on patient outcomes. By using genetic and surrogate immunohistochemical markers, a classification of key groups was made. These groups are POLE ultramutated (POLEmut), MMR deficient (MMRd), non-specific molecular profile (NSMP), and p53 abnormal (p53abn) endometrial cancer (11). Molecular markers can also be combined with

immunohistochemical investigations on tumor biopsy samples before planned treatment and clinical parameters to create a reliable prediction model (12).

A recent study including 81 women with endometrial cancer has shown that the incidence of CTNNB1 somatic gene mutation was higher in early-onset endometrial cancer and the immunohistochemical accumulation of beta-catenin was inversely correlated with patients' age (13). It has been proposed that overexpression of beta-catenin could be a treatment failure in fertility-sparing management. A growing body of indicator evidence indicates the clinical importance of CTNNB1 mutation. Especially in young patients, there are propositions for establishing CTNNB1 status as the 5th molecular classifier of endometrial cancer. While also several other biomarkers have shown potential in predicting outcomes of endometrial cancer, they have yet to be understood in terms of the Cancer Genome Atlas (TCGA) risk profiles. Currently, we do not understand how a specific molecular profile of the tumor is connected to the signaling pathways that are important in endometrial cancer.

Molecular markers and the future of Fertility Sparing management in endometrial Cancer

There are many future challenges in improving risk stratification for fertility-sparing management in women with endometrial cancer. In patients currently classified as low-risk early stage according to established recommendations, there are still patients with increased risk of disease recurrence and spread. This is supported by recent reports showing recurrence rates in well-differentiated stage IA cancers, where in a cohort of 2691 women in a median follow-up time of 6.1 years, the incidence of recurrences was 7.2% (14). The initial studies that are available show that endometrial cancer molecular classification and different molecular markers further refine the patient risk profiles and not all stage IA, grade 1 patients bear the same disease biology. As Bosse et al. showed by evaluating endometrioid cancer samples that are grade 3 and generally deemed to have a higher risk of recurrence, their biological risk profile differs greatly if molecular classification is applied to them (15). It was shown, that the currently grade 3 tumor group (n = 381) was assembled of 12.9% of POLE ultramutated tumors, 20.7% of p53 abnormal tumors, 30.2% non-specific molecular profile (NSMP) tumors, and 36.2% of MMR deficient tumors. Further analysis of recurrence-free survival showed that POLE ultramutated and MMR-deficient remained independent prognostic factors for improved recurrence-free survival in the grade 3 endometrioid cancer group. Although the molecular classifiers are promising for the future management of women, currently available data do not allow for clinical applicability to extend the potential candidates for fertility-sparing management. Even the new ESGO/ESHRE/ESGE guidelines suggest performing molecular characterization of tumors in patients, however, this can still not be used in routine clinical practice and for the selection of candidates for fertility-sparing management. As new genetic signatures are identified through the transcriptional endometrial cancer landscape, finding a signature that could be incorporated into a prognostic model combined with the other molecular identifiers will be needed. Considering all this, large studies to show the usefulness of molecular tumor characterization in the context of fertility-sparing management are needed soon.

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LIMITATIONS OF PATHOLOGICAL DIAGNOSTICS IN ONCOFERTILITY TREATMENTS

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The biological behavior of a tumor, its prognosis, and therapy are determined by its origin and differentiation, grade and size, as well as infiltrative growth, which at the same time determines the stage of the disease.

In the oncofertility spearing treatment, we often encounter atypical hyperplasia (AH) of endometrium, i.e. EIN change, which has to be distinguished from numerous benign conditions as well as the presence of well-differentiated adenocarcinoma. Due to insufficiently clearly defined morphological criteria, several new biomarkers (in addition to currently used PAX2 and PTEN) are introduced and a new term "AH from which well-differentiated adenocarcinoma cannot be excluded" is defined. A major issue is also the FIGO classification of tumor grade (FIGO I, II, and III) based on the representation of the solid pattern considering the glandular component. According to the WHO classification, grades I and II correspond to cancer with a low degree of malignancy, whilst grade III is classified as a group of tumors with a high degree of malignancy (binary classification). As the grade of the tumor affects the decision on further treatment of patients who are treating sterility, the question of its reclassification and the representativeness of the material obtained by curettage (according to the sample size) arose [1]. The solution was found in the creation of a new molecular model that includes microsatellite instability (MSI) and p53 mainly by the immunohistochemistry (ICH), with the determination of POLE mutational status [2]. Considering the new FIGO staging classification of endometrial cancer 2023, histological prognostic parameters of the cancer are included as a criterion for the first time, classifying them into the favorable or unfavorable prognostic group [3]. Sometimes, tumor morphology characteristics, such as papillary pattern, can indicate serous differentiation as an aggressive type of tumor, but it can also be the basic type of structure in villoglandular changes (non-aggressive type) – therefore, the diagnosis cannot be established without the use of additional biomarkers [4].

Some types of tumors can occur primarily on the cervix and in the endometrium (endometrioid or mucinous adenocarcinoma). As different types of tumors require different treatments, appropriate antibody panels have been proposed for differentiation, none of which gives a definitive answer, but a certain probability of estimating the site of origin. The once-promising p16 marker (the surrogate marker for HPV infection and oncogenic transformation) did not fully meet expectations. It was shown that in addition to only focal positivity in the primary endometrial tumor and diffuse intense positivity in most cervical cancers, post-cervical cancers are not p16+ (such as serous, clear cell, or gastric adenocarcinoma), which is why additional determination of HPV status by PCR technique is suggested. Pathological diagnosis is further complicated by the introduction of the new term "colonization". It refers to the possibility of the spread of primary intraepithelial changes (either squamous or glandular) from the cervix "per continuitatem" to the endometrium and even to the lining of the fallopian tubes [5].

A similar situation is when it is necessary to delineate where the tumor originates from, when the same type exists simultaneously in the endometrium and the ovary, which is sometimes not possible - so far not a single marker has been defined that would confirm the ovarian or endometrial origin. For example, it is believed that in serous carcinomas, WT1 is more often

positive in ovarian tumors, whilst in determining the type of tumor, SOX17 (which has not been used so far) indicates endometrioid differentiation [6]. In order to assess response to therapy, the status of estrogen receptors is often requested, but while some authors take 1% as the limit value of positivity, for others it is 10%, which makes it difficult for the pathologist to interpret the obtained results.

In cases of mesenchymal tumors, the issue is also substantial. For certain types, including mixed epithelial-mesenchymal tumors, the criteria are unclear, so it is sometimes difficult to tell whether it is a malignant or benign tumor, which is why a wrong diagnosis is made. Typical examples are the diagnosis of adenosarcoma, endometrial stroma tumors and even smooth muscle tumors. Due to unclear criteria, adenosarcoma is often recognized as an endometrial or cervical polyp (application of ICH has no decisive influence).

When using additional biomarkers the origin of the tumor is determined, from the endometrial stroma or smooth muscle, for the evaluation of the biological behavior a border with the surrounding unchanged myometrium is necessary, which is very difficult to obtain by applying diagnostic procedures. The presence of infiltrative growth determines the malignant nature of the disease, but not always. In some benign conditions, infiltration of the environment to a depth of up to 3mm is allowed. When it comes to endometrial stroma, the term Endometrial Stromal Tumor (EST) is introduced, because it is not possible to make a differential diagnosis in the material usually obtained by hysteroscopy between Endometrial Stromal Nodule (ESN) and Endometrial Stromal Sarcoma (ESS) of low degree of malignancy. In the group of smooth muscle tumors, we are talking about Smooth Muscle Tumors of Unknown/Uncertain Malignant Potential (STUMP), as a transitional category between leiomyoma (LM) and leiomyosarcoma (LMS) with several proposed criteria needed for diagnosis, some of which are sometimes difficult to define (including the type of necrosis in the tumor). STUMP and LMS are difficult to distinguish from leiomyoma with atypical - bizarre nuclei (LMBN), which is a benign change, with the obligatory note that it is necessary to take extensive tissue sampling and obtain a border according to the surrounding myometrium. Given that operations in the treatment of oncofertility are performed as hysteroscopic - laparoscopic, it is not realistic to expect to evaluate infiltration or the existence of limited fields of malignant features in the particulated material, the term “smooth muscle neoplasm with atypia” is recommended, without clearly defining its biological behavior. Recent genetic studies show that LMBN is more similar to STUMP and LMS than LM. They can be divided into two groups, with normal FH/2SC status or with abnormal FH/2SC expression and FH mutation, when patients are advised genetic testing and a long follow-up interval, due to the possibility of kidney cancer.

The most common changes on the ovary that are defined as functional, non-tumorous are follicular cysts. Among sex cord-stromal ovarian tumors the most frequent is the granulosa cell tumor (the adult type), which has a different histological patterns. The macrofollicular form is sometimes very difficult to distinguish from follicular cysts, so it is necessary to perform a molecular FOXL2 analysis (the ICH profile of the cells is identical) in order to make differential diagnosis between these tumor and non-tumor lesions, that is, between malignant and benign conditions **[**7**[**.

The development of technology and its application in pathology undoubtedly contribute to better and more accurate diagnostics, but at the same time they complicate everyday work, diagnostics and treatment. The number of entities, i.e. pathological diagnoses, is increasing, with more and more of those representing “border line” forms. The use of new methods and the introduction of new diagnostic terms require continuous education of both the pathologist, who recognizes the

disease and determines the prognostic parameters, as well as the gynecologist and oncologist who need to respond to the increasing demands and possibilities for treatment. Also, there is the question of a sufficient number of employed pathologists and adequate equipment of their laboratories to keep up with technological development in diagnostics. Continuous cooperation within the Council for Oncofertility in making the best decision for the woman, who is not only a patient but also an active participant, is accepted as imperative.

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ADNEKSALNE MASE U REPRODUKTIVNOM PERIODU – DIJAGNOSTIČKI I TERAPIJSKI PRISTUP

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Termin adneksalna masa obuhvata širok spektar oboljenja ginekološkog i neginekološkog porekla. Iako je diferencijalna dijagnoza široka, većina adneksalnih masa u reproduktivnom periodu je ovarijalnog porekla i uglavnom su dobroćudne. S druge strane, iako redak, kancer jajnika je najsmrtonosniji ginekološki malignitet i zahteva posebnu pažnju. Za razliku od ostalih ginekoloških maligniteta, kod adneksalnih promena preoperativna histopatološka verifikacija nije moguća, što otežava planiranje operativnog zahavata.

Prilikom odluke o potrebi za hirurškom intervencijom uzimamo u obzir demografske karakteristike pacijentkinje, reproduktivne želje, kliničku simptomatologiju, ultrazvučne karakteristike uočene lezije, kao i rezultate dodatnih ispitivanja, u prvom redu tumorskih markera i dodatnog imidžinga.

Dijagnostički pristup

Transvaginalni ultrazvučni pregled predstavlja osnovnu imidžing metodu u proceni adneksalne patologije. Obzirom da postoji dobra korelacija ultrazvučne slike i makroskopskih karakteristika tumora, iskusan kliničar, pored diferencijacije na benignu i malignu promenu, može na osnovu patognomoničnih ultrazvučnih karakteristika predvideti i histološki podtip analizirane promene u približno 75% slučajeva. Pored subjektivne procene, u upotrebi su prediktivni modeli koji uključuju demografske karakteristike pacijentkinje, različite ultrazvučne karakteristike lezije i vrednost kancer antigena 125 (CA 125). Treba naglasiti da niti jedan model nije opšte prihvaćen, ali se po svojim karakteristikama u novije vreme izdvajaju modeli Međunarodne grupe za analizu ovarijalnih tumora (International Ovarian Tumor Analysis – IOTA) i to model jednostavnih pravila i ADNEX model.

Tumorski markeri imaju ograničenu vrednost u proceni rizika od maligniteta. U praksi se koristi ROMA (Risk of Malignancy Algorithm) indeks koji uzima u obzir vrednost CA 125, humanog epididimisnog antigena 4 (HE 4) i menopauzalnog statusa, a pacijentkinja sa na osnovu rezultata klasifikuje u grupu niskog ili visokog rizika za postojanje ovarijalnog kancera. Ipak, studije ukazuju da su performanse ovog prediktivnog modela lošije u odnosu na subjektivnu procenu ili ultrazvučne prediktivne modele. Kod mlađih pacijentkinja, tumorske markere je preporučljivo uraditi ukoliko se radi o kompleksnoj ultrazvučnoj promeni ili ukoliko nalaz zahteva praćenje. Ostali tumorski markeri se određuju u pojedinačnim slučajevima.

Dodatni imidžing (metoda izbora je magnetna rezonanca) se koristi u cilju dalje diferencijacije suspektnih promena, prvenstveno u cilju procene ekstraovarijalnog širenja bolesti i procene odnosa tumora sa okolnim strukturama.

Terapijski pristup

Benigne promene se mogu pratiti serijskim ultrazvučnim pregledima i određivanjem tumorskih markera. Preliminarni rezultati IOTA 5 studije pokazuju da je dugoročno praćenje adneksalnih promena bezbedno. Kod 1900 pacijentkinja koje su praćene u toku dve godine spontana rezolucija je uočena u 20% pacijentkinja, dok je hirurška procedura urađena kod 16% pacijentkinja. Malignitet

(invazivni i border-line tumori jajnika) je dijagnostikovan u manje od 1%, dok su torkvacija i ruptura ciste uočeni u 0,6% operisanih pacijentkinja. Na žalost, ne postoji opšte prihvaćeni konsenzus o tri važna pitanja: koliko često, na koji način i do kada pratiti adneksalnu promenu. U praksi se naredni ultrazvučni pregled često planira za 2-3 meseca kako bi se dokumentovala spontana rezolucija u slučaju funkcionalnih cisti, ili kako bi se utvrdila dinamika rasta promene. Naredna kontrola se može planirati za 6 meseci, a u slučaju stabilnih nalaza koji ne menjaju svoje karakteristike, kontrole mogu biti jednom godišnje (manji endometriomi, dermoidne ciste, cistadenomi). Ukoliko se tokom praćenja pojave karakteristike suspektne na malignitet, dođe do rasta tumora ili elevacije tumorskih markera praćenje se može prekinuti i planirati hirurška intervencija.

Hirurški tretman se preporučuje kod adneksalnih tumora kod kojih je poželjna histološka evaluacija, ali i kod benignih promena kod kojih je povišen rizik od torkvacije ili rupture ciste, kao i kod pacijentkinja sa izraženom simptomatologijom. Obim operativnog zahvata zavisi od većeg broja faktora i uključuje starost pacijentkinje, reproduktivne želje, stepen sumnje na malignitet (na osnovu ultrazvuka, dodatnig imidžinga i tumorskih markera) i intraoperativni nalaz. Poštedne procedure (cistektomija ili enukleacija solidnog tumora) imaju za cilj očuvanje reproduktivne i/ili hormonske funkcije jajnika, dok se ovariektomija ili adneksektomija mogu razmotriti kod žena koje su završile reproduktivnu funkciju.

Poseban problem predstavljaju nalazi koji su visoko suspektni na malignitet. Opsežnost hirurškog postupka i mogućnost ponovne hirurške intervencije mora biti jasno predočena pacijentkinji. U zavisnosti od nalaza, odlučujemo se za cistektomiju ili ovariektomiju (adneksektomiju), pri čemu se u istom aktu može načiniti i stejdžing procedura. Biopsija kontralateralnog jajnika se ne preporučuje ukoliko je jajnik normalnih makroskopskih karakteristika. U slučaju dijagnostikovanog maligniteta, pacijentkinji se može predložiti stejdžing procedura ukoliko prethodno nije urađena ili radikalizacija ukoliko je pacijentkinja završila reprodukciju.

Operativni zahvat se može izvesti laparotomijom ili laparoskopijom. Prednosti laparoskopije, pored estetskog efekta, uključuju brži oporavak i nižu učestalost postoperativnog bola, kraću hospitalizaciju i niže troškove lečenja, ali i manji rizik od formiranja adhezija što je od značaja za infertilne pacijentkinje. Pacijentkinje sa unilokularnim cistama, posebno ukoliko na osnovu imidžinga možemo proceniti verovatni histološki tip promene (funkcionalna cista, endometriom, dermoidna cista, cistadenom), predstavljaju idealne kandidate za laparoskopiju. Kompleksna adneksalna promena ne predstavlja kontraindikaciju za laparoskopiju, ali je u tim slučajevima pristup individualan i zavisi od stepena sumnje na malignitet. Veličina ciste generalno ne predstavlja limitirajući faktor za laparoskopiju. S druge strane, nedostatak laparoskopije je veći rizik od rupture ciste i time jatrogenog rasipanja potencijalno malignog sadržaja. Prema literaturi, rizik od incidentalnog nalaza maligniteta tokom laparoskopije je nizak i kreće se ispod 0,5%. Odgovarajućom selekcijom pacijentkinja i intraoperativnim manipulacijama se ovi rizici mogu svesti na minimum. Ukoliko je indikovana ponovna hirurška procedura zbog nalaza border-line tumora ili kancera jajnika, ova procedura se može izvesti laparoskopskim pristupom, jer je primarni tumor prethodno uklonjen i nema rizika od rasejavanja bolesti.

Plodnost nakon jednostrane ovariektomije

Iako ovariektomija značajno smanjuje fertilni potencijal, stvarni efekti ove procedure na reprodukciju nisu dovoljno poznati. Većinu informacija dobijamo iz malih studija u kojima su učestvovale pacijentkinje kod kojih je poštedno tretiran malignitet jajnika (uključujući i border-line tumore), pri čemu je stopa trudnoća bolja u ovoj grupi (42 do 88 %) u odnosu na pacijentkinje kod kojih je poštedno tretiran karcinom grlića ili tela materice. U meta-analizi koja je obuhvatila 21

retrospektivnu studiju, pacijentkinje sa jednim jajnikom su očekivano imale manji broj folikula po ciklusu, ali sa uporedivim kvalitetom jajnih ćelija i stopama trudnoća u odnosu na pacijentkinje sa oba jajnika.

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FERTILITY PRESERVATION IN GYNECOLOGICAL CANCERS

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Almost all standard therapies for gynecologic cancer, including surgical intervention, gonadotoxic chemotherapy, and radiation therapy, threaten a woman's childbearing potential. Preservation of fertility should be discussed with premenopausal women with early-stage gynecologic cancer shortly after diagnosis and, for women who desire to preserve fertility, during treatment planning. Many authors have investigated both oncologic and reproductive outcomes following fertility-sparing therapy, and there is ongoing development of assisted reproduction techniques available to cancer patients and survivors.

Women with early-stage (IA1-IB1) cervical cancer may be candidates for fertility-sparing cervical conization, simple or radical trachelectomy. In women with stage I epithelial ovarian cancer, fertility-sparing surgery appears safe overall, although controversy remains in patients with high-risk features (eg, high pathologic grade, clear cell histology, or stage IC disease). In women with low-grade, early-stage endometrial cancer, hormonal therapy has emerged as a viable option. Criteria for patient selection for fertility-sparing therapy are not well defined, thus patients and providers must carefully discuss potential risks and benefits. In general, in carefully selected patients, survival outcomes do not appear to differ significantly between radical and fertility-sparing approaches. Women who undergo fertility-sparing therapies may experience a number of fertility and obstetric complications. Preconception counseling with high-risk obstetric specialists is important to optimize health before a woman attempts to conceive. Identifying appropriate candidates for fertility-sparing treatments, assessing fertility potential, and helping women conceive after cancer treatment is best accomplished through multidisciplinary collaboration between gynecologic oncologists and fertility specialists. The effect of cancer treatments on fertility and pregnancy outcomes is a distressing concern among the increasing population of reproductive-age women with gynecologic cancer. The 2012–2016 Surveillance, Epidemiology, and End Results (SEER) statistics report 36.5% of cervical cancers, 6.5% of uterine cancers, and 7% of ovarian cancers were diagnosed in women <45 years old. Among all gynecologic cancers 44% of women with cervical cancer are diagnosed at an early stage, and almost 70% of endometrial cancers are diagnosed while still confined to the uterus. For ovarian cancer, about 14% are diagnosed with early stage disease only. As women continue to delay childbearing, the number of young women with cancer who face fertility preservation decisions grows. Surgical interventions, gonadotoxic chemotherapy agents, and radiation therapy can have long-term detrimental effects on a woman's ability to conceive and/or successfully carry a pregnancy. However, fertility preservation techniques have improved over the last two decades, and observational studies have led to careful implementation of a variety of fertility-sparing treatment options for selected reproductive-age women with early-stage gynecologic cancer. Determining which women with gynecologic cancer are appropriate candidates for fertility sparing treatments, assessing fertility potential, and helping women conceive after cancer treatment is best accomplished through multidisciplinary collaboration between gynecologic oncologists and fertility specialists.

Early involvement of fertility specialists during treatment planning is imperative in optimizing opportunities for counseling and outcomes.

In addition, since fertility-sparing cancer treatment can lead to complications that might increase obstetric risks during future pregnancy, a preconception counseling consult with a maternal-fetal medicine specialist is helpful to identify potential problems and strategies to optimize health prior to pregnancy. Fertility has been reported by patients as one of the most important determinants of their quality of life after treatment. One study found that only 46% of patients with gynecological cancers reported receiving reproductive counseling prior to treatment, consistent with data from similar studies in other cancer types. These data suggest a gap in patient education regarding fertility preservation options, although, reassuringly, rates of fertility preserving surgery in the USA have increased in the past 10 years.

The American Society of Clinical Oncology has published guidelines that highlight fertility preservation options as well as the important of addressing fertility risk and making early referral to fertility specialists prior to initiating cancer therapy.

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OČUVANJE FERTILITETA NAKON LEČENJA GTN

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Neoplastična oboljenja koja nastaju iz tkiva posteljice nazivaju se gestacijskim trofoblastnim bolestima (GTB). Ova oboljenja karakteriše nekoliko zajedničkih osobina: trofoblastno (placentno) poreklo, invazivnost, rana sposobnost metastaziranja, velika prokrvljenost i mogućnost očuvanja fertiliteta nakon lečenja. U gestacijske trofoblastne bolesti ubrajaju se sledeća oboljenja koja imaju svoje histološke i kliničke specifičnosti:

- parcijalna hidatiformna mola (pHM),
- kompletna hidatiformna mola (cHM),
- invazivna hidatiformna mola (iHM),
- horiokarcinom (CC),
- trofoblastni tumor placentnog ležišta (PSTT),
- epitelioidni trofoblastni tumor (ETT),
- nodus placentnog ležišta (PSN),
- atipični nodus placentnog ležišta (APSN).

Kako većinu populacije pacijentkinja obolelih od gestacijskih trofoblastnih bolesti čine osobre u reproduktivnom periodu, očuvanje fertiliteta u lečenju od ovih bolesti ima veoma važno mesto.

Parcijalna i kompletna hidatiformna mola predstavljaju benigne (premaligne) bolesti i osnova njihovog lečenja je evakuaciona kiretaža nakon čega nastupa period praćenja koji se zasniva na periodičnoj kontroli serumskog ili urinskog nivoa beta-horionskog gonadotropina (beta-hCG-a). Ukoliko trend kretanja beta-hCG-a ukaže na uspešnost tretmana evakuacionom kiretažom i time isključi postojanje postmolarne trofoblastne bolesti ili maligne alteracije u horiokarcinom, kod pacijentkinja lečenih od parcijalne i kompletne mole nema prepreka za ostvarivanje trudnoće nakon što protekne dovoljno vremena od lečenja. Ukoliko (u malom procentu slučajeva) dođe do razvoja postmolarne gestacijske neoplazije (tzv. perzistentne trofoblastne bolesti), ova oboljenja se leče primenom hemioterapije i kod njih pitanje fertiliteta ima isto mesto kao u lečenju invazivne mole i horiokarcinoma.

Pre uvođenja hemioterapije u lečenje GTN-a, tretman invazivne mole i horiokaricnoma je podrazumevao histerektomiju (sa ili bez adneksektomije) što je automatski isključivalo mogućnost očuvanja fertiliteta. Čak i u slučajevima kada je radikalno operativno lečenje (histerektomija) imalo dobar onkološki ishod (što nije bio čest slučaj), mlade pacijentkinje su se suočavale sa ozbiljnim padom kvaliteta života zbog gubitka reproduktivne funkcije. Zbog toga je uvođenje hemioterapije 1956. godine unelo revoluciju u lečenje GTN jer lečenje hemioterapijom, bez histerektomije i adneksektomije, ostavlja prostor za očuvanje reproduktivne sposobnosti.

Invazivna mola, postmolarna gestacijska trofoblastna bolest i horiokaricnom se danas primarno leče mono- ili polihemioterapijom, dok se histerektomija izvodi samo u slučajevima krvarenje koje nije moguće zbrinuti drugim postupcima ili kod pacijentkinja koje su ispunile reproduktivnu funkciju i jako su motivisane u smislu histerektomije. U isto vreme, primena hemioterapije je u mnogome poboljšala onkološke ishode lečenja GTN-a tako da savremeni podaci ukazuju na stopu izlečenja od preko 90 % čak i u slučajevima metastatske bolesti. Zbog ovoga je pitanje očuvanja

reproduktivne funkcije postalo još važnije, ali je ovo pokrenulo pitanje uticaja hemioterapije na ovarijalnu funkciju, rizik od pojave prevremene menopauze i rizik od mutagenog i teratogenog uticaja hemioterapije na buduće trudnoće.

U tretmanu GTN se rutinski koriste sledeći hemioterapijski lekovi: metotreksat, aktinomicin D, etopozid, ciklofosfamid, vinkristin i platinski derivati. Kako su gestacijske trofoblastne bolesti retke bolesti, podaci o uticaju lečenja na reproduktivnu funkciju ovih pacijentkinja su dosta oskudni. Međutim, navedena hemioterapijska sredstva se koriste i za lečenje drugih maligniteta (karcinom dojke, limfomi, leukemije, tumori germinativnih ćelija itd) od kojih neki takođe pogađaju žene reproduktivnog doba.

Godine starosti pacijentkinje su jak nezavisni faktor fertiliteta pacijentkinja lečenih od GTN-a, gde 40. godina predstavlja granicu nakon koje fertilnost opada. Monohemioterapija je bezbednija po reprodukciju i naredne trudnoće od polihemioterapije. Metotreksat, aktinomicin D i vinkristin nose nizak rizik za indukciju prevremene ovarijalne insuficijencije (POF), platinski derivati su lekovi srednjeg rizika, ciklofosfamid je lek visokog rizika, dok za etopozid nema pouzdanih podataka [1]. Upotreba samog metotreksata nema rizika od izazivanja prevremene menopauze [2,3,4], kao ni aktinomicin [5]. Monohemioterapija ne utiče na fertilitet niti na ishod trudnoće, dok je stopa spontanih pobačaja povišena samo u slučaju trudnoća ostvarenih u prvih šest meseci po završetku lečenja [5]. Kombinovana hemioterapija obično izaziva prolaznu amenoreju, ali obično ne izaziva infertilitet, pogotovo kod žena mlađih od 40 godina [5]. Takođe, analizom stopa sponatnih pobačaja, prevemenih porođaja, ektopičnog graviditeta, mrtvorođenosti ili pojave kongenitalnih anomalija, podaci ukazuju da na povoljan ishod trudnoća nakon primene monohemioterapije i niskodozne polihemioterapije u lečenju GTN-a [5,6]. Opisani su brojni slučajevi uspešnih, nekomplikovanih trudnoća nakon lečenja horiokarcinoma kombinovanom produženom hemioterapijom [6].

Standardno lečenje PSTT-a i ETT-a i danas podrazumeva histerektomiju, pre svega zbog znatno slabijih rezultata hemioterapijskog lečenja u poređenju sa molama i CC-om. Nakon histerektomije, većina ovih pacijentkinja biva lečena visokodoznim hemioterapijskim režimima koji se sastoje od etopozida, cis-platine, metotreksata, aktinomicina D i floksuridina. Međutim, i ovi tumori mogu da se jave kod žena koje nisu završile reprodukciju i motivisane su za očuvanje reproduktivne funkcije. U odabranim slučajevima se može razmotriti eksciozina (histeroskopska ili otvorena) hirurška procedura uz hemioterapiju. Visokodozni hemioterapijski režimi često izazivaju trajnu amenoreju i do sada nema podataka o ostvarenim trudnoćama nakon primene ovih protokola za lečenje GTN-a.

Savremeno lečenje GTN-a u slučajevima rezistencije na hemioterapiju obuhvata i primenu imunoterapije lekovima pembrolizumab (blokator PD-1 receptora) i avelumab (blokator PD-L1). Kako se ovaj lek tek odskora primenjuje, nema još uvek pouzdanih podataka o uticaju na reprodutkivnu funkciju niti na ishode trudnoća, ali su početni rezultati obećavajući. Ovo je posebno važno kao moguća alternativa visokodoznim režimima u lečenju PSTT i ETT.

Ukoliko se ostvari trudnoća nakon lečenja GTN-a, prenatalna zaštita treba da bude standardna tj. nije potrebna modifikacija kontrole trudnoće zbog prethodno lečene GTN. Po završetku trudnoće (bilo pobačajem, bilo porođajem) savetuje se histopatološki pregled posteljice. Takođe, savetuje se kontrola beta-hCG-a šest nedelja nakon završetka trudnoće. Važno je savetovati pacijentkinju da tokom perioda praćenja (koje zavisi od prirode oboljenja i sprovedenog lečenja) rigorozno koristi kontracepciju. Odlaganje trudnoće je podjednako važno zbog samog praćenja (jer praćenjem beta-hCG-a nije moguće pouzdano razlikovati normalnu trudnoću u praćenju od progresije bolesti) i zbog ishoda trudnoće (odlaganje trudnoće za 6-12 meseci značajno smanjuje

rizik od spontanog pobačaja i teratogenosti hemioterapije). Način završavanja porođaja kod ovih pacijentkinja je određen akušerskim indikacijama.

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MINIMALLY INVASIVE GYNECOLOGICAL SURGERY

THE ROLE OF TECHNIQUE IN LAPAROSCOPIC PELVIC LYMPHADENECTOMY

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Pelvic lymphadenectomy as an integral part of the surgical treatment of genital malignancies has been established for many years in the clinical treatment of oncology patients. By improving the techniques of the classical surgical approach, a revolution was experienced with the introduction of laparoscopy in the field of pelvic lymphadenectomy. Advances in technology and surgical techniques today bring numerous positive moments to clinical practice for oncology patients with gynecological malignancies. With a minimally invasive approach, pelvic laparoscopic lymphadenectomy is today the method of choice in the treatment of patients with malignant neoplasms of the female genital system.

Key words: malignant genital tumors in women, laparoscopic pelvic lymphadenectomy

Introduction.

It is certain that pelvic lymphadenectomy as an integral part of the surgical treatment of genital malignancies has been established for many years in the clinical treatment of oncology patients. We can rightfully assert that the surgical technique for pelvic lymphadenectomy underwent a revolution with the introduction of laparoscopy. It is certain that the progress of technology and surgical techniques has brought numerous positive effects to clinical practice for oncology patients with gynecological malignancies. It is indisputable that as a minimally invasive method, pelvic laparoscopic lymphadenectomy is today the method of choice in the treatment of patients with malignant neoplasms of the female genital system. Minimally invasive gynecological surgery today represents the gold standard in the treatment of gynecological and gynecological-oncological patients. The mentioned approach first imposes the need for high-quality preoperative preparation and treatment of patients, which is a guarantee for the best possible treatment success. In all gynecological malignancies, endoscopy and minimally invasive gynecological surgery play a significant role, both in premalignant lesions and in malignant lesions. Even the former controversies about the use of endoscopic methods in ovarian cancer have been resolved today, because their area of application has been precisely determined, with the avoidance of rupture or puncture of a malignant ovarian tumor. Ovarian cancer is still associated with the fact that in about 60% of patients it still occurs in advanced stages, so laparoscopic lymphadenectomy plays an important role in the restaging of ovarian and fallopian tube cancer. Even when using laparoscopy, the prognosis of patients with gynecological cancer correlates with the stage of the disease, which is determined according to the FIGO classification. Surgical staging of the disease is a diagnostic and therapeutic standard, both because of the possibility of obtaining a histological diagnosis, and because of the very accurate representation of tumor extension during surgery. The status of the lymph nodes is the most important prognostic factor in gynecological cancers,

whereby pelvic and para-aortic lymphadenectomy, for histological analysis of the nodes, is part of the exact surgical determination of the stage of the disease [1,2].

Laparoscopic pelvic lymphadenectomy was first described in the literature by Dargent and Salvat (1989), and at the same time by Querleu et al. In 1991, Nazhat published his first experiences with laparoscopic para-aortic lymphadenectomy. The advantages of endoscopy and minimally invasive gynecological surgery compared to conventional surgery are indisputable. Today, the laparoscopic approach has its place in cervical and endometrial cancer, but also in early ovarian cancer [3,4,5].

Even today, the biggest controversies are related to the role of endoscopy in the treatment of ovarian cancer. Today, it is considered that the laparoscopic approach is applied when ovarian cancer is staged as IA, the same when it comes to "second look" operations after surgical R0 and performed neoadjuvant chemotherapy, as well as staging and/or biopsy. Thus, laparoscopy plays a role in assessing tumor resectability, histological verification of the origin of peritoneal carcinomatosis. In doing so, one should adhere to the rule that the laparoscopic approach must not compromise the survival of patients and that the laparoscopic approach can only be used by highly experienced surgeons. Along with many others, the main risks associated with laparoscopy in gynecological oncology can be reduced to aerosolization of cells, "under staging" - lack of training, and "trocar sites" implants. At the same time, although laparoscopic operations last longer than conventional ones, it is undeniable that the visualization and quality of the surgical procedure is undoubtedly better with the endoscopic approach [6,7].

Presentation of the technique of pelvic lymphadenectomy

It is extremely important to present the very technique of laparoscopic pelvic and para-aortic lymphadenectomy, which are an integral part of the surgical treatment of gynecological malignancies. In doing so, the patient is placed in the lithotomy position, with the absence of flexion in the knees and flexed lower legs, with fixed holders. The operator is usually on the left side of the patient, with the image displayed on two monitors. The trocars themselves are placed with the primary trocar placed infraumbilically. Two 5 mm working trocars are placed in the lower quadrants, while a third working trocar is usually placed in the upper left quadrant. There is always the possibility of introducing an additional working trocar. Every endoscopic surgical procedure should always begin with an inspection of the abdomen and surgical area, whereby the inspection begins with the upper abdomen, liver, gall bladder, stomach, omentum, intestines, appendix, other organs in the abdomen and pelvis, as well as with a detailed inspection of the parietal and visceral peritoneum. Due to the development of instrumentation, today we have numerous high-quality laparoscopic instruments and modern generators that allow us to efficiently and safely use different forms of energy in hemostasis and to perform efficient and fast endoscopic surgical procedures. Even with endoscopic operations, we behave in such a way that washings for cytodiagnostics and biopsies for pathohistological analysis are taken [4,8,9].

The levels of lymphadenectomy were very precisely classified by Querle, and below we present an overview of his division, which is often applied. According to Querle, there are 4 levels or degrees of lymphadenectomy. At the same time, stage 1 represents the resection of the interiliac lymph nodes. The mentioned stage can be divided into anterior (stage 1a – nodes from the obturator fossa and nodes between the artery and external iliac vein) and posterior (stage 1b – nodes between the artery and external iliac vein and deep obturator nodes located in the corner between the external iliac vein and the first hypogastric veins). Furthermore, stage 2 enables a complete pelvic dissection of the lymph nodes, and is divided into three parts: stage 2a (includes the lateral chain of lymph nodes of the external iliac artery bilaterally), stage 2b (includes the lateral chain of nodes

of the common iliac artery bilaterally) and stage 2c, which is located medial (includes the medial chain of nodes of the left and right iliac arteries and the presacral nodes). When performing stage 3, the para-aortic nodes below the inferior mesenteric artery are removed. Grade 4 is reserved for infrarenal nodes (between the inferior mesenteric artery and the left renal vein). Grade 3, as well as grade 4, are included in para-aortic lymphadenectomy.4,10,11

The endoscopic surgery itself begins with the opening of the parietal peritoneum and the obligatory identification of the ureter. At the same time, the lig. rotundum is raised and an incision is made in the fold of the peritoneum thus created. In this case, the lymph nodes are separated by blunt or sharp dissection according to the previously mentioned scheme, with the treatment of hemostasis with modern instruments, with extreme caution in the vicinity of the ureter or large blood vessels. In case of early cervical or endometrial cancer, we perform an interiliac dissection considering the fact that involvement of the lymph nodes around the iliac common or aorta is rare (less than 2%). Interiliac lymphadenectomy covers the area between the external and internal iliac arteries, where it always begins with the dissection of the lymph nodes of the external iliac artery and vein, from the iliac communis to the femoral artery. This is followed by dissection of the lymph nodes of the obturator fossa and finally the nodes of the internal iliac artery. In doing so, we rarely decide on complete node dissection of the common iliac artery, as well as extremely rarely on inframesenteric para-aortic lymphadenectomy (in the case when a solitary enlarged lymph node is visible). At the end of the procedure, the peritoneum itself is left open for lymphatic drainage, with the usual placement of drains. The obtained lymphatic tissue samples are sent separately with an indication of the exact localization. The same samples are taken intraoperatively through a 10 mm trocar, after completion of certain stages of the surgical procedure. Complications are far less than in classic surgery and are related to possible bleeding, ureteral lesions or injured obturator nerves [4,12,13].

Conclusion

Considering the exceptional technical possibilities and advances in the field of visualization, gynecological endoscopy today has an indispensable place in the treatment of gynecological malignancies, with a far lower number and proportion of complications compared to classical surgery. It is indisputable that, as with any advanced technique, great experience and technical dexterity are needed to perform the aforementioned surgical procedures, but ultimately the advantages of the endoscopic approach are immeasurable. Today, the minimally invasive, including endoscopic, approach has indeed become the gold standard in the treatment of gynecological malignancies, and it is certain that robotic surgery will be the one that will bring an additional revolutionary step forward in the aforementioned field [14,15].

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ENDOMETRIOSIS – NEW INSIGHTS

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Introduction: Endometriosis is an inflammatory condition occurring in 5–10% of women of reproductive age associated with debilitating pelvic pain and infertility [1]. It is characterized by the presence of endometrial-like tissue outside the uterus, mainly on pelvic organs.

Pathophysiology: Regarding pathophysiology, no great progress has been made in recent years. However, new therapeutic targets are based on previously established pathophysiology [2]. Estimates from twin studies suggest 47-51% total heritability of endometriosis, with 26% estimated to be from genetic variation [3]. Genome-wide association studies keep identifying significant genome loci and those associations with certain disease types and prognosis, as well as genetic correlations between endometriosis and other conditions including asthma and osteoarthritis, thereby aiding individual approach therapy [4].

Diagnosis: Laparoscopy is no longer the diagnostic gold standard and it is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate [5]. In the diagnostic work-up for endometriosis, imaging plays an important role, although, clinicians need to be aware that a negative finding does not exclude endometriosis, particularly superficial peritoneal disease.

The IDEA consensus statement remains the best systematic approach in the sonographic evaluation of the pelvis in women with suspected endometriosis [6]. It proposes four step approach with accessing uterus, ovaries, anterior and posterior compartment of pelvis with dynamic evaluation as well [7].

Ultrasound characteristics of typical endometrioma according to IOTA criteria include adnexal mass with ground-glass echogenicity of the cyst fluid in premenopausal patients, one to four loci and no papillary strctures with detectable blood flow [8] IOTA classification has good overall accuracy for ultrasound diagnose of endometroma [9]. In addition, clinicians should be aware of atypical ovarian endometrioma, in order to avoid unnecessary surgical treatment and reduction of ovarian reserve [8}. While papillary projections with blood flow should always raise suspicion on underlying malignancy, in pregnancy it could be a normal finding due to decidualization of ovarian endometriomas.

It is recommended to always look for adenomyosis as well as deep endometrial nodules in the case of a detected endometriosis, especially in the case of visible endometriomas. Diagnosis of adenomyosis should be according to MUSA criteria [10]. Echogenic subendometrial lines and buds as individual criterion showed the best diagnostic performance with sensitivity of 23-58% and specificity of 92% [11]. The typical translesional vascularity that helps to distinguish adenomyosis from fibroid is difficult to obtain with regular power Doppler and new studies are directed towards usage of MV-flow to access blood flow through small vessels [12].

In order to detect the obliteration of pouch of Douglas, the mobility of retrocervix against rectum in anteverted and uterine fundus against rectum in retroverted uterus should be accessed.

Positive sliding sign excludes the pathology [13]. Additionally, clinicians are encouraged to look for anterior muscularis of rectum and a presence of endometrial nodules.

Treatment: NSAIDs may be offered in order to reduce endometriosis-associated pain, especially in adolescents if first line hormone treatment is not an option [5]. Tricyclic antidepressants (e.g. amitriptyline, nortriptyline), selective serotonin uptake inhibitors (e.g. duloxetine) and anticonvulsants (e.g. gabapentin and pregabalin) have all shown promise in the treatment of endometriosis-associated pain. However, in randomized clinical trials for the management of chronic pelvic pain, they have not been proven to be clearly superior to placebo and are sometimes associated with severe, dose-limiting side effects [14].

Hormone therapy is based on the evidence that endometriosis is a 'steroid dependent' condition. Combined hormonal contraceptives and progestogens are used as the first line hormone therapy for endometriosis associated pain [5]. A systematic review and meta-analysis by Muzii and colleagues compared continuous versus cyclic OCP use for the treatment of endometriosis-associated pain and reported that the continuous regimen appears to be more efficacious with regards to dysmenorrhea recurrence (RR 0.24; 95%CI 0.06-0.91) [15]. Although preferentially prescribed from clinicians, dienogest is not proved to be superior from norethisterone-acetate, that is financially more affordable [16].

Anti-progestogens and danazol are no longer included in ESHRE recommendations due to their severe side effects.

However, one-third of patients are non-responders to estro-progestins and progestin-only medication due to progesterone resistance and they could benefit from GnRH agonists and GnRH antagonists that are prescribed as a second line hormonal treatment [17, 18].

GnRH agonists are effective at treating endometriosis symptoms, but have numerous limitations, including a delayed therapeutic impact because of the flare-up effect and suppression of E2 to less than 20pg/mL, consequently leading to reduction of bone mineral density after long-term treatment [19]. There are many combinations of add-back regimens that are effective in preventing bone loss when administered with GnRH agonists. These add-back regimens include progestin monotherapy such as norethisterone/norethindrone acetate (NETA), estrogen-progestin combinations, selective estrogen receptor modulators, bisphosphonates, tibolone, and testosterone [20]. ESHRE recommends to consider the addition of add-back therapy when prescribing GnRH agonist [5].

GnRH antagonists have been added as the second line therapy to the ESHRE guideline update in 2022 [5]. The main advantages of GnRH antagonists are oral administration, immediate suppression of FSH and LH secretion without flare-up effect, rapid recovery of hormone secretion after stopping treatment, as well as dose-dependent estrogen suppression [17]. Elagolix and relugolix are FDA approved GnRH drugs, but their effectiveness in treatment of endometriosis related pain is proven only in comparation with placebo, and not with first line estrogen-progestin/progestin only therapy [21, 22, 23]. That is the reason, in addition to the high price, why certain authors strongly argue against their usage [24]. Nevertheless, it should always bare in mind the prescribed safe time of use of GnRH analogues.

In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonists **[5]**.

Surgical treatment of endometriosis is the therapy of choice in case of persistent pain after the use of drugs [5]. Before the potential implementation of the surgical procedure, the potential improvement in the quality of life should be weighed against the inevitable damage to the ovarian reserve. Also, patients should be informed that pain may persist even after removal of the uterus, due to central sensitization [25]. Medical pre-treatment is not recommended, as there is no proved improvement [5]. However, if patient do not plan pregnancy after surgically treated, medical treatment, i.e. COC, LNG-IUD or oral progestins should be prescribed in order to prevent recurrence of disease and disease-induced pain [5].

Surgery is also a therapeutic option in case of suspected malignancy, which is evaluated according to the IOTA criteria. In the treatment of infertility, surgery is performed in the case of an estimated high EFI score to ensure a greater chance of natural conception. If a spontaneous pregnancy does not occur after 18 months, IVF is recommended for the couple [26]. On the other hand, if the patient is referred for in vitro fertilization, surgical pretreatment is not recommended because it does not improve the outcome and leads to a decrease in the ovarian reserve5. It is performed only in rare cases of estimated difficulties in aspiration of the follicles and, as previously stated, in the case of an estimated risk of malignancy or refractory pain.

Numerous researches are conducted with the aim of finding a safe and effective medical non-hormonal therapy, affecting primarily angiogenesis and inflammation. However, there is a long way from preclinical studies to the official recommendations, as well as their availability on the market.

Endometriosis and pregnancy: Women with superficial peritoneal and ovarian endometriosis do not appear to be at considerably increased risk of major obstetric and neonatal complications, whereas women with severe endometriosis, whether operated or not, are at several-fold increased risk of placenta previa. Overall, women with adenomyosis are at increased risk of various adverse obstetric outcomes, including preeclampsia, preterm delivery, fetal malpresentation, postpartum hemorrhage, low birth weight, and small for gestational age [27].

Conclusion: Endometriosis affects a large percent of women of reproductive age and is frequently associated with lowered quality of life as well as certain health risks, and continuous education and keeping up with new updates related to the disease enables clinicians to provide the patient with the best individualized treatment.

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MINIMALLY INVASIVE GYNECOLOGICAL SURGERY (MIGS) AND GYNECOLOGICAL EMERGENCIES

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Starting as a diagnostic procedure MIGS has evolved, mainly due to instrumental evolution and surgeons acceptance, to become the gold standard in managing most gynecological benign pathology and even in more advanced procedures such as pelvic organ prolapse and urinary incontinence management techniques.

Acute gynecological emergencies are conditions that threaten the woman's life. Also, the same conditions could jeopardize patients fertility. Common gynecological emergencies present as acute abdomen, abnormal vaginal bleeding, or a combination of both.

The main gynecological emergencies could be divided into:

- early pregnancy problems (abortus, ectopic pregnancy...)
- gynecological causes of severe pelvic pain (acute pelvic inflammatory disease, pelvic endometriosis, torsion and rupture of an ovarian neoplasm, torsion or degeneration of a uterine leiomyoma, ovarian hyperstimulation syndrome) [1].

New technologies are making big improvements in surgery, especially in laparoscopic surgery.

By laparoscopy, it is possible to treat the patients with serious diagnosis including those with high-risk life-threatening conditions. Emergency laparoscopy enables us to immediately diagnose the cause of abdominal pain as well as to manage and treat such urgent patients.

Today, laparoscopic surgery is the standard procedure in different fields of medicine, solving the most delicate problems. Laparoscopic approach is the best choice for most urgent situations, especially in gynecological pathology.

In gynecology, laparoscopic operations are almost standard procedures for treatment of:

- ectopic pregnancies
- ovarian cysts
- pelvic or ovarian endometriosis
- adnexal masses.

Urgent laparoscopy could be performed even in pregnant patients!

Minimally invasive surgical procedures, compared with the traditional open surgery, are associated with:

- significantly less blood loss during surgery
- less scarring
- less postoperative pain
- quicker recovery and shorter hospital stay
- fewer infections.

This allows patients to recover faster and return to their lives and daily activities with improved quality of life. Benefits of laparoscopy (vs laparotomy) is: the procedure is safer, cost-effective (use of less medicaments: antibiotics, pain killers...), less traumatic (postoperative recovery is quick),

significantly decreases number of hospital days, and thus enables quicker return to normal social and working activities.

Patient are usually dismissed the first postoperative day after laparoscopic surgery.

Indications for urgent laparoscopy in gynecology:

- Tubal abortion/rupture - hemoperitoneum
- Rupture of the ovarian cyst
- Adnexal or ovarian cyst torsion
- Rupture of the endometriotic cyst [2].

Contraindications for laparoscopy:

- Cardiopulmonary disease
- Ileus
- Adhesions (prior operations, inflammations, STDs...)
- Large intraabdominal tumors
- Pregnancy
- Progressive malignant disease
- Huge intraabdominal bleeding – shock hemorrhagic
- Extreme obesity

Conditions for laparoscopy operations in acute gynecological emergencies:

- Accurate diagnosis
- Adequate decision on the type of surgical procedure
- Training and coordination of the team in OP room
- Anesthesia
- Apparatus and instruments (laparoscopic equipment and cell-saver).

Before making a decision and starting laparoscopic surgery, it is important to assess how quickly and safely the bleeding can be stopped with this approach.

Complications during laparoscopy:

- Injury during the introduction of the first and assistant trocars
- Lesions of large blood vessels
- Bowel or bladder perforations
- CO2 insufflation problem, emphysema
- Injuries of the ureter
- Pulmonary embolism
- Complications from anesthesia [3].

Minimally invasive surgery could be very demanding especially for emergency cases in gynecology. The main condition even for regular laparoscopy is teamwork of well trained and skillful team, including experienced anesthesiologist and adequate op. room with equipment (instruments). In case of hemoperitoneum, we should have available cell saver. For emergency cases, all of this must be available all the time during duty, 24/7.

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KARCINOM ENDOMETRIJA – ULOGA HISTEROSKOPIJE

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Introduction:

Hysteroscopy is an endoscopic method, which has a very important place in minimally invasive gynecological surgery. Its significance is multi-layered and today it is indispensable in the diagnosis of many conditions in gynecology. Hysteroscopy has an indispensable place in the diagnosis of endometrial cancer.

Discussion:

Ever since the pioneering works of Bozzini, and even earlier, the human mind has been trying to penetrate the uterine cavity. visualization of changes inside the uterine cavity has always been an unfulfilled dream for many generations of gynecological oncologists. Today we can proudly say that we are inheriting the realization of the dream of many of our honorable predecessors, who did not have the opportunity to apply such a sophisticated technique in clinical practice. And hysteroscopy, as an endoscopic method, is not only very important in minimally invasive gynecological surgery, but today it is indispensable in the diagnosis of endometrial cancer. It is indisputable that today the importance of hysteroscopy is increasing. We can explain the mentioned by the fact that there have been a number of generations of gynecological endoscopists who have undergone the most demanding education. In addition to the aforementioned progress in surgical techniques, as well as technological progress, which until yesterday was not even possible to comprehend, brings an additional dimension to the routine application of hysteroscopy in the diagnosis of endometrial cancer.

Conclusion:

The Republic of Croatia was and is a leader in minimally invasive gynecological surgery. It is undeniable that the Croatian Society for Gynecological Endoscopy of the Croatian Medical Association has been operating in Zabok since 2000. We are proud to point out that almost a thousand gynecological endoscopists from the Republic of Croatia and Southeast Europe have been educated through twenty-three international endoscopy postgraduate courses “Kurt Semm”. In addition to the fact that the first laparoscopic hysterectomy was performed in Zabok General Hospital in 1994, performed by prof. Kopjar and Dr. Knezović, we must emphasize that great strides have been made in terms of the development, introduction and routine clinical application of hysteroscopy in the diagnosis and surgical treatment of benign and malignant neoplasms of the uterus. Today, we are proud to witness the fact that in the Republic of Croatia and in Southeastern Europe, the application of hysteroscopy has entered daily clinical practice. The use of classic fractionated curettage is extremely rare today, and is practically reserved for manifest and extreme uterine bleeding. For all other procedures, primarily in the diagnosis of

benign and malignant endometrial neoplasms, the primary and preferred diagnostic and therapeutic procedure is precisely hysteroscopy. And in the future, with various state-of-the-art technological achievements, especially in terms of the development of artificial intelligence, we expect further progress in the clinical application of hysteroscopy, to the benefit of our patients.

Regardless of the technological progress we are witnessing, there are still moments in the diagnosis and treatment of endometrial cancer that require thoughtful and multidisciplinary team action by experts from numerous fields. The personalization of medicine and the personalization of the relationship with each individual patient, in front of the entire healthcare system, imposes numerous challenges. Raising the quality of diagnostics in the treatment of endometrial cancer is an imperative for all of us in our daily clinical work. By improving the quality of our work and continuously improving it, we ultimately contribute to better results in the diagnosis, treatment and follow-up of our patients. The mentioned approach imposes on all of us a paradigm shift in the diagnostic and therapeutic procedure. It is certain that until recently, in many areas, the method of choice in diagnostics was the application of classical fractional curettage. Fractional curettage has been used routinely in the detection of endometrial cancer for many years. With the advancement of technology and past experience, the application of hysteroscopy has given us a very powerful tool in the diagnosis and treatment of endometrial cancer. The great advantages of hysteroscopy are, first of all, its minimal invasiveness and very high accuracy, as excellent visualization enables accurate sampling of suspicious samples. All of the above guarantees very good and high-quality results in dietetics and treatment of patients with endometrial cancer.

Key words: Hysteroscopy, endometrial cancer, endometrial cancer diagnosis

Endometrial cancer – global challenges

The incidence of endometrial cancer in the world speaks in favor of a continuous increase in the number of newly diagnosed women. Estimates say that every year around 142,000 women are diagnosed with endometrial cancer in the world, and about 42,000 of them die from the same disease every year. Based on statistical and epidemiological research, it is evident that endometrial cancer is most often diagnosed after menopause. Its incidence is highest around the seventh decade of life [1,2]. Endometrial cancer rarely occurs in younger patients, so that only 4% of them are in the age group younger than 40, and it most often occurs in postmenopausal patients. [3] Based on recent literature, we now know that endometrial cancer is the fourth most common malignant tumor in women. population in the world. It was estimated that there were 65,620 newly diagnosed endometrial cancer patients in the United States, while 12,590 of them died in the same year [4]. The underlying cause of the increase in incidence is thought to be the obesity epidemic and the resulting hyperinsulinemia [5,6,7].

A review of recent literature verifies that endometrial cancer is the most common gynecological malignancy in Europe and North America. The traditional classification of endometrial cancer is based on clinical and endocrine features (eg types I and II) or on histopathological characteristics (eg endometrioid, serous or clear cell adenocarcinoma). The subtypes defined by different classification systems correlate to some extent, but there is considerable heterogeneity in biological, pathological, and molecular features within tumor types from both classification systems. In this Review, we provide an overview of traditional and newer genomic classifications of endometrial cancer. We discuss how a classification system incorporating genomic and histopathological features to define biologically and clinically relevant disease subsets would be useful. Such an integrated classification could facilitate the development of treatments tailored

to specific subsets of the disease and could potentially enable the delivery of precision medicine to patients with endometrial cancer [8].

And a smaller number of hysterectomies for benign endometrial pathology has contributed to the current increase in the incidence of endometrial cancer, but the main cause of this is the growing prevalence of obesity in the population. however, obesity poses challenges for diagnosis and treatment, and more research is needed to offer primary prevention to high-risk women and to optimize endometrial cancer survival. Early onset of postmenopausal bleeding ensures the cure of most endometrial cancers with hysterectomy. On the other hand, patients with advanced disease have a worse prognosis. A minimally invasive surgical strategy and sentinel lymph node biopsy provide an alternative for our patients. It is a very high-quality alternative to the classic radical surgical treatment. Adjuvant radiotherapy also reduces locoregional recurrences in cases of medium and high risk. Advances in our understanding of the molecular biology of endometrial cancer have paved the way for targeted chemotherapy strategies, and clinical trials will determine their benefit in the setting of adjuvant, advanced, and recurrent disease in the coming years [9]. Endometrial cancer is the fourth most common cancer in the United States after breast, lung, and colon cancer. Risk factors are associated with excessive exposure of the endometrium to estrogens, including estrogen therapy, early menarche, and late menopause. Risk factors also include tamoxifen therapy, nulliparity, infertility or absence of ovulation, and polycystic ovary syndrome. Additional risk factors for endometrial cancer are the increasing life expectancy of women, obesity, hypertension, diabetes mellitus and hereditary colorectal cancer [10].

Specifics of diagnosis and treatment of endometrial cancer

What is a relatively favorable fact, however, is precisely the appearance of vaginal bleeding as a symptom of the disease itself. The mentioned also explains the fact why most women with endometrial cancer are diagnosed at an early stage. The total five-year survival in endometrial cancer for all stages is about 80%. Endometrial tumors of histological grade I have the best prognosis, and they also respond better to hormonal therapy. Grade II and III tumors have a worse prognosis, with a tendency to relapse. What is really crucial is the fact that surgical treatment is the basic procedure in the treatment of endometrial cancer. It enables accurate determination of the stage of the disease and later determination of further adjuvant treatment for patients who need it [1]. Since the primary treatment for endometrial cancer is surgery, we all face numerous challenges related to younger patients with endometrial cancer who would like to retain their reproductive capacity. Recently, several studies have been published that indicate encouraging results in the treatment of younger patients with endometrial cancer, precisely with the use of high doses of progestin [3]. In this case, conservative treatment may be indicated for younger women who want to maintain their fertility. it is undeniable that lifestyle changes, such as diet and exercise, can modulate the risk of developing endometrial cancer, as well as prevent recurrence and other obesity-related comorbidities [5].Based on state-of-the-art knowledge, an overview of the current molecular classification of endometrial cancer, imaging findings in early and advanced disease, and current treatment strategies is provided, with an emphasis on new systemic therapies for advanced EC. In recent years, the treatment of endometrial cancer has changed significantly. Molecular characterization of endometrial cancer has shed new light on the biological behavior of this disease, the staging system of the International Federation of Gynecology and Obstetrics has recently been revised, and imaging itself is officially included in the treatment of endometrial cancer. Recent genomic analysis of endometrial cancer has led to the approval of new molecularly targeted therapies and immune checkpoint inhibitors. At the same time, the imaging itself enables the assessment of myometrial invasion, expansion of the cervical stroma, involvement of lymph

nodes and distant metastases, and plays a key role in treatment planning. Modern treatment strategies, which include surgery, radiation and systemic therapies, are based on accurate staging and risk stratification. The mentioned strategies improve the quality of our treatment and give patients a better prognosis [6].The American Cancer Society recommends that all women over the age of 65 be informed about the risks and symptoms of endometrial cancer and that they be advised to contact their doctor if symptoms occur. According to available literature references, there is currently no evidence supporting endometrial cancer screening in asymptomatic women. In the case of profuse bleeding, it is necessary to first rule out pregnancy in women of reproductive age and to determine the complete blood count and determine the prothrombin and partial thromboplastin times. We recommend a transvaginal ultrasound as well as an endometrial biopsy, which determines the further diagnostic and therapeutic procedure for the patient. The prevailing opinion is that the primary therapy for endometrial cancer is surgical with total hysterectomy and bilateral salpingo-oophorectomy and indicated pelvic lymphadenectomy. Recently, more and more emphasis has been placed on the minimal invasiveness of the surgical treatment with the removal of the Sentinel's sentinel node. Pre-invasive endometrial changes can be treated conservatively without atypia, while the presence of atypia requires surgical treatment in endometrial hyperplasia. Postoperatively, in advanced stages, radiation and chemotherapy have their place. The very survival of patients with endometrial cancer is determined by the stage of the disease itself. Prevention of endometrial cancer also contributes to the control of risk factors, such as obesity, diabetes and hypertension [10,11].

The stage of endometrial cancer is determined according to the FIGO classification - International Federation of Gynecology and Obstetrics. Early and accurate diagnostic assessment of disease status is important for optimal treatment planning and outcome prediction. Preoperative evaluation and workup can help assess local spread and detect distant metastatic disease, guiding the optimal course of treatment. Several imaging methods, such as transvaginal ultrasound, computed tomography, and magnetic resonance imaging, are used as tools for preoperative staging of endometrial cancer. Positron emission tomography/computed tomography and more recently, positron emission tomography/magnetic resonance imaging are also used in the treatment of endometrial cancer. Cross-sectional imaging, particularly MRI, may reveal extensive myometrial invasion or tumor extension into the cervical stroma, which may alter treatment. Imaging studies can also assess the presence of lymph node involvement and detect local and distant metastatic disease at diagnosis. In addition, imaging methods play a major role in the monitoring of treatment and supervision of patients, and enable the detection of early recurrences of the disease [12,13,14,15].

The role of hysteroscopy and new perspectives in the treatment of endometrial cancer

With increasing life expectancy, women now live up to one-third of their lives in menopause. Postmenopausal bleeding is a common gynecological problem encountered by clinicians. Endometrial cancer is present in about 10% of patients with postmenstrual bleeding. However, many other conditions such as endometrial or cervical polyps, genital atrophy or non-gynecological conditions may be present. Hysteroscopy has replaced blind diagnostic procedures and is now considered the gold standard in the diagnosis and treatment of intrauterine pathology. Gynecologists in clinical practice should be familiar with the use of hysteroscopy in the diagnosis and treatment of menopausal patients with gynecological complaints. Recent findings indicate exact evidence of the role of hysteroscopy in the evaluation and treatment of postmenopausal patients with intrauterine pathology [15].

The Cancer Genome Atlas publication was the first to describe the genomic landscape of endometrial cancer and characterize these cancers into four molecular subtypes with different prognoses. A proactive molecular classifier for endometrial cancer was developed to more easily and inexpensively classify endometrial cancer into four similar molecular subtypes called POLE, mismatch repair deficiency, abnormal p53, and no specific molecular profile. In addition to these four subtypes, other molecular biomarkers may influence clinical behavior and response to targeted therapies and include beta-catenin, Her2 amplification, PI3K/mTOR/AKT alterations, L1CAM, hormone receptor expression, tumor mutational burden, and ARID1A. There are numerous clinical trials investigating treatment escalation and de-escalation within the four molecular subtypes, as well as matching targeted therapies to specific mutational or biomarker profiles. All endometrial cancers should undergo basic molecular classification that includes assessment of mismatch repair status. POLE and p53 status are prognostic and may become actionable in the future. Clinicians treating patients with endometrial cancer should understand the role of molecular classification in guiding treatment. These studies aim to provide patients with endometrial cancer with the best possible prognosis [7]. The team work, in which doctors of numerous profiles participate, at the oncology council, determines only the treatment, prognosis and treatment perspectives of our patients, in order to provide them with the best prospects [1]. In order to be able to direct all necessary efforts for better treatment, monitoring and prognosis of endometrial cancer patients, it is necessary to respect and accept a number of preconditions. In doing so, it is necessary to include a detailed review of etiology, diagnostics, protocols, treatment, monitoring and controversies related to endometrial cancer. It is necessary to continuously monitor the recent literature and the guidelines prescribed by the relevant societies and institutions. As one of the most common gynecological oncological diseases, endometrial cancer poses great challenges to all of us. In addition to the public health component, endometrial cancer poses a number of other dilemmas for the health care system, starting from primary surgical treatment with the stage of the disease itself, to adjuvant treatment with radiation and chemotherapy. In all of the above, patient education will have a great effect on the prognosis, how to deal with the disease itself, treatment and subsequent recovery, rehabilitation and socialization of patients as well as possible [2]. As the prognosis is worse for advanced stages of endometrial cancer, new treatment protocols are being explored. The aim is to provide an overview of the current situation, especially in relation to the genetic and metabolic characteristics of tumors. At the same time, newer technologies are being researched and nanotechnology tests are being carried out in the early diagnosis of endometrial cancer, the determination of metastases and the treatment itself. The above is supported by a systematic analysis of recent references taken from Pub med. Based on the aforementioned, it was verified that hypoxia-inducible factor-1 and the Von Hippel-Lindau factor participated in the oncogenesis and progression of endometrial cancer, as well as the Nrf2 factor. Various genetic changes were found in endometrial cancer, and it was verified that abnormal inactivation of the X chromosome can help in the diagnosis of endometrial cancer and its precancerous lesions. Likewise, disorders in glucose and lipid metabolism were found in endometrial cancer. Today, therapeutic strategies are focused on the HIF-1α pathway, the mTOR pathway as well as immunotherapy. It is evident that today endometrial cancer is understood in numerous segments, but the underlying mechanisms still remain relatively unknown. The aforementioned presents us with challenges for new diagnostic, prognostic and therapeutic goals, as well as further research [4].The first joint consensus conference of the European Society of Medical Oncology (ESMO), the European Society of Radiotherapy and Oncology (ESTRO) and the European Society of Gynecological Oncology (ESGO) on endometrial cancer was held on 11 and 13 December 2014 in Milan, Italy. Elaboration of four problems: prevention and screening, surgery, adjuvant treatment

and advanced and recurrent disease. All relevant scientific literature, identified by experts, was previously reviewed. During the consensus conference, the panel developed recommendations for each specific issue and a consensus was reached. The results of this consensus conference gave recommendations with evidence for the treatment of endometrial cancer, which greatly helped all specialists who take multidisciplinary care of patients with endometrial cancer [11]. The prognosis for women with endometrial cancer is generally good. This is because the disease is often diagnosed at an early, treatable stage, as women seek care for postmenopausal bleeding. The prognosis, however, is worse for women with high-risk endometrial cancer. These women may benefit from more extensive surgery, including pelvic and para-aortic lymph node dissection, whereas such surgery is not beneficial for women with low-risk cancer. Therefore, it is important to correctly identify women with high-risk cancer before surgery. Imaging methods can help us identify and recognize women with high-risk cancer and can help us assess local tumor extension in women with endometrial cancer [13]. Although hysteroscopy is currently the undisputed gold standard for examination of the uterine cavity in women with suspected endometrial cancer, it remains controversial as a procedure that may promote the spread of metastases. Endometrial cancer cells can be detached during hysteroscopy and passively transported with fluid flow into the peritoneal cavity. Today, there is an open discussion about the risk of metastasis in women who undergo diagnostic hysteroscopy and what conditions must be met for the procedure to be safe. We searched PubMed, Ovid, Medline and Scopus databases for data published in the years 1985-2017. The following search criteria, “MeSH headings”: hysteroscopy, endometrial cancer, intraperitoneal or metastatic spread were used to find relevant papers. Based on the previous data analysis, it was concluded that diagnostic hysteroscopy performed in women with endometrial cancer, especially in the early stages, is a very useful, effective and safe diagnostic method. It was also concluded that distension media used for endoscopic interventions in the uterine cavity must be applied with relatively low pressures to prevent an increase in the risk of intraperitoneal spread of endometrial cancer. The mentioned approach reduces the possibility of metastases [14,15,16].

Hysteroscopy is performed in many indications. Today, it is in clinical practice that doctors are educated on hysteroscopic models, before they begin the clinical application of hysteroscopy on female patients. The aforementioned is determined by numerous ethical, legal and economic limitations, which are connected with the incompatibility of hysteroscopic education on female patients. Virtual reality simulation also helps as a hysteroscopy training tool. It is planned to establish specific curricula for the education of specific hysteroscopists. The mentioned curricula should primarily be based on the requirements for hysteroscopy skills, and their standardization will enable better preparation of future hysteroscopists [16].

Today, hysteroscopy is the gold standard in the diagnosis and treatment of intrauterine pathologies because it is a safe and minimally invasive procedure that allows visualization of the entire uterine cavity. In the last few years, numerous technological innovations have appeared that have contributed to the development and widespread use of this technique. In particular, the new small-diameter hysteroscopes are equipped with an operating channel into which various mechanical instruments can be inserted, and allow not only the examination of the cervical canal and uterine cavity, but also the performance of biopsies or the treatment of benign diseases in a relatively short period of time. The aforementioned also does not require anesthesia to perform surgical procedures in outpatient settings. In this scenario, the operator must be able to perform hysteroscopy in the correct way to make this procedure as safe and painless as possible for the patient, which requires previous training and experience [16,17,18,19]. Regardless of the technological progress we are witnessing, there are still moments in the diagnosis and treatment

of endometrial cancer that require thoughtful and multidisciplinary team action by experts from numerous fields. The personalization of medicine and the personalization of the relationship with each individual patient, in front of the entire healthcare system, imposes numerous challenges. Raising the quality of diagnostics in the treatment of endometrial cancer is an imperative for all of us in our daily clinical work. By improving the quality of our work and continuously improving it, we ultimately contribute to better results in the diagnosis, treatment and follow-up of our patients. The mentioned approach imposes on all of us a paradigm shift in the diagnostic and therapeutic procedure. It is certain that until recently, in many areas, the method of choice in diagnostics was the application of classical fractional curettage. Fractional curettage has been used routinely in the detection of endometrial cancer for many years. With the advancement of technology and past experience, the application of hysteroscopy has given us a very high-quality tool in the diagnosis and treatment of endometrial cancer. The great advantages of hysteroscopy are, first of all, its minimal invasiveness and very high accuracy, as excellent visualization enables accurate sampling of suspicious samples. All of the above guarantees very good and high-quality results in the diagnosis and treatment of patients with endometrial cancer [20,21,22,23,24,25,26,27].

Perspectives and projections

Endometrial cancer presents new challenges to the public health system, which are increasing, given the continuous increase in incidence and mortality. Minimally invasive treatment, including the use of hysteroscopy in diagnostics, is sure to gain more and more importance. Ultimately, the most important thing is to provide our patients with the best and highest quality treatment as well as the prognosis [28,29,30,31,32,33,34,35,36].

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PREOPERATIVNA PRIPREMA I ANESTEZIJA ZA LAPAROSKOPSKE GINEKOLOŠKE PROCEDURE

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Ginekologija je jedna od prvih hirurških grana koja je počela da razvija laparoskopske tehnike - da bi danas mogli reći, da nema te ginekološke operacije koja se ne može izvesti laparoskopskim pristupom. Vremenom je laparoskopija stekla veliku popularnost kao minimalno-invazivna hirurgija sa manjim procentom i težinom komplikacija, te se sve češće izvodi i u uslovima dnevne bolnice. Posmatrano sa ekonomskog aspekta ovaj pristup hirurgiji je daleko povoljniji, i kao takav se nameće i preuzima primat. Sa druge strane, za anesteziologe, laparoskopija uvodi nove izazove i moguće komplikacije uzrokovane pre svega pneumoperitoneumom i Trendelenburgovim položajem, kao i aditivnim efektom ova dva faktora. Potreban je naročit oprez kod starijih osoba, osoba sa komorbiditetima i gojaznih.

Intraoperativni efekti laparoskopske operacije se odnose na primenu pneumoperitoneuma koji podiže intra-abdominalni pritisak.

Pneumoperitoneum odvaja trbušni zid od visceralnih organa i omogućava bezbednu inserciju instrumenta kao i vizuelizaciju operativnog polja. Različiti gasovi su u prošlosti koriršćeni za insuflaciju i postizanje pneumoperitoneuma. Počev od kiseonika koji je ubrzo napušten zbog svoje zapaljivosti u kombinaciji sa elektrohirurgijom i laserom, zatim vazduh koji se takodje nije pokazao kao bezbedan imajući u vidu da u daleko većoj učestalosti dovodi do gasne embolije u odnosu na ugljen dioksid. Azotni oksidul (N2O) i ugljen dioskid su danas najčešće u upotrebi, od čega se ugljen dioksid koristi u 90% slučajeva. Ugljen dioksid nije zapaljiv i brzo se apsorbuje preko peritoneuma i izlučuje plućima, što može da rezultira hiperkarbijom koja se registruje kao povećanje parcijalnog pritiska ugljen dioksida na kraju ekspirijuma (End-tidal Carbon Dioksid - EtCO2). Kotrolisana ventilacija sa hiperventilacijom može spustiti nivo EtCO2. Fatalna gasna embolizacija je daleko ređa, kada se ugljen dioksid koristi kao distenzioni medijum u odnosu na vazduh. Potrebno je da u krvni sud dospe 200 ml CO2 da bi došlo do drastičnih negativnih efekata na kardiovaskularni sistem, dok je za vazduh dovoljno 20 ml.

Fiziološke promene uzrokovane povećanjem intra-abdominalnog pritiska su minimalne ako je on *<15 mmHg*. Fiziološki efekti uključuju: pomeranje dijafragme, smanjenje zapremine pluća, povećani otpor vazdušnih puteva, povišeni V/Q, hipoksija usled hipoventilacije, hiperkarbija takođe usled hipoventilacije ali i apsorpcije CO2, povećani rizik od regurgitacije, povišen sistemski vaskularni otpor, povišen srednji arterijski pritisak, smanjeni venski dotok, smanjen udarni volumen uz smanjenje renalnog protoka krvi i stope glomerularne filtracije. Stoga, neophodno je prilagoditi anesteziološke tehnike promenama koje se dešavaju tokom laparoskopskih operacija.

Ginekološke laparoskopske operacije se obično izvode u Trendelenburgovom položaju, a često i u kombinaciji sa ginekološkim položajem. Ovi položaji adidtivno deluju na fiziološke promene respiratornog i kardiovaskularnog sistema koje nastaju usled pneumoperitoneuma.Smatra se da kod pacijenta bez komorbiditeta tokom laparoskopije u opštoj anesteziji Trendelenburgov položaj *> 20°* ne dovodi do značajnih promena parcijalnog pritiska kiseonika alveolarne krvi (PaO2). Takođe, neophodno je obratiti pažnju da naglašen Trendelenburgov položaj može uticati na povećanje

intrakranijalnog pritiska, te je potreban oprez kod pacijentkinja sa glaukomom i intrakranijalnom patologijom. Viđene su i retinalne hemoragije kod primene značajnog Trendelenburgovog položaja. Pri postavljanju pacijentkinja u ginekološki položaj, važno je voditi računa da ne dođe do povrede femoralnog, peronealnog, obturatornog nerva - obavezno je zaštiti prevoje sunđerima. Značajna abdukcija ruke kod Trendelenburg položaja može potencirati povrede aksilarnih i brahijalnih nerava.

Komplikacije

Komplikacije laparaskopske hirurgije i prateće anestezije variraju od lakih do veoma teških, uključujući i letalni ishod. Laparaskopska hirurgija je minimalno-invazivna, i kao takva ima prednost nad otvorenom hirurgijom zbog manjeg procenta komplikacija i posledično bržeg oporavka pacijenta. Kraće je zadržavanje u bolnici i brži povratak svakodnevnim aktivnostima. Komplikacije su svakako manje ako se gleda hirurški aspekt, dok su se za anesteziju pojavili novi izazovi na koje se mora obrati pažnja. Pre svega pneumoperitoneum i Trendelenburgov položaj i njihov pojedinačni kao i udruženi uticaj na pacijenta u anesteziji. Takođe, važno je napomenuti da sa rastućom popularmošću laparoskopije, sve je više pacijenata u starijoj životnoj dobi i sa brojnim komorbiditetima koji se operišu laparoskopski putem.

- Bol u leđima i ramenima- dovodi se u vezu sa stvaranjem pneumoperitoneuma i distenzijom krvnih sudova i nerava. Javlja se u učestalosti od 35 - 63%, što predstavlja ozbiljan diskomfor za pacijentkinju. Nastaje iritacijom freničnog nerva. Može da traje od jednog do tri dana. Prevencija ovog bola je u pažljivoj evakuaciji gasa. Za lečenje postoperativnog bola koriste se neopioidni analgetici, a često se pribegava i primeni lokalnih anestetika preventivno u okviru procedure. Primer je aplikacija lokalnog anestetika na dijafragmu da bi se izbegao neprijatni, a veoma čest bol u ramenima koji prati laparaskopske procedure.
- Postoperativna mučnina i povraćanje (Postoperative Nausea and Vomiting - PONV). Najčešća je komplikacija laparaskopske hirurgije, što je i najveća učestalost ove komplikacije kod laparaskopije u odnosu na sve druge vrste hirurgije. Zahteva pravovremen pristup i tretman, jer dovodi do značajnih subjektivnih tegoba pacijenta, produžen je postoperativni nadzor i hospitalno zadržavanje - što utiče na efikasnost minimalno invazivne hirurgije kao takve. Preventivne mere PONV su daleko efikasnije od tretmana, te je potrebno prilagoditi anesteziološke tehnike, pažljiv odabir pacijenta kao i primenu antiemetika u premedikaciji, prema lokalnom protoloku.
- Hiperkapnija i potkožni emfizem se neretko viđaju, i mogu se tolerisati različito u zavisnosti od starosti i komorbiditeta pacijenta. Hiperkapnija vodi ka acidozi i njenim poznatim negativnim efektima. Rešava se kontrolisanom hiperventilacijom pacijenta, a u ukoliko to ne pomogne, neophodno je konvertovati laparaskopsku u otvorenu, klasičnu operaciju.
- Pneumotoraks, pneumomedijastinum, gasna embolija i kardiorespiratorne komplikacije uključujući i srčani zastoj, su najteže komplikacije na koje moramo misliti. Neophodan je monitoring saturacije krvi kiseonikom, nivo endekspiratornog ugljen dioksida (EtCO2), EKG, neinvazivno merenje krvnog pritiska, kao i monitoring diureze. Za povredu velikih krvnih sudova i visceralnih organa najveća je mogućnost prilikom kreiranja pneumoperitoneuma i insercije instrumenata. Retke, ali viđene komplikacije su neuropatije i retinalno krvarenje koje nastaju usled pozicioniranja pacijenta.

Anesteziološke tehnike

Postoje tri mogućnosti anesteziioloških tehnika za ginekološke laparoskopske operacije:

- lokalna anestezija (blokada perifernih nerava) sa ili bez sedacije,
- regionalnu anestezija (neuroaksijalna, spinalna i periduralna) i
- opšta anestezija.

Potrebno je imati na umu mogućnost konverzije lokalne i regionalne u opštu anesteziju. Odabir tehnike se vrši na osnovu indikacija za operaciju i opšteg stanja pacijentkinje, uključujući i komorbiditete.

Blokada perifernih nerava i regionalna anestezija se primenjuju u pojedinim centrima za dijagnostičku i mikrolaparoskopiju. Sedacija se preporučuje uz lokalnu i regionalnu anesteziju da umanji diskomfor pacijentkinja i obezbedi bolju saradnju u toku operacije.

Opšta anestezija je najčešći i dalje najoptimalniji vid anestezije za većinu laparoskopskih operacija. Obezbeđuje optimalnu relaksaciju, kontrolisanu ventilaciju i eventualnu potrebu sa hiperventilacijom, analgeziju i amneziju. Opštoj anesteziji prethodi premedikacija anksioliticima i antiemeticima. Uvod u anesteziju može biti inhalacionim ili intravenskim anesteticima. Najčešće primenjivan je intravenski uvod propofolom ili Na-tiopentonom, a održavanje inhalacionim anesteticima, sevofluranom ili desfluranom. Primenjuje se i tehnika totalne intravenske anestezije (TIVA), koja podrazumeva uvod i održavanje anestezije propofolom, putem infuzione pumpe u kombinaciji sa opioidnim anelgeticima, remifentanilom ili alfentanilom. Po nekim autorima nije uočena značajna razlika u brzini buđenja i oporavka u odnosu na održavanje anestezije inhalacionim volatilnim anesteticima. Uočena je izvesna razlika u smislu manje učestalosti PONV u fazi ranog oporavka, kod primene propofola za održavanje anestezije u odnosu na volatilne anestetike. Ovaj podatak nije bez značaja, ako imamo u vidu visok procenat PONV kod laparaskopske hirurgije, kao i činjenicu da se laparaskopija smatra minimalno invazivnom hirurškom procedurom kod koje se očekuje brži oporavak i otpust iz bolnice.

Laparoskopija u trudnoći

Laparoskopska hirurgija u trudnoći danas se rutinski izvodi. Može se izvoditi tokom cele trudnoće ali je rizik najmanji tokom 2. trimestra. Laparoskopske tehnike smanjuju morbiditet majke i rizik od prevremenog porođaja, zbog manje manipulacije sa gravidnim uterusom. Prednosti ove tehnike su, takođe, manji postoperatvni bol, brži oporavak respiratorne i gastrointestinalne funkcije, brži povratak normalnim dnevnim aktivnostima, kraći boravak u bolnici. Sa druge strane, opisani su i specifični rizici, kako po majku, tako i za plod. Tu spadaju, rizik od povrede gravidnog uterusa i posledične fetalne traume, rizik od fetalne acidoze nastale apsorpcijom ugljen dioksida, snižavanje CO majke, kao i kompromitovana uteroplacentna cirkulacija usled povišenog intraperitonealnog pritiska. Pneumoperitoneum, nastao insuflacijom CO_2, elevira dijafragmu, smanjuje komplijansu grudnog koša, povećava pritisak u disajnim putevima i dovodi do povećanja $PaCO_2$ u krvi majke. Kao respiratorne komplikacije mogu nastati subkutani emfizem, pneumotoraks i gasna embolija.

Društvo Američkih gastroitestinalnih i endoskopskih hirurga (Society of American Gastrointestinal and Endoscopic Surgeons - SAGES) izdalo je preporuke za laparoskopiju tokom trudnoće koje uključuju:

1. odlaganje hirurške procedure do početka drugog trimestra;
2. intraoperativna intermitentna pneumatska kompresija donjih ekstermiteta kao profilaksa duboke venske tromboze;
3. monitoring srčane radnje fetusa i kontrakcija uterusa tokom operacije;
4. obavezan kapnografski monitoring;
5. ulazak u trbuh otvorenom tehnikom;

6. izbegavanje aortokavalne kompresije i hipotenzije;
7. održavanje niskih pritisaka pneumoperitoneuma (ispod 15 mmHg);
8. konsultacija akušera neposredno posle operacije.

Perioperativnu upotrebu tokolitičkih agenasa trebalo bi razmotriti ukoliko postoje znaci prevremenog porođaja.

Opšta endotrahealna anestezija je anestezija izbora za laparoskopske procedure tokom trudnoće. Kontrolisanom ventilacijom tokom anestezije postiže se održavanje normokapnije sa parcijalnim pritiskom između 30 i 35 mmHg u izdahnutom vazduhuna kraju ekspirijuma (EtCO2), čime se prevenira nastanak fetalne acidoze. Do acidoze može doći i usled apsorpcije ugljen dioksida preko peritoneuma. Pneumoperitonem sa pridruženom acidozom može dovesti do povećanja srčane frekvence i arterijskog pritiska majke. Hiperventilacija pluća može biti neophodna mera u ovakvim situacijama.

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OBSTETRICS

POSTPARTUM HAEMORRHAGE: TREATMENT OPTIONS IN UP TO DATE OBSTETRICS

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Postpartum hemorrhage (PPH) is defined as blood loss in the first 24 hours following the delivery in a volume greater than 500ml during vaginal delivery, or more than 1000ml during caesarean section. It complicates 1% to 10% of all births and is one of the leading causes of maternal mortality. Considering that the assessment of blood loss is often subjectively evaluated, ACOG (American College of Obstetricians and Gynecologists) completed and updated the definition of postpartum hemorrhage, defining it as blood loss equal to or greater than 1000 ml, or blood loss accompanied by symptoms and signs of hemorrhagic shock within 24 hours from birth.

Several etiological factors have been recognized as a risk factor for PPH, but in most cases the etiological factor remains unidentified. Uterine atony most commonly occurs during deliveries lasting for unusually long time, especially if they are complicated by chorioamnionitis, high parity, general anesthesia, as well as conditions that lead to excessive uterine distension, such as multiple pregnancies, polyhydramnios, and fetal macrosomia. Tissue trauma is most often associated with lacerations of the cervix and perineum, episiotomies, hematomas of the perineum and rupture of the uterus. Residual placental tissue increases the risk for PPH up to 3.5 times.

Coagulation disorders can be divided into congenital and acquired. The most common congenital coagulation disorders are von Willebrand's disease, hemophilia and idiopathic thrombocytopenic purpura. Acquired coagulation disorders are related to the use of anticoagulant drugs and disseminated intravascular coagulopathy (DIC). Other etiologic factors include uterine inversion and abnormal placentation.

FIGO (International Federation go Gynecology and Obstetrics) recommendations recommended to use of the Schock Index (SI) in the initial assessment and treatment of PPH. SI is defined as the ratio of heart rate to systolic blood pressure. SI shows an inverse, linear relationship with left ventricular function in acute heart failure. In conditions such as hemorrhage, trauma or sepsis, there is a reduction in the work of the left ventricle, a reduced stroke volume and an increase in SI. Due to the existence of compensatory mechanisms, that in a healthy woman can tolerate blood loss up to 1000 ml without a significant drop in blood pressure, SI is a promising marker that indicates blood loss. SI values greater than 0.9 indicate hemodynamic instability of the patient in labor, while values above 1 indicate the need for blood transfusion.

Guidelines are defined as systematically developed recommendations that may help medical professionals make the best decisions in a given situation. There are a large number of national as well as international guidelines for PPH, and all of them are primarily based on the prevention, diagnosis and therapy of PPH. The mutual differences between these guidelines arise primarily because they are based on observational studies, clinical evaluations, and expert opinions.

Active management of the third stage of labor is a frequent topic of controversy among different guidelines. It is recommended that uterotonics should be prescribed to all patients after childbirth, and the most commonly used drug for this purpose is oxyticin. The dose in which this drug is given, as well as the route of administration, are the subject of controversy among

different guidelines. In 2018, the World Health Organization (WHO) issued a recommendation for intramuscular or intravenous administration of 10 International Units (IU) of oxytocin. In case of lack or immediate unavailability of oxytocin, WHO recommends the use of carbetocin, ergot alkaloids and misoprostol. In case of contraindications, such as hypertension, according to WHO guidelines, mozoprostol is the drug of choice. For the prevention of PPH, along with the use of 10 IU of oxytocin, FIGO recommends controlled traction of the umbilical cord and postpartum assessment of uterine tone. If the condition of the newborn does not indicate otherwise, early ligation of the umbilical cord is not recommended.

The therapeutic approach to PPH depends on the identified cause of bleeding and ranges from a less invasive approach to more complex and radical. Initial care should include the placement of two venous lines, oxygen support, continuous monitoring of the woman in labor, administration of crystalloid solutions and taking measures to prevent hypothermia and to find the cause of bleeding as soon as possible. If atony is recognized as the cause of bleeding, most guidelines recommend uterine massage with bimanual uterine compression, followed by a simultaneous administration of uterotonics. If adequate uterine contractility is not established by the use of oxytocin, the use of other drugs is recommended, such as ergot derivatives, parenteral administration of prostaglandins or misoprostol.

Another recommendation given by the WHO includes the use of tranexamic acid (TXA) in the first three hours after delivery at a dose of 1 g intravenously. Some guidelines recommend the use of recombinant activated factor VII in the case of massive PPH.

If pharmacological measures do not give the desired result, uterine balloon tamponade, placement of compressive uterine sutures, ligature of pelvic blood vessels, embolization of the uterine artery, and in case of extreme necessity postpartum hysterectomy. In the cases of severe haemorrhage, when transfer to a tertiary level obstetric institution is indicated, aortic compression can be used as a temporary measure, or if available, the application of non-pneumatic anti-shock garment.

TXA is an inhibitor of fibrinolysis and FIGO recommends its administration immediately after the diagnosis of PPH, if no more than three hours have passed since delivery. The recommended dose is 1 gram of TXA administered intravenously over 10 minutes, regardless of the cause of the bleeding. If the haemorrhage continues after 30 minutes, or is repeated within 24 hours of the first dose, FIGO recommends the use of the second dose of TXA.

FIGO does not recommend the prophylactic use of TXA, but it can be prescribed in cases where greater blood loss is expected, including placenta accreta spectrum, placenta previa or if the previous delivery was complicated by PPH. TXA is most often given within 10 minutes of delivery, with the use of uterotonics (oxytocin), controlled umbilical cord traction and uterine massage. The most common side effects that occur after the administration of TXA are headache, pain in the stomach, back and musculoskeletal system.

Uterine balloon tamponade can be both a diagnostic and a therapeutic measure to control PPH and FIGO recommends its use in cases of PPH that are refractory to medical therapy. If adequate control of bleeding is not established with its application, the causative agent of PPH should be reevaluated. According to the results of observational studies, the success of balloon tamponade as a therapeutic measure for PPH ranges from 83% to 95%, and its application has led to a significant reduction in the performance of more invasive and radical procedures, such as ligation of pelvic blood vessels, uterine artery embolization and postpartum hysterectomy.

Uterine artery embolization is recommended in cases of refractory bleeding, whose control cannot be established with medication and less invasive, non-surgical procedures. The success rate of this method is greater than 90%, but its application requires the involvement of an interventional radiologist as well as trained personnel. This method is very successful in controlling bleeding caused by placental disorders, such as placenta accreta spectrum disorders.

Placing hemostatic sutures on the uterus is the method of choice when medical and non-surgical procedures fail to provide adequate bleeding control. Complications related to this surgical technique are rare, and the most common are uterine synechiae, ischemia, necrosis, and infections. The following hemostatic sutures are most commonly applied: B-Lynch, Hayman, Pereira and Cho.

In the case when application of a hemostatic sutures does not lead to the desired outcome, ligature of the uterine arteries is considered as the next measure. This method is a quick and relatively simple surgical solution that preserves a woman's reproductive capacity. The success rate of this method ranges widely, from 42% to 88%. Bilateral ligature of the internal iliac artery has a success rate between 40% and 100%, but it is a method that obstetricians rarely choose, primarily because of the anatomical proximity of the surrounding structures and the possibility of their injury. In the presence of massive PPH, such as those caused by rupture of the uterus or extensive lacerations of the genital organs, ligation of these blood vessels reduces intrapelvic bleeding, facilitates the work of the operator, as well as the performance of the hysterectomy when it is indicated.

Peripartum hysterectomy is the last therapeutic measure in the control of PPH, and is resorted to if all other medical, non-surgical and surgical procedures have been exhausted. Globally, there is an increase in the performance of this operation, which is primarily related to the increased rate of caesarean sections. The most common indications for its performance are related to placentation disorders, placenta previa, placenta accreta spectrum, placental abruption, atony and uterine rupture. Peripartum hysterectomy is accompanied by the highest maternal morbidity, higher incidence of blood transfusions, coagulopathy, urinary tract injuries, relaparotomy, and postoperative febrile morbidity. Subtotal hysterectomy should always be performed when intrapartum hysterectomy is indicated, since the duration of this operation is shorter and hemostasis is established more quickly. Total hysterectomy is indicated in cases of bleeding from the lower uterine segment, cervix or vaginal fornix.

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PROSTAGLANDIN E1 AS A PREFERENCE IN SECOND TRIMESTER PREGNANCY TERMINATION – EXPERIENCE IN CLINICAL CENTRE OF MONTENEGRO

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Second-trimester pregnancy termination comprises approximately 10 to 15 percent of abortions performed annually worldwide. Implicated with various maternal, fetal or combined indications, second trimester abortion is associated with more morbidity and mortality and, for some patients, more social or emotional challenges than first-trimester abortion.

Choices for these procedures are surgical, with dilation and evacuation (D&E), or with induction (medication).

Misoprostol is a synthetic analogue of prostaglandin E1, which has gastric antisecretory and mucosal protective effects, with additional effects in contracting smooth muscle fibers of the myometrium and cervical ripening. The oral form of misoprostol is approved in many countries for the treatment and prevention of gastroduodenal ulcers, but not for use in pregnancy. The FIGO and WHO latest update from 2018. support medical way of termination of pregnancy with misoprostol only regimen in many cases. Also, there is misoprostol in various combinations with mifegyne, antiprogesterone agent.

Our experience with misoprostol use in pregnancy termination started in 2017, when we used it for the first time in pregnancy termination. In the last five years we treated more than 300 patients with this medication. Compared with previous modalities used in the past, misoprostol alone or in combination with mifegyne premedication seems to be safe and efficient.

Keywords: misoprostol, mifegyne, prostaglandin E1, second trimester pregnancy termination

Uvod

Najnoviji revidirani protokol za upotrebu misoprostola u procesu prekida trudnoće, izdat je 2017. godine od FIGO-a, podržan od strane WHO. Lako dostupan, veoma informativan i sažet, sa preciznim dozama vezanim za starost trudnoće, načinima aplikacije u nekoliko češćih situacija iz prakse, može naći primjenu u svakodnevnim izazovima perinatologije. Uprkos cilju da se očuva svaka trudnoća, imamo situacije u kojima je neizbježna intervencija prekida trudnoće: iz razloga koji ugrožavaju majku ili fetusu ne pružaju perspektivu. Veoma dozno zavistan lijek, misoprostol treba koristiti po preporučenim dozama zavisno od starosti trudnoće ili veličine uterusa (od 800 mcg za prvi trimester do 25 mcg u trećem trimestru). Glavni nedostatak ovog protokola je što u analizu koja opravdava upotrebu nisu bile uključene pacijentkinje sa značajnim komorbiditetima, npr. prethodni ožiljci na uterusu tj. prethodni carski rezovi, koji predstavljaju logičan rizik u procesu prekida trudnoće, a svakodnevicu u praksi s obzirom na globalni porast broja carskih rezova. Iz manjih radova i podataka ustanovljeni su rizici rupture uterusa (0.3-0.4%) tako da je prihvaćena opcija upotrebe i u ovim situacijama do 26. nedjelje gestacije, uz oprez i eventualno korigovanje doze. Takođe, jedan broj radova analizira iskustva kombinacije misoprostola i mifegyna u procesu prekida trudnoće i prijavljuju čak i bolje rezultate (bolja priprema grlića materice, brži završetak čitave procedure, manje doze misoprostola...).

Rezultati

U proteklih pet godina sa preko 300 pacijenata upotrebljavali smo u većini slučajeva samo misoprostol, a u 20% premedikaciju mifegynom. Kod 10% pacijentkinja kod kojih pobačaj ne bi nastupio 24h od indukcije, bio bi plasiran Folley kateter intracervikalno opterećen tegom, kao pomoć za augmentaciju procesa. Sve trudnoće bile su starosti od 12-26 nedjelje gestacije. U tekućoj godini za prvih 9 meseci bilo je 67 pacijenata, najveći broj - njih 27 zbog uginuća ploda in utero, 19 zbog težih anomalija dijagnostikovanih ultrazvučnim pregledom (cistični higrom, spina bifida, hidrocefalus, anomalije srca, sakrokokcigealni teratom), hromozomopatija 10 (od čega 6 Tr 21), vPPROM 7, oligoamnion-anamnion 3 i jedna pacijentkinja sa karcinomom dojke. Kod 8 pacijentkinja rađen je feticid (starost preko 24 NG ili potreba za uzorkovanjem fetalne krvi zbog dalje dijagnostike). Kod pacijentkinja koje su to tražile, obezbjeđena je epiduralna analgezija u toku indukcije ili kratkotrajna analgosedacija za reviziju uterusa nakon pobačaja, kao i podrška kliničkog psihologa. U oko 25% slučajeva ehosonografski se isključila potreba za instrumentalnom revizijom nakon pobačaja, ali je ipak u 3 takva slučaja ustanovljena rezidua pa je kiretaža rađena naknadno. Sve pacijentkinje su pobacile u roku od 48h (sa prosječnim vremenom 14h) bez većih komplikacija, dvije su primale transfuzije krvi, nije bilo rupture uterusa kao teže komplikacije u ovoj grupi.

Diskusija

Od dvije pacijentkinje koje su primale transfuzije, jedna je imala marginalnu placenta previju i prethodno prolongirano krvarenje praćeno anemijom i vPPROM, a druga sindrom hronične abrupcije-oligoamniona. U oko 25% slučajeva pacijentkinje su imale opterećenu anamnezu sa jednim ili više prethodnih carskih rezova u istoriji.

Jedna od pacijentkinja je u anamnezi imala rupturu materice na ožiljku od prethodnog carskog reza prilikom indukcije pobačaja prije godinu dana (isto na protokolu misoprostola zbog uginule druge trudnoće sa 12 NG – kada je radjena hitna laparotomija i sutura uterusa, oporavak dobar, da bi nakon godinu dana došla sa trećom, uginulom trudnoćom starosti 15 NG i bez komplikacija ovog puta indukovana kombinacijom mifegyn/misoprostol).

Takođe je vrijedna pomena i pacijentkinja koja se pojavila u drugoj trudnoći (prethodna završena carskim rezom) granične starosti trudnoće za upotrebu prostaglandina (26/27 NG) sa intrauterinom smrću ploda, u dijabetičnoj ketoacidozi, težeg opšteg stanja koja je uspješno tretirana konzervativno, takođe kombinacijom mifegyn/misoprostol.

Zaključak

Indukcija pobačaja misoprostolom a naročito kombinacijom mifegyn/misoprostol pokazala se kao veoma efikasna, sigurna i bez većih i češćih komplikacija u odnosu na metode iz prošlosti. Lakši način aplikacije (bukalna primjena) kao i bolje tolerisanje neželjenih efekata (manji nagon na povraćanje, manji osjećaj bola, manja učestalost dijareja i osjećaja iscrpljenosti) evidentno je u odnosu na druge vrste prostaglandina, što definitvno stavlja ovaj metod i kao prvu liniju izbora.

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NAUČNE OSNOVE ZA RAZVOJ PARTOGRAMA – OD FRIEDMANOVE KRIVE DO "LABOUR CARE GUIDE"

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Partogram je grafički prikaz napredovanja porođaja, kao i stanja majke i ploda u toku porođaja. Razvijen je i ekstenzivno testiran od strane Svetske zdravstvene organizacije i u upotrebi je već skoro 30 godina. Partogram omogućava akušeru, odnosno babici da rano identifikuje sporo napredovanje porođaja i preduzimanje adekvatnih intervencija u cilju sprečavanja prolongiranog i obstruisanog porođaja.

Do obstruisanog porođaja dolazi u slučaju značajne disproporcije između dimenzija ploda/ neadekvatne fetalne prezentacije i karlice majke. Smatra se da je incidenca obstruisanog porođaja između 5-10%. Izvještavane učestalosti maternalnog mortaliteta kao posledice obstruisanog porođaja se kreću od 1% do 20% u različitim populacijama. Od oko 42 000 smrti majki koje su se desile 2000. godine vezanih za porođaj, procijenjeno je da je oko 8% bilo uzrokovano obstruisanim porođajem. Ovi podaci su vjerovatno nepotpuni i nekonzistentni i smatra se da navedene cifre podcjenjuju problem, jer se maternalne smrti uzrokovane obstruisanim porođajem često klasifikuju pod dijagnozama sepse, postpartalne hemoragije ili rupture uterusa.

Pristupi procjene rizika od obstruisanog porođaja su se mijenjali tokom vremena. U prošlosti, nizak rast čak i veličina obuće su korišćeni kao indirektni markeri adekvatnosti male karlice i potencijalne cefalopelvične disproporcije. Takođe, koristila se spoljašnja i unutrašnja pelvimetrija, a u literaturi se opisivala i rendgenska pelvimetrija. Pokazano je da ni procjena težine ploda bilo klinički bilo ultrazvučno nije efektivna u predviđanju obstruisanog porođaja. Sve navedene metode imaju nisku prediktivnu vrijednost zbog činjenice da se promjene dimenzija glavice ploda i karlice majke tokom porođaja ne mogu adekvatno predvidjeti njihovim korišćenjem. Tako da sama procjena adekvatnosti napredovanja porođaja treba identifikovati one žene koje su u riziku za cefalopelvičnu disproporciju, a partogram je upravo i kreiran kao alatka za paravovremeno prepoznavanje zastoja u porođaju.

Prvo istraživanje koje je prethodilo kreiranju partograma sproveo je Friedman 1954 godine na 500 prvorotki u jednoj bolnici u Americi i opisalo je obrazac normalne dilatacije grlića u toku porođaja. Friedman je podijelio porođaj funkcionalno na dvije faze. Latentna faza je trajala 8-10 h i odnosila se na dilataciju grlića do 3cm, a zatim je nastupala aktivna faza koja se karakteriše fazom akceleracije (od 3-9 cm) , a zatim fazom deceleracije Vremenski početak porođaja je bio zasnovan na subjektivnoj percepciji trudnice da su kontrakcije počele. Bilježenjem dilatacije grlića u odnosu na vrijeme dobijena je tipična krivulja u obliku slova S.

Philipott je zatim nastavio sa istraživanjem koristeći inicijalno principe Friedmanove studije i konstruisao tzv. cervikograf koji je testiran na porođajima prvorotki. Njegova studija je sprovedena u Africi u pokušaju da efikasno iskoristi praćenje porođaja od strane babica u regionima gdje nije bilo dovoljno ljekara. Od cervikografa je nastao partogram, koji nije bilježio samo dilataciju grlića nego i ostale parametre od značaja u porođaju. Kasnije je dodata „alert" linija koja je predstavljala prosječnu stopu napredovanja dilatacije najsporijih 10% pacijenata u posmatranoj populaciji Afričkih prvorotki. „Alert" linija je konstruisana prema brzini dilatacije od 1 cm/h počevši od vremena prijema. Svrha „alert" linije je da omogući babicama i ljekarima koji nadziru porođaj

da u slučaju nenapredovanja porođaja očekivanom dilatacijom od 1 cm/h upute pacijentkinju u odgovarajući centar gdje je moguće sprovesti aktivni tretman porođaja. Sledeći korak u razvoju partograma je ucrtavanje „action“ linije. Akciona linija je ucrtana 4h udesno od „alert“ linije ukazujući na to da bi se transfer pacijenta trebao omogućiti prije nego što se pređe akciona linija. Nastanakovog prvog partograma,odnosno cervikografa je je bio uslovljen namjerom da se na ispitivanom uzorku prvorotki u porođaju sprovede aktivni menadžment porođaja. Aktivni menadžment porođaja je uveo O Driscoll u irskoj sredinom 60-tih godina prošlog vijeka. Ovaj protokol vođenja porođaja je podrazumijevao prenatalnu pripremu i edukaciju trudnica, ranu amniotomiju, korekciju nenapredovanja porođaja sa oksitocinom i kontinuiranu podršku u toku porođaja. Vaginalni pregledi su se sprovodili na sat vremena od strane iskusnog i vještog akušera, rana amniotomija je vršena odmah nakon postavljanja dijagnoze početka aktivne faze porođaja. Normalno napredovanje porođaja je prema aktivnom vođenju definisano brzinom dilatacije grlića od 1cm/h. Procenat stimulacije porođaja oxitocinom je iznosio i do 55%. U to vrijeme, širom svijeta se sprovodilo aktivno vođenje porođaja koje je smatrano antidotom prolongiranom porođaju, ali je samo nekoliko porodilišta uspjelo da reprodukuje dobre rezultate ovakvog aktivnog vođenja porođaja sa stopom od 1% obstruisanog porođaja i 5% carskog reza. S obzirom da se u tercijarnom centru u Harareu, Zimbabve gdje se ispitivanje sprovodilo porađao samo dio žena pod nadzorom istraživača i da se većina trudnica porađala u perifernim centrima gdje nije bilo obučenog osoblja, Phillipot i Castle su upravo organizovali da babice šalju trudnice onda kada se na partogramu pređe „alert“ linija. Tako je i nastala modifikacija protokola predloženog od strane O Driscolla. Intervencije nisu vršene odmah po uspostavljanju dijagnoze aktivne faze, nego su čak odložene za vremenski period od 4 h od postavljanja dijagnoze nenapredovanja porođaja. Interesantno je da akciona linija nije statističi izvedena već je samo predstavljala procijenjeni vremenski period u toku kojeg će trudnica biti transpotovana iz perifernog centra. Takođe, obučeni akušer se uključivao mnogo kasnije u aktivno vođenje porođaja a rutinski vaginalni pregledi su bili predviđeni na svaka 4h.

Partogrami SZO

Prvi partogram razvijen i testiran od strane SZO je bio tzv. kompozitni partogram (Sl. 1) koji je u upotrebi od 1994 godine. Uključivao je latentnu fazu u trajanju od 8h i aktivnu fazu koja je počinjala sa 3cm dilatacije. Akciona linija je ucrtana 4h udesno i paralelna je sa „alert“ linijom. Ovaj partogram je omogućavao i bilježenje spuštanja prednjačećeg dijela, indikatora stanja majke i ploda i ljekova koji su primijenjeni u toku porođaja. ,,Ovaj partogram je uspješno testiran u međunarodnoj multicentričnoj studiji koja je sprovedena na preko 35 000 žena u Jugoistočnoj Aziji, u kojoj je uvođenje partograma sa dogovorenim protokolom menadžmenta porođaja smanjio i broj prolongiranih porođaja (6.4% na 3.4%) i proporciju porođaja koji zahtijevaju stimulaciju porođaja (od 20.7% na 9.1%). Pad stope carskog reza je bio najizraženiji kod prvorotki gdje je zabilježen pad sa 6.2% na 4.5%.

Modifikovani partogram SZO (Sl. 2) predviđen za upotrebu u bolnicama objavljen je 2000 godine. Latentna faza je isključena iz ovog partograma, a aktivna faza počinje sa 4 cm dilatacije, ostale karakteristike su iste kao kod prethodnog partograma. Jedan od razloga za isključivanje latentne faze je taj što su intervencije u porođaju bile češće ukoliko se trudnica primi u latentnoj fazi porođaja. Dilatacija od 4 cm kao marker početka aktivne faze je određena da bi se smanjio rizik od intervencija kod višerotki koje mogu imati prolazan i dilatiran grlić iako još nisu u porođaju.

Sledeća modifikacija je napravljena za upotrebu od strane obučenih ljekara u bolnicama i navodi se kao pojednostavljeni (simplifikovani) partogram.(Sl. 3) i karakteriše se obojenim površinama.

Površina lijevo od „alert“ linije je obojena zeleno i predstavlja normalan progres porođaja. Površina desno od akcione linije je obojena crveno i ukazuje na opasno sporo napredovanje porođaja, dok je površina između dvije linije obojena bojom ćilibara i ukazuje na potrebu za pojačanom pažnjom u nadzoru porođaja. Na ovom partogramu se ne bilježi spuštanje prednjačećeg dijela. Studija koja je upoređivala kompozitni i simplifikovani partogram naišla je na slične maternalne i perinatalne ishode, ali u slučaju kompozitnog partograma bilježene vrijednosti u porođaju su češće prelazile action liniju a samim tim povećavao se broj carskih rezova.

Ostali tipovi partograma koji su razvijani od strane istraživača su okrugli partogram, partogram drugog porođajnog doba, elektronski partogram, sonopartogram itd.

Uprkost značajnih debata i istraživanja koja su sprovođena prethodnih decenija, koncept „normalnosti“ u porođaju nije univerzalno standardizovan. SZO je 2018. godine izdala preporuke u vidu vodiča:“ Intrapartalna njega za pozitivno iskustvo u porođaju“. Preporuke su skrenule pažnju na značajan porast u primjeni porođajnih praksi u cilju iniciranja, ubrzavanja, završavanja, regulacije i nadzora fiziološkog procesa porođaja, sa ciljem poboljšanja ishoda po majku i bebu. Zaključeno je da povećana medikalizacija porođajnog procesa ima tendenciju da podminira prirodnu sposobnost žene za fiziološki porođaj i negativno utiče na iskustvo žene vezano za porođaj. Vodič prepoznaje ,,pozitivno iskustvo u porođaju“ kao značajan ishod porođaja. Ono definiše pozitivno iskustvo u porođaju kao iskustvo koje ispunjava ili prevazilazi lična i sociokulturna očekivanja i uvjerenja , uključujući rađanje zdravog djeteta u klinički i psihološki sigurnom okruženju sa kontinuiranom praktičnom i emocionalnom podrškom od strane pratioca na porođaju i nježnog, profesionalno kompetentnog kliničkog osoblja. Bazirano je na pretpostavci da većina žena želi fiziološki porođaj i da ima osjećaj ličnog dostignuća i kontrolu kroz uključivanje u donošenju odluka, čak i kada su potrebne medicinske intervencije. Vodič se sastoji 56 preporuka koje se odnose na njegu tokom porođaja-prvo doba porođaja, njegu tokom drugog porođajnog doba, preporuke vezane za treće porođajno doba, njegu novorođenčeta i njegu žene nakon porođaja.

Prema najnovijim naučnim istraživanjima koja su sproveli Abalos E. i Oladapo OT 2018. godine zaključeno je da je trajanje porođaja individualno i veoma varira i zavisi od antropometrijskih karakteristika majke i ploda, i da brzina dilatacije manja od 1 cm/h može da rezultira normalnim spontanim porođajem. Takođe, aktivna faza porođaja počinje tek sa 5-6 cm dilatacije i shodno tome je SZO 2020. godine predložila partogram nove generacije tzv.“Labour Care Guide“ (Sl. 4) gdje su takođe uključeni principi „pozitivnog iskustva u porođaju“.

U Porodilištu Kliničkog Centra Crne Gore trenutno se koristi prilagođeni partogram (Sl. 5) koji je izrađen na bazi modifikovanog partograma SZO. Implementacija naprednog partograma „Labour care Guide“ je planirana, ali je otežana zbog tercijarnog karaktera našeg Porodilišta, velikog broja porođaja, opterećenosti osoblja, a takođe postoje i izvjesna prostorna ograničenja.

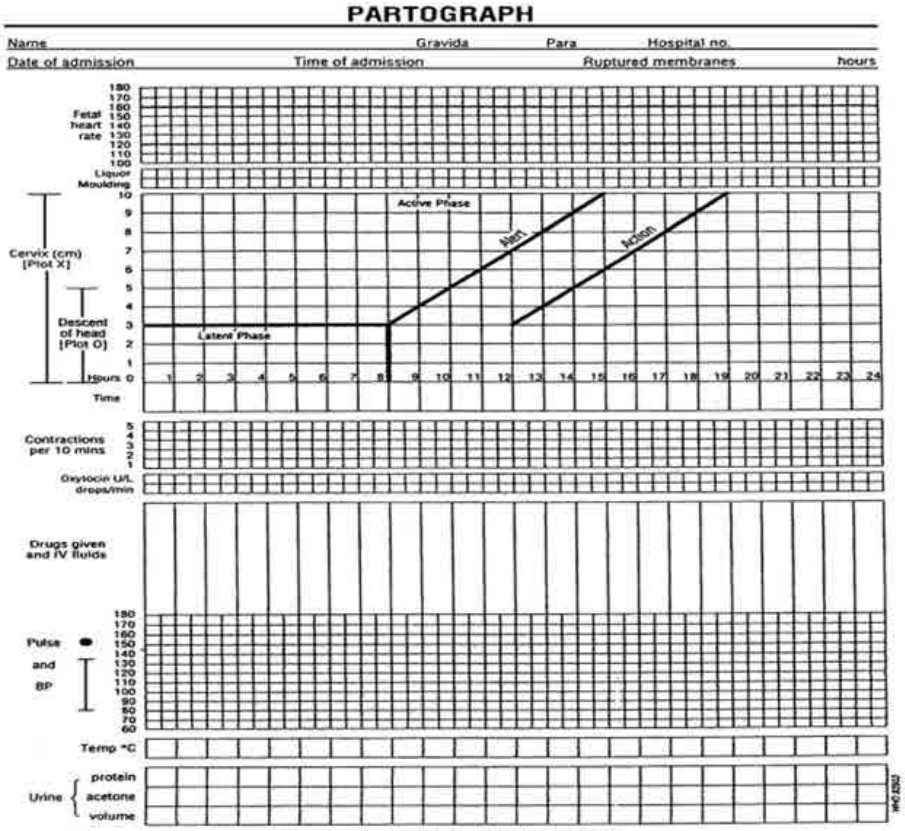
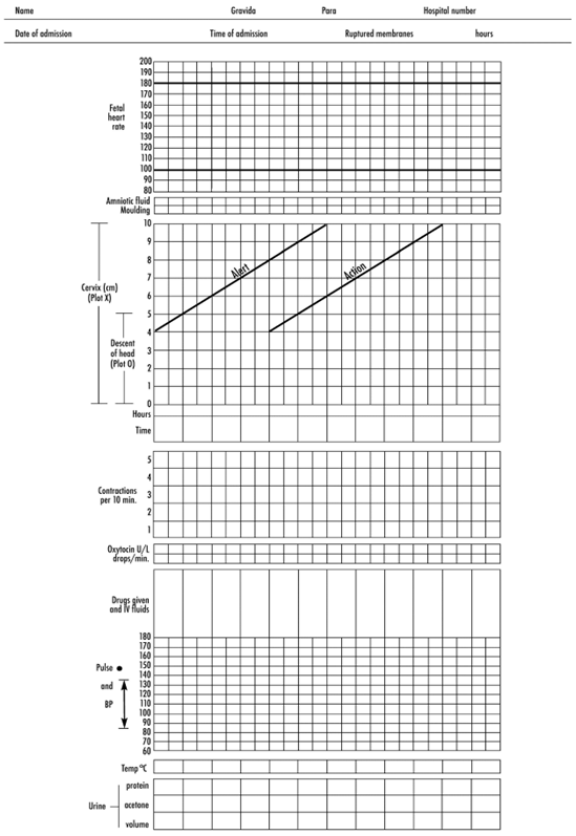
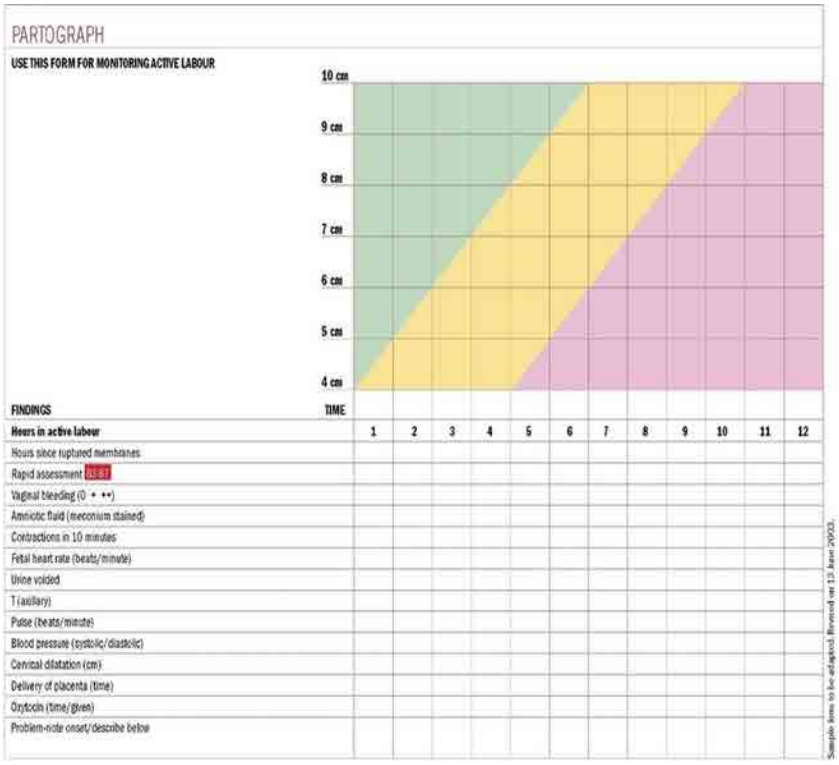


Fig. 1: composite Partograph (WHO, 1994)

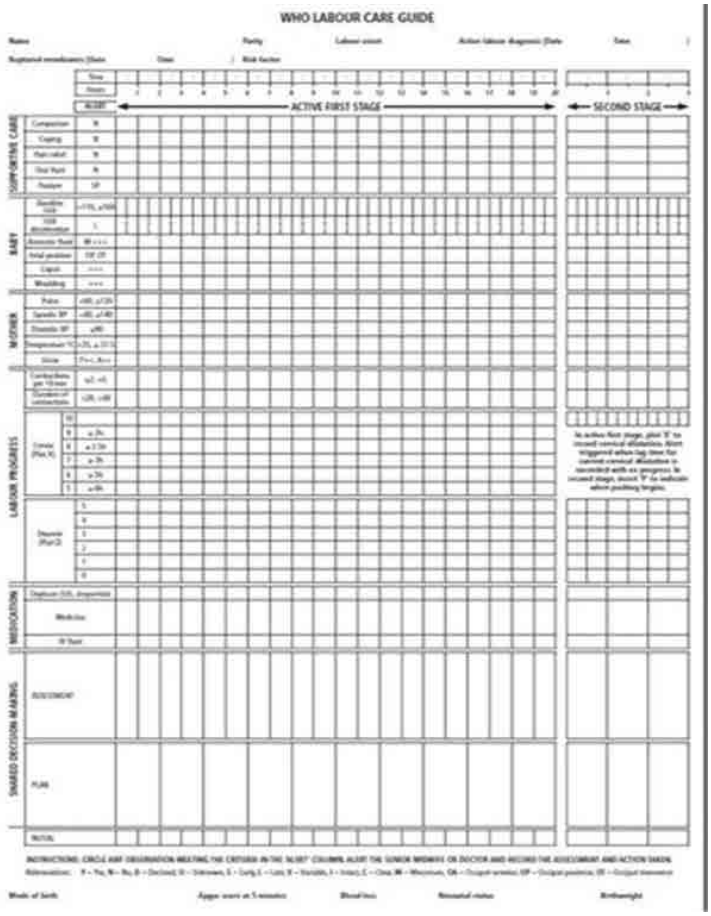
Slika 1. Kompozitni partogram



Slika 2. Modifikovani partogram



Slika 3. Simplifikovani partogram



Slika 4. „Labour Care Gide“

KLINIKA ZA GINEKOLOGIJU I AKUSERSTVO

PARTOGRAM

Prezime i ime, starost _____ Z.M. _____
Datum i sat prijema _____ Porod. _____
Prsnuće vodenjaka (datum i sat) _____ VTP: _____
B - bistra **M** - mekonijalna (+++) **K** - krvava Prednjač. dio G K T

DILATACIJA (cm)	10															
	9															
	8															
	7															
	6															
	5															
Sati u aktivnom prodaju	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Vrijeme pregleda																
Vrsta pred. dijela	Ulaz karlice															
	U karlici															
	Izlaz karlice															
	Vagina															
Vodenjak	Intaktan															
	Spontano prsnuće															
	Amniotomija															
	Boja plodove vode															
Srčani ton. u min.																
Kontrakcije u 10min	≤2, >5															
Dužina trajanja kontrakcije	<20, >60															
Terapija																
Potpis akušera																

Slika 5. Partogram porodilišta KCCG

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MANAGEMENT OF PREMATURE RUPTURE OF MEMBRANES

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Prelabor rupture of the fetal membranes (PROM) refers to the spontaneous rupture of the amniotic membranes before the onset of labor, resulting in a high risk of maternal and neonatal adverse outcomes. PROM that occurs before 37 weeks of gestation is defined as preterm premature rupture of membranes (PPROM). The World Health Organization (WHO) classifies preterm birth into three categories, namely, extremely preterm (below 28 gestational weeks), very preterm (between 28 and 32 gestational weeks), and moderately to late preterm (between 32 and 37 gestational weeks). Previous literature reported that PROM and preterm PROM occurred in 12 ~ 19% and 2 ~ 3 % of pregnancies, respectively.

The rate of premature birth differs between countries, and it is thought to be between 5% and 18%. In addition, the rate of premature births appears to be on the rise, with the United States reporting an increase from 10.1% in 2021 to 10.5% in 2022.

PPROM increases neonatal and maternal disease risks, which are among the main causes of premature birth. PPROM leads to approximately 18%–20% of perinatal deaths. In particular, PPROM, which usually occurs before the gestational age of 28 weeks, increases the incidence of extremely premature infants. Due to the immaturity of various organs, the prognosis of these infants is relatively poor. Studies reported that the occurrence of PPROM increased the incidence and even mortality of diseases such as respiratory distress syndrome, sepsis, severe bronchopulmonary dysplasia, severe retinopathy of prematurity, intraventricular hemorrhage, and necrotizing enterocolitis. In addition to neonatal complications, PPROM may also lead to complications in pregnant women. Intrauterine infection with clinical evidence has been observed in 15%–35% of women with PPROM, while postpartum infection occurs in approximately 15%–25% of PPROM cases. Moreover, placental abruption occurs in 2%–5% of pregnancies with PPROM. These maternal and infant complications pose a serious burden on society and families.

The etiology of PROM is multifactorial. Various pathological mechanisms, acting either alone or in combination with other factors, can lead to PPROM. Novel theories recognized that PPROM may result from complex and multifaceted pathways contributing to a weakening of the membrane morphology through alteration of the collagen network and/or activation of matrix metalloproteinases triggered by bacterial products or pro-inflammatory cytokines. Risk factors for PPROM are generally similar to those for spontaneous preterm labor with intact membranes, although microbial invasion of the amniotic cavity is identified, generally in a subclinical stage of infection, in up to one-half of all PPROM cases, particularly at earlier gestational ages and in 70% of patients with PPROM who go into labor.

There is a wide array of mechanisms that cause prelabor rupture of membranes. It can result from a physiologic weakening of the membranes combined with the forces caused by uterine contractions. Intramniotic infection is commonly associated with PPROM. The major risk factors for PPROM include a history of PPROM, short cervical length, second or third-trimester vaginal bleeding, uterine overdistension, nutritional deficiencies of copper and ascorbic acid, connective

tissue disorders, low body mass index, low socioeconomic status, cigarette smoking, and illicit drug use. Despite a variety of etiologies, often there is no obvious cause that is identified in a patient who presents with PROM.

PPROM is followed by a period of latency before the onset of labor, which can range from hours to several weeks. The latency period is negatively correlated with gestational age at PPROM and is shorter in cases of oligohydramnios. Regardless of obstetric management or clinical presentation, 50% of patients with PPROM will deliver within 1 week.

When PPROM occurs, in the absence of clinical signs of chorioamnionitis or labor, expectant management is recommended and generally consists of hospital admission with strict monitoring for signs of infection, placental abruption, fetal distress, and labor. Broad-spectrum antibiotics are routinely used in the management of PPROM to prolong pregnancy and decrease maternal and neonatal mortality. The management of PPROM represents a clinical challenge owing to the lack of specific signs that may predict the development of chorioamnionitis and latency for delivery.

Aim

We conducted a study at General Hospital Kotor to analyze the treatment protocol for PPROM and measure predictors and neonatal outcomes in pregnancies with and without PPROM.

Method

The study included 25 pregnant women with PPROM in the test group and 25 women with similar characteristics but without PPROM in the control group. Various parameters were analyzed in both groups, including gestation, vaginal pH, AFI, leucocytes count, vaginal and cervical swabs, delivery outcomes, birth weight, APGAR score, and duration of hospital treatment for both mothers and neonates. Additionally, specific characteristics related to the diagnosis and treatments of PPROM were examined in the test group.

The research focused on treating and delivering patients with PPROM. A proper diagnostic procedure confirmed the clinical condition of the pregnant women in the study group. A standardized protocol, aligned with current treatment guidelines, was employed as per recommendations for managing PPROM.

Results

The study group revealed the profound importance of PPROM parameters and their consequences. Elevated maternal leucocytes, CRP levels, and fetal heart rate notably accelerated the time between PPROM and delivery. Neonatal gestational age, birth weight, maternal corticosteroid, and antibiotic usage emerged as crucial predictors of neonatal respiratory immaturity. Decisions regarding the termination of PPROM pregnancies were primarily guided by intra-amniotic infection indicators, including increased leucocytes, CRP levels, and fetal heart rate.

Compared to the control group, pregnant women with PPROM exhibited significant differences. These included lower gestational age at delivery, an extended time from water breaking to delivery, higher vaginal pH, altered biophysical profiles (low AFI and fetal tachycardia), as well as elevated CRP and leukocyte levels in the blood. Post-delivery, women with PPROM had longer hospital stays than those in the control group. The study group's infants showed highly significant prematurity-related outcomes, including gestational immaturity, lower birth weight, and reduced APGAR scores. Furthermore, a notably higher number of children from the study group required referral to specialized institutions for further treatment.

Regarding labor completion in PPROM cases and its impact on newborns, the study found that pregnant women in the 28th to 34th gestational week received more intensive treatments, including dual antibiotics, tocolytics, and corticosteroids. Additionally, a higher proportion of PPROM pregnancies accompanied by comorbidities and unfavorable fetal positioning resulted in cesarean section deliveries.

Novel research

Serum amyloid A expression, an acute-phase protein that plays a crucial role in the inflammatory response, has been reported to be faster and more sensitive than other acute-phase proteins, such as C-reactive protein. The measurement of SAA levels in serum provides a valuable tool for assessing the severity of inflammation and monitoring the effectiveness of anti-inflammatory therapies. High levels of maternal SAA are associated with preterm birth who were diagnosed with pre-labor premature rupture of membranes. It is worth mentioning that SAA is a non-specific marker of inflammation and may not be specific to PROM. Therefore, further studies should be conducted to determine the predictive role of SAA in PTB/PROM and cut-off levels for the use of this marker in clinical practice.

The abnormal vaginal microbiota is an important risk factor for PPROM. Hypothetically, the colonization of pathogenic bacteria in the local and upper cervix and fetal membrane can lead to an inflammatory cascade reaction, and in turn, the remodeling and destruction of membrane structure and premature rupture. The dysbiotic vaginal microbiota signatures in patients with PPROM include a higher bacterial diversity, decreased autochthonous bacteria, and increased pathogenic bacteria. These results may be beneficial for developing biomarkers for screening and early diagnosis of PPROM and may provide effective preventative treatments. Results of a Chinese study by Yan et al., showed that the diversity of vaginal microbiota in patients with PPROM increased compared with controls. The relative abundance of *Lactobacillus iners*, *Gardnerella vaginalis*, *Prevotella bivia*, *Ochrobactrum* sp., *Prevotella timonensis*, and *Ureaplasma parvum* were more abundant in patients with PPROM, while *Lactobacillus crispatus* and *Lactobacillus gasseri* were more abundant in controls. They concluded that *Ochrobactrum* sp., *Prevotella timonensis*, and *Gardnerella vaginalis*, could serve as biomarkers for PPROM.

Environmental factors, such as air pollution, have also been suggested to participate in the pathogenesis of PROM. These pollutants include nitrogen dioxide (NO2), nitrogen oxides (NO_x), ozone (O_3), and particulate matter with aerodynamic diameters of ≤ 2.5 μm ($PM_{2.5}$) and ≤ 10 μm (PM_{10}). Investigations regarding air pollution and PROM conducted in Barcelona, China, Australia, and Southern California revealed a significant correlation between pregnancy exposure to air pollutants, especially $PM_{2.5}$ and PROM. Wang et al. found that both acute and chronic maternal exposures to ambient $PM_{2.5}$ during the second trimester of gestation increased the risk of PROM, particularly preterm PROM. Women who were less educated or obese, or gave birth in a cold season appeared to be more sensitive to ambient $PM_{2.5}$ exposure.

Expectant Management

According to recent guidelines, expectant management is done in cases of preterm (<34 weeks) and late preterm (34-36 weeks + six days) PROM if no contraindications exist. It consists of admitting the patient, administering a course of corticosteroids, short-term tocolysis, rectovaginal swabs for group-B streptococci screening, and starting the group-B streptococci prophylaxis. Antibiotics are stopped if the screening is negative. Magnesium sulfate is administered for neuroprotection if the gestational age is less than 32 weeks. Management of PPROM between 34-37 weeks + six days

is the same as that of <34 weeks, except that tocolytics are not administered, and induction of labor is performed if there are indications for the same. Monitoring maternal vitals is of paramount importance to rule out the presence of chorioamnionitis. It is a clinical diagnosis suggested by the presence of fever, tachycardia, and/or uterine tenderness. A speculum examination can also confirm the diagnosis if it shows the presence of pus leaking from the cervix. Maternal monitoring is done for temperature, uterine tenderness, and uterine contractions. Fetal monitoring is done by a daily non-stress test (NST) and biophysical score if the NST is non-reactive. Periodic USG is done to monitor fetal growth. An elevated WBC count, elevated lactate dehydrogenase (LDH), and reduced glucose seen on amniotic fluid sampling may also point toward the diagnosis. In such cases, delivery of the fetus is initiated immediately, followed by the administration of broad-spectrum antibiotic therapy.

Recommended therapy

Antibiotics have become the mainstay of therapy for patients with pre-labor membrane rupture. According to the information currently available, a seven-day course of latency antibiotic therapy with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 weeks of gestation to reduce maternal and neonatal infections and gestational-age-dependent morbidity. Corticosteroids decrease the occurrence of respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis if given to a woman with intact membranes in the case of preterm labor. A similar benefit of corticosteroids can also be seen in preterm PROM, why all patients with preterm PROM between 24-34 weeks of pregnancy should consider using corticosteroids to accelerate lung maturation. Unlike corticosteroids and antibiotics, tocolysis should only be used when there is a proven clinical advantage, such as in transporting a pregnant woman to a tertiary care center with the availability of a neonatal intensive care unit. According to available evidence, magnesium sulfate given before an expected early premature birth lowers the chance of cerebral palsy in infants. Physicians who choose to employ magnesium sulfate for fetal neuroprotection should set precise protocols for eligibility, therapy regimens, simultaneous tocolysis, and surveillance.

Recommendations to take home

- Accurate diagnosis is required for appropriate counseling and management of PROM.
- Early term and term patients (37 0/7 weeks of gestation or more): proceed to delivery and Group B Streptococcus prophylaxis should be administered as indicated
- Late Preterm (34 0/7- 36 6/7 weeks of gestation): either immediate delivery or expectant management up to 37 weeks is recommended
- Preterm (24 0/7 – 33 6/7 weeks of gestation): expectant management, latency antibiotics, single course of corticosteroids, GBS prophylaxis as indicated
- Less than 24 weeks of gestation: patient counseling, expectant management or induction of labor, antibiotics can be considered as early as 20 0/7 weeks of gestation, GBS prophylaxis/corticosteroids/tocolysis/magnesium sulfate are not recommended before viability
- Delivery is recommended for term PROM, chorioamnionitis, and for patients with pre-viable PROM who do not desire expectant management.

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KOMPLIKACIJE EPIDURALNE ANALGEZIJE U AKUŠERSTVU

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Epiduralna analgezija je zlatni standard za terapiju bola tokom porođaja i preporučuje se od strane Svjetske zdravstvene organizacije, pri čemu se procjenjuje da 10-64% porodilja koristi epidural u razvijenim zemljama (1). Tokom porođaja, kontrakcije uterusa i dilatacija cerviksa stimulišu nociceptore, koji preko aferentnih vlakana spinalnih nerava na nivou Th10-L1 prenose impuls, dovodeći do teško lokalizovanog visceralnog bola. Spuštanjem ploda, širenjem perineuma i vagine, bol se prenosi putem pudentalnih nerava i spinalnih korjenova S2-S4. Modifikacija ovih ushodnih puteva, odnosno bol, kupiraju se različitim kombinacijama lokalnih anestetika, opioida i adjuvanasa koji se mogu ordinirati putem epiduralnog katetera (2). Različite kombinacije i koncentracije lijekova se koriste za analgeziju, stoga se i očekivani efekat razlikuje, kako tokom porođaja, tako i u postpartalnom periodu.

Komplikacije koje se javljaju kao rezultat izvođenja regionalnih tehnika u akušerstvu mogu se definisati kao:

- Toksičnost uzrokovana lokalnim anesteticima
- Totalni spinal
- Postpunkciona glavobolja
- Epiduralni hematom
- Oštećenja nerava

Iako se radi o sigurnim tehnikama analgezije, istraživanja o sigurnosti epidurala su heterogena, zbog odsustva standardizacije postupaka i posmatranja ishoda. Podaci o hipertermiji, dojenju, postpartalnoj depresiji, kao i dogotrajnim efektima u razvoju djece, zahtjevaju dalja detaljnija istraživanja.

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PERINATOLOGY

POLIPRAGMAZIJA U TRUDNOĆI

Vesna Ećim Zlojutro

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Pojmom polipragmazije (grč.) označava se neopravdana i nepotrebna istovremena upotreba više lijekova pri čemu se ne vodi briga o njihovim mogućim međudjelovanjima, što za posljedicu može imati opasne nuspojave. Šteta od polipragmazije je narušavanje zdravlja korisnika, ali i neracionalno trošenje ionako ograničenih sredstava za zdravstvo.

Na propisivanje lijekova kod nas često utiču i želje bolesnika koje se ne podudaraju s medicinskim potrebama, pa ljekari pod pritiskom pacijenata ponekad propisuju i nepotrebne lijekove. Na tržištu se nalazi veliki broj lijekova, suplemenata i različitih preparata koji stvaraju zbrku i nesnalaženje i kod ljekara i kod pacijenata.Veliku ulogu ima i sve veće reklamiranje različitih proizvoda putem različitih medija kai i njihova slobodna kupovima bez medicinskih nalaza i recepata.

Mnogobrojne studije pokazuju da 80-99% trudnica uzima lijekove, i to prosječno od 4 do 7 lijekova. Većina lijekova može proći kroz posteljicu, pa tako može imati i štetno djelovanje na samu trudnicu ,kao i na embrion i fetus.

Lijekovi koji se koriste tokom trudnoće mogu kroz posteljicu doći i do fetusa iako odgovor fetusa na primijenjenu dozu lijeka može biti različit. Razlike u djelovanju lijeka na fetus ovise o sljedećim faktorima:

- vrsti lijeka
- doze ,dužine davanja i učestalosti davanja lijeka
- koliko lijekova je korišteno
- svaka individua ima svoj vlastiti odgovor na primijenjeni lijek.

Svi lijekovi uz svoja pozitivna svojstva mogu imati i nuspojave. Pod nuspojavama se podrazumijevaju štetni i neželjeni učinci lijeka koji je primijenjen u pravoj dozi uz odgovarajuće indikacije. Dijele se u dvije grupe:

- tipa A i
- tipa B.(ADR, od eng. adverse drug reaction) .

Nuspojavama se smatraju i štetni učinci lijeka koji nastaju kao posljedica pogrešne upotrebe ili zloupotrebe lijeka .

Nuspojave tipa A posljedica su uobičajenoga farmakološkog djelovanja lijeka ..

Svaka promjena učinka određenoga lijeka u prisutnosti drugoga lijeka, hrane ili biljnoga proizvoda naziva se interakcijom . One mogu imati željene i neželjene učinke . Neke se interakcije koriste kako bi se postigao bolji učinak samog lijeka,ali mogu dovesti i do smanjenja djejstva ili ćak do štetnih nuspojava.Nekontrolisana upotreba bezreceptni lijekovi mogu pogoršati stanje pacijentkinje ili stupiti u interakciju s lijekovima propisanima receptom. Prema učestalosti, nuspojave lijekova se mogu podijeliti na:

- **vrlo česte** (javljaju se kod jednog od deset bolesnika koji uzima lijek),
- **česte** (kod jednog od sto),
- **manje česte** (kod jednog od hiljadu),
- **rijetke** (kod jednog od deset hiljada) te

- **vrlo rijetke** (manje nego kod jednog na deset hiljada bolesnika).

Pojava teških i ozbiljih nuspojave mogu dovesti do teškog oštećenja kako kod trudnice, tako i kod fetusa.Velikiproblem se javlja i zbog toga što ispitivanja lijekova u trudnoči nisu izvodiva iz etičkih razloga. Zato su od izuzetnog značaja objavljeni radovi o slučajevima kada su trudnice ne znajući da su trudne uzimale neki lijek ili su zbog svoje bolesti morale uzimati određeni lijek usprkos riziku štetnosti za plod koji taj lijek eventualno ima. Najpoznatija je FDA (FDA - Food and Drug Administration - Američka uprava za hranu i lijekove) klasifikacija (kategorije rizika A, B, C, D, X) lijekova u trudnoći koja je temeljena na podacima iz kontroliranih studija u žena i studija provedenih na životinjama.

Podaci iz literature govore da su nuspojave četvrti uzrok smrti u SAD-u . Učestalost nuspojava kreće se u rasponu od 10 do 20%, a učestalost klinički značajnih interakcija iznosi od 3 do 5%, postotak koji raste usporedno s povećanjem broja istodobno korištenih lijekova . i uzrokuju 200 milijardi dolara godišnjih troškova zdravstvenome sustavu. Navodi se i kako u Nizozemskoj više ljudi umire od nuspojava nego od posljedica saobraćajnih nesreća..

Prema Svjetskoj zdravstvenoj organizaciji (WHO), u nekim zemljama troškovi uzrokovani nuspojavama, uključujući hospitalizacije, operacije i gubitak produktivnosti, premašuju troškove lijekova . Procijenjeno je da troškovi od započinjanja bolničkoga prijema zbog posljedica neželjenoga događaja lijeka iznose 422 – 7062 USD . Troškovi hospitalizacije zbog nuspojava u Nizozemskoj mogu se kretati od 2128 do 4915 eura .

Definicija racionalne farmakoterapije prema WHO-u je odabir adekvatnog lijeka kroz odgovarajući vremenski period u dozi koja zadovoljava kliničke potrebe pacijenta s najnižim troškom za njega i zajednicu . Odabir lijekova treba biti vođen poštivanjem pravila medicinske struke i nauke te načelima racionalne farmakoterapije.

Trudnice mogu biti izložene brojnim lijekovima uz različite indikacije. Brojne su studije pokazale visoku stopu izloženosti trudnica lijekovima, među kojima su i lijekovi za koje se zna da su teratogeni. Jedna studija provedena u Norveškoj između 2004. i 2006. godine pokazala je da je 57% trudnica primilo lijek na recept, a studije provedene u Francuskoj i Njemačkoj pokazale su da taj postotak iznosi čak 85% . Trudnice prosječno uzimaju od 3-15 lijekova . Pri odabiru lijeka koji će biti propisani trudnici, treba dobro razmotriti omjer koristi i rizika, pri čemu pomaže FDA klasifikacija tog omjera. Upotreba nekih lijekova za vrijeme laktacije može dovesti do prekida laktacije, smanjenja refleksa sisanja i do pojave nuspojava u dojenčeta. Nuspojave su ipak rijetke jer ukupna dnevna doza za većinu lijekova u dojenčeta iznosi manje od 1% majčine. Niske koncentracije lijeka koje dospiju u majčino mlijeko mogu uzrokovati hipersenzitivne reakcije u dojenčeta. Za vrijeme laktacije uz pojedine se iznimke mogu koristiti lijekovi koji su dopušteni u trudnoći. Lijekove za koje se ne zna pouzdano škodljivost i novije lijekove treba izbjegavati

Nekoliko je istraživanja vezanih za primjenu lijekova u trudnoći u Americi i Europi pokazalo visoke stope propisivanja lijekova na recept trudnicama, uključujući i lijekove s poznatim teratogenim učinkom . Wettach i suradnici pokazali su da je najveća povezanost između nuspojave lijeka i poremećaja fetusa prisutna kod primjene lijekova koji djeluju na nervni sistem (antidepresivi, antiepileptici i anksiolitici), a najčešći poremećaj je malformacija . Zato s obzirom na težinu nuspojava i posljedica, kao i mišljenje ispitanika da nisu dovoljno edukovani o toj problematici, dodatna edukacija, kao i bolja suradnja sa kliničkim farmakolozima, mogli bi uticati na smanjenje stope fetalnih poremećaja uzrokovanih primjenom lijekova u trudnoći .

Švajcarska nacionalna ADR baza podataka VigiFlov je predstavila izveštaje od 1. januara 1990. do 31. decembra 2009. kategorizovano u klasu organskih sistema (SOC) kategoriju br. 1500 (fetalporemećaji) sistema SZO-terminologije neželjenih reakcija (ART)

Ova kategorija se sastoji od unaprijed definisanih termina abnormalnog fetusa,stanja ili razvoja koji se javljaju tokom trudnoće ili drugih negativnih ishoda trudnoće . Slučajevi izlaganja lijekovima tokom trudnoće bez negativnih fetalnih ishoda su takođe uključeni u ovu kategoriju.

Primarna krajnja tačka bila je izloženost lijekovima (vrsta i broj lijekova, gestaciono doba) u odnosu na uočene fetalne poremećaje (fokus na malformacije). Podjela je izvršena u odnosu na broj lijekova koji je korišten ibkreatao se od 1 do 9.

Pošto su trudnice često isključene iz kliničkih ispitivanja, još uvek postoje veoma ograničene informacije o riziku i bezbjednosti lijekova koji se izdaju na recept tokom trudnoće.

Pod pojmom farmakovigilacija se podrazumijeva skup aktivnosti vezanih za otkrivanje,procjenu,razumijevanje,prevenciju i postupanje u slučaju nuspojava lijekova kao i novih saznanja o škodljivosti primjene lijekova.

Jedan od objavljenih radova je prospektivna studija koja je sprovedena u nastavnom porodilištu u Brazilu tokom šest mjeseci. Prevalencija neželjenih dejstava među 294 ispitana pacijenta bila je 8,8%. Prosječna starost bila je 27,14 (±7,5) god. Starost pacijentkinje je bila povezana sa prisustvom neželjenih reakcija, dok ispoljavanje ovih događaja nije bilo povezano sa bilo kakvim neželjenim ishodom trudnoće. 75,9% neželjenih reakcija prijavljenih u studiji bile su blage, a 24,1% umjerene težine. Značajno povećanje krvnog pritiska primijećeno je kod svih pacijenata koji su istovremeno koristili metildopu i gvožđe sulfat.

Studija koja se bavila izućavanje dejstva metformina koji je prva linija farmakološkoga liječenja šećerne bolesti tipa 2 s procjenom da se rutinski propisuje 120 milijuna bolesnika s dijabetesom širom svijeta. Dokazana je povezanost između dugotrajne upotrebe metformina i niske razine vitamina B12 u do 30% liječenih dijabetičara

Nekoliko studija je istraživalo prirodu i učestalost problema povezanih sa lijekovima (ADR) kod hospitalizovanih trudnica. Nedavno je studija na 1117 etiopskih trudnica otkrila 29% pojavljivanja jedne ili više nuspojava . Australijska studija na 241 hospitalizovanoj trudnici otkrila je prevalenciju ADR-a (83%) identifikovanih u kratkom periodu od pet nedelja . Druga studija je istraživala pojavu kod trudnica (42%), ali je navela lijekove koji se koriste samo kod kuće . Jedan brazilski rad objavio pojavu od oko 60% ADR kod 600 puerpera sa dijagnozom preeklampsije.

U ovoj prospektivnoj kohortnoj studiji zasnovanoj na reprezentativnom uzorku trudnica sa hipertenzijom i dijabetesom, istaknuta je visoka pojava ADP-a prvenstveno vezana za terapijsku neefikasnost i neželjene reakcije. Detekcija je dominirala u prvih 48 sati, naglašavajući neefikasnost povezanu sa nedovoljnom dozom insulina i neželjenim reakcijama na metildopu. Niža starost majke, niža gestacijska dob, prethodna istorija preosjetljivosti na lijekove, duže vrijeme liječenja i broj prepisanih lijekova bili su povezani sa pojavom ADR.

Sa sličnim pristupom i nalazima našim, izdvajamo australsku kohortu sa 241 hospitalizovanom trudnicom koju svakodnevno procenjuje klinička apotekarska služba .Autori su identifikovali pojavu ADR-a kod oko 80% pacijenata sa dominacijom dozoloških neadekvatnosti kao glavnih uzroka. Nasuprot tome, studija na 1117 etiopskih trudnica otkrila je pojavu od 29% jednog ili više ADR-a. Glavni otkriveni DRP je potreba za dodatnom terapijom (73%).

Magnezij se nalazi u brojnim namirnicama. Tako ga ima u mliječnim proizvodima, hljebu, žitaricama, sjemenkama, mahunarkama, brokuli, bademima i drugim orašastim plodovima, zelenom povrću, mesu i čokoladi. prevelike količine magnezija mogu uzrokovati nepravilan rad srca, niski krvni pritisak, usporeno disanje te u rijetkim slučajevima komu.

Kada se radi o injekcijama magnezija kod trudnica, on se uzima isključivo na preporuku ginekologa kod određenih komplikacija jer u suprotnome može izazvati probleme s kostima i mozgom kod djeteta.

Ion-izmjenjivačke smole kao što su kolestiramin, kolestipol ili kalcijeve i natrijeve soli polistiren sulfonske kiseline, inhibiraju apsorpciju levotiroksina vežući hormone štitne žlijezde u gastrointestinalnom traktu, te ih je zato potrebno primijeniti 4 – 5 sati nakon primjene ovog lijeka. Inhibitori protonske pumpe (IPP) mogu smanjiti apsorpciju levotiroksina iz gastrointestinalnog trakta. U bolesnika koji uzimaju levotiroksin s IPP-ima, potrebno je pratiti razinu TSH-a i prema potrebi prilagoditi dozu.

Umjesto zaključaka:

Postavlja se pitanje koliko su ginekolozi i ostali specijalisti upoznati da interakcijom i eventualnim nuspojavama odrđenih lijekova koje propisujemo?

Da li naše trudnice piju neopravdano ogroman broj lijekova, suplemenata i drugih pripravaka?

Da li smo bitno time uticali na zdravlje naših trudnica i fetusa ili čak naprotiv?

Da li je uz sve to sve veći broj dijabetičnih trudnica, dermatitisa, alergija uz sve veći broj carskih rezova ,a broj prijevremenih nije smanjen?

Da li smo davanjem enormnih količina hormona, vitamina , minerala i raznih drugih preparata poboljšali zdravstveno stanje naših trudnica i njihove djece?

Koliko to sve košta naš zdravstveni sistem?

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CONTEMPORARY PERINATOLOGICAL CONTRIBUTIONS TO THE QUALITY OF BIRTH RATES IN SERBIA

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The concept of fetal programming explores how intrauterine conditions can lead to long-term health implications by influencing fetal growth and development. Intricate relationship between genetic potential, intrauterine environment, and nutrient transfer through the placenta, results in various birth weight states, particularly on growth restriction and macrosomia. Different patterns of fetal growth impairment, such as symmetric and asymmetric growth restrictions, are examined. Epidemiological studies establish links between birth weight, body proportions, and chronic diseases like cardiovascular disease (CHD), hypertension, and type 2 diabetes. Beyond birth weight, factors such as placental weight, body proportions, and neonatal growth rate contribute to the concept of fetal programming. The text explores accelerated childhood growth as a response to intrauterine growth restriction, potentially leading to metabolic diseases later in life. The correlation between fetal growth, blood lipid profiles, and coagulation factors is discussed. Low birth weight and altered body proportions are associated with unfavorable lipid profiles and elevated cardiovascular disease risk. The complexity of fetal programming, its intergenerational effects, and challenges in epidemiological studies due to confounding variables are highlighted. The impact of intrauterine and postnatal factors on blood pressure is emphasized, alongside the influence of birth weight on insulin resistance and metabolic disturbances. The role of twins studies and famine-exposed populations provides insights into the concept of fetal programming, revealing non-genetic factors impact on disease susceptibility. The text also explores potential links between birth weight and immune-related diseases, breast tumors, and PCOS. Early developmental factors influence on immune system function and disease susceptibility is discussed. Overall underscore the significance of early life factors, particularly birth weight, in shaping long-term health outcomes. Fetal programming, driven by genetic and environmental factors, influences various physiological systems, potentially contributing to chronic diseases and conditions later in life. The complex mechanisms underlying these associations warrant further investigation for potential interventions.

Introduction

Fetal Programming and Its Impact on Chronic Diseases

Fetal programming, often referred to as the "developmental origins of health and disease" (DOHaD) hypothesis, is a captivating concept that delves into how environmental factors encountered during fetal development can exert profound and enduring effects on an individual's health and susceptibility to disease later in life. This theory postulates that the prenatal period represents a critical window during which exposures to various factors, including maternal nutrition, stress, and toxins, can significantly shape the development of organs, tissues, and physiological systems, thereby influencing health outcomes in adulthood [1].

Birth rates in Serbia

From the period 2017 to 2021, we have extracted birth statistical data from Batut, Republic of Serbia, which speak about the quality of health care and the birth rate trend. We have come to the

conclusion that the number of live births in Serbia has significantly decreased over a period of 5 years, in percentage terms this amounts to 5.5%. The natural increase has reached an even greater decline, but the corona virus pandemic had an overriding impact here, both in the world and in Serbia. With a negative increase of -38828, we reached -74442 in 2021. Increasing natality, or the birth rate, in a country is a complex and multifaceted challenge that involves various societal, economic, and healthcare factors. We can contribute to this effort by providing healthcare services and guidance to expectant parents. However, influencing the overall birth rate requires a broader approach involving government policies, social initiatives, and economic incentives.

Critical Periods of Development

Central to the concept of fetal programming is the notion that specific timeframes during gestation are especially sensitive to external influences. These critical periods align with the development of various organ systems, and disruptions during these critical junctures can give rise to enduring consequences. In essence, the blueprint of an individual's health destiny begins to take shape during these pivotal moments in fetal development [2].

Epigenetics, the study of heritable changes in gene expression that do not involve alterations to the underlying DNA sequence, plays a pivotal role in fetal programming. Environmental factors encountered during pregnancy can trigger epigenetic modifications such as DNA methylation and histone modifications. These changes can subtly or significantly alter gene expression patterns without changing the fundamental DNA code. Importantly, these epigenetic modifications can endure throughout an individual's life, exerting a lasting influence on health and disease risk [2].

One fascinating aspect of fetal programming is the fetus's remarkable ability to adapt to its intrauterine environment based on the signals it receives from the mother's physiology. These adaptive responses can profoundly shape fetal development and may serve as a survival strategy in response to perceived conditions [1]. For instance, when faced with maternal undernutrition, the fetus may adjust its growth patterns and metabolic processes to optimize chances of survival in a resource-scarce environment.

Metabolic Disorders

Fetal exposure to poor maternal nutrition or overnutrition can significantly increase the risk of metabolic disorders in adulthood. Individuals who experienced suboptimal nutrition in the womb may be at a higher risk of obesity, type 2 diabetes, and metabolic syndrome as they grow older. This underscores the enduring impact of early-life nutrition on metabolic health [3].

Adverse prenatal conditions can contribute to the development of cardiovascular problems such as hypertension, atherosclerosis, and cardiovascular disease. The links between fetal development and cardiovascular health highlight the intricate interplay between early-life experiences and long-term well-being.

Fetal programming may extend its influence to brain development, potentially leading to cognitive deficits, mood disorders, and behavioral problems later in life. The developing brain appears to be particularly susceptible to environmental factors during gestation, emphasizing the importance of a nurturing intrauterine environment [4].

Factors like maternal smoking during pregnancy can elevate the risk of respiratory disorders in offspring, including conditions like asthma. The fetal programming concept sheds light on how prenatal exposures can affect respiratory health in the long term.

Fetal exposures can perturb the development of the endocrine system, potentially resulting in disorders such as thyroid dysfunction. These disruptions in endocrine function can have far-reaching consequences for an individual's health [5].

Fetal programming has been shown to influence immune function and may impact susceptibility to autoimmune diseases. The intricate connections between early-life experiences and immune health continue to be a subject of research and discovery.

Placental Function

The placenta serves as a vital intermediary between the maternal environment and the developing fetus. Its role in transmitting signals, nutrients, and other factors is pivotal in fetal programming. Placental function can significantly impact the developmental trajectory of the fetus [6].

Modern Medicine and Insights

Modern medicine has provided invaluable insights into the intricate relationships between genetic potential, the influence of the intrauterine environment, placental nutrient transfer, and the ultimate outcomes in neonatal development. The variation in fetal body weight, ranging from growth retardation to macrosomy, represents a spectrum of developmental changes that can have profound implications for the neonate's subsequent growth and health [7].

Newborns with limited growth represent a diverse group, and analyzing body proportions can provide more nuanced insights than birth weight alone. Newborns with proportional intrauterine growth restriction (normal PI) may exhibit reduced overall size, while those with disproportional intrauterine growth restriction (low PI) may have a thinner physique but nearly normal body length [7]. The underlying factors contributing to these differences can be multifaceted.

Children with disproportional growth restriction are at a heightened risk of chronic diseases and insulin resistance later in life. The connection between neonatal growth patterns and the risk of chronic diseases underscores the intricate interplay between early-life experiences and long-term health [8].

Conclusion

In conclusion, the concept of fetal programming, as encapsulated by the ,,developmental origins of health and disease" hypothesis, unveils the remarkable complexity of human development and its enduring impact on health. It underscores the critical importance of the prenatal period as a window of vulnerability and adaptability, where environmental factors can sculpt the trajectory of an individual's life.

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KLINIČKE IMPLIKACIJE NOVIH NAUČNIH SAZNANJA O GENETIČKOM SKRININGU I DIJAGNOSTICI U PRVOM TRIMESTRU TRUDNOĆE

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Osamdesetih godina prošlog veka, sa pojavom skrininga maternalnog seruma na aneuploidije, započinje nezaustavljiva evolucija jedne od najvažnijih i najprogresivnijih oblasti savremene perinatologije.

Prenatalni genetički skrining se koristi da bi identifikovali fetuse pod povišenim rizikom od postojanja određenog genetičkog poremećaja. U prvobitnoj formi, prenatalno genetičko testiranje se primarno fokusiralo na trizomiju 21 (Down sindrom), ali se danas može detektovati širok raspon drugih genetičkih poremećaja.

U savremenoj perinatologiji, genetički skrining obuhvata četiri modaliteta: ultrasonografiju, maternalni status nosioca specifičnog genetičkog poremećaja, maternalne serumske biohemijske markere indikativne za postojanje fetalne aneuploidije i najsavremeniji – iz maternalne plazme dobijen cell-free fetal DNA (cfDNA).

Pre odabira bilo koje metode skrininga/dijagnostike genetičkih poremećaja, ne sme se izgubiti iz vida genetičko savetovanje koje mora obezbediti lako razumljivu i kompletnu informaciju pacijentu, koja će mu omogućiti da donese informisanu odluku o skriningu i dijagnostici, a posledično i kasniju reproduktivnu odluku [1]. Drugi, izuzetno važan preduslov adekvatnog odabira metode testiranja fetusa je ultrazvučni pregled fetusa u prvom trimestru. Detaljan ultrazvučni pregled u kasnom prvom trimestru trudnoće identifikovaće više fetusa sa potencijalnim abnormalnostima, nego što će to uraditi primena samo neinvazivnog prenatalnog testiranja. Stoga, ultrazvuk prvog trimestra ostaje neizostavni i veoma značajan deo prenatalnog skrininga, koji treba koristiti u kombinaciji sa drugim formama neinvazivniog prenatalnog testiranja [2]. Studije pokazuju da nuhalnu transluscencu (NT) ≥99th percentila i fetalne abnormalnosti treba smatrati ekskluzionim kriterijumima za cfDNA skrining. Stoga izostanak merenja NT, kao i detaljnog, sistematičnog ultrazvučnog pregleda u 12-13.nedelji gestacije predstavlja stručnu grešku. Još jednom je važno podvući značaj merenja NT kao markera kongenitalnih abnormalnosti, koje ne mogu biti otkrivene putem cfDNA. Najšire korišćen prag za NT kao markera za dodatni ultrazvučni pregled i genetičko ispitivanje je 3,5mm, što korespondira sa 99.percentilom [3]. Noviji rezultati podržavaju ovaj prag, kao najsenzitivniji i najspecifičniji u detekciji kongenitalnih abnormalnosti. Međutim, 23,4% abnormalnosti nalazi se u trudnoćama sa NT između 95 i 99.percentila. Štaviše, skorašnje studije preporučuju NT ≥3,0mm kao indikacija za invazivno testiranje, metodom chromosomal microarray analysis (CMA) [4] .U prisustvu detektovanih strukturnih anomalija, CMA je indikovana kao prva linija testiranja [5] .

Postoje dve opcije kliničke implementacije cfDNA analize maternalne krvi u skriningu trizomija 21, 18 i 13: prva, rutinski skrining cele populacije i druga, kontigent skrining baziran na rezultatima prve linije skrininga drugom metodom, preferabilno kombinovanim skriningom prvog trimestra. Kontigent skrining rezultuje u vrlo visokoj stopi detekcije i veoma niskoj stopi invazivnih procedura, kao i manjoj ceni koštanja, u odnosu na opciju cfDNA kao prve linije skrininga [6]. Rezultati

kombinovanog skrininga bi stratifikovali populaciju na visoko rizičnu grupu, koju je najbolje testirati invazivnom procedurom, intermedijernu grupu koja bi imala koristi od cfDNA testiranja i nisko rizičnu grupu koja ne mora zahtevati dalje testiranje za trizomije. I ovde je od nemerljivog značaja ultrazvučni pregled u prvom trimestru koji će detektovati veliki broj major anomalija.

Skrining putem analize cfDNA u maternalnoj krvi u monofetalnim trudnoćama može detektovati preko 99% fetusa sa trizomijom 21, 98% trizomija 18 i 99% trizomija 13, sa kombinovanom stopom lažno pozitivnih rezultata (FPR) od 0,13%. Broj objavljenih slučajeva aneuploidija polnih hromozoma je još uvek suviše mali za preciznu procenu performansi ovog skrininga [7]. U blizanačkim trudnoćama, cfDNA u maternalnoj krvi obezbeđuje efektivan skrining za trizomiju 21. Ova metoda može biti korišćena ili kao primarni skrining, ili kao kontigent na osnovu rezultata kombinovanog skrininga prvog trimestra. Ukoliko se cfDNA koristi kao skrining prve linije u blizanačkoj trudnoći i dalje ostaje imperativ da trudnici treba da bude urađen ultrazvučni pregled u 11-14.nedelji gestacije, kako bi se odredila gestaciona starost, horionicitet, vitalnost fetusa, kao i njihove NT ili major anomalije, koje bi indikovale invazivno testiranje [8].

Godine 2015. velika studija koja je koristila bazu podataka California Prenatal Screening Program, zaključila je da tradicionalni cfDNA skrining za uobičajene aneuploidije i polne hromozome, ima sposobnost da detektuje oko 70-80% fetalnih i neonatalnih abnormalnosti nasledne osnove fetusa [9]. Preostalih 20-30% abnormalnosti koje neće biti detektovane tradicionalnim cfDNA skriningom, obuhvataju klinički releventne nalaze kao što su submikroskopske delecije/duplikacije, retke autozomne aneuploidije i poliploidije, što predstavlja prostor za dalji razvoj prenatalnih skrining testova.

Tokom prethodne dekade, sa pojavom i širokom kliničkom primenom cfDNA testiranja radi skrininga na fetalne aneuploidije, pojavio se interes za patogene genomske copy number variants (pCNVs) [10]. Velikim delom ovo je bila posledica saznanja da su pCNVs, kumulativno gledano, uzrok humanog morbiditeta i mortaliteta veće prevalence nego same aneuploidije [11]. Sve češće korišćenje chromosomal microarray (CMA), kao alternative veće rezolucije u odnosu na konvencionalni kariotip u invazivnim prenatalnim genetičkim analizama, sa ili bez nalaza fetalnih strukturnih anomalija, potvrdilo je značaj CNVs [12].

Genome-wide cfDNA (GW-cfDNA) skrining je razvijen kako bi se proširilo polje abnormalnosti detektabilnih prenatalnim skriningom [13].Međutim, uprkos godina iskustva sa ovom vrstom testiranja, stručna udruženja još uvek ne podržavaju GW-cfDNA skrining u prenatalnom period, navodeći da su neophodni dodatni podaci i dokazi [14] .Najnovije studije, fokusirane samo na CNVs podgrupu abnormalnosti, sugerišu da GW-cfDNA skrining može ponuditi pacijentima i lekarima mogućnost da identifikuju dodatne klinički relevantne hromozomske abnormalnosti koje ne bi bile detektovane tradicionalnim cfDNA skriningom, uz upozorenje da ovaj skrining test ne može biti zamena za dijagnostičko testiranje. Preporučuju da pacijentima koji žele da maksimiziraju detekciju hromozomskih abnormalnosti treba ponuditi invazivno dijagnostičko testiranje CMA metodom. Podaci od preko 86000 skrining uzoraka svakako obezbeđuju kliničarima i stručnim udruženjima podatke koje će podržati i verovatno uskoro obezbediti kritičnu masu dokaza o korisnosti upotrebe ovog testa [15].

Najnovi publikovane studije međutim sugerišu da uprkos interesovanju i upotrebi skrininga za detekciju CNVs pomoću cfDNA skrininga, pravo neinvazivno sveobuhvatno profilisanje fetalnog genoma za mikrodelecije i mikroduplikacije nije moguće, zbog ograničenja koja se odnose na lošu rezoluciju cfDNA testiranja za disbalanse manje veličine [16]. Stoga, cfDNA test koji ukazuje na nizak rizik i dalje ostaje udružen sa određenim rezidualnim rizikom. Upravo objavljene, kao i studije

koje su u toku, pokazuju da većina ovih limitacija, koja se odnosi na veličinu disbalansa, može biti prevaziđena razvojem metode koja podrazumeva neinvazivno uzorkovanje intaktne fetalne ćelije, sa subsekventnom analizom čistog kompletnog fetalnog genoma [17, 18].

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OBESITY – OBSTETRIC CHALLENGES

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Obesity in women of childbearing age is a growing global problem [1]. The prevalence of obesity is increasing worldwide and this trend also affects women of reproductive age. Maternal obesity is now the most common risk factor for maternal mortality in developed countries and is also associated with a wide spectrum of adverse pregnancy outcome [1].

Maternal obesity presents several specific challenges to the labor and delivery process, including compromised myometrial contractility, prolonged labor, and challenges in monitoring. Interventions without demonstrated benefit may, in fact, subject patients to harm. This is especially true as obese women undergoing cesarean delivery are at increased risk for anesthetic, infectious, and thromboembolic complications [3].

Studies of gestational age in obese pregnancies have shown that a high maternal BMI increases the risk of a longer pregnancy (>41 weeks of gestation), which is associated with the risk of labor induction. Induction of labor (IOL) increase the risk of instrumental delivery, such as vacuum extractions and cesarean section (CS). Overweight and obesity are also associated with longer periods of active labor. For cervical ripening and reaching active labor, studies have shown that obese women have a different course of labor compared with women with a normal weight (BMI <25). Cervical ripening is slower, which means that it takes longer to reach the active phase of labor and that they may need more doses of prostaglandins during IOL. Studies have also suggested that overweight and obese women may need higher doses of oxytocin during labor. Nevertheless, obese women have an increased risk of CS due to dystocia compared to normal-weighted women in normal deliveries, especially during IOL [4].

The rates of onset of spontaneous labor in term obese pregnancies were lower and scheduled delivery rates were higher than in non-obese pregnancies. Furthermore, as BMI increased, lower rates of onset of spontaneous labor and higher rates of scheduled delivery were determined. There are only a few studies in literature on this subject and in those studies, the rate of onset of spontaneous labor in term obese pregnant patients has been shown to be lower than in term non-obese pregnant patients, which is similar to the current study results. Although the pathophysiology of this decrease in the onset of spontaneous labor rates in term obese pregnancies compared to non-obese pregnancies is not fully understood, in vitro studies have shown that obese women have abnormal contractility in the myometrium and that when oxytocin is required, higher doses are used in obese pregnancies. Therefore, this decrease in the onset of spontaneous labor rates in obese pregnancies may be due to this abnormal myometrium contractility [5].

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AKUŠERSTVO U CRNOJ GORI, NEKAD I SAD

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Opstertrička struka je jedna od najstarijih medicinskih struka. Dva velika prokletstva pratila su prirodni porođaj od davnina, smanjena karlica i otežan porođaj. S urbanizacijom i hospitalizacijom, puerperalna groznica postala je uobičajena. Budući da su majke često umirale pri porođaju, a djeca u djetinjstvu, stavovi prema rođenju i bebama bili su drugačiji od naših. Roditelji su očekivali da će djeca umirati u djetinjstvu, a smrt pri porođaju bila je očekivana tragedija.

U razvijenim zemljama smrtnost djece je sada niska, a smrtnost majki rijetka katastrofa. Dokumentovani zapisi još od pre Hrista, preko mračnog srednjeg vijeka, kada su babice proganjane vode do Njemačke 1452. kada je izašao prvi zakon o regulisanju porodiljstva. Stotinjak godina kasnije izlazi prvi udzbenik za babice. Tek u XVII vijeku porođaju prisustvuje doktor, po zapisima iz evropskih zemalja. Sa razvojem medicinskih nauka ubrzano se razvija i porodiljstvo.

U Crnoj Gori prije početka XX vijeka, sam čin porođaja tretira se "ispod ljudskog dostojanstva i biva prepušten samoj porodilji i eventualno ženskim članovima porodice ili zajednice". Prva bolnica Danilo I na Cetinju otvorena 1897. Prva školovana babica, Milica Amović, radila je na Cetinju, a od početka XX vijeka u Podgorici i u Nikšiću sa radom počinju školovane babice.

Mnogi pisani dokumenti, legende i podaci govore o prvom carskom rezu. Sa razvojem anestezije, asepse i antisepse, krajem XIX i u XX vijeku, ova operacija koja spašava živote dobija svoj zamah. Progesivno povećanje stope carskog reza u svijetu indikuje preporuke WHO 1985. da stopa carskog reza veća od 10-15% nema opravdanje, ni za jedan region, ni za bolji maternali i perinatalni ishod.

Stopa carskog reza i dalje ima postojano povećanje širom svijeta, i taj trend rasta se nastavlja tokom tekućeg desetljeća, gdje se očekuje da će koegzistirati i nezadovoljene potrebe i prekomjerna upotreba carskog reza.

Prema podacima od 2010. do 2018. godine po WHO iz 154 zemlje, pokazuju da je prosječan postotak carskog reza 21,1%, od 5% do 42,8% u Africi i Latinskoj Americi.

Prema podacima Monstata, Uprave za statistiku, 2020. godine je prvi put u Crnoj Gori od Drugog svjetskog rata zabilježen negativni prirodni priraštaj. Iako je porast smrtnosti u Crnoj Gori veći iz godine u godinu, do ove godine nije zabilježeno da je broj umrlih veći od broja rođenih. Podaci pokazuju da je šezdesetih, sedamdesetih i osamdesetih godina prošlog vijeka broj porođaja bio iznad deset hiljada na nivou godine. Nakon toga broj novorođenih se spušta na nivo oko devet hiljada, da bi u poslednjih deset godina ta brojka bila između 7200 do 7500 novorođenih.

Crna Gora takođe poslednih decenija pokazuje trend rasta stope carskih rezova. Prema WHO podacima u 1997. 9%, do 2002. 230/1000 živorođenih i 2012. 260/1000 živorođenih. U 2021. 28,5% je stopa carskog reza u Crnoj Gori.

Posmatrajući regione Crne Gore prema podacima Uprave za statisku Monstat velika je razlika zastupljenosti carskog reza. Obzirom da je klinički centar, tercijarna ustanova u kojoj se slivaju najteži slučajevi trudnoća, očekivani procenat operativnog porođaja iako u trendu rasta nije najveći u Crnoj Gori. U poslednjih dvadeset godina, od 6% koliko je bilo 2005, postotak stidljivo raste do 2015, a zatim od 2017. procenat se održava iznad dvadeset, da bi u 2022. bio 28,5%.

Prošla godina je za našu instituciju godina najvećeg procenta operativnog porađaja unazad dvadeset godina. Analiza podataka ne obeshrabruje. Naime, obrada podataka po Robsonu pokazuje da je grupa sa najvećim brojem pacijentkinja u skladu s okruženjem. VBAC, vaginalni porođaj nakon carskog reza, iako sigurna procedura, zbog straha od rupture materice je sve rjeđi. Tako da veličina grupe 1+2 i 3+4 po Robsonovoj klasifikaciji ukazuju na značajan broj pacijentkinja koje rađaju više od jednog djeteta.

Šta primijeniti u budućosti? Koje tehnologije implementirati, pitanja na koja zajedno moramo odgovarati.

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NOVELS IN UNDERSTANDING OF FUNCTIONAL CHANGES OF GASTROINTESTINAL TRACT DURING PREGNANCY

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Pregnancy has little effect on gastrointestinal secretion or absorption, but it has a major effect on gastrointestinal motility due to increased levels of progesterone and the displacement of bowel by enlarging uterus. Knowledge of the gastrointestinal adaptation to pregnancy is necessary for accurate interpretation of laboratory tests as well as imaging studies in the gravid patient.

Oral health conditions during pregnancy include gingivitis, tooth mobility or erosion, oral gingival lesions, dental caries and sometimes excessive salivation. Gastrointestinal reflux is common in pregnancy because of decreased lower esophageal sphincter pressure and inhibition of the adaptive responses of the sphincter. The prevalence of symptoms is increasing from the first to the third trimester, with relief postpartum. Pregnant women are predisposed to gastric aspiration due to increased intraabdominal pressure and relaxation of the lower esophageal sphincter. They are at the highest risk of occurrence during labor or soon after delivery, presumably as a consequence of sedation and recumbent position.

Serum aminotransferase, bilirubin, and fasting total bile acid concentrations remain within the normal range during pregnancy. Serum albumin and gamma-glutamyl transpeptidase levels are significantly reduced, whereas lipids and alkaline phosphatase levels are significantly increased. Treatment of elevated lipid levels is not indicated during pregnancy and women who are receiving statin therapy ideally should stop statin treatment three months prior to conception. Gallbladder volume and the lithogenicity of bile are increased. Amylase levels appear to remain in the normal range or be slightly elevated. Acute pancreatitis during pregnancy is rare. Abdominal bloating and constipation during pregnancy are likely caused by hormonal changes - increased progesterone concentration that reduce small bowel and colonic motility, in addition to the bowel compression caused by the growing uterus. Fecal incontinence and flatus are more common during pregnancy. Hemorrhoids are common in pregnancy, due to increased local venous pressure and an increased prevalence of constipation. Constipation exacerbates these symptoms, so adequate hydration and a high-fiber diet are advisable.

The overwhelming majority of gastrointestinal changes that occur with pregnancy will resolve with delivery and can be managed with supportive care. However, conditions such as gallstone pancreatitis, appendicitis, cholelithiasis with cholecystitis, and acute hepatitis require urgent consultation from a gastrointestinal expert. The maternal gut microbiome is influenced by pregnancy. The microbiome is now considered to be essential as both a commensal and symbiont integral to immune and metabolic health. Gut bacteria stimulate lymphoid tissue associated with the gut mucosa to produce antibodies to pathogens and play a role in the expression of Toll-like receptors in the intestines (pattern recognition receptors), that may influence oral tolerance and immune memory. The maternal gut microbiome changes across gestation. Massive bacterial colonization of the newborn gut occurs during labor and vaginal birth upon exposure to maternal vaginal, fecal, and skin microbiota. Because cesarean-born neonates do not experience the same exposure to the maternal microbiome, restoration of normal neonatal colonization iatrogenically - vaginal seeding has been suggested, but is discouraged outside of research studies. Prenatal

and post-natal supplementation with lactobacilli alone or lactobacilli with Bifidobacterium spp. seems to be protective. Probiotics may improve insulin resistance and consequently reduce the risk of gestational diabetes.

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THE POTENTIAL ROLE OF AI IN PRENATAL DIAGNOSIS OF FETAL HEART ANOMALIES

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Fetal echocardiography is a specialized ultrasound examination that focuses on evaluating the structure and function of the fetal heart. Congenital heart defect (CHD) refers to the structural abnormality of the heart or large blood vessels in the thoracic cavity, with the incidence rate of about 30% of congenital defects. It is also the most common and easily missed congenital defect, with some countries detecting only 14% of severe CHD cases before birth.Antenatal screening is state of the art of the contemporary prenatal care and is used to identify pregnant women carrying fetuses at sufficient risk of a congenital disorder to warrant an offer of further investigation and medical interventions after birth.

Advances in artificial intelligence (AI) have been transforming various aspects of healthcare, and one particularly promising application is in the field of fetal ultrasound echocardiography. This revolutionary technology holds the potential to significantly enhance prenatal care by providing more accurate and timely information about the developing fetal heart.It could integrate data from multiple sources, such as fetal echocardiography, clinical parameters, risk factors, and other imaging modalities in order to provide CHD detection, personalized outcome predictions and automatic quantification.Another important aspect is the standardization of the evaluation process, reducing inter-operator variability and ensuring consistent, high-quality assessments across different healthcare facilities.It can also automate the process of image acquisition and analysis, reducing the dependency on highly specialized sonographers and making the procedure more accessible and cost-effective.

Machine learning (ML) is an integral part of AI. ML can be defined as the use of computer programs that automatically improve with experience and become better in their defined task. Deep learning (DL) is a specific type of ML that uses neural networks. These networks are composed of multiple layers of perceptrons, which can extract more abstract and high-level features from the input data, allowing complex interpretation and prediction.

One recent study done in UK compared AI model with a current screening programme. The human-AI collaboration has been highlighted so far, since either the highly sensitive or highly specific calibration of AI models affects false positive and false negative findings, respectively. In order to accomplish this real-time feedback to sonographers during the ultrasound examination is needed, assisting them inmodifying imageacquisition basedontheAImodeloutput.

The vast majority of medical AI research has been performed using retrospectively acquired data, which has been used both for training and testing the algorithms.Although there are many favorable results indicating excellent model performance, very little work has been done examining how to apply these models to a real world setting, on prospectively acquired data, for actual clinical benefit to the patients. High quality randomized controlled trials are needed in the future to overcome this limitation. A recent systematic review found only two published randomized controlled trials comparing the performance of AI versus humans in medical

imaging tasks, and identified a high risk of bias in the majority of the published literature using retrospective data.

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SIGNIFICANCE OF EXOME SEQUENCING FOR PRENATAL DIAGNOSIS

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Congenital anomalies, as defined by the World Health Organization (WHO), are structural or functional abnormalities that occur during the intrauterine life, with severe consequences including intrauterine and newborn demise, chronic diseases and lifelong disability, posing a significant burden on the families affected and the medical system. Isolated or multiple congenital anomalies (MCA) affect around 3% to 4% of all livebirths, mainly due to genetic disorders. These disorders are a genuine medical challenge, particularly because of their perinatal mortality that is around 20%. Over the past decade, the implementation and accuracy of prenatal screening programs including first and second trimester ultrasonography (US) have significantly increased. Therefore, more congenital malformations are detected early in pregnancy, with higher precision.

Ultrasound scanning in pregnancy can reveal fetal structural abnormalities from the first trimester onwards, ranging from isolated minor anomalies to severe, multisystem disorders. These abnormalities may indicate an underlying genetic condition but making a definitive diagnosis can be difficult because many conditions have overlapping fetal presentations. A genetic diagnosis can clarify the prognosis for the fetus, informing parental decision making and clinical management during perinatal period.

The rapid identification of a causal diagnosis is therefore essential for adapting perinatal management and providing genetic counseling for the current pregnancy and any subsequent pregnancies. Modalities of prenatal testing that lead to diagnoses and facilitate decision making have evolved significantly over the past decade as part of the unprecedented progress registered in the field of genetics.

For over 30 years, the standard diagnostic investigations for fetal anomalies have included conventional prenatal cytogenetic analysis via karyotyping. Rapid aneuploidy detection for the identification of specific common fetal aneuploidies (trisomy 13, 18 and 21, sex chromosome aneuploidy and triploidy) has replaced karyotyping and, when normal, is followed by chromosomal microarray analysis to improve resolution and detect both microscopic and submicroscopic pathogenic copy number variations (CNV). Chromosomal microarray analysis accounts for an increased diagnostic yield dependent on the anomalies, and ranges from approximately 3%–6% in fetuses with an isolated anomaly to greater than 10% when multiple anomalies or other fetal findings are present (e.g., intrauterine growth restriction, oligohydramnios/anhydramnios). However, in more than half of the fetal structural anomaly cases, the molecular etiology is unknown, resulting in challenges in parental counseling.

The gradual introduction of next generation sequencing (NGS) over the past decade has marked a shift in the approach to genetic diagnosis either by a targeted gene panel approach that incorporates a differential diagnosis when a diagnostic handle can be identified, or by a comprehensive genomic approach when the diagnosis is non-specific or too complex through exome (ES) and, exceedingly rare at the moment, genome sequencing.

Next-generation sequencing technology has been proven to be a powerful tool for the clinical diagnosis of Mendelian disorders. Given the success in postnatal patient populations and the

limitations of current genetic testing for prenatal cases, ES is now applied to prenatal diagnosis (pES) more widely.

Hereof, the next step in the diagnosis of monogenic disorders prenatally is to use next generation sequencing (NGS) techniques. In this context, NGS utilises test DNA from the fetus obtained by amniocentesis, chorionic villous or fetal blood sampling and involves trio (both parents and fetus) exome sequencing (ES) and potentially whole genome sequencing (WGS).

Exome sequencing entails analysis of the protein-coding regions of the genome, which are referred to as the exons. There are approximately 20000 protein-coding genes, although not all of these are associated with known human diseases. A smaller number of disease-associated genes (around 5000) are evaluated in some laboratory settings; this is sometimes termed the "clinical exome ".

As there are increasing novel sequence variants being detected by laboratories, in 2015 the American College of Medical Genetics and Genomics (ACMG) released guidance on the classification of variants. The understanding that the clinical significance of a variant lies on a spectrum from almost certainly pathogenic to benign is reflected by the update. Variants are classified as either pathogenic, likely pathogenic, uncertain significance, likely benign or benign according to a series of criteria with levels of evidence to support this. Their consensus is that a variant is likely pathogenic/pathogenic or likely benign/benign when there is more than 90% certainty that the variant is causative or not causative of the disease.

The most commonly used method of next generation sequencing in the prenatal setting is exome sequencing. This evaluates the protein-coding exons, which although comprise only around 1–2% of the genome, are responsible for more than 85% of all pathological variants which cause disease. ES is often the preferred method of NGS used in clinical practice. Although a compromise in some respects as it does not evaluate the whole genome and therefore limits the potential for making a genetic diagnosis, it can detect single nucleotide variants (SNVs), small insertions and deletions and some copy number variants at a relatively lower cost whilst still achieving significant diagnostic yield with a rapid turnaround time, and reducing the discovery of incidental findings.

In prenatal diagnosis, trio-based sequencing (trio-exome), including both parents and the fetus is often used because this approach can filter out uninformative variants, identify de novo variants and determine inheritance of recessive variants.

Over the past few years, a flurry of studies has showed a wide range of diagnostic yields anywhere between 6% and 89%, demonstrating its overall clinical utility. As showed by a recent meta-analysis the highest yields are associated with multiple anomalies, and recurrent anomalies are highly suspected to be genetic.

An important increase in diagnostic yield from NGS compared to conventional testing has been demonstrated in fetuses with congenital malformations, particularly with multisystem differences where the likelihood of monogenic etiology is increased.

Diagnostic yields are highest with nonimmune fetal hydrops, skeletal dysplasia and central nervous system anomalies.

The highest diagnostic yields of exome sequencing (ES) for prenatal diagnosis of fetal structural anomalies, where karyotype/chromosomal microarray (CMA) is normal, occur in fetuses with skeletal abnormalities 53%, neuromuscular abnormalities, usually presenting as fetal akinesia deformation sequence (FADS) 37%, and abnormalities in multiple systems 29%.

Previous studies showed that nearly 23% of fetuses with increased nuchal translucency (NT) and other anomalies had a causative variant, whereas only 1.8% of those with an isolated increased NT (which remained isolated throughout) had a diagnostic variant detected. The diagnostic rate increased from 1.6% with NT 3.5–4.4 mm to 28.6% with NT > 7.5 mm.

A systematic review demonstrates that when pES is used as a secondary genetic test for fetuses with prenatal non-immune hydrops fetalis (NIHF), the additional diagnostic yield is 29%, when karyotyping and/or CMA is non-diagnostic. Even in those fetuses with isolated NIHF there was significant diagnostic yield, with a RASopathy the most common diagnosis. This data supports its clinical utility in all cases of NIHF diagnosed prenatally.

Studies report on the diagnostic yield of pES in fetuses with CNS malformations show a promising rate of 45%–75%.

The additional yield for ES in all congenital heart disease was reported to be 12.7%, in isolated CHD this was 11.5% and where CHD was associated with extra-cardiac anomalies (ECA) the additional yield was 14.7%

In the analysis of the WES use in a large group of Congenital anomalies of the kidney and urinary tract (CAKUT) fetuses with normal karyotypes and CMA results, the total yield of clinical diagnosis reached 13.3%.

A recent systematic review and meta-analysis performed as sub-group analyses on specific fetal phenotypes to determine the incremental yield of ES for single system congenital abnormalities showed that diagnostic yield varied significantly according to fetal phenotype. Pooled estimated diagnostic yield for each isolated system was as follows:

- skeletal 53%,
- neuromuscular/fetal akinesia deformation sequence 37%,
- multisystem 29%,
- hydrops/edema 22%,
- central nervous system (CNS) 17%,
- cardiac 11%,
- craniofacial 9%,
- congenital anomalies of the kidneys and urinary tract (CAKUT) 9%,
- fetal growth restriction (FGR) 4%,
- isolated increased nuchal translucency (NT) 2%,
- gastrointestinal 2%,
- respiratory/chest 0,
- abdominal wall 0.

Factors such as the rigour of eligibility criteria, testing platforms, trio (parents and fetus) versus singleton (fetus only) sequencing and, in particular, whether there has been selection following genetic review all impact on diagnostic yield. A growing number of studies have demonstrated the clinical utility of prenatal ES and recent guidelines from professional bodies have considered the evidence for the use of this test.

Next generation sequencing is also utilised postnatally for neonates and infants requiring intensive care and thought to have a potential monogenic disease, as well as an additional diagnostic test at postmortem examination in the absence of an antenatal diagnosis, forasmuch establishing a diagnosis aids accurate genetic counselling for parents, which will include accurate recurrence risks and planning for future pregnancies.

It is well known that ES is typically a phenotype-driven test. Correlating the genotype with the prenatal phenotype is challenging. In general, the fetal phenotype of many conditions has not been well described and may deviate quite substantially from the known postnatal phenotype. Despite the advances in prenatal imaging, the fetal genotype-phenotype correlation remains the major practical challenge of prenatal ES, due to limited prenatal phenotypic information which makes gene variant interpretation difficult. Furthermore, some phenotypes are impossible to determine from prenatal imaging, such as developmental delay, intellectual disability, metabolic abnormality, and subtle dysmorphic features. Currently, there is no fetal variant database equivalent to postnatal ones. Variable presentations of fetal disorders and the appearance of ultrasound abnormalities at late gestational age can only complicate the pES data interpretation. Cataloguing the phenotype of prenatal-onset syndromes is of utmost importance to guide healthcare providers in recognizing these syndromes at an early stage and know their evolution throughout the pregnancy.

It is well known that many syndromes have postnatal features that cannot be detected prenatally on routine or expert ultrasound scans, e.g., intellectual disability or hypotonia. In cases of a treatable anomaly, the association with or absence of intellectual disability is the most important information for the parents in their decision to terminate or continue the pregnancy. In these cases, the detection of a genetic cause of fetal anomalies may be of special value as a molecular diagnosis may have more impact on decision-making during pregnancy than the anomalies seen on the fetal scan. Several studies show a large clinical impact of pES in ongoing pregnancies on either decision-making potentially resulting in a termination of pregnancy or on pre- or perinatal management.

Offering pES to an increasing number of prospective parents asks for a critical reflection on prenatal counseling practices. In pre-test counseling, it is not only important to share the knowledge on the possible outcomes and limitations of the genomic test to enable deliberative decision-making, but it is advised to obtain informed consent including patients' preferences on the possible outcomes that are going to be reported.

In the families with a de novo variant, genetic testing in future pregnancies should be discussed because of the possibility of parental gonadal mosaicism.

Ethically, the most demanding issue is the possibility of incidental findings in both fetus and parents. Although rigorous filtering can reduce the number of incidental findings, they can never be fully excluded as this would jeopardize the identification of the primary variant(s) explaining the phenotype. Therefore, a genetic pretest counseling as well as informed consent by both parents are mandatory, so that they are well aware of the possible outcomes.

pES is performed for an agreed panel of genes known to cause disorders that present prenatally, after discussion with clinical geneticists. Rapid aneuploidy testing via quantitative fluorescence polymerase chain reaction (QF-PCR) is performed first, and those with no diagnosis proceed to pES, with chromosomal microarray analysis (CMA) and pES done in parallel, if indicated. This service can provide parents with a definitive genetic diagnosis and information with which to evaluate options for the pregnancy, plan neonatal care and consider the risk of recurrence.

To conclude, exome sequencing increases the detection rate in fetuses with structural anomalies and improves genetic counseling. Moreover, turnaround time is of particular significance in the prenatal setting because of the biological time frame of pregnancy; trios should, therefore, be analyzed simultaneously to expedite interpretation.

Accurate genetic diagnosis allows tailored parental counselling about prognosis, informs decision-making about pregnancy management, and aids planning for delivery and perinatal management. It also circumvents the pre- and postnatal 'diagnostic odyssey' and allows accurate counselling about recurrence risk for subsequent pregnancies, as well as for other family members.

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DETEKCIJA ANOMALIJA PRVOG TRIMESTRA FETUSA – GRUDNI KOŠ I ABDOMEN

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Sa usavršavanjem ultrazvučnih aparata i ovladavanjem veština ultrazvuka kao i velikim brojem istraživanja poslednju deceniju je značajno poboljšano rano detektovanje anomalija fetusa već u prvom trimestru.

Tokom proteklih 25 godina, embrionalni i fetalni period trudnoće imaju sve veću pažnju. Savremene visoko-frekventne ultrazvučne sonde omogućavaju dobijanje detaljne slike od početaka razvoja embriona, čime se pomera fokus pretraživanja anatomije i anomalija od drugog ka prvom tromesečju graviditeta, te je danas sve više radova o detekciji embrionalnih i fetalnih strukturnih abnormalnosti u prvom trimestru. Treba reći da se u tom ranom period, do oko 10. nedelje, kada je embrion mali primenjuje transvaginalni ultrazvuk, a opserviranje tokom kasnijeg perioda se obično vrši pomoću transabdominalne sonde. Rane abnormalnosti prvog trimestra se često uočavaju slučajno i zasnovane su na kliničkim indikacijama, dok je otkrivanje kasnih abnormalnosti prvog trimestra rezultat sistematskog skrininga pomoću ultrazvučnih markera.

U 10. nedelji embrion je manji od polovine dužine odraslog palca, ali poseduje već nekoliko hiljada identifikovanih struktura i praktično svaka od njih može imati razvojna odstupanja. Većina urođenih anomalija se i pojavi u tom periodu te je njihova rana detekcija ultrazvukom naš cilj.

Tačna definicija prelaza između trimestara nije moguća jer nema konkretnih razvojnih faza koje bi ukazivala takve granice [4]. Uvođenje 11-13+6 nedelje fetusa je uspostavljen kao praktični period opservacije kao i 13+6 do 14 nedelja završetkom prvog tromesečja. Treba napraviti razliku između skrininga tokom 11-13+6 nedelje i onog pre ovog perioda tokom embrionalnog perioda [5-7]. Transvaginalna pristup je poželjan za sve preglede pre 11-12 nedelje trudnoće.

Skoro kod svih pobačaja u prvom trimestru se ultrazvukom obično uočavaju poremećaji kao što su prevelika ili premala žumančana kesa, prevelika amnionska šupljina, embrion je premali ili nenormalnog izgleda, ili je rad srca usporen. Za opserviranje su interesantne one anomalije u kojima embrion nastavlja da živi i da se razvija. U takvim slučajevima, možemo očekivati sledeće ultrazvučne nalaze: abnormalne konture glave, tela i ekstremiteta; abnormalno smanjenje ili povećanje tečnosti u moždanim šupljinama, abnormalno povećanje tečnosti u grudnom košu, stomaku i digestivnom traktu kao i abnormalan broj prstiju; odstupanja u biometrijskom merenju CRL, biparietalnog prečnika (BPD) i žumančane kese kao i značajna odstupanja u srčanom ritmu.

Hidrops i polimalformisan fetus

Interesantno je navesti podatke koje je prikazao Grande sa saradnicima 2012 godine vezano za prisustvo fetalnog hidropsa u prvom trimestru graviditeta. Fetalni hidrops je imao stopu detekcije u prvom trimestru od 89% (osam od devet slučajeva)[4]. Nasuprot tome, samo 31% (četiri od 13) kod fetusa su bile prisutne dve ili više većih strukturnih anomalija koje uključuju različite sisteme (Hidrocefalus + pupčana kila; hidrops + megacista; transpozicija velikih krvnih sudova + dijafragmalnom kile; i hipoplazija desnog srca + hidrops)[4]. Uvećanje NT ili patološki protok kroz DV je bio prisutan kod 64% ovih fetusa i 8% je imalo odsutvo nosne kosti [4].

Urođene srčane mane

Podaci o specifičnim grupama srčanih anomalija i njihovom ranom otkrivanju u euploidnih fetusa iz 14 studija koje su dale takve detalje su prikazani u tabeli.

Tabela 1. Detekcija CHD u I trimestru

Studies providing details on the early diagnosis of specific cardiac abnormalities in euploid fetuses.

Cardiac abnormality	Screening study[a]														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Coarctation of the aorta		0/1		0/3		0/1		0/1	2/5	0/2	0/8	4/15	0/1		6/37 (16.2%)
Tetralogy of Fallot		1/2	0/1	0/2		0/1	0/1		0/3	0/2	0/9	3/10	2/3		6/34 (17.6%)
Hypoplastic left heart		1/2	0/2	1/3				0/1	1/2	1/3	0/6	5/10	2/2	10/10	21/41 (51.2%)
Transposition of the great arteries				0/2	0/1			0/3	0/3	0/1	0/8	2/5	2/2	2/8	6/33 (18.2%)
Atrioventricular septal defect		0/3		0/7							0/2	3/9	8/9	4/5	15/35 (42.9%)
Pulmonary stenosis			0/1	0/1		0/1		0/1	0/4		0/1	0/5	1/1		1/15 (6.7%)
Aortic stenosis		1/3							0/2			0/1	2/3		3/9 (33.3%)
Tricuspid atresia	0/1								0/2			1/1	1/1		2/5 (40.0%)
Ebstein's anomaly								0/1			0/2	0/5			0/8 (0.0%)
Double outlet right ventricle					0/2							4/7			4/9 (44.4%)
Anomalous pulmonary venous return		0/1									0/1				0/2 (0.0%)
Mitral atresia											0/1		1/1		1/2 (50.0%)
Interrupted aortic arch											0/1		1/1		1/2 (50.0%)
Pulmonary atresia											0/1	1/3			1/4 (25.0%)
Double inlet left ventricle									0/1						0/1 (0.0%)
Common truncus arteriosus											0/1				0/1 (0.0%)
Ventricular septal defect	1/2			0/7	1/1	0/4		0/8	0/1	0/2	0/7	0/16	5/8		7/56 (12.5%)
Total	1/3	3/12	0/4	1/25	1/4	0/7	0/1	0/15	3/23	1/10	0/48	23/87	25/32	16/23	74/294 (25.1%)

Adapted from Syngelaki et al.[11]

[a] 1, Hernandi and Torocsic[11]; 2, D'Ottavio et al.[4]; 3, Bilardo et al.[13]; 4, Taipale et al.[5]; 5, Chen et al.[6]; 6, Cedergren and Selbing[7]; 7, Dane et al.[16]; 8, Chen et al.[15]; 9, Mavrides et al.[17]; 10, Michailidis and Economides[18]; 11, Hyett et al.[12]; 12, Syngelaki et al.[3]; 13, Volpe et al.[8]; 14, Grande et al.[28].

Najčešće detektovana srčana anomalija je bila hipoplazija levog srca 51% pa do najredje detektovanih tetralogije Fallot i transpozicije velikih arterija 18% koarktacija aorte 16%. I najmanje VSD12 % [5].

Najveća studija, koji uključuje 44 859 jednoplodnoj trudnoći prikazuje pregled srca u prvom trimestru kao deo rutinskog skrininga za aneuploidije pokazuje stopa detekcije glavnih urodjenih srčanih anomalija od 34% [5]. Dijagnostikovano je oko polovine slučajeva dvostrukog izlaza desne komore, hipoplazije levog srca i transpozicije velikih krvnih sudova, oko jedne trećine slučajeva atrio-ventriculal septalnog defekta-ASD, Koarktacija aorte, tetralogije Fallot i pumonalne atrezije, ali nijedan od slučajevaventrikularnog septalnog defekta- VSD, Ebštajnove anomalije, aortne ili pulmonalne stenoze, trikuspidne atrezije ili srčanog tumora. Skoro objavljeni rezultati na 36 237 trudnoća u periodu od 1993. do 2008. godine, u osam centara, sugeriše da je ukupna stopa otkrivanja velikih urođenih anomalija od 11-13 nedelje bila 29% a stopa detekcije srčanih defekata 17% [6].

NT i loš ishod trudnoće

Pored snažne povezanoti sa detekcijom aneuploidija fetusa, uvećanje NT je povezano sa rizikom od neželjenog perinatalnog ishoda uključujući fetalne malformacije, displazije, deformitete, i genetske sindrome. Ovi rizici nemaju značaj sve dok NT nije ≥ 3,5 mm (> 99 procenata)[7]. Stopa mortaliteta fetusa zavisi od stepena abnormalnosti NT (od 3,5-4,4 mm smrtnosti = 2,7%, preko> 6,5 mm smrtnosti = 19%) [8]. Nasuprot tome, ako fetus preživi do sredinjeg trimestra i na ultrazvučnom pregledu se neuoče abnormalnosti, rizik od nepovoljnog ishoda se neće značajno povećati [9].

Treba istaći da je potrebna specijalizovana obuka i sertifikacija za sonografe koji mere NT.

NT i urođene srčane mane

Kod fetusa bez hromozomopatija, učestalost urođenih srčanih mana je povećana kod onih fetusa gde je vrednost NT iznad 95. percentila, što je prisutno u približno 1/3 fetusa sa teškim srčanim defektima [5]. Rizik zavisi od stepena abnormalnosti NT i kada je NT ≥ 3.5 mm, defekti srca su prisutne u 1 od 43 jednoplodnih trudnoća [10]. Goetzl i saradnici su izneli podatak da kada je NT ≥ 3,5 mm, učestalost srčanih anomalija je 6,0% (5.2-6.8%); kada je NT od 3,5 do 4,4 mm, učestalost je 3,2% (2.3-4.1%); i kada NT > 4,5 mm, učestalost je 11.8% (9.8 do 13.8%)[11].

Urođene srčane mane u rizičnim trudnoćama

Kombinacija povećane NT i prisustvo trikuspidne regurgitacije kao i nedostatka "a" talasa u ductus venosusu - DV predstavljaje veliku mogućnost prisustva teških srčanih defekata [12]. Kada je NT iznad 99 procenata ili je protok kroz duktus venozus odsutan ili obrnuto, stopa otkrivanja velikih srčanih defekata je 47% uz lažno pozitivnu stopu od 2,7% [13].

Trikuspidna regurgitacija (TR)u prvom trimestru prisutna je u oko 7% normalnih fetusa i ima značajnu vezu sa fetalnim aneuploidijama, posebno u prisustvu drugih markera ali kao izolovani marker TR pokazuje nizak skrining potencijal za fetalne aneuploidije i urođene srčane mane [14]. Sa kvalifikovanum osobljem i opremom, otkrivanje velikih urodjenih srčanih mana u visoko rizičnim grupama (TR, povećana NT, abnormalni protok kroz DV) osetljivosti u prvom i početkom drugog tromesečja može biti i 78,5% [14].

Rana detekcija srčanih anomalija ima ograničenja i procena fetalnog srca u ovoj gestacionoj starosti zahteva visok stepen stručnosti i opreza [15]. Prikazani su u literaturi podaci gde je lažno pozitivna stopa bila čak 33% [11], dok je kod dobro edukovanih sonografa stopa lažno pozitivnih rezultata bila daleko manja.

Defekt prednjeg trbušnog zida

Zbog fiziološkog defekta prednjeg trbušnog zida "fiziološke onfalokele" koja je jasno vidljiva ultrazvukom od 10-11 nedelje, mora se biti oprezan sa donošenjem dijagnoze kao što su pupčana kila pre 12 nedelja. Normalna veličina i razvoj fiziološkog središnje uzdužne herniacije je opisana od 7-12 nedelje graviditeta [2] i može pomoći u razlikovanju normalnih defekata abdominalnog zida.

Kontemplacije o patogenezi defekata prednjeg trbušnog zida ima tendenciju da kategoriše ove defekte u zavisnosti na njihove lokacije u odnosu na pupak [17]. Nastaje podela na kranijalne defekte (npr ektopično srce, epigastrična onfalokela); centralne defekte (npr centralna pupčana kila, gastrošiza); kaudalne defekte (npr. ekstrofija bešike, Kloakalna ekstrofija, onfalokela-ekstrofija-imperforatni anus-spinalni defekt kompleks); i kompleksni defekti (npr ud-telo-zid-kompleks), uključujući body stalk anomaliju, i body stalk anomaly izazvane rupturom ovojaka [18]. Pre 12 nedelje trudnoće, diferencijacija ultrazvukom ovih podgrupa izgleda neprikladno iako postoji u literature samo nekoliko izveštaja o slučajevima velikih složenih defekta, kao što su ud- telo-zid-kompleks i ektopčnog srca [19] pre 10 nedelje kao čak i rani opis gastrošize u 9 nedelji [20].

Body stalk anomalija se detektuje skoro uvek od 11 nedelje a karakteriše je malformisan fetus sa defektom prednjeg trbušnog zida i jedan deo tela fetusa dodiruje placentu, a ključni nalaz je savijenost kičme fetusa i kifoskolioza.

Abdomen – Gastrointenstinalni i urogenitalni sistem

Većina kongenitalnih gastrointestinalnih anomalija su opstrukcije gastrointestinalnog trakta. Takve anomalije su atrezije, stenoze, i duplikature gastro-intestinalnog trakta, ciste ili tumori, i

bolesti jetre, slezine ili pankreasa. Promena u količini plodove vode zbog moguće neravnoteže u proizvodnji i resorpciji gastrointestinalnog i urinarnog sistema nije značajna do drugog trimestra. Tečnost koja se može naći u embrionalnom stomaku već od 8 nedelje ne predstavlja progutanu amnionsku tečnost već potiče verovatno od želudačne sekrecije [3]. Dakle, ne može se očekivati rani oligo- ili polihidramion kao marker za gastrointestinalne ili urogenitalne anomalije. Slučajevi ezofagealne atrezije se opisuju od 12 nedelje graviditeta mada je opisan jedan slučaj u 10 nedelji [18]. Kao i kod gastrointestinalnog trakta, razvoj genitourinarnog trakta nije kompletan pre post-embrionalnog perioda. Genitourinarne anomalije trakta obično nisu otkrivena pre 11-13+6 skeniranja skeniranja. Dijagnoze gastrointestinalnih I genitourinarne anomalije tokom embrionalnog perioda nisu opisani.

Pupčana kila se javlja kada postoji hernijacija fetusa creva iza 12 nedelje trudnoće sa insercijom pupčanika na vrhu kilne kese. Gastrošiza i onfalokela se detektuju sa stopom detekcije i do 100% u kasnom prvom trimestru [5].

Tokom prvog tromesečja, bešike se obično vizuelizuje u oko 90% slučajeva [21]. Velika studija tima prof. Nicolaidesa iz 2011 godine na 44 859 slučajeva je detektovala exomphalos, gastroschizu, megacystu i body stalk anomaly u 100% slučajeva [4], a dijafragmalna hernija u 50% [2] ili 33% slučajeva [4] dok se cistični bubrezi uočavaju u 25% 21 do 33% [2] a hidronefroza u 6% [4]. Cista jajnika fetusa nikada nije uočena u prvom trimestru.

Ishod trudnoće

Prekid trudnoće je opcija za sve žene koje nose fetus sa teškim strukturnim anomalijama CNS-a (Akranija-eksncephalija, alobarna holoprozenkefalija i Encefalocela), u nekim vrstama srčanih defekata (teškim defekata levog i desnog srca), kod artrogripoze, fetalnog hidropsa i u jasno definisaniom cistichnog higroma [4].

Prekid se sprovedi u više od polovine sledećih anomalija: spina bifida, AV kanala, megaciste, osteochondrodisplazije, defekima udova, i u polimalformisanih fetusa [4].

Prekid nikada nije sproveden kod fetusa sa rascepima lica, dijafragmalnom hernijom, cističnim bubregom [4].

Preporuke [15,22]

Prvi trimestar je podeljen na embrionalni, rani fetalni period 10-11 nedelje i kasniji period od 11-13+6 nedelja.

Transvaginalni ultrazvuk je poželjan u embrionalnom periodu, dok se transabdominalna sonografija obično primenjuje kasnije.

Preduslov za bilo kakvu anatomsku evaluaciju i dijagnostiku strukturnih abnormalnosti u I trimestru je znanje normalnog embrionalnog razvoja.

Skeniranje treba da sadrži određene standarna merenja: merenje CRL, prečnik amnionske kese, prečnik žumance kese, i frekfence srca. Kod fetusa od 10-11 nedelja treba pridodati merenje biparijetalnog dijametra- BPD, prečnikaili obima trbuha, nuhalnu translucneciju- NT , i dužinu butne kosti -FL

U kasnom periodu I trimestra od 11-13+6 nedelja, upotreba soft markeraza aneuploidije pomaže da se identifikuju fetusi sa rizikom za strukturne anomalijama. U tim slučajevima, osim odgovarajuće daljeg ispitivanja kao što je kariotipizacija, treba sprovesti temeljan ultrazvučni pregled na anomalije uz prednost korišćenja trasvaginalne sonde i uz pomoć trodimenzionalnog ultrazvuka.

Razvijati algoritam za skrining za urodjene srčane mane -CHD u prvom trimestru, koristeći kombinaciju karakteristika majke i trudnoće, nuhalne translucencije, protoka kroz ductus venosus-DV i trikuspidne rekurgitacije -TR.

Usavršavanje i rutinska primena transvaginalne ultrazvuka i STIC-a za fetalno srce sa ciljem povećanja stope detekcije CHD.

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PRENATAL DIAGNOSIS, MANAGEMENT, AND TREATMENT OF FETAL CARDIAC DISEASE

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Congenital heart defects (CHD) represent the one third of all major congenital anomalies with a prevalence of 4-9 per 1000 live births. [1]

The American College of Cardiology/American Heart Association classification of recommendations and level of evidence for practice guidelines were applied to the current practice of fetal cardiac medicine. The components of a fetal echocardiogram are described in detail, including descriptions of the assessment of cardiac anatomy, cardiac function, and rhythm [2].

First trimester screening recently started to play a pivotal role in the management of pregnancies. By the combination of maternal age, serum biochemistry, ultrasound anomaly scan, and additional ultrasonographic markers, this screening can identify most fetal aneuploidies and structural abnormalities in the fetus [1,3]. The first step in the analysis is the detection of risk factors, mother and family. A multitude of factors are associated with an increased risk of identifying CHD in the fetus. The leading reason for referral for fetal cardiac evaluation is the: suspicion of a structural heart abnormality on obstetric ultrasound (fetal conditions), which results in a diagnosis of CHD in 40% to 50% of fetuses referred; maternal metabolic disease (DM, phenylketonuria...); family history of CHD. Many of these indications have been estimated to carry a <5% to 10% risk. [2]

In addition, most CHD can be detected in the first trimester using increased nuchal translucency (NT) and by color Doppler assessment, absent/reverse a-wave following atrial contraction in ductus venosus (DV) and tricuspid regurgitation (TCR) [2-12].

Risk levels of ≥2% to 3% defined by prenatal screening tests result in a recommendation to consider additional testing; indicated fetal echocardiography. If the initial risk exceeds 3%, fetal echocardiography should be performed as soon as possible. When the risk approaches that of the general population (≤1%), fetal echocardiography is not indicated [2].

Simple cardiac scan, which is in accordance with ALARA principle (as low as reasonably achievable), giving a certain diagnostic accuracy in revealing CHD in first trimester, might become a part of routine clinical strategy [14,15].

In the second trimester, between 18-24 weeks of gestation, a standard ultrasonographic examination of the fetal heart is indicated, which includes the following anatomical sections: four chamber view, left ventricular outflow tract, right ventricular outflow tract, three vessels trachea view, aortic arch, ductal arch, bicaval view, high short axis and low short axis view [2]. The second trimester is also the right time for a consultative ultrasonographic examination by a pediatric-fetal cardiologist [2].

Knowing the genetic cause of the heart defect will enable a more accurate and appropriate assessment of the risk of recurrence for the parents of the fetus.

It is known that up to 40% of all trisomy 21, 90% of trisomy 18, 80% of trisomy 13 are associated with cardiac anomalies. Monosomy 22q11.2, better known as DiGeorge syndrome, is second in frequency after trisomy 21, is inherited in an autosomal dominant manner and is associated

with anomalies of the heart and in 30% of cases with mental health deficits. All these are the reasons why the first step in the diagnosis of cardiac anomalies is karyotyping (15% to 30% risk of chromosomal abnormality) and micro-array (22q11, Holt-Oram, Williams, and Alagille) [2-12].

Prenatal counseling should be offered in temporal sequence shortly after the fetal echocardiogram, ideally on the same day. Counseling should offer information on the natural history in utero, the potential for a change in or progression of disease, and prognosis for the remainder of the pregnancy.

Expectant parents should be informed about the possible range of treatment and management strategies in utero and after birth. It is important that they understand the limitations of our knowledge in this respect and the challenge in fully predicting lifelong morbidity and impact on life span for many forms of CHD [2].

In 2010, McElhinney created a Cardiovascular profile score (CVPS) system for assessing the severity of fetal CHD. Scoring of the 5 categories (2 points for each), including hydrops, venous Doppler, heart size, heart function and arterial Doppler. If it's CVSP <5 - recommendation termination of pregnancy (TOP); CVSP 6-7 - the decision to continue the pregnancy should be carefully considered in accordance with the involvement of fetal lesions, the mother's health condition, as well as the overall situation in the family; CVCP >7 fetal heart function should be carefully monitored every 2 weeks. No medical therapeutic intervention is required during that period. The CVPS system helps the perinatologist/fetal cardiologist to approximate the current situation and help the parents to make the right decision about the further course of the pregnancy [16].

Recommendation for delivery in fetuses with CHD: elective delivery until 39 completed weeks of gestation has been shown to improve neonatal outcomes; close communication between obstetric and cardiology services is essential; the data that are available do not show any inherent advantage to cesarean section/vaginal birth. [2].

Conclusion

In the modern era, it is expected that structural CHD and arrhythmias will be diagnosed with precise detail in utero. The goal of the perinatologist and fetal cardiologist has now become to understand the fetus as a patient, knowing that the fetal circulation is different from the postnatal circulation, that CHD may progress in utero, and that cardiac function and stability of the cardiovascular system play important roles in fetal wellness.

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IMMUNOLOGY OF PREGNANCY

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Successful pregnancy depends on maternal tolerance of the fetal "semi-allograft". A protein called progesterone-induced blocking factor (PIBF), by inducing a Th2 dominant cytokine production mediates the immunological effects of progesterone. PIBF is produced by PR-positive pregnancy lymphocytes and by several pregnancy-related tissues and malignant tumors. The expression of PIBF seems to be crucial for normal progression of pregnancy. Reduced production of the full-length PIBF protein results in disturbed cell cycle regulation and dysregulated trophoblast invasion. PIBF inhibits arachidonic acid release by a direct action on the phopholipase A2 enzyme. Its immunological effects include inhibition of NK activity and an action on the cytokine balance. PIBF alters the profile of cytokine secretion of activated lymphocytes by shifting the balance toward Th2 dominance. During a normal uneventful pregnancy, the concentration of PIBF continuously increases while in patients with a threatened miscarriage or premature labour PIBF levels failed to increase.

Out of 37 patients with threatened preterm birth 11 delivered pre-term and three groups of patients were formed: the preterm delivery group, patients with threatened preterm delivery, and healthy pregnant women. In samples that were taken within 5 days before labor started (6/11, 54.5%), PIBF concentrations were significantly lower than in those obtained more than 5 days before labor (5/11, 45.5%; the mean interval between sampling and the onset of labor was 4.1 ± 1.8 days). Multiple regression analysis of the individual contributions of each observed parameter for preterm delivery demonstrated the significant contribution of a lack of PIBF to preterm birth ($p = 0.002$). Receiver operating characteristics (ROC) analysis was performed to evaluate the diagnostic accuracy of PIBF for the prediction of preterm birth of women with symptoms of pre-term delivery. The PIBF demonstrated an excellent diagnostic value in the prediction of preterm birth with an area under the ROC curve (AUC) of 0.956 (95% CI = 0.884-0.989; $p < 0.0001$).

Five (16.7%) pregnancies in the study group ended missed abortion vs. none in the control group ($P<0.05$). Five (20%) threatened abortions delivered between 24 (th) and 37 (th) weeks of gestation, whereas two (10%) preterm deliveries occurred in the controls ($P>0.05$). PIBF concentrations in urine (19.5+/-12.9 ng/mL) and serum (214.4+/-120.6 of patients with threatened abortion were significantly lower than in healthy pregnant women (45.3+/-33.7 ng/mL and 357.3+/-159.9 ng/mL, respectively). Women with threatened abortion had significantly lower serum levels of anti-inflammatory cytokine, but levels of proinflammatory cytokines were higher in this group compared with healthy controls.

Urine and serum were collected from 120 women, undergoing IVF. 87.5% of patients had primary infertility. 69.2% faced female causes of infertility: 10.8% tubal cause, 11.7% ovulation disorder, and 46.7% other causes of infertility. 30.8% of patients had male factor of infertility. Among non-pregnant women (42) mean concentrations of PIBF in urine and serum were significantly lower (15.8 ng/mL; 148.4 ng/mL) than in women with positive beta HCG value (78) (19.1 ng/mL; 225.9 ng/mL). In 49 patients pregnancy terminated with a term delivery, in 10 patients with pretem delivery, while in 19 patients the pregnancy terminated with a miscarriage. PIBF concentrations in

urine (13.9 ± 2.8 ng/mL) and serum (124.6 ± 46.7 ng/mL) samples of women with miscarriage were significantly lower of those with preterm delivery (180.6 ± 54.4 ng/mL; 18.1 ± 4.4 ng/mL) and of those with term delivery (20.4 ± 8.5 ng/mL; 208.7 ± 114.3 ng/mL). Our data suggest that pregnancy termination can be predicted by lower than normal pregnancy PIBF values within 5 days before labor and can contribute to the diagnosis of preterm birth. Determination of progesteron-induced blocking factor level in body fluids in early pregnancy might be used for the diagnosis and prognosis of threatened abortion. Measuring PIBF and cytokine concentrations in serum during pregnancy is feasible and may be important for understanding immunological causes of pre-term delivery.

NEONATALNA DISBIOZA- ZNAČAJ I FAKTORI RIZIKA

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Sve je više dokaza da je mikrobiom jedan od najznačajnijih faktora koji određuju naše zdravlje, uzimajući u obzir brojne i veoma važne funkcije koje obuhvataju različite nutritivne, fiziološke, metaboličke i imunske efekte mikrobioma. Tako je, uz značajnu ulogu u preradi i digestiji hranljivih materija, kao i metabolizmu žučnih kiselina, mikrobiom značajan za sintezu esencijalnih mikronutrijenata kao što su vitamin B12 i folati. Podstičući razvoj creva i crevnog epitela, formiranja intestinalne mukozno-epitelne barijere i sinteze antimikrobnih produkata, mikrobiom sprečava kolonizaciju creva patogenim bakterijama. Istovremeno doprinosi razvoju i održavanju senzornih i motornih funkcija creva, produkciji različitih metabolita i regulisanju energetske homeostaze. Doprinoseći razvoju imunskog sistema i odgovarajuće oralne tolerancije, mikrobiom ima veliki značaj u zaštiti deteta od razvoja inflamatornih, atopijskih i autoimunih bolesti.

Poremećaj ili disbalans mikrobioma udružen sa bolešću nazivamo „disbioza“. Veza između disbioze creva i različitih patoloških stanja naslućena je odavno, mnogo pre nego što se znalo za mikrobiom. Još je Hipokrat, 400 godina pre nove ere, govorio da „smrt sedi u crevima“ i da je „loše varenje koren svih zla“. Ipak, poslednjih par dekada interesovanje za uticaj mikrobioma na naše zdravlje, i mogućnosti njegove korekcije, značajno raste.

Problemi vezani za disbiozu vidljivi su već u najmlađoj životnoj dobi. U prvim mesecima, života ispoljavaju se kao različiti digestivni poremećaji, uključujući i infantilne kolike. Neposredne posledice dizbioze kod deteta u razvoju mogu biti i teške infekcije, među kojima se posebno izdvaja nekrotični enterokolitis. Nekrotični enterokolitis (NEK) je jedan od najznačanijih uzroka morbiditeta i mortaliteta nezrele novorođenčadi. Kod novorođenčadi veoma male porođajne telesne mase (<1500 g) javlja sa učestalošću od 1,5 do 10% i mortalitetom koji je, uprkos svim naporima, i dalje veoma visok, čak do 30%, kao i veoma ozbiljnim sekvelama kod preživele novorođenčadi. Iako su već decenijama istraživanja usmerena na proučavanje patofiziologije NEK-a, ona još uvek nije sasvim razjašnjena. Ono što je postalo jasno je da bakterijski sastav creva ima veliki značaj i da se ne radi o jednom specifičnom uzročniku, već o izmenjenom mikrobiotskom sastavu creva, odnosno disbiozi. Više studija je istaklo da se mikrobiom novorođenčeta sa NEK-om značajno razlikuje od zdravog novorođenčeta, i da zavisno od svog sastava, može imati kako protektivnu tako i patogenu ulogu u razvoju intestinalne inflamacije i nekroze, koji su patogenetska osnova NEK-a.

Pored neposrednih efekata, disbioza se dovodi i u vezu sa dugoročnim narušavanjem zdravlja, smatrajući se faktorom rizika za razvoj širokog spektra patoloških stanja uključujući alergije, autoimune, kardiovaskularne i metaboličke bolesti, digestivne poremećaje, pa čak i različite psihološke probleme.

Prvih 1000 dana, počevši od koncepcije i nadalje tokom fetalnog života, neonatalnog i odojačkog uzrasta i tokom druge godine života, smatraju se jedinstvenim i izuzetno značajnim periodom za rast i razvoj individue. Ovaj period istovremeno predstavlja i veoma značajan vremenski prozor za uspostavljanje interakcije domaćin - mikrobiom. Više veoma značajnih faktora određuju mikrobiotski sastav u ranom detinjstvu, ali se uz genetsku predispoziciju, vertikalna transmisija sa majke na dete tokom trudnoće, način završetka porođaja, gestacijska starost, tretman i ishrana u prvim danima života uzdvajaju kao posebno značajni za razvoj mikrobioma.

Kolonizacija creva počinje već tokom fetalnog života i nastavlja se tokom porođaja i ranog detinjstva. Hipoteza da je materica sterilna, koju je početkom dvadesetog veka postavio franscuski pedijatar Tisje, dugo je ostala dogma i svako prisustvo bakterije u uterusu se do nedavno smatralo opasnim po dete. Intrauterusna infekcija i inflamacija zaista predstavljaju značajan uzrok prevremenog porođaja, na šta ukazuju brojne studije. Međutim, relativno mali broj studija je proučavao mikrobiom uterusa kod zdravih, terminskih trudnoća. Tokom poslednje dekade, tragovi prisustva više uobačajenih bakterijskih vrsta su otkrivene u umbilikalnoj krvi, plodovoj vodi, placenti i mekonijumu dece bez ikakvih znakova inflamacije, što sugeriše na izloženost mikroorganizmima već tokom intrauterusnog života fetusa. Sa napredovanjem trudnoće, u organizmu trudnice se odvijaju značajne hormonske, imunološke i metaboličke promene i uporedo sa ovim promenama menja se i broj i struktura njene mikrobiotske flore. Tako se, u sklopu ostalih fizioloških promena, kod trudnice uočavaju i promene mikrobioma usne duplje, urinarnog i genitalnog trakta, kao i mlečne žljezde. Na taj način favorizuje se prelazak određenih bakterijskih vrsta ka fetusu i dojci, ali tačno poreklo, vreme i značaj ove intrauterusne kolonizacije fetalnih creva tek treba da bude razjašnjeno.

Način završetka porođaja i gestacijska zrelost na rođenju su od izuzetnog značaja za formiranje mikrobioma novorođenčeta. Za razliku od dece rođene vaginalnim putem, čiji je mikrobiom sličan onom u vagini i crevima majke, kod novorođenčadi rođene carskim rezom on po sastavu više odgovara majčinoj koži i hospitalnom okruženju. Tako, deca rođena carskim rezom imaju manji ukupni broj bakterija, uz predominaciju stafilokoka i korinebakterijuma i manji broj ili čak odsustvo bifidobakterija. Uz to, profilaktička primena antibiotika, standardni pristup u mnogim zemljama i mnogim vodičima za carski rez, kao i odloženo uspostavljanje podoja, dodatno menjaju mikrobiotsku strukturu ove novorođenčadi. Bojazan da se tako izmenjen model kolonizacije odvijao u kritičnom uzrastu metaboličkog i imunskog razvoja, i da je na taj način bio osnov razvoja brojnih različitih oboljenja u kasnijem dobu, potvrđuju nalazi da se kod dece rođene carskim rezom, uočava slabiji Th1 imunski odgovor tokom prve 2 godine života. Epidemiološke studije ukazuju na veću prevalenciju atopijskih bolesti, astme, tip 1 diabetesa i alergije na hranu, kod dece rođene carskim rezom u poređenju sa decom rođenom vaginalnim putem.

Prevremeno rođenu decu karakteriše odložena kolonizacija uz smanjenu raznolikost bakterijskih vrsta, kao i manja zastupljenost bifidobakterija i povećana sklonost naseljavanju patogenih bakterija. Uz strukturnu i funkcionalnu nezrelost creva, faktori koji dodatno usporavaju i menjaju kolonizaciju ove dece su češća primena totalne parenteralne ishrane, odloženo uspostavljanje enteralne ishrane, aseptično okruženje intenzivne nege, učestala antenatalna i postnatalna primena antibiotika, kao i perinatalni faktori uključujući produženu rupturu vodenjaka i izloženost patogenim mikroorganizmima. Za razliku od zdravih osoba, kod kojih je crevni mikrobiom komensalan i kao takav reguliše različite metaboličke, imunske i inflamatorne procese, kod novorođene dece, naročito one nezrele, ovaj komensalni odnos tek treba da se razvije. Uz to, njihov nerazvijeni imunski sistem ima ograničenu mogućnost odbrane od patogenih bakterija i tolerancije komensalnih bakterija.

Među faktorima koji u prvim mesecima utiču na formiranje mikrobioma, posebno se ističe vrsta ishrane. Već krajem prve nedelje života, u crevima zdrave, terminske, dojene novorođenčadi predominiraju bifidobakterije i laktobacili, za razliku od novorođenčadi hranjene mlečnom formulom čija je mikrobiota slična adultnoj i obiluje potencijalno patogenim bakterijama. Očigledno je da prisustvo majčinog mleka u crevima značajno doprinosi formiranju zdravog mikrobioma novorođenčeta. Pored optimalnog nutritivnog sastava i brojnih imunomodulatornih

zaštitnih faktora majčinog mleka, ono je i bogat izvor prebiotika i probiotika, veoma značajnih u prevenciji disbioze.

Primena antibiotske terapije, uz sav svoj značaj u prevenciji i lečenju teških bakterijskih infekcija novorođenčadi, istovremeno predstavlja i veoma značajan faktor rizika za razvoj disbioze i posledične neonatalne sepse. Primena antibiotika značajno menja mikrobiom creva, usporavajući i otežavajući naseljavanje bifidobakterija i laktobakterija i istovremeno olakšavajući naseljavanje patogenih bakterija. Studije su pokazale da čak jedna trećina bakterija može biti uništena antibiotskim tretmanom u ranom detinjstvu, ali od ne manjeg značaja je i antibiotska terapija ordinirana majci antenatalno ili tokom laktacije. Ovako izmenjen mikrobiom može perzistirati nedeljama, pa i mesecima, sa mogućim dugoročnim posledicama po dete u razvoju.

I okruženje u kome dete boravi tokom najranije životne dobi, sa svoje strane utiče na razvoj njegovog mikrobioma i imunskog sistema. Pored higijenskih navika roditelja i prisustva braće i sestara u porodici, postoje i brojni dodatni faktori koji, iako ne možemo da odredimo egzaktno doprinos svakog od njih, imaju nesumljivi značaj. Među njima se posebno ističe rani kontakt sa domaćim životinjama. Brojne epidemiološke studije su ukazale na značaj života na selu, i ranog kontakta sa domaćim životinjama, u smislu prevencije astme i drugih alergijskih bolesti. Uz to, sve je više i studija koje ukazuju na činjenicu da i pristvo kućnog ljubimca u gradskim uslovima ima sličan efekat.

Vremenom se dizbioza koriguje. Kao i odrasli, i novorođenče i mlado odojče, ima sposobnost da nakon dejstva nekog faktora, koriguje sastav svog mikrobioma. Međutim, izmenjen model kolonizacije se odvijao u kritičnom uzrastu metaboličkog i imunološkog razvoja, što može biti osnov razvoja različitih bolesti i imati dugoročne posledice po zdravlje.

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PRENATALNA ULTRAZVUČNA PROCJENA FETALNE MATURACIJE PLUĆA

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UVOD

Fetalna maturacija je proces strukturnog, biohemijskog i funkcionalnog razvoja i rasta svih organskih sistema fetusa-kontinuum koji osposobljava fetus za samostalan ekstrauterini život.

Brojna opstetrička, maternalna, fetalna, placentna ili uterina stanja zahtevaju porođaj prije 39 nedjelja gestacije, pa je ACOG, u Februaru 2021. godine, napravio preporuke u vezi sa vremenom završavanja takvih, komplikovanih trudnoća (1).

Smatra se da 30-35% prevremenih i ranih terminskih porođaja je jatrogeno, indikovano od strane ginekologa, pre spontanih kontrakcija ili rupture plodovih ovojaka i poslednjih decenija ima tendeciju rasta (2).

Potencijalne neonatološke komplikacije i respiratorni morbiditet, RDS i/ili tranzitorna tahipneja, povezane sa jatrogenim prođajima pre 39 nedelje gestacije i deficitom surfaktanta su dobro poznate (3,4). Incidencija RDS varira između 26-30% kod prematurusa rođenih pre 34 NG i 5-20% kod onih rođenih nakon 34 NG. Rizik za neonatalni mortalitet i morbiditet opada sa gestacijskom starošću ploda, i značajno je manji kod neonatusa nakon 34 NG. Međutim, zbog fragilnosti i imaturiteta ne samo pluća, već i mozga, imunološkog i gastrointestinalnog sistema, bubrega, kože i očiju itd, neonatusi rođeni između 34-36 NG imaju 4 puta veću, a oni rođeni između 36 -39 NG dva puta veću stopu mortaliteta u komparaciji sa terminskim. RDS, sleep apnea, nekrotizirajući enterokolitis i periventrikularna hemoragija kao posledica fetalnog imaturiteta, su najčešće komplikacije kasnih prevremenih porođaja.

Potreba za respiratornom potporom neonatusa, hiperbilirubinemija i hipoglikemija koje iztiskuju tretman, Apgar skor <7, i pored dokumentovanog fetalnog plućnog maturiteta, su češći kod ranih terminskih porođaja, u odnosu na terminske, ustanovljeno je u velikoj kohortnoj studiji sprovedenoj nad 115,502 porođaja u 25 bolnica u SAD (5). Ustanovljena je češća pojava motornih i kognitivnih poremećaja, hroničnih bolesti i ranih smrti u odraslom dobu kod rođenih prije navršene 39 0/7 nedjelje gestacije.

Zbog svega navedenog, dobro izbalansirana odluka o vremenu jatrogenih porođaja kod komplikovanih trudnoća je kompleksna i podrazumijeva individualan pristup u procjeni maternalnog, fetalnog i neonatalnog rizika u slučaju preterminskog porođaja, nasuprot riziku ekspektativnog pristupa i odgađanja porođaja u cilju bolje fetalne maturacije.

Aktuelne su otvorene, stručne debate o upotrebljivosti i vrednostima invazivnih testova za procenu fetalne plućne maturacije u komplikovanim i graničnim kliničkim situacijama koje iziskuju jatrogeni preterminski porođaj.

ACOG i SMFM od 2021. godine ne preporučuju primenu amniocenteze u cilju utvrđivanja fetalne maturacije, smatrajući da jatrogenom preterminskom porođaju treba pribegavati samo u slučaju postojanja jasnih medicinskih indikacija, u situacijama signifikatnog maternalog ili fetalnog rizika kada trudnoću treba završiti, nezavisno od rezultata testa plućne maturacije. Sugerišu da su

testovi imperfektni u predikciji RDS /imaju visoku specifičnost, a nisku senzitivnost/ i da obavezno ne reflektuju maturitet drugih organskih sistema (1).

Ipak, prenatalna procena fetalne plućne maturacije u cilju smanjenja jatrogenog prematuriteta, ostaje bitan činilac u evaluaciji vremena jatrogenih preterminskih porođaja. Posebno u kontekstu razmatranja: potrebe za arteficijalnom maturacijom pluća kortikosteroidnom terapijom, razmatranja transporta trudnice u tercijarnu ustanovu sa najboljom intenzivnom neonatološkom negom, kod pretećeg prevremenog porođaja radi odluke o inicijaciji ili obustavljanju tokolitičke terapije, u stanjima neadekvatnog prenatalnog nadzora i nepoznavanja tačne gestacijske starosti, loše regulisanog dijabetesa u trudnoći, ponavljanih carskih rezova, itd.

Zbog invazivnosti procedure dokazivanja fetalne plućne maturacije amniocentezom i retkih, ali ipak mogućih komplikacija (prevremenog prsnuća plodovih ovojaka, placentne hemoragije i abrupcije, direktne i indirektne fetalne povrede, horioamnionitisa, fetalne smrti, krvarenja u trbušnom zidu trudnice) (6), zbog nedovoljne obučenosti kadra ili nedovoljnosti uslova za njeno izvođenje, kao i umanjenja diskomfora trudnica, neinvazivna ultrazvučna procena fetalne plućne maturacije se stalno ispituje i unapređuje.

Poslednjih godina je nekoliko studija utvrdilo da neinvazivna, ultrazvučna i doplerska mjerenja imaju prihvatljiv nivo senzitivnosti, specifičnosti i prediktivne vrijednosti u procjeni fetalne maturacije pluća. Kao ultrazvučni indikatori plućne maturacije fetusa se razmatraju: BPD veći od 92mm, gradus III placente, ehogenost fetalnog intestinuma i dijametar kolona, ehogenost pluća, prisustvo slobodnoplutajućih partikula u plodovoj vodi (FFP-free floating paricles), dužina bubrega >4cm, prisustvo centara osifikacije dugih kostiju, doplerske analize fetalne plućne arterije, hiperehogeni talamus itd.

CILJ I METODOLOGIJA

U prospektivnoj studiji sprovedenoj na GAK Narodni Front u Beogradu, u periodu od Januara 2021 do Decembra 2021. godine na uzorku od 79 hospitalizovanih trudnica ispitivana je povezanost ultrazvučnih parametara sa koncentracijom lamelarnih tiela u amnionskoj tečnosti, kao i dijagnostička tačnost ultrazvučnih parametara u proceni zrelosti fetalnih pluća. Analizirane su sve trudnice koje su na osnovu utvrđenih indikacija podvrgnute kasnoj, dijagnostičkoj amniocentezi u cilju određivanja fetalne maturacije pluća, merenjem broja lamelarnih tijela u plodovoj vodi. Isključene su trudnice sa hromozomskim i strukturnim anomalijama ploda. U centrifugiranim uzorcima od 3ml plodove vode je pomoću hematološkog brojača ćelija, tipa Cell Dyn Emerald: na kanalu za trombocite, određivan broj lamelarnih tiela i notirane su kao apsolutan broj. Vrednosti > ili jednake 50000/mcL su smatrane indikatorom zrelosti fetalnih pluća. Svakoj od ovih trudnica je prije intervencije utvrđena gestacijska starost i notirane dijagnoze. Ultrazvučnim pregledom na aparatima GE Voluson E 10 su mereni biometrijski parametri: Gradus placente je određen prema Grannum klasifikaciji. Ehogenost pluća je određivana u longitudalnom, desnom parasagitalnom presjeku fetusa. Ehogenost pluća je određivana u komparaciji sa ehogenošću jetre, i klasifikovana kao hipoehogena, izoehogena i hiperehogena.

Maksimalni poprečni dijametar kolona je mjeren u longitudinalnoj, lijevoj parasagitalnoj ravni ili koronalnoj ravni, i klasifikovan je u tri grupe: <10mm, 10-14mm, 15mm ili više.

Ehogenost intestinuma je klasifikovana u 4 grupe, na osnovu ehogenosti mekonijuma unutar kolona i u komparaciji sa ehogenošću jetre:

- Gradus I: Abdomen izgleda uniforman i kolon se ne indetifikuje,
- Gradus II: Kolon se prikazuje kao anehogene strukture u abdomen,

- Gradus III: Ehogenost intestinuma i kolona je veća od m. bešike i želuca, manja od jetre,
- Gradus IV: Ehogenost kolona je ista kao ehogenost jetre uz prsutne haustre i perstaltiku.

Prisustvo slobodno plutajućih partikula /FFP/ odnosno verniksa u plodovoj vodi je notirano u svim džepovima plodove vode i klasifikovana je kao: odsutna, srednje prisutna i veoma pristne u plodovoj vodi.

Statistička analiza je izvršena korišćenjem paketa IBM SPSS 21.

REZULTATI I DISKUSIJA

Prosečna starost ispitivanih trudnica je bilo 34 godine tj bilo je starije od prosečne starosti prvorotki, i u Srbiji i svijetu. U Evropi i SAD prosečna starost prvorotki je 29.8 godina, dok je u Srbiji prosečna starost prvorotki 2020. godine iznosila 28,8 godina pokazuju podaci Republičkog Zavoda za statistiku Republike Srbije (7,8).

Broj lamelarnih tela veći ili jednak od 50000/mcL u centrifugiranom uzorku je smatran indikatorom zrelosti fetalnih pluća. Neerhof i saradnici su 2004. godine konsenzusom 4 institucije usvojili da je zrelost fetalnih pluća indikativna kada je LBC veća ili jednaka 50000/mcL (9). U našem ispitivanju 67,09% uzoraka je bilo "zrelo" (mature amniocenthesis) tj. imalo LBC jednak ili viši od 50000/mcL.

Najmanja nedelja gravidnosti bila je 30 a najkasnija 39, pri čemu je polovina trudnica koje su podvrgnute kasnoj amniocentezi bilo između 36 i 38 nedjelja gestacije.

Minimalni broj lamealarnih tijela po mcL iznosio je 15000, a maksimalni 213000. Lamelarna tela se pojavljuju u plodovoj vodi od 28 nedjelje gestacije i sa napredovanjem gestacije rastu.

U našem uzorku je jedna trudnica starosti 30 nedelja gestacije imala neočekivano visok LBC 30000/mcL, a 4 trudnice starosti 38 nedjelja gestacije su imale vrijednosti LBC 20000/mcL ili manje.

Rezultati Petrovića i saradnika (10), u studiji sprovedenoj sa 155 uzoraka plodove vode su ukazali da u fiziološkim uslovima lamelarna tela tokom trudnoće ne rastu linearno, i da se samo na osnovu gestacijske starosti a pre donešenosti, ne može pouzdano prognozirati stanje fetalne / neonatalne plućne zrelosti, niti konkretna vrednost lamelarnih tela u plodovoj vodi.

Najčešći komorbiditeti ili stanja žena podvrgnutih kasnoj amniocentezi u cilju utvrđivanja fetalne plućne maturacije su bila hipertenzivni poremećaji u trudnoći, dijabetes i stanje nakon carskog reza (44,3%, 39,24% i 32,91% respektivno). Navedeni komorbiditeti/stanja nisu bili indikacija za amniocentezu per se, izuzev u slučajevima preteće ugroženosti majke i/ili ploda i razmatranja najoptimalnijeg vremena za završetak trudnoće.

Svi ultrazvučni parametri koje smo ispitivali su bili u visokim, pozitivnim i statistički značajnim korelacijama sa brojem lamelarnih tela. Veći gradus placente, veća ehogenost pluća i intestinuma, veći dijametar kolona i veća zastupljenost FFP bili su praćeni većim brojem lamelarnih tijela.

- PLACENTA

Sa rastom i maturacijom fetusa, događaju se promjene na posteljici kao i u sastavu i količini plodove vode. Ćelije posteljice prestaju da proliferišu u 34. nedjelji trudnoće, a od 36. počinju regresivne promene u posteljici zbog taloženja fibrina u interviloznim prostorima i obliteracije krvnih sudova u horionskim resicama.

Veći gradus placente je korelirao sa većim brojem lamelarnih tela (Rs= 0,747, p < 0,001), (AUC=0,909, 95% CI 0,846-0,973, p<0,001). Ustanovili smo da je gradus III placente visoko specifičan i dobar

pozitivan prediktor plućne maturacije tj. LBC > od 50000, ali sa niskom senzitivnošću i negativnom prediktivnom vredosti (Se 0.58, Sp 1.00, PPV 1.000, NPV 0.542). Sve trudnice sa gradusom III placente su imale zreli nalaz amniocenteze, ali odsustvo ovog gradusa ne isključuje zadovoljavajuću fetalnu maturaciju. Loret de Mola I saradnici (11) su u svom ispitavnju imali slične rezultate, gdje je Gradus III placente imao Se 64% i Sp od 98% u korelaciji sa "zrelim" nalazom amniocenteze. Kandil i saradnici (12) su 2021. korelirali gradus placente sa neonatalnim RDS statusom, i ustanovili da je gradus III placente (Se 81%, Sp 74%, PPV 94% I NPV 42%), dobar prediktor plućne maturacije.

- EHOGENOST INTESTINUMA

U našem istraživanju, najvišu pozitivnu korelaciju dobili smo između ehogenosti intestinuma i broja lamelarnih tijela (Rs=0.881, p < 0,001), (AUC 0.947, 95% CI 0,901-0,993, p < 0,001). III i IV gradus ehogenosti intestinuma i kolona (itraluminarna ehogenost kolona veća od m. bešike i želuca a manja od jetre ili ista kao ehogenost jetre, uz vidljive haustre i peristaltiku) u predikciji nalaza „zrele" amniocenteze ima senzitivnost 0.868, specifičnost 0.962, PPV 0.979 i NPV 0.781.

Mekonijum, bogat epitelnim ćelijama, žuči i mukusom, se akumulira i ispunjava kolon sve više sa rastom ploda. Zbog povećanja masnih i aminokiselina u njemu, organskih kiselina, sterola i ketonskih tela ehogenost itraluminarnog mekonijuma postaje intenzivnija sa maturacijom ploda. (13)

U studiji iz 2017. godine koja je korelirala ultrazvučne parametre fetalne maturacije sa lamelarnim telima, ustanovljeno je da je gradus IV intestinuma visoko specifičan (98.9%) i manje senzitivan (62.5%) prediktor fetalne plućne maturacije (14). Goldstein i saradnici su 1987. objavili da je prisustvo peristaltike tankih creva, intraluminarne ehogenosti i haustri fetalnog kolona uz progresivno povećanje transverzalnog dijametra kolona povezano sa terminski zrelim plodovima (15).

- DIJAMETAR KOLONA

Veliki broj studija je ispitivao povezanost poprečnog dijametra kolona i gestacijske starosti ploda, i sve su ustanovile njihovu statističi značajnu i signifikantnu pozitivnu linearnu korelaciju (27,28). Ustanovili su da je prosečni dijametar kolona u 34. NG 8-9mm, a u 40. NG 17-18mm. (16,17,18,19)

Međutim, u do sada objavljenoj, stručnoj literaturi nismo uspeli da pronađemo radove o povezanosti dijametra kolona sa koncentracijom lamelarnih tijela u plodovoj vodi, kao objektivnim pokazateljom fetalne plućne maturacije. Svi dostupni radovi su se odnosili na ultrasonografske promene fetalnog intestinuma u funkciji gestacijske starosti i/ili neonatolnog RDS statusa.

Caravalho i saradnici (20) 2011. godine su u studiji sprovedenoj na 1296 fetusa između 33. I 40. nedelje gestacije ustanovili da je 86,6% fetusa sa dijametrom kolona 14mm bilo u 37. ili većoj nedelji gestacije.

2016. godine u studiji Arora R i saradnika (19) svi fetusi sa dijametrom kolona 16mm i više su bili 37 ili više nedelja gestacije (Sp 100%, Se 12%).

U našem radu je nađena statistički signifikantna pozitivna korelacija između dijametra kolona i broja lamelarnih tijela (Rs=0.858, p<0.001), sa najvećom prediktivnom moći ove varijable u pogledu broja lamelarnih tijela(AUC=0.981, 95% CI 0.954-1,008 p<0,001). Ustanovili smo da je dijametar kolona jednak ili veći od 15mm visoko specifičan (Sp 1.000 Se 0.755) i dobar pozitivan prediktor (PPV 1,000) plućne maturacije i LBC >50000. Svih 40 trudnica sa poprečnim dijametrom fetalnog kolona 15mm je imalo nalaz „zrele" amniocenteze. Dijametar kolona manji od 10mm imao je specifičnost od 0.981 i senzitivnost od 0.923 u detekciji „nezrelog" rezultata amniocenteze tj. 98% trudnica sa dijametrom fetalnog kolona manjim od 10mm imalo je LBC< 50000.

- EHOGENOST PLUĆA

Literaturni podaci o povezanosti fetalne plućne ehogenosti u predikciji plućne maturacije su kontradiktorni. Veliki broj radova nije ustanovio klinički značajnu povezanost između ehogenosti fetalnih pluća i gestacijske starosti ploda, testova plućne maturacije i RDS. Sa druge strane, 1992. godine su Sohn i saradnici utvrdili da je ehogenost jetre u trećem trimestru relativno konstantna i nezavisna od gestacijeke starosti, dok se ehogenost pluća povećava, naročto nakon 35. nedelje gestacije (21). Takesin i saradnici (22) su 2004 godine objavili da se odnos ehogenosti pluća/jetra mijenja sa napredovanjem gestacije, i da pluća ehogenija od jetre ukazuju na zrelost.

U našem ispitivanju hiperehogena fetalna pluća u odnosu na ehogenost jetre su se pokazala kao signifikantan marker fetalne plućne zrelosti u trećem trimestru trudnoće i statistički značajno koreliraju sa koncentracijom lamelarnih tela (Rs =0.807, p<0.001) (AUC 0.922 95% CI 0.866-0.977), sa visokom specifičnoću i PPV, nižom senzitivnošću i NPV (1.000, 1.000, 0.774, 0.684 respektivno). Svih 41 fetusa sa hiperehogenim plućima je imalo LBC>50000, dok je 68% onih sa izo/hipoehogenim plućima imalo LBC <50000.

Da li će kvantitativna analiza teksture fetalnih pluća zasnovana na najsavremenijim ultrazvučnim softverima i algoritmima (Quantus FLM) u predikciji fetalnog maturiteta I RDS ući u rutinsku perinatološku praksu aktuelna i buduća istraživanja će dati odgovor. Palaco I saradnici (23) su 2017. godine u velikoj, prospetivnoj i multcentričnoj studiji utvrdili da QuantusFLM u predikciji neonatalnog respiratornog morbiditeta ima sličnu dijagnostičku tačnost (86.5%) kao I invazivni testovi plućne maturacije.

- VERNIKS U PLODOVOJ VODI (FFP)

Prisustvo verniksa tj. slobodno plutajućh partikula u plodovoj vodi se pojavljuje oko 35. nedjelje trudnoće i ultrasonografski se detektuje kao pojedinačni hiperehogeni odjeci u plodovoj vodi, manji od 2mm koje obično detektujemo u jednom od slobodnih džepova plodove vode. Nakon 37. nedjelje trudnoće tj 1-2 nedjelje uoči porođaja dolazi do rapidnog porasta broja, veličine i distribucije FFP, ultrasonografski se detektuju gusti, hiperehogeni odjeci u plodovoj vodi, 4mm ili veći, sa ekstenzijom u sve džepove plodove vode. Da u kasnom trećem trimestru turbiditet plodove raste sa napredovanjem gestacije i maturacije ploda, potvrdile su brojne studije.

Gross i saradnici (1985) su u studiji koja je uključivala analizu 467 uzoraka plodove vode, ustanovili da slika tzv snežne mećave plodove vode 100% specifičan, ali 35% senzitivan marker u predikciji zrelog L/S odnosa i fetalne maturacije pluća (24). Ram I saradnici (2020) su korelirajući prisustvo i veličinu FFP sa optičkom denzimetrijom (650nm) uzoraka plodove vode i neonatalnim RDS statusom ustanovili da su partikule veće od 4mm dobri prediktori fetalne plućne maturacije i odsustva RDS(25). Matsumoto i saradnici (2023) su koristeći se ultrazvučnom histogramskom, kvantitativnom analizom ehogenosti plodove vode i upoređujući ehogenost plodove vode sa ehogenošću fetalnog urina u bešici, ustanovili da hiperehogenija plodova voda u odnosu na fetalni urin, sa cut off-om 20.3 histograma, statistički značajno korelira sa neonatalnim RDS statusom (26) Mi smo ustanovili da je prisustvo FFP iako manje od prethodno analiziranih markera, statistički signifikantan parametar plućne maturacije fetusa I LBC >50000 (Rs 0.722, p<0.001) ((AUC = 0,900, 95%CI[0,816-0.984, p < 0,001) (Se 0.981, Sp 0.769, PPV 0.897 i NPV 0.952). Visoka negativna prediktivna vrednost ovog parametra, upućuje na zaključak da odustvo FFP u plodovoj vodi značajno korelira sa nedovoljnom maturacijom fetalnih pluća.

ZAKLJUČAK

Najčešće indkacije za evaluaciju fetalne maturacije su hipertenzivni poremećaji u trudnoći, dijabetes i stanje nakon carskog reza.

Prisustvo gradusa III placente, dijametra kolona>15mm, gradusa III/IV ehogenosti intestinuma, pluća ehogenijih od jetre i prisutnih FFP su se pokazali kao veoma dobri i dijagnostički tačni prediktori fetalne maturacije pluća.

Prisustvo Gradusa I placente, ehogenosti intestinuma I/II, dijametra kolona <10mm i odsustvo FFP, pluća hipo ili izoehogena u odnosu na jetru upućuju na nedovoljnu zrelost pluća i LBC <50000, pa se provera fetalne maturacije pluća invazivnom metodom nameće kao racionalan postupak u ovakvim i klinički indikovanim situacijama.

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PREVENCIJA I SKRINING U NEONATOLOGIJI

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U neonatologiji je prevencija postigla više nego i u jednoj drugoj grani medicine, a i sama neoonatologija je preventivna medicina odrasle dobi. Prevencija je usmjerena na sprječavanje razvoja bolesti prije nego što se pojave simptomi ili događaji opasni po život, i najbolje je rješenje za trenutnu krizu. Bez rutinskih preventivnih postupaka bilo bi teško pružiti kvalitetnu univerzalnu zdravstvenu njegu svakom novorođenčetu. Neki preventivni postupci su nastali u svakodnevnom rutinskom radu a neki na osnovu spoznaje o pojavi neonatalnih oboljenja koja se mogu spriječiti ili liječiti.

Spontana prevencija hipotermije kao i pranje ruku , ekskluzivno dojenje, prevencija i tetman boli bili su ključni za smanjenje oboljenja i smrtnosti novorođenčadi. Danas se u gotovo svim porodilištima sa ciljem prevencije i otkrivanja bolesti provodi nekoliko preventivnih mjera; Prevencija neonatalne oftalmije, prevencija hemoragijske bolesti davanjem vitamina K vitamin, vakcinacija protiv tuberkuloze (BCG) i hepatitisa B (Hib). Ispitivanje sluha metodom otoakustične emisije radi otkrivanja gluhoće ili nagluhosti. Selektivni skrining kukova, rano otkrivanje ROP-a, prevencija RSV infekcija Synagisom.

Jedna trenutno dobro uspostavljena procedura, za koju se „čini da je oduvijek postojala“, ali je uvedena prije manje od 50 godina, je skrining za metaboličke bolesti korištenjem krvnih mrlja na filter papiru. Prvi test, uveden u Massachusettsu, bio je test na fenilketonuriju, nazvan Guthrie test. Skrining za kongenitalnu hipotireozu uveden je ranih 1970-ih, a zatim i skrining na mnoge metaboličke bolesti i hormonske probleme te hemoglobinske bolesti. Rano otkrivanje rijetkih bolesti, prije pojave simptoma kada je povezan sa odgovarajućim tretmanom može promijeniti život, pa čak i spasiti život. Skrining za druge bolesti, kao što su teške kombinovane imunodeficijencije (SCID) ili spinalna mišićna atrofija (SMA) implementiraju se u nekim zemljama i dobijaju sve veću pažnju

Zaključak

Prevencija i skrining u neonatologiji još uvijek su na nivou nacionalnih odluka, ali zahtjevaju timski rad i globalizaciju prevencije, što se postiže umrežavanjem učesnika u prevenciji i razmjeni podataka, znanja i mudrosti.

ZNAČAJ INFEKCIJE RESPIRATORNIM SINCICIJALNIM VIRUSOM U NOVOROĐENAČKOJ POPULACIJI

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Respiratorni sincicijalni virus (RSV) prouzrokuje akutne infekcije respiratornog trakta kod ljudi svih uzrasta i jedan je od najvažnijih i najčešćih uzročnika infekcija donjih disajnih puteva kod odojčadi i male dece. Odgovoran je za više od 80% infekcija donjeg respiratornog trakta kod dece mlađe od godinu dana [1]. Oko 70% dece se inficira u prvoj godini života, a skoro sva deca do kraja druge godine [2]. Imunitet nakon preležane infekcije je kratak, pa su reinfekcije česte tokom života i obično su sa lakšom kliničkom slikom u odnosu na primarnu infekciju. Rizik od hospitalizacije je najveći kod odojčadi mlađe od 3 meseca, prevremeno rođene dece, dece sa kardiopulmonalnim i neuromišićnim bolestima.

Prema podacima iz 2019. godine RSV je bio odgovaran za 12,9 miliona infekcija donjih disajnih puteva kod dece mlađe od godinu dana, 2,2 miliona hospitalizacija i 66 300 smrtnih slučajeva kod ove dece [3].

S obzirom na visoku stopu hospitalizacije i značajno povećanje troškova zdravstvenog sistema, RSV je jedan od glavnih globalnih zdravstvenih problema. Posebno je zabrinjavajuća činjenica da RSV infekcija može nepovoljno uticati na razvoj pluća i dovoditi do dugoročnih respiratornih poremećaja. Poznato je da su odojčad koja su imala težak oblik RSV infekcije u većem riziku za razvoj rekurentnog vizinga do 10. god. života [4].

Dodatni problem predstavljaju bolničke infekcije uzrokovane RS virusom. Na pedijatrijskim odeljenjima RSV je jedan od najčešćih uzročnika bolničkih infekcija koje su povezane sa lošijim kliničkim ishodom, uključujući povećan mortalitet, češću potrebu za primenom mehaničke ventilacije i produženu hospitalizaciju [5]. Objavljeni podaci o epidemiologiji bolničke RSV infekcije su još uvek limitirani. Kod novorođenčadi i odojčadi je opisan ozbiljan tok bolesti, naročito kod dece sa komorbiditetima, čak i ozbiljniji kod bolnički stečene RSV infekcije u odnosu na infekciju stečenu u zajednici [6].

Humani respiratorni sincicijalni virus je RNK negativan virus sa omotačem, koji pripada rodu Pneumovirus, familiji Paramyxoviridae [2,7]. Postoje dva antigena podtipa: A i B, koji se primarno razlikuju na osnovu genetske i antigenske varijabilnosti G proteina [2]. Svaki podtip ima više sojeva, do sada je identifikovano 16 sojeva RSV A i 22 soja RSV B podtipa [8]. Podtipovi mogu da cirkulišu istovremeno u populaciji, iako je podtip A prevalentniji. U nekim studijama je pokazano da je podtip A virulentniji od podtipa B, sa većim virusnim opterećenjem i kraćim transmisionim vremenom [2,8].

Respiratorni sincicijalni virus je virus srednje veličine (120-300 nm), većinom sferičnog oblika [2]. Virusnu česticu čine nukleokapsid (jednolančana, nesegmentirana RNK i proteinski matriks) i bilipidni omotač [2]. Kompletan genom RSV je sekvencioniran. Virusna RNK se sastoji od 15 222 nukleotida koji čine 10 gena, koji kodiraju 11 proteina: 9 strukturnih i 2 nestrukturna proteina [2].

Protein F i protein G su glavni antigeni proteini na koje se stvara većina antitela nakon infekcije RSV i imaju bitnu ulogu u virulenciji virusa [1].

U umerenim klimatskim područjima RSV infekcija se ispoljava u godišnjim epidemijama tokom zime i ranog proleća, na severnoj hemisferi od novembra do aprila[2].

Ljudi su jedini izvor infekcije [7]. Prenos virus je direktnim ili bliskim kontaktom sa kontaminiranim sekretima ili preko zaraženih predmeta. Virus može preživeti na površinama (radne ploče, kreveti, mobilni telefoni) do 6 sati, na gumenim rukavicama do 90 minuta a na rukama 30 minuta i duže [3,5] . Infekcija kod zdravstvenog osoblja se može dogoditi samoinokulacijom preko ruku kontaminiranih sekretima.

Nakon ulaska u organizam domaćina, inkubacioni period traje od 2 do 8 dana, najčešće 4-6 dana [7]. Inficirane osobe su uobičajeno kontagiozne 3-8 dana, mada period izlučivanja virusa može iznositi 3-4 nedelje i duže, naročito kod odojčadi i imunokompromitovanih osoba [7,8]. Procenjuje se da jedna osoba inficirana sa RSV može da inficira 5-25 drugih osoba [5].

Skoro sva deca se inficiraju bar jednom do 2. godine života, a najveća stopa obolevanja je u uzrastu između 2. i 6. meseca, što se poklapa sa padom koncentracije transplacentrano prenesenih protektivnih majčinih IgG antitela [1]. Preležana infekcija ne ostavlja trajni imunitet čak i u prisustvu značajnog titra antitela, iako viši titar antitela može ublažiti tok bolesti. Stoga su ponavljane infekcije česte i moguće čak i u istoj sezoni [1].

Osobenosti imunskog odgovora

Imunski sistem novorođenčeta i odojčeta se značajno razlikuje od imunskog sistema odraslih i to ima glavni uticaj na podložnost ka respiratornim virusnim infekcijama. Nedostatak prethodne izloženosti patogenima vodi ka nedostatku imunske memorije. Postoji i tendencija ka hiporeaktivnosti imunskog odgovora u ranom životu koja je karakteristična i za urođeni i za stečeni imunitet.

Nakon rođenja novorođenče se oslanja na transplacentarno prenesena majčina antitela i urođeni imunitet, i ima ograničenu sposobnost da se brani od patogena. Prisustvo majčinih IgA antitela u kolostrumu pruža dojenoj deci izvestan stepen zaštite. Kritični period podložnosti ka RSV infekciji je od 2. do 6. meseca što se poklapa sa padom transplacentarno prenesenih majčinih antitela ispod protektivnih vrednosti a pre nego što nivo neutrališućih antitela odojčeta dostigne dovoljan titar [4,9].

Osobenosti respiratornog trakta novorođenčadi

Disajni put dece se značajno razlikuje od disajnog puta odraslih. Anatomija disajnih puteva odojčadi predisponira ih za teže oblike bolesti. Kod novorođenčadi nozdrve su uske i otpor u nosu čini 50% ukupnog otpora u disajnim putevima, pa i najmanja opstrukcija sekretom ili otokom sluzokože kompromituje disanje novorođenčeta i povećava disajni rad [10]. Kod laminarnog protoka otpor u disajnim putevima je obrnuto proporcionalan četvrtom stepenu prečnika disajnog puta, što znači da suženje disajnog puta za 50% dovodi do porasta otpora u disajnim putevima za 16 puta.

U poređenju sa odraslima zid grudnog koša novorođenčeta ima veću komplijansu, lako kolabira u inspirijumu zbog generisanja visokog negativnog pritiska, što rezultira paradoksalnim disanjem. Za razliku od grudnog koša, plućni parenhim ima manju komplijansu kod novorođenčadi u poređenju sa odraslima, naročito kod prematurusa zbog nedostatka surfaktanta.

Dijafragma i međurebarni mišići sadrže manji procenat mišićnih vlakana tipa I koja su otporna na zamor, što uz manje depoe glikogena i masti u respiratornim mišićima dovodi do njihovog bržeg zamaranja [10].

Novorođenčad dolaze na svet sa polovinom ukupnog broja alveola odraslih, a uvećanje broja alveola se nastavlja i nakon rođenja. Faktori koji mogu imati negativan efekat na alveolarizaciju su: mehanička venitilacija, ante i postnatalna primena kortikosteroida, proinflamatorni medijatori, horioamnionitis, hiperoksija i hipoksija, loša ishranjenost. Zbog nedovoljnog broja alveola i nezrelog elastičnog vezivnog tkiva povećan je rizik od kolapsa disajnih puteva.

Klinička slika infekcije respiratornim sincicijalnim virusom

Klinička slika infekcije RSV zavisi od uzrasta i prethodnog zdravstvenog stanja deteta. Nakon inkubacionog perioda od 3-5 dana, većina odojčadi inficiranih sa RSV ispolji simptome infekcije gornjeg respiratornog trakta: nazalnu kongestiju, rinitis, kijanje, konjuktivitis, temperaturu (uobičajeno nižeg stepena), slabije uzimanje obroka [2].

Razvoj infekcije donjih respiratornih puteva (bronhiolitis i/ili pneumonija) zavisi od uzrasta i ispolji se kod oko 45% odojčadi mlađe od 6 meseci i kod oko 20 % dece uzrasta 2-5 godina [2,11].

Progresivno nagomilavanje ugljendioksida i respiratorna acidoza se razvijaju kao znaci razvoja zamora respiratorne muskulature i razvoja respiratorne insuficijencije koja zahteva ventilatornu podršku [1].

Infekcija RSV kod novorođenčadi, posebno među preterminskom novorođenčadi, može da dovede do minimalnih znakova respiratorne infekcije, letargije, iritabilnosti, otežanog hranjenja, ponekad udruženo sa epizodama apnee, koje mogu biti životno ugrožavajuće [12]. Apnee se javljaju sa učestalošću i do 20% kod odojčadi mlađe od 6 meseci koja zahtevaju hospitalizaciju [1]. Kada su prisutne apnee se javljaju rano, pre simptoma infekcije donjih respiratornih puteva.

Oko 0,5-1% odojčadi zahteva hospitalizaciju. Većina hospitalizovanih se oporavi uz pomoć suportivne terapije i budu otpuštena na kućno lečenje nakon 3 do 4 dana [2,4]. Odojčad sa faktorima rizika zahtevaju dužu hospitalizaciju, imaju veću stopu prijema u jedinice intenzivne nege i često potrebu za mehaničkom ventilacijom. Smrtnost kod hospitalizovane dece je 2-37% u grupi dece sa bolestima srca i pluća i manje od 1% u grupi zdrave dece [2].

Faktori rizika za teži oblik bolesti i hospitalizaciju

- Prevremeno rođena deca: iako je najveći rizik za težak oblik bolesti kod prevremeno rođene dece pre 29. GN, dostupni podaci pokazuju povećan rizik kod sve dece rođene pre 37. GN (13).
- Uzrast mlađi od 6 meseci u vreme infekcije,
- Deca sa hroničnom plućnom bolesti (bronhopulmonalnom displazijom ili cističnom fibrozom),
- Deca sa kongenitalnim srčanim bolestima (naročito udruženim sa plućnom hipertenzijom),
- Deca sa kongenitalnom ili stečenom imunodeficijencijom i
- Deca sa neuromišićnim bolestima

Epidemiološke karakteristike bolničke infekcije respiratornim sincicijalnim virusom

Na pedijatrijskim odeljenjima RSV je jedan od najčešćih uzročnika bolničkih infekcija. Oko 40% bolničkih infekcija RSV je povezano sa infekcijama donjih respiratornih puteva kod odojčadi. Faktori rizika za pojavu bolničkih infekcija su mlađi uzrast, pridružene hronične bolesti, duga hospitalizacija i veliki broj pacijenata na odeljenjima.

Bolničke infekcije RSV mogu biti naročito teške na odeljenjima neonatalne intenzivne nege, sa neočekivanom kliničkom slikom (apnee, bradikardija, promene u ishrani) i visokim mortalitetom.

RSV infekcija kod bolničkog osoblja često može biti blaga, nalik prehladi ili asimptomatska. Više od 50 % bolničkog osoblja biva inficirano RSV u sezoni RSV u zajednici, od toga 15-20%

su asimptomatski nosioci virusa tako da osoblje može biti okultni ali efikasan vektor u prenosu infekcije na odeljenjima.

Nozokomijalna infekcija preterminske novorođenčadi respiratornim sincicijalnim virusom na Odeljenju neonatologije KGA UKCS

Naša studija je sprovedena na Klinici za ginekologiju i akušerstvo Univerzitetskog kliničkog centra Srbije, tokom decembra 2018. i januara 2019. godine i obuhvatila je 54 preterminska novorođenčeta, lečena na Odeljenju za prevremeno rođenu decu i Odeljenju neonatalne intenzivne nege, u tom periodu. U odnosu na prisustvo RSV infekcije novorođenčad su podeljena u dve grupe:

- RSV grupa- koju je činilo 24 prevremeno rođena novorođenčeta sa dokazanom RSV infekcijom i
- Kontrolna grupa- formirana od 30 preterminskih novorođenčadi hospitalizavanih u istom periodu a kod kojih nije došlo do razvoja infekcije.

Rezultati

U ispitivanoj grupi novorođenčadi sa RSV infekcijom dečaci su imali statistički značajno češće težu kliničku sliku u odnosu na devojčice (70% dečaka je imalo težu kliničku sliku u odnosu na 30 % devojčica sa težom kliničkom slikom, p<0,045).

I u drugim istraživanjima je opisano da su novorođenčad muškog pola sklonija težim oblicima RSV infekcije jer su njihovi disajni putevi manjeg dijametra (uži i kraći) što ih potencijalno čini osetljivijim na virusne respiratorne infekcije, dovodi do odloženog klirensa patogena i povećava rizik za infekcije donjih disajnih puteva, koji su skloniji opstrukciji u poređenju sa novorođenčadi ženskog pola (14,15). U radu Leonarda D. Krilova je pokazan da se dečaci dva puta češće hospitalizuju zbog RSV infekcije u odnosu na devojčice [11].

I hronološki uzrast u vreme RSV infekcije je faktor rizika za težu kliničku sliku. U našoj ispitivanoj RSV grupi prosečan hronološki uzrast ispitanika u vreme infekcije RSV je bio 25 dana. Najmlađe novorođenče u našem istraživanju u vreme infekcije RSV je bilo uzrasta 8 dana, što je u skladu sa podacima iz literature da je infekcija RSV opisana i u prvoj nedelji života [16]. Najstariji ispitanik u vreme RSV infekcije bio uzrasta 40 dana. Iako nije utvrđeno postojanje statistički značajne razlike u težini kliničke slike u odnosu na hronološki uzrast, oba novorođenčeta koja su ispoljila RSV infekciju u prvih 14 dana života, su imala i težu kliničku sliku infekcije.

U našoj ispitivanoj RSV grupi dve trećine novorođenčadi (66,7%) je imalo telesnu masu na rođenju malu za gestacijsko doba (MGD), dok je u kontrolnoj grupi je 76,7% ispitanika bilo eutrofično, a samo 23,3% je bilo sa TM na rođenju MGD. Razlika između grupa je visoko statistički značajna (p<0,001), pa se može zaključiti da je telesna masa mala za gestacijsko doba je značajan faktor rizika za razvoj infekcije RSV.

Kod 23 dece (95,8%) je primenjena suplementarna oksigenoterapija, a samo jedno novorođenče sa lakšom kliničkom slikom je nije zahtevalo. Kod četvoro novorođenčadi (16,7%) je započeta primena neinvazivne respiratorne podrške putem nCPAP-a, ali je zbog daljeg pogoršanja respiratorne funkcije kod njih bilo neophodno primeniti invazivnu mehaničku potporu. Kod ukupno desetoro novorođenčadi (41,7%) je zbog razvoja respiratorne insuficijencije ili ponavljanih apnea bilo neophodno primeniti mehaničku ventilaciju. Klinički tok kod jednog deteta se komplikovao u 10. danu od početka RSV infekcije pojavom plućne hemoragije.

Prema podacima iz literature mortalitet od primarne RSV infekcije kod inače zdrave dece je 0,005% do 0,02% , dok je mortalitet kod hospitalizovane dece od 1% do 3% [17]. Veći procenat mortaliteta je kod imunokompromitovane dece i dece sa kardiopulmonalnim bolestima, pa se procenjuje da

je mortalitet kod odojčadi sa bolestima srca i do 37%, a čak i do 73% kod pacijenta sa plućnom hipertenzijom [17]. U našoj studiji u obe ispitivane grupe nije bilo smrtnih slučajeva.

Poznato je da RSV infekcija produžava dužinu hospitalizacije što značajno povećava troškove lečenja. I u našoj studiji dokazana je statistički značajna razlika u odnosu na dužinu hospitalizacije u ispitivanoj i kontrolnoj grupi (p<0,001). U grupi dece sa RSV infekcijom prosečna dužina hospitalizacije je iznosila 49 dana, dok je u kontrolnoj grupi dece iznosila 29 dana.

Mere prevencije infekcije respiratornim sincicijalnim virusom

Prema podacima iz literature širenje RSV infekcije se najčešće dešava direktnim kontaktom sa inficiranim sekretom, ili putem velikih inficiranih kapi ili preko zaraženih predmeta i posledičnom samoinokulacijom [11]. S toga je u cilju prevencije širenja infekcije najbitnije pranje ruku i dezinfekcija radnih površina.

Nekoliko studija je pokazalo da striktne mere kontrole infekcije mogu smanjiti širenje bolničke infekcije za 39-67% [18].

Jedna od mera prevencije teških oblika RSV infekcije je i primena pasivne imunoprofilakse humanizovanim monoklonskim antitelom (Palivizumab) u visokorizičnim grupama dece. U našoj zemlji na predlog ekspertske grupe neonatologa i pulmologa Srbije, Republička stručna komisija za zdravstvenu zaštitu žena, dece i omladine je 2009. odobrila primenu Palivizumaba kao obaveznog vida pasivne imunizacije za visikorizične grupe dece [19]. Na odeljenju neonatologije KGA UKCS Palivizumab se daje visokorizičnoj grupi dece od 2018. godine.

Kao zaključak možemo izvesti da uvek treba misliti na moguću cirkulaciju RSV u populaciji. Plan prevencije širenja infekcije u bolničkoj sredini treba inicirati pre očekivane sezone RSV, i striktno sprovoditi čim se u populaciji detektuje prvi slučaj RSV. Uvek treba misliti na moguću prikrivenu cirkulaciju RSV u bolničkoj sredini, stoga su nadzor i sumnja na prisustvo RSV od ključnog značaja.

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ONCOLOGY

PSTT, ETT I APSN: POTPUNO DRUGAČIJI IZAZOV

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Gestacijske trofoblastne neoplazije predstavljaju maligna oboljenja porekla trofoblasta. To su maligna oboljenja koja su uvek povezana sa trudnoćom, invazivna su, imaju veliki potencijal angiogeneze i u velikom procentu su osetljiva na hemioterapijske lekove. U gestacijske trofoblastne bolesti ubrajaju se sledeća oboljenja: parcijalna hidatiformna mola (pHM), kompletna hidatiformna mola (cHM), invazivna hidatiformna mola (iHM), horiokarcinom (CC), trofoblastni tumor placentnog ležišta (PSTT), epitelioidni trofoblastni tumor (ETT), nodus placentnog ležišta (PSN), atipični nodus placentnog ležišta (APSN). pHM i cHM predstavljaju benigna oboljenja koja se leče evakuacionom kiretažom nakon čega je potrebno praćenje zbog male, ali nezanemarljive, mogućnosti perzistiranja bolesti ili prelaska u klinički znatno ozbiljniji horiokarcinom. CC, PSTT i ETT su maligna oboljenja koja imaju lošu prognozu ukoliko se ne leče. APSN predstavlja poseban fenomen.

Iako je ranije lečenje ovih oboljenja bilo u onkološkom smislu najčešće neuspešno jer se uklanjanjem materice nije mogla kontrolisati metastatska bolest, danas zahvaljujući primeni hemioterapije, lečenje invazivne mole, horiokarcinoma i postmolarne gestacijske neoplazije je uspešno u više od 90 % slučajeva. Ovo važi i za slučajeve uznapredovale (metastatske) bolesti i to bez radikalnog hirurškog lečenja (histerektomije). Pored hemiosenzitivnosti, ovome je značajno doprinelo i postojanje pouzdanog i dostupnog tumorskog markera - beta horionskog gonadotropina (beta-hCG-a) - koji je omogućio lako praćenje pacijentkinja nakon prve linije lečenja i blagovremeno otkrivanje relapsa bolesti.

Nasuprot svemu izloženom o CC i iHM, stvari stoje značajno drugačije sa trofoblastnim tumorom placentnog ležišta i epiteloidnim trofoblastnim tumorom. U poređenju sa CC i iHM, ovo su bolesti su još ređe prema svojoj incidenciji, značajno su sporijeg prirodnog toka, češće metastaziraju u limfne čvorove, značajno manje osetljive na hemioterapiju i neuporedivo manje sekretuju beta-hCG (u odnosu na volumen tumora) te se on ne može koristiti za njihovo praćenje.

PSTT potiče od intermedijernog trofoblasta placentnog ležišta. Značajan procenat pacijentkinja će imati povišen nivou humanog placentnog laktogena (HPL).

Dijagnoza PSTT i ETT je prevashodno histopatološka na tkivu dobijenom kiretažom, histeroskopijom ili biopsijom metastatske lezije. Nakon postavljanja dijagnoze, potrebno je izvršiti radiološko (CT/MR) stadiranje bolesti prema FIGO klasifikaciji. Za ove tumore se ne koristi FIGO sistem skorovanja za procenu rizika od razvoja rezistencije na monohemioterapiju. Po postavljanju dijagnoze, pacijentkinju je potrebno uputiti u referentni centar gde će se savetuje verifikacija histopatološke dijagnoze od strane referentnog patologa.

U tretmanu PSTT i ETT jedini faktor za koji je utvrđeno da utiče na prognozu bolesti i koji sledsteveno utiče na terapijski pristup jeste vreme proteklo od trudnoće iz koje je nastao tumor. Zbog toga se u dijagnostičkoj obradi pacijentkinje ponekad koriste i različite genetičke analize koje imaju za cilj određivanje iz koje od njenih prethodnih trudnoća je nastao tumor. Ukoliko je period od trudnoće do započinjanja lečenja kraći od 48 meseci i radi se o bolesti u I stadijumu,

lečenje se sastoji od histerektomije i praćenja. Ukoliko je od trudnoće do započinjanja lečenja prošlo više od 48 meseci, nakon histerektomije se savetuje adjuvantna hemioterapija bazirana na preparatima platine. U stadijumima II i III, u slučajevima kod kojih je prošlo manje od 48 meseci od trudnoće, tretman se sastoji od histerektomije i hemioterapije po režimu EP-EMA. Kada se radi o II i III stadijumu bolesti kod kojih je prošlo više od 48 meseci od trudnoće, kao i u IV stadijumu bolesti, nakon histerektomije potrebno je sprovesti visokodoznu hemioterapiju.

U zavisnosti od nalaza, klasična ili radikalna histerektomija mogu biti indikovane. Takođe, neophodno je uraditi limfadenektomiju svih (klinički i radiološki) suspektnih nodusa.

Dodatni problem u lečenju PSTT i ETT predstavljaju mlade pacijentkinje koje imaju želju za daljom reprodukcijom. Kod ovakvih pacijentkinja u I stadijumu bolesti kada je od trudnoće prošlo manje od 48 meseci, može se razmotriti nestandardni, poštedni hirurški tretman koji se sastoji od uklanjanja tumora histeroskopskom resekcijom ili histerotomijom uz imperativ dobijanja čistih hirurških margina. Nema jasnih smernica je da li kod ovih pacijentkinja treba primeniti i hemioterapiju.

Praćenje pacijentkinja je pre svega radiološko tj. imidžing metodama. Beta-hCG se može koristiti samo kod pacijentkinja kod kojih je ovaj marker bio visok pre započinjanja lečenja. Takođe, HPL nije dovoljno pouzdan za praćenje, ali može biti koristan.

U slučaju rekurentne bolesti, uz vrlo ograničene uspehe, mogu se razmotriti druge linije hemioterapije, resekcija metastatske bolesti ili imunoterapija. Imunoterapija se zasniva na lekovima koji blokiraju PD-1 receptor (pembrolizumab) i lekovima koji blokiraju PD-L1 ligant (avelumab).

Atipični nodus placentnog ležišta (APSN) po svojim histološkim i kliničkim karakteristikama predstavlja leziju koja je slična nodusu placentno ležišta od kog se razlikuje po izraženoj celularnosti, izraženoj nuklearnoj atipiji i povišenoj pozitivnosti na Ki-67. Iako je u ovom momentu teško precizno utvrditi prirodu ovog oboljenja, standardni tretman predstavlja histerektomija zbog mogućnosti razvoja PSTT-a iz ove lezije. U slučaju da se radi o pacijentkinji u reproduktivnom periodu koja ima želju za ostvarivanjem trudnoće, može se ponuditi nestandardni tretman histeroskopske resekcije (eventualno histerotomije i ekstirpacije tumora) uz pažljiv monitoring imidžing metodama i eventualno beta-hCG-om.

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MRI IN CERVICAL CANCER: AN UPDATE

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Although advancements in prevention of cervical cancer have decreased its incidence, cervical cancer still contributes significantly to women's morbidity and mortality worldwide (1, Patel). Cervical cancer is fourth most frequent malignancy among women of all age and second most common cause of death among women under the age of 40 (2, WHO).

Management and survival rates of these patients are based on staging classification. The International Federation of Gynecology and Obstetrics (FIGO) system is used for disease staging. Since the previous studies have shown the importance of tumor size and nodal involvement in survival rates, the revision of FIGO staging classification was made in 2018. The aim of these changes was to increase the accuracy of staging in order to guide treatment and to stratify patient's survival better. Revised FIGO system points out the necessity of MRI as a method of choice for accurate measurement of tumor size, parametrial invasion and nodal involvement as a prognostic indicator (3, Salib). Introduction of the imaging as part of proper evaluation proved to better determinate local invasion than physical examination which was previously used for local assessment in 2009 FIGO staging classification. Also, lymph nodes were not evaluated in 2009 FIGO system (4, Pecoreli).

Revision was made for stage IA as well as for IB, and new IIIC substage was introduced. Stage IA is based only on depth of the tumor and previous width of the tumor was removed in order to avoid artefacts (5, Bhatla). IA1 stage is defined as microinvasive tumor ≤3 mm in depth and IA2 as micoinvasive tumor >3 mm and ≤5 mm in depth. Although stage IA tumors are not visible at MRI, MRI examination is crucial for excluding skip lesions and nodal metastasis (3, Salib). Stage IB is now subdivided in three subgroups: IB1 is tumor ≤2 cm, IB2 >2 cm and ≤4 cm and IB3 is tumor that is >4 cm in depth. This division was based on the results of National Cancer Institute's Surveillance, Epidemiology, and End Results database which showed that survival rate of patients with tumors measuring less then 2 cm was two times higher than in patients with tumor size between 2 and 4 cm (6, Matsuo). New IIIC substage refers to nodal lymph involvement. If pelvic lymph nodes are positive, the disease is staged IIIC1 and if para-aortic lymph nodes are positive it is IIIC2. Studies have showed that the most important prognostic parameter for increased 5-year survival is the presence of disease in lymph nodes (7, Singh). So, sophisticated imaging techniques may lead to upstage of the disease influencing the method of treatment and future prognosis. According to 2018 FIGO classification, 5-year survival rate for patients in IIIC1 stage is 60,8% and in IIIC2 is 37,5% (3, Salib).

The MRI evaluation is also important for adequate selection of patients who are candidates for fertility-sparing surgery. In this case, apart from general MRI report which includes tumor size, parametrial invasion, vaginal invasion (upper two-thirds or lower one-third), pelvic side wall invasion, presence of hydronephrosis, lymphadenopathy and adnexal mass, invasion of bladder or rectum, MRI should also report the distance between tumor and internal cervical os (8, Manganaro). Sensitivity of MRI detection of internal cervical os involment is high, 90-98% (9, Saleh). *Additionally, involvement of internal cervical os increses the risk for lymph node metastasis (10, Bourgiot).*

The reason why MRI is preferred diagnostic tool over CT is because of its soft tissue contrast resolution and multi-planar capability (8). Patient preparation prior to MRI imaging could enhance its sensitivity. Bladder and rectum should be emptied 30 minutes before the exam, although fasting before the examination is recommended. Antiperistaltic agents help reducing gut motion and uterine contractions, and usage of vaginal gel is optional (3, Salib, 8, Manganaro).

Cervical tumors usually show intermediate T2-weighted signal intensity that should be differentiated from normal fibrous stroma od the cervix (3, Salib). Vaginal involvement is suspected when there is a loss of the normal low T2-weighted signal intensity, while lymph node involvement is assessed by size, morphology and drainage pathway (3, Salib).

The aim of our study was to compare MRI tumor classification with definite histopathological finding. We analyzed 58 patients with cervical cancer who undergone radical hysterectomy with pelvic lymphadenectomy. Average patient age was 53 years. According to MRI imaging, there were 23 (39.65%) patients with tumor in size less than 20 mm, 23 (39.65%) with tumor size between 20 and 40 mm and 3 (5.18%) patients with tumor size more than 40 mm. In 9 patients (15.53%) tumor was not recognized on MRI. Definitive histopathological finding showed 15 (22.41%) patients with tumor in size less than 20 mm, 32 (41.38%) with tumor size between 20 and 40 mm and 8 (13.79%) patients with tumor size more than 40 mm. Microinvasion was present among 3 (4.17%) patients. Vaginal involvement was described in 6 cases on MRI (10.34%), whereas it was verified later in 9 patients (15.52%). Parametrial invasion was seen in 13 patients on MRI (22.41%), but was histopathologically proved in 11 patients (18.96%). MRI imaging detected 9 patients (15.52%) with lymph node involvement, while lymph nodes were truly positive in 11 patients (18.96%). These results showed that MRI imaging was most accurate for tumor size between 20 and 40 mm. The precise measurement of tumor size is important while it affects treatment decision and corresponds with recurrence and survival rate (3, Salib). Patients with tumors measuring less than 20 mm are eligible for fertility sparing treatment (trachelectomy). Also, 5-year survival rate mostly depends on nodal metastasis. Stage IA could only be established on histopathology because these lesions are not visible on MRI (11, Nicolet). Our results were concordant in the fact that characteristic MRI findings based on signal intensity have been proved to have very high specificity in detecting parametrial involvement (12, Saala). On the other hand, MRI invasion of upper two-thirds of vagina could be hard, so the bimanual clinical examination should not be omitted (13, Otero-García).

To conclude, MRI imaging plays significant role in the latest FIGO classification revision. In order to carefully plan and choose best treatment MRI helps determining tumor size and disease spread. Adequate pre-operation evaluation is important for patient's prognosis and overall outcome.

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VY KLIZAJUĆI FASCIOKUTANI REŽANJ U REKONSTRUKCIJI VULVOPERINEALNIH DEFEKATA

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Karcinom vulve je spade u retke malignitete koji čine 3%- 5% svih ginekoloških maligniteta. [1,2]. Najčešći maligni tumor vulve je planocelularni karcinom koji čini preko 90% svih karcinoma genitoperinealne regije [3,4]. Prema podacima CDC iz 2020. godišnje se registruje 6200 novih slučajeva karcinoma vulve [5]. Prema statističkim podacima iz literature karcinom vulve je dijagnostikovan u 39% slučaja u stadijumu III ili IV bolesti [6]. Kod ekstenzivnijih tumora, lokalni recidivi su učestaliji od udaljenih metastaza i mogu se uspešno lečiti hirurgijom i zračnom terapijom. Kod pacijentkinja u odmaklim stadijumima FIGO III i IVa i koje zahtevaju radikalnu vulvektomiju sa bilateralnom ingvinalnom disekcijom, pokrivanje resekcionih defekta predstavlja hirurški izazov. Pokrivanje ekstenzivnih defekata vulvo-perinealne regije, nakon radikalnih ekscizija tumora, primenom lokalnih, regionalnih i miokutanih režnjeva, doprinosi smanjenju postoperativnih komplikacija i poboljšanju funkcionalnog i kozmetskog izgleda, čime se značajno poboljšava kvalitet života pacijenta. [2,7, 8]. Karcinom vulve se tretira radikalnom hirurškom ekcizijom, tj. en block vulvektmijom, obzirom na visok procenat recidiva. Postoperativne komplikacije poput dehiscencija, hematoma, infekcija i limfedema su prijavljene u literaturi u 64%–85% slučajeva [2]. Sastavni deo lečenja karcinoma vulve je rekonstrukcija ekstenzivnih mekotkivnih postonkoloških defekata tkiva. Primarno zatvaranje defekta je moguće ukoliko su manjih dimenzija, ali tenzija koja nastaje na mestu ušivanja može dovesti do dehiscencije i produženog zarastanja rane, što produžava hospitalizaciju, a samim tim i troškove lečenja. Brojne hirurgije recidiva, zračne terapije i široke ekcizije tumora dovode do nastanka ekstenzivnih mekotkivnih defekata, koji odlažu zarastanje rana i povećavaju postoperativni morbiditet, što sve negativno utiče na kvalitet života pacijentkinja.

U praksi se primenjuju različite metode rekonstrukcija, u cilju smanjnja postoperativnih komplikacija, skraćenja hospitalizacije i bržeg oporavka, čime se poboljšava kvalitet života pacijentkinja [2,8,9]. Rekonstruktivne metode podrazumevaju primenu slobodnih kožnih transplantata, lokalnih režnjeva, regionalnih peteljkastih i slobodnih režnjeva, vodeći se pravilima rekonstruktivne lestvice od jednostavnije rekonstrukcije ka kompleksnijoj, u zavisnosti od zahteva defekta tkiva koje se rekonstrujiše.

Svaka od potencijalnih metoda rekonstrukcije ima svoje prednosti i mane. Poslednjih godina, učestala je primena mišićnih i mišićno kožnih režnjeva kod pacijentkinja sa ginekološkim malignitetima [10,11]. Primena mišićnih i slobodnih režnjeva produžava vreme operacije, i povećava mogućnost nastanka komplikacija poput parcijalne ili totalne nekroze režnja, usled kompromitovane cirkulacije u režnju. [2,7,8]. Česte postoperativne komplikacije kod direktne aproksimacije nategnutih ivica defekta su pre primene režnjeva bile dehiscencije i usporeno zarastanje rane [2]. Postoperative dehiscencije i limfedemi su zastupljeni u 64- 85% slučaja. Primenom režnjeva, tj. rekonstrukcijom defekta tkivom koje se mobiliše iz obližnje regije, gde ga ima u višku, omogućilo je primarno zatvaranje defekta u istom hirurškom aktu kada i radikalno uklanjanje tumora uz disekciju regionalnih limfatika, a bez bojazni od dehiscencije. Pored kozmetskog izgleda, koji je primenom režnjeva poboljšan, očuvana je i funkcija mikcije i defekacije.

U ovom radu su prikazani klinički slučajevi pacijentkinja kod kojih su nakon radikalnih ekscizija ekstenzivnih tumora vulvo-perinealne regije uz bilateralnu ingvinalnu disekciju, defekti pokriveni V-Y lokalnim klizajućim režnjevima, lokalnim fasciokutanim režnjevima i vertikalnim miokutanim režnjem m. rectus abdominus-a, a poseban osvrt je na prednosti lokalnih fasciokutanih klizajućih VY režnjeva, u odnosu na ostale rekonstruktivne opcije.

Perinealne i ingvinalne dehiscencije kao komplikacija su česte kod direktnog ušivanja defekta nakon onkoloških resekcija tumora vulve i kreću se od 68,4% do 78,9%, dok je taj procenat znatno smanjen na 10,5% do 36,8% kada se primeni neka od rekonstruktivnih tehnika pokrivanja defekata mekih tkiva. Veće studije Di Donato i sradnika koje su uključile analizu 24 studije ukazuju da je većina režnjeva bila po tipu prednjačećih, klizajućih ili advancement i transpozicionih režnjeva sa sličnom incidencom komplikacija 26,7% - 22,3%. Kada se donosi odluka o tipu rekonstrukcije i primeni režnja, osnovno je uzeti u obzir karakteristike defekta, veličine, dubine, lokalizacije, ali i kozmetski izggled vulvo perinealne regije. Neke studije preferiraju transpozicione u odnosu na VY klizajuće režnjeve zbog manje vidljivih ožiljaka. Sa druge strane srednji i veći defekti zahtevaju primenu prednjačećih režnjeva jer obezbedjuju manje tenzije na mestu defekta.

VY klizajuci režanj je lokalni fasciokutani režanj kojim se mobiliše fascija i koža oko defekta kako bi se rekonstruisao primarni defect nastao nakon radikalne ekcizije tumora. Ovaj režanj se može upotrebiti kada ima dovoljno rastegljive kože davajuće regije za pokrivanje defekta, u istom aktu kada i uklanjanje tumora [2,12,13]. Početni rez na koži je u obliku slova V, a nakon rekonstrukcije dobija oblik slova Y uz direktno zatvaranje sekundarnog defekta. Ovaj režanj se može upotrebiti kada postoji dovoljno mobilne kože u obližnjoj glutealnoj regiji [2,12]. U predstojećem postoperativnom periodu režanj će nedeljama biti edematozan i eritematozan, sto se vremenom gubi, kako se uspostavlja limfna drenaža i ožiljak sazreva. Prednosti VY klizajućeg režnja su jednostavnost izvođenja, sigurni su u smislu vaskularizacije i preživljavanja i dobre su teksture kože. Režanj se ishranjuje putem perforatora a. pudende interne i muskulokutanim perforatorima mišića koji leži ispod režnja. Senzitivna inervacija potiče od pudendalnog i zadnjeg kožnog nerva butine. Rekonstrukcije VY klizajućim režnjem su siguran metod pokrvanja vulvarno- perinealnih defekata mekih tkiva, sa niskom stopom komplikacija u većini slučaja. Rekonstrujisana zona tj. režanj može biti otečen i crveno prebojen danima i nedeljama koje slede, a finalnu formu dobija nakon 3 do 6 meseci od operacije.

Vertikalni režanj m. rectus abdominisa je pored miokutanog režnja m. gracilisa, najprimenljiviji režanj u pokrivanju ekstenzivnih defekta genitoperinealne regije. To je aksijalni peteljkast režanj čija se vaskularizacija bazira na a. epigastrici inferior i komitantnim venama. Režanj je kompozitan, jer se sastoji od m. rectus femorisa i kože iznad njega. Rotacijom oko vaskularne peteljke za 180 stepeni može pokriti trodimenzionalne defekte vulvo perinealne regije. Davajuća regija na trbuhu se direktno ušiva, tako da je morbiditet davajuće regije minimalan.

U prikazanim slučajevima pacijentkinja nije bilo većih komplikacije poput nekroza i parcijalnih nekroza režnjeva. Pacijentkinje su kontrolisane prvih mesec dana od strane plastičnog hirurga, a zatim naredne dve godine na svaka tri meseca od strane ginekologa onkologa. U okviru prve godine od operacije nije bilo znakova recidiva bolesti.

Cilj ovoga rada je da prikažemo naše rezultate rekonstrukcija defekata vulvo-peinealne regije, uzimajući u obzir pre svega karakteristike defekta tkiva koje rekonstrujišemo, sa posebnim osvrtom na prednosti i mane fasciokutanog VY režnja u odnosu na druge rekonstruktivne opcije.

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MESTO IMUNOTERAPIJE U CERVIKALNOM KARCINOMU. NOVI HORIZONTI

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Standardni tretman prve linije za metastatski rak grlića materice je hemioterapija na bazi platine i bevacizumab (GOG-240). Isti protokol se koristi za rekurentnu bolest. Petogodišnja stopa preživljavanja ranog stadijuma raka grlića materice je oko 91,6% (95% CI, 91,1-92,0), ali je za pacijente sa udaljenim metastazama i dalje niska, 17,2% (95% CI, 16, 2-18,3)(1). Postoje neke promene u lečenju ovih pacijenata, ali još uvek nema jasnih indikacija, biomarkera ili protokola lečenja. Neki obećavajući rezultati ukazuju na imunoterapiju. Proučava se određeni broj imunoterapeutika za grupu pacijenata sa metastatskim karcinomom grlića materice.

Inhibitori imunoloških kontrolnih tačaka su uveliko proučavani. Racionalno za imunoterapiju je da su promene tumorskog mikrookruženja povezane sa progresijom u viši stepen displazije, a bolesnici sa karcinomom grlića materice sa tumorom infiltriranim limfocitima (TIL) u tumorskom tkivu imaju bolje preživljavanje. HPV infekcija je povezana sa ekspresijom PD L1 u displastičnim ćelijama i skvamoznom karcinomu grlića materice (SCC).

Sa kliničkog aspekta najznačajnije studije su ispitivanje faze 3, KEINOTE-826, PFS i OS bili su značajno duži kod pacijenata koji su primali pembrolizumab plus hemloterapiju zasnovanu na platini sa ili bez beacizumaba, nego u placebo grupi, koji su primali samo hemloterapiju sa ili bez bevacizumaba. PFS i OS su analizirani kod pacijenata sa PD-L1 kombinovanim pozitivnim rezultatom (CPS) ≥ 1, u populaciji ITT (eng. the intention-to-treat population), i PD-L1 CPS ≥ 10. U prvoj grupi (CPS ≥1), 548 pacijenata, medijana PFS je bila 10,4 meseca i 8,2 (odnos opasnosti 0,62; 95% CI, 0,50-0,77; p<0,001) u grupi koja je primala pembrolizumab i placebo. Ukupno preživljavanje za 2 godine bilo je 53% i 41,7% (HR za smrt, 0,64; 95% CI, 0,50-0,81; p<0,001) u grupi koja je primala pembrolizumab i placebo. U populaciji ITT (617) PFS je bio 10,4 i 8,2 meseca u grupi sa pembrolizumabom i placebom (odnos rizika (HR) 0,65; 95% CI, 0,53-0,79; p<0,001). Ukupno preživljavanje je bilo 50,4% i 40,4% (HR, 0,67; 95% CI, 0,54-0,84; p<0,001). U grupi sa PD-L1 CPS ≥ 10 PFS 10,4 u grupi pembrolizumaba i 8,1 meseci u placebo grupi (HR 0,58; 95% CI, 0,44-0,77; p<0,001) i OS je bio 54,4% i 44,6% (HR;, 95% CI, 0,44-0,84; p=0,001).

U fazi ispitivanja I/II, CheckMate 358, nivolumab je predstavljen kao obećavajuća monoterapija kod pacijenata sa rekurentnim ili metastatskim karcinomom grlića materice sa ORR od 26,3% (95% CI, 9,1%-51,2%). Medijan OS je bio 21,9 meseci (95% CI, 15,1-nije dostignut), a trajanje odgovora na srednjem praćenju (19,2 meseca) nije postignuto. Kasnija privremena analiza pacijenata sa rekurentnim ili metastatskim grlićem materice koji su primali nivolumab plus ipilimumab sugeriše da postoji korist od ove kombinacije lečenja bez obzira na status PD-L1. Kombinacija nivolumaba i ipilimumaba praćena nivolumabom do progresije ili neprihvatljive toksičnosti imala je povoljnu efikasnost u poređenju sa kombinacijom nivolumaba i ipilimumaba samog kod pacijenata sa prethodnim sistemskim terapijama (ORR 36% prema 23%; medijan OS 25,4 meseca (17,5-nije dostignut); meseci (7,9-15,2)).

Analiza rezultata ispitivanja EMPOVER-Cervical/GOG-3016/ENGOT-ck9 pokazala je da je cemiplimab bio bolji od hemioterapije sa jednim lekom kod pacijenata sa rekurentnim ili metastatskim karcinomom grlića materice. Ukupno preživljavanje kod karcinoma skvamoznih

ćelija bilo je 11,1 mesec u cemiplimabu i 8,8 u grupi hemioterapije (HR o,73; 95% CI, 0,58-0,91; p=0,003). Za pacijente sa adenokarcinomom ili adenoskvamoznim karcinomom OS je bio 13,3 meseca i 7,0 (HR 0,56; 95% CI, 0,36-0,85; p<0,005) (13).

Kliničko ispitivanje faze I, GOG 9929, koristi inhibitor anti-CTLA-4 imunološke kontrolne tačke, ipilimumab, kod pacijenata FIGO stadijuma IB2-IIB i IIIB-IVA nakon standardne hemioradioterapije (CRT). Maksimalna tolerisana doza bila je 10 mg/kg. Bilo je 19 pacijenata koji su primali ipilimumab 2-6 nedelja nakon CRT, 90% 4 ciklusa i 10% 2 ciklusa. Toksičnost stepena 3 primećena je kod 3 pacijenta i sama se rešila. Većina akutnih toksičnosti je bila nižeg stepena (1-2) i bilo je osipa, gastrointestinalnih tegoba i endokrinopatija bez kasnih toksičnosti nakon 12 meseci praćenja. Jednogodišnji DFS je bio 74%. Detekcija povećane ekspresije ICOS i PD-1 sugeriše da bi imunoterapiju trebalo proučavati u lečenju te grupe pacijenata.

Drugo randomizovano ispitivanje faze III koje procenjuje efikasnost atezolizumaba istovremeno sa standardnom hemioterapijom (cisplatin i paklitaksel plus bevacizumab) kod pacijenata sa metastatskim, rekurentnim ili perzistentnim karcinomom grlića materice.

Ispitivanje VolATIL A (NCT03946358) još uvek regrutuje pacijente za ispitivanje kombinacije terapijske vakcine protiv raka (UCPVak) i atezolizumaba za lečenje HPV pozitivnih karcinoma.

Trenutne studija (NCT04483544) regrutuje pacijente sa uznapredovalim ili rekurentnim karcinomom grlića materice nakon standardne hemoterapije za procenu odgovora na kombinaciju lekova pembrolizumab i olaparib (PARP inhibitor). PARP inhibitor dovodi do oštećenja DNK što čini ćelije privlačnim za imunoterapiju.

Efikasnost primene imunoterapije u metastatskoj/rekurentnoj bolesti raka grlića materice otvara nove mogućnosti koje se danas ispituju sa jasnim ciljem pomeranja primene terapije na I liniju tretmana raka grlića materice.

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SLN U GINEKOLOŠKOJ ONKOLOGIJI

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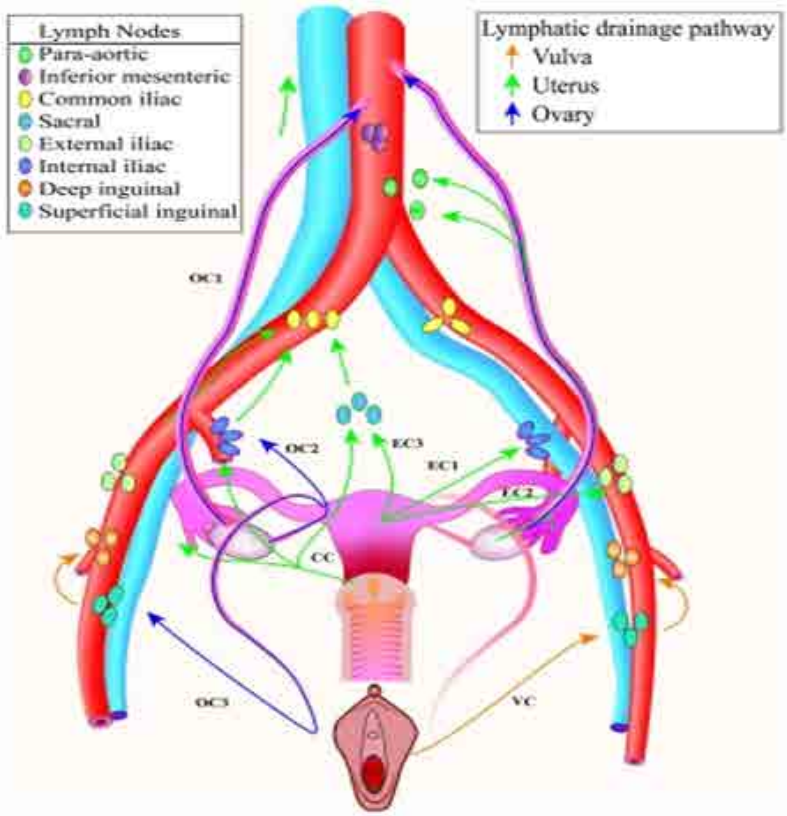
Limfni nodus "stražar "(sentinel lymph node, SLN) je limfna žlijezda u koju se drenira područje zahvaćeno tumorom i prva prima aferentnu limfnu drenažu iz malignog tumora. To je mjesto gdje se pojavljuju prve meta promjene i ukazuje na status limfnih nodusa u datom regionu.

Da bi se ova tehnika mogla primjenjivati neophodno je dobro osnovno poznavanje anatomskih struktura kao i limfne drenaže iz ginekoloških organa [1].



Slika 1. ,,Limfna drenaža male karlice''

Prvi put je metoda urađena i opisana od strane Gould et al.1960. god. tokom operacije karcinoma parotidne zlijezde [2]. Mada se najčešće kao prvi pominje Cabanas 1977. god. sa operacijom karcinoma penisa [3]. Od tada je procedura primjenjena kod melanoma, a onda je zaživjela kod karcinoma dojke. Koncept SLN našao je ubrzo svoju primjenu u ginekološkoj onkologiji i to prvo kod karcinoma vulve, a kasnije kod karcinoma grlića i endometrijuma.

SLN procedura se preduzima da bi se utvrdilo da li je tumor razvio limfne matastaze. Ako se PH analizom utvrdi da je SLN negativan, smatra se da u tom regionu nema limfnih metastaza, a to nam omogućava da odredimo prognozu bolesti i kakav će biti dalji tretman.

Prednost ove tehnike je svakako manja invazivnost u toku operacije te manje postoperacionih komplikacija. Ovom metodom se uklanjaju samo označeni limfatici. Time su značajno umanjene učestalosti limfedema, limfociste, oštećenja nerava, dehiscencije rana. Kraće je vrijeme trajanja

hirurškog zahvata, manji je broj infektivnih komplikacija operacije. Zbog smanjenog obima operacije manji je intraoperacioni gubitak krvi. Na kraju cost-effective saldo je pozitivan, a ušteđena sredstva se mogu usmjeriti npr. na unapređenje patohistoloških analiza.

Mane ove metode su faktori koji utiču na uspješno mapiranje i pronalaženje SLN kao što su:

- faktor hirurg - vještina i iskustvo neophodni za pronalaženje svih mapiranih SLN u očekivanim regionima drenaže, ali i misliti na rijetke neobične lokalizacije za svaki malignitet posebno;
- različiti tragači u upotrebi

Među tragačima na tržištu se mogu naći: blue dye (methylene blue, patent blue, isosulfan blue), indocijanin zelena (ICG), tehnecijum koloid (nanokoloid, kalcijum phytat, sulfur koloid). Uz ICG se obavezno koristi near- infrared svijetlo koje prolazi do 8mm dubine tkiva pa vidi i dublje postavljene noduse. Upotreba tehnecijuma zahtjeva detektor (SPECT CT). ICG povećeva stopu detekcije SLN u odnosu na blue dye. Ako se koristi tehnecijum, mora se voditi računa da neki čvorovi mogu promaći, jer ne emituju potrebnu dozu zračenja. Mana metode je i mogućnost alergijske reakcije na tragač kao i jonizujuće zračenje [4].

Slabost SLN metode je i mogućnost da se u toku procedure propusti nodus sa metastazama (retrogradni metastatski nodusi, jump metastaze). Vidljivost blue dye je lošija jer je boja manje penetrantna od ICG, a neki su limfni sudovi dublje postavljeni pa se nodusi ne uoče. Tumor takođe može da opstruira limfni sud i nema protoka limfe, pa izgleda da je područje neobojeno. Klinički je ova situacija rijetka jer znači da je nodus u velikoj mjeri zablokiran malignim ćelijama, da je vjerovatno i klinički manifestan.

Osnovni koraci SLN procedure obuhvataju: pripremu pacijenta, injekcija tragača, intraoperacionu lokalizaciju i biopsiju nodusa kao i postoperacioni ultrastaging.

Karcinom endometrijuma

Endometrijalni karcinom je među najčešćim karcinomima žena u razvijenim zemljama. U svijetu se po GLOBOCAN-u registrije oko 382069 novih slučajva ovog karcinoma, a umre oko 89909 [5,6]. Dijagnostikuje se najčešće u ranom stadijumu. Osnovni način liječenja ovog karcinoma je hirurgija. Kod ranog stadijuma bolesti pelvična i paraaortalna limfonodektomija ne utiče na preživljavanje (OS), niti na period bez bolesti (DFS), ali značajno povećava perioperativni i postoperativni morbiditet kod pacijentkinja, vrijeme trajanja operacije i finansijska sredstva koja se u tu svrhu dodatno izdvajaju. Od kada je SLN tehnika prvi put urađena kod ovog karcinoma napravljeni su vodiči čiji je cilj da smanje varijetete u tehnici izvođenja procedure i indikacijama za izvođenje. Uglavnom se vodiči (ESGO, NCCN, SGO) poklapaju kad su u pitanju niskorizična i bolest sa srednjim rizikom, kada se i predlaže izvođenje procedure. Kod visokorizične forme bolesti (gradus 3 endometrijalni, serozni, clearcell, CaSa) se predlaže limfonodektomija mada SLN može biti alternativa limfonodektomiji [7,8,9]. Incidencija izolovanih tumorskih celija (ITC) raste sa dubinom invazije miometrijuma. Zaključak je da se kod pacijentkinja bez invazije miometrijuma ne radi ultrastaging.

Veći dio tijela uterusa drenira limfu u ilijačne limfne noduse (eksterne/interne) i obturatorne noduse. Manji dio u presakralne, eventualno paraaortalne.

Kod ovog karcinoma tragač se može ubrizgati u cerviks ili histeroskopski u tumor. Studije nisu našle veću stopu detekcije kod ubrizgavanja u tumor u odnosu na ubrizgavanje u cerviks. Medju tragačima blagu prednost u skoro svim studijama poslednjih godina ima ICG u odnosu na blue dye i tehnecijum. Kada se upotrebljavaju druga dva tragača onda obično idu zajedno [10].

Nekada se SLN ne oboje tragačem i to se dešava u oko 6% slučajeva [11]. Vodiči preporučuju da se u slučajevima kada se ne uoče mapirane SLN, na toj strani uradi limfonodektomija. Kako se pregledaju odstranjeni SLN zavisi od vodiča kojim se rukovode patohistolozi. Svi se slažu da je neophodan ultrastaging, ali da li će to biti hematoksilin-eozin (HE) bojenje, pa onda imunohistohemija (IHH) ili jedan rez HE, a drugi rez IHH (cytokeratin AE1/AE3) ... Jasno je da samo uklanjanje limfatika nije terapija ali obezbeđuje bitnu informaciju o PH statusu žlijezdasta što je bitna informacija za planiranje daljeg adjuvantnog tretmana. Sve u svemu u velikoj većini postupanja,različiti vodiči se poklapaju u preporukama. Kada je u pitanju SLN u visokorizičnoj bolesti, kao i metodologija i protokol o patohistološkom pregledu materijala, neophodna su dalja iscrpna istraživanja [10].

Po važećim vodičima SLN kao procedura se preporučuje kod bolesti niskog rizika i one sa srednjim rizikom. Za visokorizičnu bolest ostaje po protokolu procedura limfonodektomije. Međutim ipak su rađene neke studije sa pacijentima koji su imali visokorizičnu bolest i kod polovine pacijenata je rađen samo SLN, a kod druge polovine SLN, a nakon toga PLND. Senzitivnost samo SLN procedure je bila 96%, a NPV 99% u odnosu na SLN +PLND, kad je riječ o onkološkoj sigurnosti i prognozi za ove pacijente [12,13].

Karcinom grlića materice

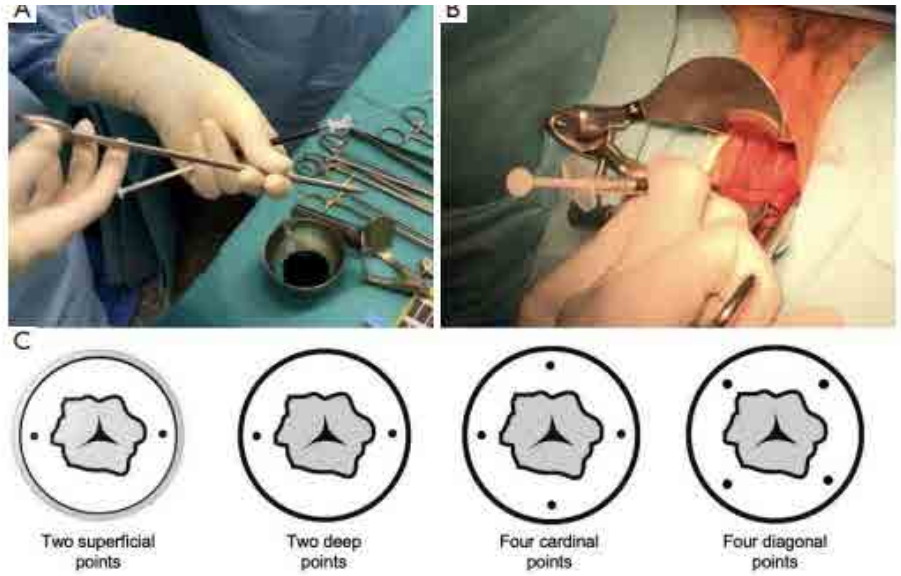
Karcinom grlića materice je na četvrtom mjestu po učestlosti maligniteta među ženama u svijetu. Procjenjuje se da godišnje oboli oko 604000 žena a umre oko 342000. Skoro 90% novih slučajeva otkrije se u nerazvijenim ili srednje razvijenim zemljama u svijetu [14].

Ovaj malignitet se može izliječiti ako se otkrije u ranoj fazi, a takođe se može i spriječiti. naime, primjenom primarne i sekundarne prevencije, u odgovarajućem algoritmu, sigurno se može svesti na rijetku bolest.

Rani karcinom nakon hirurške intervencije ima dobar ishod pa je period bez bolesti (DFS) u 96,5% slučajeva, za 4,5 godine. Status limfnih čvorova je značajan prognostički factor i DFS pada sa 88% na 57% u slučaju pozitivnih limfatika [15]. FIGO je u klasifikaciju iz 2018. god. dodao status limfatika. Limfatučki status je od velike važnosti jer saznanje o pozitivnim limfaticima može zahtjevati dalje paraaortalno uzorkovanje ili HTRT umjesto radikalne hirurgije. Za stadiranje kod karcinoma grlića potrebno je uraditi pelvičnu limfonodektomiju (PLND). Ova procedura iziskuje utreniranog i iskusnog hirurga ali i veže za sebe povećani peri i postoperativni morbiditet pacijentkinje.

Koje su činjenice važne kod širenja bolesti u limfatike karlice? Kod ranog karcinoma srednja stopa pozitivnih nodusa je oko 20%. Broj pozitivnih nodusa po pacijentu je 1-3. Kad se radi pelvična limfonodektomija u prosjeku se vadi oko 15 čvorova. Skoro 80% pacijenata koji imaju negativne noduse dobilo je opsežnu operaciju sa mogućim brojnim komplikacijama, produženim trajanjem zahvata, obaveznom nadoknadom krvi itd. A opet će 10%-15% pacijenata razviti recidiv u karlici zbog toga što se zna da limfatični putevi mogu da imaju i neke nestandardne puteve derivacije limfe [16].

Prema ESGO-u u svrhu SLN tehnike se može koristiti ICG ili blue dye+ Tc 99m. Primjena ICG se proširila jer je jednostavnija za upotrebu, jeftinija, i manji je rizik od alergijske reakcije u odnosu na blue dye. Ne zahtjeva scintigrafiju i navedenu tehničku logistiku u tom smislu. Odobrena je od strane FDA I EMA. Tragač se ubrizgava u grlic metodom 2 ili 4 uboda.



Slika 2.,,Mesta ubrizgavanja kontrastra na grliću''

Nakon aplikacije tragača pristupa se pronalaženju SLN. Hirurški pristup sa kojim se počelo bio je minimalno invazivni, do pojave rezultata LACC studije. Poželjno je da se identifikuju SLN obostrano i odstrane. Ako se ne pronađu nakon pažljivog pregleda onda se radi pelvična limfonodektomija

Čitava procedura se najbolje uči kada se prije svake pelvične limfonodektomije uradi SLN procedura. To je i osnovni koncept učenja (learning curve) da bi se steklo iskustvo i opisana je u literaturi. SENTICOL I i II kohorte to su jasno pokazale [17].

Limfa grlica se drenira u obturatorne, interne, eksterne ilijačne, presakralne i paraortalne limfne noduse.

Uprkos mnogobrojnim rezultatima o primjeni SLN kod karcinoma grlića materice, metoda se još uvijek ne smatra zlatnim standardom. Optimalna veličina tumora kada se može raditi je <2cm. Preporučeni stadijumi za ovu metodu su: IA1+LVI, IA2, IB1, IB2 i IIA1. Postojanje LVI ima značajan uticaj na uspješnost SLN metode, kao i veličina tumora, gojaznost i starost pacijentkinje >70 godina života. Mada vodiči preporučuju SLN ultrastadiranje, ove procedure treba dalje standardizovati, kako se ne bi propustila low-volume bolest (MIC, ITC). Preživljavanje i onkološki ishod pacijentkinja koje su bile podvrgnute samo SLN umjesto PLND još uvijek nije dovoljno ispitano [17].

Karcinom vulve

Prema IARC podacima, svake se godine dijagnostikuje oko 45000 novih slucajeva karcinoma vulve. Od toga preko 50% je u visoko razvijenim zemljama [18]. Misli se da je oko 45% vulvarnih skvamocelularnih karcinoma izazvano HPV infekcijom. Prosječna starost žena sa vulvarnim karcinomom je 69 godina. U studiji Kang et al. pokazan je 38% porast incidencije ovog karcinoma u dobi ispod 60 godina [19]. Tumor se dijagnostikuje isključivo biopsijom. Zlatni standard terapije je hirurgija. Kod ovog karcinoma hirurgija je prošla dug put izmjene hirurških tehnika, od početnih veoma mutilantnih, do sadašnjih protokola operacije: široka ekscizija vulve, 1 cm do u zdravo, sa unilateralnom ili bilateralnom limfonodektomijom ingvinuma, u zavisnosti od lokacije primarnog tumora u odnosu na središnju liniju. Veoma važan faktor u daljem preživljavanju kod ranog stadijuma vulvarnog karcinoma je pravilan tretman ingvinalnih limfnih nodusa. Tumori koji su u opsegu manjem od 2cm u odnosu na središnju liniju, podliježu obostranoj limfonodektomiji, a oni koji su u širem opsegu ipsilateralnoj [20].

SLN kod karcinoma vulve prvi je opisao Levenback et al. jos 1994. godine [21]. Od tada do danas zaključuje se da je SLN tehnika sigurna. Pokazala je visoki stepen detekcije bolesti kod tumora <4cm, unifokalnih sa negativnim kliničkim i radiološkim nalazom ingvinalne regije. Efikasna je sa stopom lažno negativnih samo 3,7%, te spada u bezbjedne okološke procedure, kada je izvodi iskusan hirurg [22].

Limfa vulve se primarno drenira u površinske limfne noduse ingvinalne regije, a zatim u duboke čvorove, ispod kribriformne fascije i na kraju u pelvične noduse.

Tehnika SLN je manje invazivna od limfonodektomije, pa je zbog toga manji postoperativni morbiditet kod pacijentkinja i oporavak je brži. Tragač se ubrizgava u zonu tumora, okomito, sa 4 uboda. Ova metoda se preporučuje za T1b i T2 vulvarne karcinome sa negativnim čvorovima na radiološkim procedurama. Preporučuje se jednostrana SLN za tumore <4cm i koji su udaljeni od središnje linije 2cm ili više. Ako je tumor u zoni <2cm od središnje linije, onda se preporučuje obostrana SLN. Neophodan je patohistološki ultrastaging. Od tragača se najbolje pokazala ICG uz upotrebu near-infrared svjetla [23].

Prema studiji GROINSS- V indikacije za metodu su: unifokalni tumor vulve, manji od 4 cm, sa stromalnom invazijom više od 1mm, koji su klinički i radiološki negativni na noduse u ingvinumu [24]. Studija GOG 173 ukazuje da se ingvinofemoralna limfonodektomija može zamjeniti SLN procedurom kod pacijentkinja čiji su tumori manji od 4cm [25]. Obje studije su utvrdile SLN proceduru kao zlatni standard u tretmanu pacijentkinja sa ranim stadijumom vulvarnog karcinoma koje imaju unifokalni tumor do 4cm, ingvinalne lože koje nisu suspktne na meta. To je metoda iza čijeg sprovođenja je manji perioperativni morbiditet i incidencija limfedema nakon operacije.

Potrebna su dalja istraživanja kad je u pitanju postoperativni tretman pacijentkinja sa pozitivnim SLN. Trebalo bi da studija GROINSS-V III pruži odgovore o ulozi HTRT kod pacijenata sa SLN makrometastazama.

Lokalni recidiv bolesti se sreće i može se tretirati uspješno, za razliku od recidiva u ingvinumima ili udaljenim recidivima, čija prognoza nije dobra. Zbog toga se predlaže dugo praćenje nakon tretmana od ove bolesti.

Princip SLN u ginekološkoj onkologiji je u ekspanziji poslednjih godina. Već je našao svoje mjesto kao standard kod karcinoma vulve. Za karcinom endometrijuma i grlića materice se još čekaju neki ključni rezultati, koji se tiču onkološkokih ishoda, da bi se obezbijedila baza podataka koja garantuje bezbjednost metode.

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ICG - SENTINEL METHOD IN GYNECOLOGICAL MALIGNANCIES

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Introduction

In recent decades, minimally invasive surgery has been increasingly used in gynecology. After initial reluctance, this technique was accepted and increasingly used in gynecological oncology. It has been shown that oncological procedures such as pelvic/para-aortic lymph node dissection can be performed safely and effectively using the minimally invasive technique. Thus, this technique has become the accepted standard of care for specific pathologies such as endometrial cancer.

Recently, there have been reports in the scientific literature that the SLN technique is being used more and more often in clinical practice during oncological operations in gynecology. The identification of the first, tumor-draining sentinel lymph node through an SLN biopsy makes it possible to reduce the morbidity of a complete lymphadenectomy and improves the detection of metastatic changes (through ultra-staging protocols and identification of alternative lymphatic drainage routes).

In the past, SLN mapping was performed with the radiocolloid 99m technetium (99mTc) pure or in combination with dyes (Patent Blue V). However, the use of these markers may cause some side effects, which may include discoloration of the skin and urine, decreases in pulse oximetry readings, and occasionally severe allergic reactions. Mapping with 99Tc is logistically demanding as injection, imaging and surgery must be coordinated in a controlled environment according to a specifically defined standard protocol. These circumstances make the technology more time-consuming and expensive. Nowadays, indocyanine green (ICG) is used as a marker for lymphatic vessel mapping in various oncology departments. ICG is a fluorescent dye that binds intravascularly and has been used in ophthalmology since the mid-1990s to demonstrate the vasculature of the retina and choroid.

After a submucosal injection, the ICG enters the lymphatic system, binds to lipoproteins and is transported through the lymphatic system and nodes. This makes ICG the perfect marker for SLN mapping.

ICG has a low risk potential and the risk of allergy is 1 in 42,000.

Technique of sentinel lymph node mapping in gynecology

For cervical and endometrial cancer, the marker is injected cervically. The procedure is therefore identical for both scenarios. After removal of the SLNs, a radical or simple laparoscopic hysterectomy, appropriate for cervical and endometrial cancer, is performed.

Once the ICG solution is injected as described, the uterine manipulator is inserted. Before the retroperitoneal access is created, the camera system is switched to NIR mode in order to produce the fluorescence required for detection, which emanates from lymphatic vessels or an SLN.

The pelvic sidewall peritoneum is opened to gain access to the retroperitoneum.

The pelvic peritoneum is then incised cranially, over the psoas major muscle and laterally to the adnexa and infundibulopelvic ligament.

The ureter is identified on the posterior branch of the broad uterine ligament and pushed away medially along with the adnexa.

The iliac vessels are identified and the retroperitoneal space is carefully dissected. Blunt tissue dissection is of utmost importance as ICG leakage from transected lymphatics can affect visualization in NIR/ICG mode (Fig. 1).

The camera system is switched to near-infrared mode to locate the SLN (Fig. 2). The SLN is then excised, removed, and sent for pathologic examination (Fig. 3).

Advantages and limitations of the sentinel lymph node technique

The main advantages of SLN mapping are the possible prevention of unnecessary systematic lymphadenectomy for staging reasons and the associated morbidity, the identification of lymph nodes in atypical locations, and the possibility of applying an ultra-staging protocol.

In the meantime, this method is part of the current guidelines in the treatment of endometrial cancer and cervical cancer.

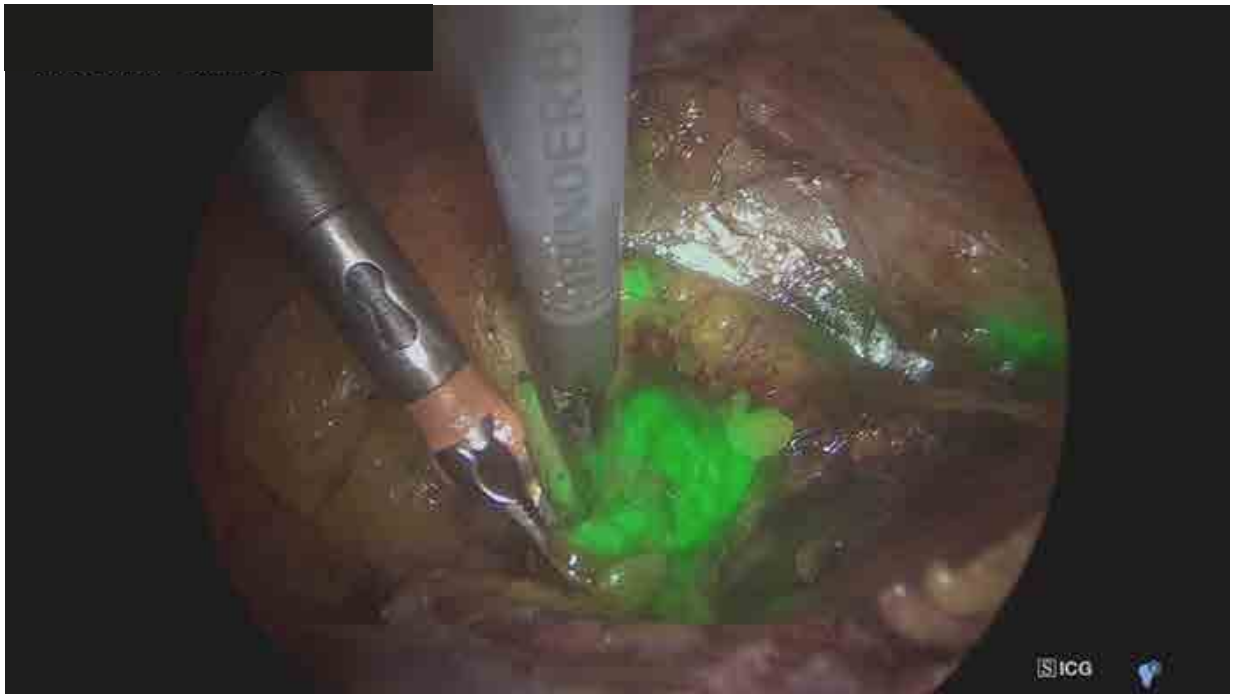

Figure 1. Blunt tissue dissection is of utmost importance as ICG leakage from transected lymphatics can affect visualization in NIR/ICG mode

Figure 2. The camera system is switched to near-infrared mode to locate the SLN

Figure 3. The SLN is then excised, removed, and sent for pathologic examination

GYNECOLOGY

FIBROTHECOMA IN ADOLESCENCE

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Ovarian tumors are rare in the pediatric population but must be considered in patients with abdominal pain and palpable masses. Although considered rare based on their incidence, they are the most common genital tumor, accounting for 60–70% of all gynecological malignancies between the ages of 10 and 19. Ovarian fibromas are benign tumors that consist of spindle cells in bundles or storiformly arranged with collagen fibers in the stroma. Thecomas resemble theca internal ovarian cells, and there is lipid material in their cytoplasm. There is a large histological and immunohistochemical overlap between the two, result-ing in the term fibrothecoma. Appearance of these tumors before the age of 20 is very uncommon. However, some authors cite two peaks in frequency: the first, after the start of menopause and, the second, between the ages of 20 and 40.

Fibroma is characterized by a benign non-hormonal tumor. On the other hand, as we have already mentioned above, it is known that fibroma is of estrogenic origin when it can cause abnormal uterine bleeding and that it can sometimes be androgenic. Functional differentiation in hormone production by luteinized theca cells or Leydig cells determines its course. In rare cases, fibrothecomas can occur with endocrine manifestations related to hormonally active tumors. Meigs syndrome is the first occurrence (ovarian fibroma, hydrothorax, and ascites), observed in 1–10% of ovarian fibromas. After ablating the tumor, hydrothorax and ascites regress rapidly. Another association is named Gorlin–Goltz syndrome, i.e., the basal nevus syndrome. Ultimately, ovarian fibromas may also be linked with familial polyposis such as Gardner's and Richard's syndromes and Peutz–Jeghers syndrome.

The diagnosis of fibrothecoma was made based on pathohistological examination.

DA LI LEČITI MIKROBIOLOŠKI NALAZ ILI INFEKCIJU VULVE KOD DEVOJČICA?

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Vulvovaginitis je najčešće ginekološko oboljenje devojčica. U zavisnosti od etiološkog činioca inflamatorni proces može da počne na vulvi ili vagini, ali zbog anatomskih i fizioloških osobenosti reproduktivnog sistema u prepubertetskom uzrastu zapaljenjem su obično zahvaćena oba organa.

Simptomi i kliničke manifestacije vulvovaginitisa

Na vulvovaginitis ukazuju bolna osetljivost spoljašnjih genitalija, peckanje, svrab, tegobe pri mokrenju i prisustvo genitalnog sekreta neuobičajene boje i mirisa. Kliničkim pregledom moguće je na spoljašnjim genitalijama zapaziti hiperemiju, edem, ekskorijacije i eflorescencije različitih karakteristika (veruke, makule, papule, vezikule, ulceracije, kruste), kao i pojačanu vaginalnu sekreciju [1].

Nespecifični vulvovaginitis

Nespecifični vulvovaginitis nije uslovljen određenim infektivnim uzročnikom, već neodgovarajućom higijenom spoljašnjih genitalija, perineuma i područja anusa. Ta vrsta zapaljenja vulve i vagine je zastupljena kod oko 70% vulvovaginitisa dečijeg uzrasta [2]. Praćena je smeđim ili zelenim sekretom neprijatnog mirisa. U mikrobiološkim brisevima iz vagine najčešće se izoluju koliformne bakterije, a ređe Streptococcus haemolyticus ili koagulaza-pozitivan Staphylococcus, koji su obično posledica autoinokulacije iz nazofarinksa devojčice (tabela 1). Pored nedovoljno razvijenih higijenskih navika, nastanku nespecifičnog vulvovaginitisa doprinosi nošenje sintetičkog donjeg rublja i tesne odeće, kao i izlaganje spoljašnjih genitalija iritantnom delovanju šampona, penušavih kupki i različitih hemijskih preparata. Nespecifični vulvovaginitis ponekad može da rezultuje hroničnom infekcijom sa značajnim psihičkim opterećenjem devojčice i njenih roditelja.

Najvažnije terapijske mere kod devojčica sa nespecifičnim zapaljenjem vulve su sedeće kupke u mlakoj vodi i nanošenje neutralne masti na područje vestibuluma vagine i stidnih usana. Ako je iritacija vulve izražena, u početnoj fazi će pomoći lokalna primena 1% krema s hidrokortizonom. Prevenciji vulvovaginitisa doprinosi adekvatna tehnika brisanja od genitalija ka anusu i dobra higijena perineuma, analnog i perianalnog područja, uz češće menjanje pamučnog donjeg rublja. Potrebno je izbegavati penušave kupke i druge vrste hemijskih i fizičkih iritacija vulve, a preporučuje se nošenje komotne odeće. Kada vulvovaginitis recidivira, a ne postoji dermatološko oboljenje, može se razmotriti sistemska primena penicilinskih ili cefalosporinskih antibiotika, kao i lokalno nanošenje estrogenskog krema [3].

Specifični vulvovaginitis

Specifični vulvovaginitis nastaje inokulacijom respiratornih ili enteričkih mikroorganizama iz drugih tkiva i organa (tabela 2). Respiratorne patogene bakterije koje mogu da izazovu zapaljenje vulve i vagine su: Streptococcus pyogenes (grupa A β-hemolitičkog streptokoka), Haemophilus influenzae, Staphylococcus aureus, Branhamella catarrhalis, Streptococcus pneumoniae i retko Neisseria meningitidis. Enterički prouzrokovači vulvovaginitisa su bakterije iz rodova Shigella i

Yersinia. Do nastanka vulvovaginitisa mogu da dovedu i pojedine vrste adenovirusa i ehovirusa, kao i neke protozoe (Trichomonas vaginalis) i helminti (Enterobius vermicularis).

Vulvovaginitis izazvan β-hemolitičkim streptokokusom grupe A se obično razvija u ranom uzrastu, s najvišom učestalošću broja obolelih u kišovitim i zimskim mesecima. Pretpostavlja se da nastaje prenošenjem piogenog streptokokusa sa inficiranog nazofarinksa na perianalno područje, perineum, vulvu i vaginu. Ova bakterija obično ima patogena svojstva i dovodi do infekcije na mestu inokulacije, odnosno retko kolonizuje spoljašnje genitalije devojčica. Zato se leči sistemskom primenom penicilina tokom 10 dana. Lečenje treba da traje od 14 do 21 dana ako je streptokokusna infekcija zahvatila perineum i perianalno područje [4].

Bakterija Haemophillusa influenzae može da dovede do rekurentnih zapaljenja vulve i vagine, a Staphylococcus aureus se smatra uzročnikom infekcije kada je jedini izolovani patogen. Infekcije genitalnih organa enteropatogenim bakterijama su retke, a nastaju kontaminacijom vagine fecesom u kome se nalaze uzročnici zaraze.

Genitalna kandidijaza je česta komplikacija tzv. dermatitisa pelena. Inače se retko razvija do početka puberteta, osim posle primene antibiotika širokog spektra ili kao prateća pojava kod devojčica sa dijabetesom melitusom i imunodeficijencijom. Sa nastupanjem puberteta vaginalni epitel kumulira glikogen i postaje pogodan za razmnožavanje kvasnica. Genitalna kandidijaza se leči lokalnom primenom antimikotika, a kada recidivira ili poprimi hronični oblik i njihovom sistemskom primenom [5].

Vulvovaginitis prouzrokovan Enterobiusom vermicularisom

Crevni parazit Enterobius vermicularis može da bude uzrok rekuretnog vulvovaginitisa. Ženka parazita polaže jaja na anus, što kod devojčice izaziva svrab i češanje tokom noći. Bolest se dijagnostikuje nalazom jaja parazita na plastičnoj samolepljivoj traci sa anusa, a leči se antihelminticima [1,5].

Vulvovaginitisi prouzrokovani polno prenosivim mikroorganizmima

Ova vrsta vulvovaginitisa u prepubertetskom uzrastu češće nastaje kao posledica seksualnog zlostavljanja devojčice, a ređe perinatalne transmisije s majke na novorođenče [1].

Genitalna infekcija virusom Herpes simplex (HSV) može da nastane pri seksualnom zlostavljanju ili samoinokulacijom uzročnika kod devojčica s herpetičnim stomatitisom. Karakteriše se papulama koje postaju vezikule ispunjene bistrom tečnošću. Po njihovom prskanju ostaju plitke ulceracije. Dijagnoza se postavlja na osnovu virusološke analize sadržaja vezikula. Prethodno treba isključiti herpes zoster. Lokalna primena aciklovira ubrzava zalečenje.

Infekcija Humanim papilloma virusom (HPV) u prepubertetskom uzrastu obično se manifestuje bradavičastim izraštajima u anogenitalnoj regiji. S obzirom na dug latentni period od nastanka infekcije do pojave prvih kliničkih manifestacija, postojanje genitalnih bradavica kod devojčica uzrasta do dve godine ne ukazuje uvek na seksualno zlostavljanje, već može da bude rezultat perinatalne transmisije. U diferencijalnoj dijagnozi treba isključiti često virusno kožno oboljenje molluscum contagiosum, koje se prezentuje kupolastim papulama sa umbilikacijom. Kod obe virusne infekcije preporučuje se uklanjanje kožnih promena.

Sa majke na novorođenče mogu da se prenesu i Chlamydia trachomatis i Trichomonas vaginalis. Zbog osobenosti reproduktivnog sistema devojčica tog uzrasta, infekcije uslovljene ovim uzročnicima obično spontano prolaze.

Vulvovaginitis može da se razvije i kod devojčica koje boluju od seboreje, psorijaze, autoimunskih buloznih dermatoza, atopijskog dermatitisa, osipnih groznica, skabiesa i Crohnove bolesti.

Tabela 1. Mikrobiološki sastav normalne vaginalne flore kod devojčica (Jarienė K, 2019)

Mikroorganizmi	Zastupljenost (%)
Aerobne i fakultativno anaerobne bakterije	
Dipteroides	78
Koagulaza-negativni staphylococci	73
β-hemolitički streptococci	39
Lactobacilli	39
Nehemolitički streptococci	34
Escherichia coli	34
Klebsiella spp.	15
Gardnerella vaginalis	13,5
Streptococcus grupe B	11
Streptococcus grupe D	8,5
Staphylococcus aureus	7
Haemophilus influenzae	5
Pseudomonas aeruginosa	5
Proteus spp.	5
Acinetobacter spp.	3
Genitalne mikoplazme	
Ureaplasma urealyticum	27
Mycoplasma hominis	6
Kvasnice	
Candida spp.	28
Anaerobne bakterije	
Peptococcus spp.	76
Peptostreptococcus spp.	56
Eubacteria spp.	32
Clostridia spp.	48
Bacteroides fragilis	24
Prevotella melaninogenica	56

Tabela 2. Uzroci vulvovaginitisa u dečijem uzrastu (Emans i saradnici, 2019)

Nespecifični vulvovaginitis
Specifični vulvovaginitis
Respiratorni patogeni
Streptococcus pyogenes (β-hemolitički- grupa A)
Staphylococcus aureus
Haemophilus influenzae
Streptococcus pneumoniae
Neisseria meningitidis
Enterični patogeni
Shigella
Yersinia
Ostala flora
Candida
Seksualno prenosivi mikroorganizmi
Neisseria gonorrhoeae

Chlamydia trachomatis

Herpes simplex

Trichomonas vaginalis

Humani papiloma virus (Condyloma accuminatum)

Enterobius vermicularis

Strano telo

Polipi, tumori

Sistemske bolesti: rubella, varicella, scarlatina, mononukleosis, Kawasakijeva bolest, histiocitoza, Crohnova bolest, Stevens-Johnsonov sindrom

Oboljenja kože vulve: lichen sclerosus et atrophicus, seborrhea, atopijski dermatitis, scabies, psoriasis, kontaktni dermatitis, deficit cinka, bulozni pemfigoid

Trauma

Psihosomatske genitalne tegobe

Ostali poremećaji: drenirajući absces male karlice, prolaps uretre, ektopični ureter

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STANJE REPRODUKTIVNOG ZDRAVLJA MLADIH NA SEVERU KOSOVA I METOHIJE U VANREDNIM OKOLNOSTIMA

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Uvod

Vlada Republike Srbije je početkom januara 2018. godine donela uredbu o Nacionalnom program očuvanja i unapređenja seksualnog i reproduktivnog zdravlja građana Republike Srbije. Ovim nacionalnim programom utvrđeni su i njegovi ciljevi i brojne, različite aktivnosti za njegovo sprovođenje.

Prema definiciji Svetske zdravstvene organizacije, reproduktivno zdravlje je stanje fizičkog, mentalnog i socijalnog blagostanja u svim oblastima vezanim za reproduktivni sistem, u svim fazama života. Reproduktivno zdravlje podrazumeva da su ljudi u mogućnosti da imaju zadovoljavajući i bezbedan polni život, slobodu da odluče da li će ga imati, kada i koliko često, kao i sposobnost da imaju potomstvo. Sastavni deo ove definicije reproduktivnog zdravlja je i pravo muškaraca i žena da budu informisani o njemu, da imaju pristup bezbednim, efektivnim, dostupnim i prihvatljivim metodama planiranja porodice po svom izboru, kao i pravo na adekvatne usluge zdravstvene zaštite koje ženi omogućavaju bezbednu trudnoću i porođaj.

Seksualno zdravlje je kontinuitet pozitivnih fizičkih, psihičkih i socio- kulturnih iskustava povezanih sa seksualnošću. Uključuje sposobnost osobe u uživanju i izražavanju svoje seksualnosti i to slobodno, bez rizika od polno prenosivih infekcija i bolesti, neželjene trudnoće, prisile, nasilja i diskriminacije.

Adolescenti predstavljaju veoma vulnerabilnu grupu podložnu prihvatanju raznih oblika rizičnog ponašanja. Rizično seksualno ponašanje podrazumeva mogućnost negativnog ishoda seksualnog odnosa, kao što su: neželjena (maloletnička trudnoća), polno prenosive infekcije i bolesti, nekorišćenje kontracepcijskih sredstava tokom polnog odnosa, konzumaciju alkohola i droga neposredno pre polnog odnosa.

Rana seksualna aktivnost, kao jedan od oblika rizičnog ponašanja, uz nepromišljeno izlaganje riziku nastanka neželjene trudnoće, može da rezultuje poremećajem reproduktivnog zdravlja sa dalekosežnim posledicama na zdravlje i reproduktivni potencijal individue. Osim značajno češćih socijalnih problema, ove trudnoće i porođaji praćeni su pojavom mnogo učestalijih komplikacija u odnosu na žene u punom generativnom periodu. Češće se javljaju: prevremeni porođaji, trudnoćom izazvana hipertenzija (PIH), nastanak krvarenja, anemija, operativno završavanje porođaja, komplikacije nakon porođaja, itd. Kod novorođenčadi adolescentnih majki češće se javljaju: intrauterini zastoj u rastu ploda, imunološki poremećaji, hromozomske anomalije, šećerna bolest.

Mogao bi se steći utisak da su danas adolescenti dobro obaveštena o seksualnom životu i kontracepciji zahvaljujući brojnim porukama koje ih prate na svakom koraku - TV, internet, muzika, filmovi, časopisi, ali to na žalost nije slučaj.

Imajući u vidu da se život i rad, posebno mlade populacije, na području naše pokrajine odvija već čitav niz godina, moglo bi se reći i decenija, u specifičnim, vanrednim uslovima života, postavili smo osnovne ciljeve rada.

Cilj rada

- Utvrditi stanje seksualnog i reproduktivnog zdravlja mlade populacije na našem terenu u vanrednim uslovima
- posebno urvrditi broj adolescentnih porođaja u odnosu na ukupan broj adolescentnih porođaja u odnosu naukupan broj porođaja
- godine života, način porađanja, paritet i starost trudnoće adolescentnih majki
- dužinu, težinu i vitalnost (A.S) njihove novorođenčadi i
- stepen informisanosti adolescenata o rizičnom seksualnom ponašanju

Materijal i metode rada

Retrospektivno je ispitano ukupno 396 porođaja adolescentkinja (starosti do navršenih 19 godina) tokom 2000.- 2009.godine na ginekološko- akušerskom odelenju Zdravstvenog centra u Kosovskoj Mitrovici.

Anonimno su anketirani učenici završnih razreda srednjih škola (starosti od 17- 19 godina) u Kosovskoj Mitrovici, Zvečanu i Leposaviću - statistički je obrađeno 433 kompletno popunjena upitnika.

Rezultati

Prosečan broj adolescentnih porođaja u odnosu u odnosu na ukupan broj porođaja na ginekološko-akušerskom odeljenju Zdravstvenog centra u Kosovskoj Mitrovici u periodu od 2000. do 2009. godine iznosio je 6,2 %, a 2005.čak 7,2%. Od tog broja je čak 13,3% bilo ekstremno mladih porodilja (od 12-16 godina života). Najmlađa porođena adolescentkinja imala je samo 12 godina. Najveći broj adolescentih trudnica je porođeno vaginalnim putem (82,1%). Najmlađa porođena adolescentna trudnica (porođena dva puta carskim rezom) imala je 14, odnosno 16 godina. Svaka peta (20 %) adolescentna porodilja porađa se drugi, treći i četvrti put.

Najveći broj novorođenčadi, 324 (81,0%) je eutrofičan, normalne porođajne težine (2500- 3999 g). Telesnu dužinu između 50 i 59 cm imalo je 87% novorođenčadi adolescentnih majki. Većina novorođenčadi, 76,5% (306) ocenjeno je A.S-om između 7 i 10. Spontanim porođajem porođeno je 86,4% adolescentskih trudnica, stimulisanim- 6%, dok je 7,6% porođeno indukcijom. Epiziotomija je urađena kod 73% adolescentnih porodilja, ali je kod 4% bio prevremeni porođaj. Blizačku trudnoću imale su 4 adolescentne trudnice (1%).

Imajući u vidu da smo u posmatranom periodu imali veliki broj adolescentnih porođaja, posebno iz grupe ekstremno mladih adolescentnih majki, hteli smo da utvrdimo stepen informisanosti adolescenata o rizičnom seksualnom ponašanju. Prijavili smo junior projekat na pomenutu temu („Polno prenosive infekcije- informisanost učenika završnih razreda srednjih škola“ odobren od strane Nastavno- naučnog veća našeg fakulteta), a organizovanje anonimne ankete u srednjim školama odobreno je od strane Ministarstva prosevete, nauke i tehnološkog razvoja Republike Srbije.

Skoro dve trećine ispitanika (63,05%) bilo je ženskog pola, svaka treća ispitanica (33%) bila je seksualno aktivna. Prvi seksualni odnos pre 17 godine imalo je ukupno 40,6 % ispitanika. Statistički značajno je utvrđeno da su osobe, koje imaju prvi seksualni odnos pre 17 godine sklone promiskuitetu. Prvo seksualno iskustvo bilo je dobrovoljno za većinu ispitanika (82,6%).

Pod uticajem alkohola, psihoaktivnih supstanci na žurkama prvi seksualni odnos imalo je 14,8% anketiranih srednjoškolaca. Kondom koristi 51% seksualno aktivnih adolescenata. Kontraceptivne pilule koristi svaka peta seksualno aktivna učenica.

Nijedan ispitanik nije čuo za spermicidne pene i pilulu za dan posle (kao kontraceptivnu metodu). Čak 40% ispitanika ne koristi zaštitu pri seksualnom odnosu sa nepoznatim partnerom. Skoro dve trećine ispitanika, kako polno aktivnih tako i onih koji to nisu, smatra da ne postoji rizično seksualno ponašanje.

Zaključak

Učestalost adolescentnih porođaja u odnosu na ukupan broj porođaja na severu Kosova i Metohije je visoka. Uzrok tome treba tražiti u lošoj informisanosti adolescenata o rizičnom seksualnom ponašanju, koje nije zadovoljavajuće, već veoma oskudno, loše i zabrinjavajuće.

Imajući u vidu da su većinu informacija dobili od medija i prijatelja, treba intenzivirati rad na zaštiti reproduktivnog zdravlja adolescenata, intezivnijim radom zdravstvene službe, organizovanjem tribina, predavanja i drugih širih društvenih aktivnosti i uvrstiti reproduktivno zdravlje u školske planove i programe.

Mada adolescentni porođaji i trudnoće spadaju u visokorizične, podaci naše studije pokazuju da su ishodi porođaja kod adolescentkinja bili dobri zahvaljujući adekvatnoj antenatalnoj i perinatalnoj službi.

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FIGIJ EDUKACIONI CENTAR PEDIJATRISKE I ADOLESCENTNE GINEKOLOGIJE U BEOGRADU – PRI BOLNICI EUROMEDIK

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Međunarodna federacija za dečiju i adolescentnu ginekologiju je osnovana 1971. godine. Subspecijalistička edukacija u ovoj oblasti se sprovodi u pojedinim zemljama Evrope, kao i u pojedinim zemljama na drugim kontinentima. Edukacije iz ove oblasti ginekologije je multidisciplinarna i zahteva saradnju lekara brojnih specijalnosti, a pre svega: pedijatara, endokrinologa, dečijih hirurga i urologa, dečijih radiologa, patologa i naravno ginekologa.

U Evropi se 2016. godine pojavila težnja da se standardizuje edukacija u oblasti dečije i adolescentne ginekologije i nastao je program edukacije koji se sprovodi kroz FIGIJ trening centre. Podrazumeva se da su svi ginekolozi završili minimum edukacije i obuke, i da znaju da urade pregled u dečijem i adolescentnom uzrastu prema tegobama i indikacijama.

Detaljnija edukacija se sprovodi u vremenskom periodu od okvirno dve godine, i kandidati se pripremaju da polažu međunarodni ispit iz ove oblasti koje organizuje FIGIJ još od 1998. godine. U Beogradu je od 2018. godine postoji FIGIJ edukacioni centar koji priprema kandidate za međunarodni ispit – IFEPAG, i on je registrovan pri bolnici EUROMEDIK. Program edukacije je predstavljen u 17 poglavlja, te obuhvata sav sadržaj koji je predviđen po Evropskoj standardizaciji edukacije te odobren od strane EBKOG.

Naravno da edukacija obuhvata i hitna stanja u ovoj oblasti. U detinjstvu i adolescenciji, hitna ginekološka stanja mogu nastati na spoljašnjim ili unutrašnjim genitalnim organima. Učestalost hitnih ginekoloških stanja razlikuje se u zavisnosti od lokalizacije, vrste bolesti i uzrasta adolescenta. Tegobe su često nespecifične, a pacijentkinje se prvo jave pedijatru, zatim budu upućene na dodatnu dijagnostiku radiologu ili hirurgu, a ponekad budu upućene i ginekologu. Pojedina hitna stanja u adolescentnoj ginekologiji zahtevaju hitan operativni tretman. Jedan od načina sistematizacije hitnih stanja u adolescentnoj ginekologiji jeste podela u zavisnosti od lokalizacije.

Naš naučni rad je kroz tretman cista, tumora jajnika i torzija, prikazao moguće probleme koji su posledica dosadašnje edukacije u ovoj oblasti. Jajnike treba štititi kako od tumora i torzija, tako i od načina lečenja koji je zasnovan na pogrešnim pretpostavkama adultnih ginekologa i hirurga o tome šta je bitno u dečijoj i adolescentnoj ginekologiji.

Zaključak

Primenom standardizovane edukacije u dečijoj i adolescentnoj ginekologiji, posebno pravovremena dijagnostika hitnih stanja, može stvoriti uslove za prevenciju komplikacija i izbor optimalnog terapijskog pristupa. Neophodan je detaljan klinički i ultrazvučni pregled spoljašnjih i unutrašnjih genitalnih organa. Lokalni ginekološki nalaz je metod izbora za diferenciranje hitnih stanja na spoljašnjim genitalnim organima, a ultrazvuk male karlice za postavljanje dijagnoze kod hitnih stanja unutrašnjih polnih organa. Izborom optimalnog pristupa lečenju hitnih stanja u dečjem i adolescentnom uzrastu povećava se i mogućnost očuvanja fertiliteta.

Za primenu postojećih znanja i veština u oblasti dečije i adolescentne ginekologije, neophodna je sistematična edukacija u ovoj oblasti.

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HORMONES ANG AGING – WHAT ARE THE CONECTIONS WITH METABOLIC CHANGES IN MENOPAUSE

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Weight gain is very common in menopause: about 30% women between ages 50 and 59 have crossed the threshold of overweight and become obese. Hypertension is the most common consequence of obesity; if the structure of the body changes and the visceral type of obesity develops, which is the case with most menopausal women, then the risk for heart diseases and diabetes increases many times over. If the waist circumference exceeds 83 cm, it is time to take serious steps in order to stop this negative trend. Why is it so difficult to maintain the body mass and structure of the body in the normal ranges? It is probably a complex and mixed influence of endocrine system aging and changes related to menopause.

ENDOCRINE SYSTEM AGING GROWTH HORMONE AXIS (GH)

Peak of growth hormone secretion is recorded in mid-puberty and after that, mean GH secretion is declining by 50% in every 10 years. After 30th year of life, the only night peaks of GH are recorded, and after 40th year of life GH does not increase even during physical effort /exercise, so there are no recordable GH in bloodstream. In menopausal women, oral estrogen supplementation inhibits hepatic IGF1 synthesis whereas IGF1 increase and contrary, IGF1 synthesis is unchanged if estrogen is replaced by transdermal route. GH is anabolic hormone, which increase protein synthesis and tissue incorporation and directs fat metabolism towards fat breakdown. Decreased output by IGF1/GH axis is associated with increased proportion of total body and visceral fat, decreased muscle mass, decreased physical fitness, decreased immune function, decreased gonadal function and decreased joy in life.

Available therapies: In children and adults with GH deficiency, GH replacement is beneficial on body composition, serum lipids, fitness and bone density and also increases growth velocity in children. Concerns of GH therapy in adults are: possible GH stimulation on malignancy, senescence and telomere shortening. In clinical trials using medication reversing age associated decline of GH concentration, there is small improvement of body structure at the expense of increased rate of adverse effects: soft tissue edema, arthralgia, carpal tunnel syndrome, increased rate of diabetes. For that reasons there is no approved therapy to reverse decline of GH secretion related to aging.

ADRENAL AXIS

The normal zona glomerulosa atrophies with aging and instead, aldosterone producing micronodules becomes numerous, manifesting autonomous aldosterone production, in the absence of angiotensin II production, which explains why the prevalence of salt sensitive hypertension increases with age. 24H – cortisol production and free cortisol concentrations are higher, diurnal rhythm is flattened with higher night cortisol level and earlier morning peak, HPA axis is more responsive to stress, in part due to reduced negative feedback inhibition. Exaggerated catabolism of aging which is visible in many tissues- skin, massless, bones - is partly caused by changes of cortisol secretion and regulation.

DHEA

DHEA, DHEAS, androstenedione and testosterone all decline from age 30 onward, reflecting a gradual reduction in the size of zona reticularis

Available therapies: Drug therapy is not well studied for subtle ACTH – independent hypercortisolemia of aging. DHEA administered as a 6,5 mg intravaginal insert improves symptoms of vulvovaginal atrophy in postmenopausal women and is FDA and EMA approved for this purpose. Systemic DHEA supplementation has not shown major benefits in older individuals.

THYROID AXIS

There is the increase of TSH secretion with age, T3 concentration are lower in older individuals suggesting the age related decline in 5-deiodinase activity. The shape of TSH distribution suggests a population shift to higher levels rather than increased incidence of hypothyroidism in older population. Subclinical hyperthyroidism – low T4 concentrations with normal concentrations of free T4 – is more common in older individuals due to increased autonomous secretion of thyroid hormones from thyroid nodules and is associated with an increased risk of atrial fibrillation, hip fracture and dementia if left untreated.

VITAMIN D

The large capacity of the skin to produce vitamin D decreases with aging, approximately 13% for each decade of life. Older individuals are still able to increase production of D vitamin as the response to UVB. A dose response meta-analysis of individuals aged 62 to 79 years indicated that serum 25OHD levels are directly correlated with the risk of frailty. Vitamin D without calcium, did not have a beneficial effect on risk of fractures. The recommended daily doses are 600 IU and 800 IU if person is older than 70 years.

THE CLINICAL CONSEQUENCES OF CESSATION OF OVARIAN FUNCTION

Ovarian aging is associated with changes in lipid profile, changes in body structure, central distribution of adipose tissue, accelerated cardiovascular risk, accelerated lumbar spine BMD loss and negative changes in sleep cognition and mood [1,2]. A truncated reproductive life span is associated with higher risk for cardiovascular events and mortality. Alternatively, cardiovascular health might be contributing factor to the timing of menopause, influencing the vascularization of the ovary, so the relations are bidirectional [3,4].

Overall changes within hormonal axes make menopausal women vulnerable to body composition changes, muscle loss and abdominal obesity; with the sedentary lifestyle, this changes affect overall energy expenditure and basal metabolic rate. In particular, increased bone marrow derived adipocytes due to estrogen loss are directed to visceral region and contribute to visceral adiposity of menopausal women. Enhanced visceral fat lipolysis by adipose tissue lipoprotein lipase triggers the excessive production of free fatty acids, causing insulin resistance and metabolic diseases. Because gens involved in beta oxidation are downregulated by estradiol loss, excess free fatty acids produced by lipolysis of visceral fat cannot be used appropriately as an energy source through beta oxidation. As the result, the catabolism of ATP production associated with beta oxidation decreases and metabolism associated with lipid synthesis increases, which leads to fat accumulation. The rate of lipolysis is higher in abdominal fat than in gluteal fat, which triggers excessive free fatty acid production from excessive visceral fat breakdown, promotes insulin resistance and leads to metabolic disease. Generally, menopause is accompanied with accelerated loss of skeletal muscle, which further decreases energy expenditure during rest and

physical activity. Thus, body function impairment originates from muscle loss in menopausal women, leading to difficulties in carrying out voluntary activities and reducing the quality of life. The most promising strategy for increasing muscle and bone mass is resistance training, as well as sufficient amount of protein (1-1,2 g/kg of body mass), vitamin D and calcium and creatinine to help to preserve this tissues during menopause. Estrogen plays the pivotal role in systemic energy homeostasis. E2 directly regulates mitochondria membrane biophysical properties and bioenergetics functions, providing a direct pathway by which estrogen state broadly influence energy homeostasis.

The primary indication for menopausal hormone therapy is treatment of symptoms. Prevention of osteoporosis is another approved indication of MHT, for postmenopausal women at significant risk for osteoporosis for whom other approved therapies are neither tolerated nor appropriate. Additional preventive indications have been considered and are currently under review [3]. Decisions regarding the optimal choice for individual women depends of degree of specific symptoms, personal preference, thromboembolic and breast cancer risk assessment and uterine status. Treatment of GSM includes vaginal moisturizers and lubricants, vaginal estrogens, DHEA and oral ospamifen or CEE/basedoxifen. Testosterone use is not approved for menopausal problems, so, titration of approved therapies for men has been recommended for treatment of hypoactive sexual desire [5].

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IVF AND INFERTILITY

INTRAUTERINE INSEMINATION

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The percentage of infertile marriages worldwide, including in our country, ranges from 12-18% [1]. Female infertility accounts for about 50%, male infertility for 20-30%, and the same percentage represents combined issues in both partners [2]. Unexplained infertility is often used for couples with ovulation, patent fallopian tubes, and a normal spermogram but does not achieve pregnancy. Some authors report a very high percentage of such couples, up to 30% [3].

Intrauterine insemination (IUI) involves the transcervical injection of processed sperm into the uterine cavity. It is a first-line procedure used in couples with unexplained infertility, cervical infertility factors, mild endometriosis, dysfunctional anovulation, mild to moderate infertility, and male sexual dysfunction.

Inseminations have been practiced for centuries. In unofficial history, it is mentioned that Henry IV attempted the first inseminations in the 15th century. In the 17th century, the first artificial insemination in a dog was performed by Lazzaro Spallinzani (Italian physiologist, 1729-1799), resulting in the birth of three puppies. The first documented insemination in human medicine, performed in a case of severe hypospadias, was carried out by John Hunter in 1770. Official reports on IUI in the human population date back to Gutmaher (1943) [4], Stoughton (1948) [5], and Kohlberg [6]. These reports marked the beginning of a new era in assisted reproduction. With scientific and technological advancements, the procedure has continuously improved, both in terms of better semen processing and, obtaining follicles and performing the procedure timely and adequately. However, unlike in vitro fertilization (IVF), where success rates are steadily increasing, they remain relatively constant in IUI.

As previously mentioned, it is crucial to select the appropriate patients referred for this procedure.

IUI is indicated in cases of the following causes of infertility: ovulatory dysfunction, cervical infertility factors, mild endometriosis, mild to moderate male infertility, sexual dysfunction, and immunological issues, as well as in cases of unexplained infertility. Contraindications include cervical atresia, blocked fallopian tubes, infections, severe male fertility disorders, and cases of long-term infertility. For women over 38 years old, IUI should only be performed during the preparation for IVF and exclusively without ovulation stimulation. The same applies to women with premature ovarian insufficiency (POI).

IUI can be performed in a natural cycle or after ovulation stimulation using medications such as clomiphene citrate (CC), letrozole, or gonadotropins. Reviewing the literature, it is observed that women stimulated with gonadotropins tend to have a slightly higher pregnancy rate and a greater risk of multiple pregnancies [7]. Controlled ovarian stimulation (COH) with gonadotropins aims to develop follicles in anovulatory women who have not responded to oral therapy or to produce more follicles in ovulatory women to increase the chances of fertilization. The American Society for Reproductive Medicine (ASRM), the European Society of Human Reproduction and Embryology (ESHRE), and many other organizations provide guidelines for ovarian stimulation in women with anovulation, emphasizing the need to minimize the risk of multiple pregnancies. They recommend discontinuing IUI when there are two or three mature follicles [8].

Women with dysfunctional anovulation are most commonly stimulated with clomiphene citrate in our practice. One issue we encounter is the thickness of the endometrium. The anti-estrogenic effect of clomiphene can reduce its thickness by 25-30%. Many studies describe a reduced endometrial thickness in the late follicular phase, although its echogenicity is not altered during vaginal ultrasound examination [9].

Cervical factors as a cause of infertility encompass all changes in the cervix and cervical canal that can hinder sperm penetration and consequently make conception more difficult. Changes associated with cervical factors include inadequate cervical mucus, cervical scarring after procedures related to HPV infections, and pronounced anteflexion, retroflection, or uterine flexion. IUI provides a sort of bypass, overcoming obstacles in the cervical canal.

Often, there is a combination of multiple infertility factors, and on the contrary, unexplained infertility (idiopathic infertility) where all investigated parameters in infertile couples fall within normal limits, yet pregnancy does not occur. IUI is recommended in many European countries and the United States for unexplained infertility because it is less expensive and invasive than IVF [10,11]. However, the National Institute for Health and Care Excellence (NICE) in 2017 did not recommend IUI for couples with unexplained infertility, male factor infertility, or mild endometriosis. The recommendation was to refer directly to IVF if pregnancy did not occur after two years. The 2019 Canadian guidelines suggest that age and the duration of infertility determine the choice of assisted reproductive technique. IVF can be a first-line procedure or considered after three unsuccessful IUI attempts.

The success rate of IUI is higher in younger patients with good ovarian reserve, shorter duration of infertility, and in cases of secondary infertility.

Male factor infertility is present in approximately 20% of infertile couples. Numerous factors can affect spermatogenesis, including congenital disorders, injuries, testicular torsion, exposure to medications, high temperatures, radiation, toxic substances, chronic diseases, varicoceles, and more. One of the main challenges in male infertility is the lack of well-defined cutoff values for sperm parameters. IUI is typically reserved for milder forms of sperm abnormalities. Establishing an exact upper limit for the number of sperm in a milliliter of ejaculation as a criterion for IUI is challenging. On average, it should not be less than 10 million per milliliter in the native sample, with preserved motility and normal sperm morphology [12]. It is much easier to establish criteria in a processed sample. The chances of a favorable outcome with IUI are low if the number of motile sperm in the processed material is below 5 million per milliliter.

Folliculometry

After clinical evaluation, including hormonal, microbiological, and ultrasound assessment, a hysterosalpingography (HSG) is performed, which is a method to examine the interior of a woman's reproductive tract. Hystero-contrast-salpingography (HyCoSy) also provides necessary information about the patency of the fallopian tubes. To proceed with IUI, at least one fallopian tube must be open. If a couple meets the inclusion criteria for the IUI procedure, an ultrasound examination with a transvaginal probe is conducted on the 2nd or 3rd day of the menstrual cycle. This examination provides information about the presence of cysts, fibroids, and endometrial polyps, as well as the number of antral follicles, which indicates the condition of the ovaries and ovarian reserve. Depending on the length of the menstrual cycle, monitoring follicle and endometrial growth begins during the dominant follicle development phase. The endometrium should follow the follicle's growth. Due to increased estradiol production, the endometrium thickens by 1-2mm per

day. In addition to thickness, it is essential to assess its quality, and during the follicular phase, it should have a typical triple-line appearance. Through repeated examinations (folliculometry), the time of ovulation and IUI, or in stimulated cycles, the time of trigger shot for ovulation, can be determined. In late follicular phase folliculometry, E2, LH, and P4 hormone levels are measured. In comparison to the pre-ovulatory LH surge, which correlates with the ultrasound findings of follicle and endometrial growth, ovulation can be accurately predicted, and the optimal timing for intrauterine insemination can be planned, which is one of the most critical factors for the success of the procedure.

In a natural cycle, ovulation occurs 36 hours after the LH surge or 16 hours after its peak. IUI is performed 24 hours after the LH surge. In stimulated cycles, when the follicle reaches a size of 18 mm, human chorionic gonadotropin (hCG) is administered as the trigger for ovulation, which occurs 36 hours later, and IUI should be done between 24 to 40 hours after hCG injection.

Typically, one IUI per cycle is recommended. Significant benefits of double insemination have been observed in cases of male infertility [13]. Couples are recommended to undergo three IUIs, although in certain cases, such as refusal of IVF or a long delay before starting the procedure, IUI can be performed up to six times. Most published studies show the pregnancy success rate ranges from 5% to 15%. Data from the ESHRE 2005 registry (A.N. Andersen) showed that the success rate of IUI in women up to 40 years of age is 12.6% per procedure, but it significantly decreases in women over 40 years to 7.4% [14].

The highest percentage of pregnancies occurs after the first IUI, significantly decreasing after several cycles [15, 16]. The highest pregnancy rates are seen in couples with ovulatory dysfunction as the cause of infertility, followed by unexplained infertility, cervical factors, and milder forms of male infertility. In contrast, the lowest rates are observed in cases of endometriosis and tubal factors [16].

Methods of Semen Processing

There are various techniques for processing semen, all aimed at achieving the maximum concentration of motile sperm while removing seminal plasma, prostaglandins, microorganisms, leukocytes, non-motile and immature sperm, and other elements that could potentially cause uterine contractions and complications such as infections. After processing, a sample with a high percentage of sperm with normal morphology and progressive motility is obtained, which can be introduced into the uterine cavity. The oldest method involves washing sperm and centrifuging it. The other two methods commonly used in most reference laboratories are the swim-up and density gradient techniques.

The swim-up technique involves centrifuging and separating sperm first, and then, using a medium, motile sperm swim up to the surface. In the density gradient technique, density gradients are used to filter the sample, separating motile sperm in the form of a pellet that is then washed and mixed with a medium. Both methods are equally used, although the second method is recommended for poorer sperm samples. There have been no observed differences in pregnancy rates when using these methods [17].

Performing IUI (Intrauterine Insemination)

When the following conditions are met: the presence of a pre-ovulatory follicle, hormone levels indicating imminent ovulation, and an appropriate endometrial lining, the IUI procedure can be planned. After obtaining the ejaculate, it undergoes processing. Since the results of sperm analysis can vary, examining the raw semen is done before processing. If the findings are inadequate,

such as a sperm count below 10 million per milliliter, reduced motility, or abnormalities in sperm morphology, the IUI procedure is canceled.

The IUI procedure is performed with the patient in a position similar to a gynecological examination. The vagina is exposed, and an IUI catheter is gently passed through the cervical canal into the uterine cavity. To facilitate this process, ensuring the catheter easily passes through the internal cervical opening, the patient is asked to have a full bladder to help straighten the uterocervical angle through pressure on the uterine body. A full bladder also aids in better ultrasound visualization if needed. The content of the syringe containing the processed sample is slowly injected. After the content is expelled, the catheter remains in the uterus for a short period before removal. The patient typically remains lying for an additional 10 to 15 minutes.

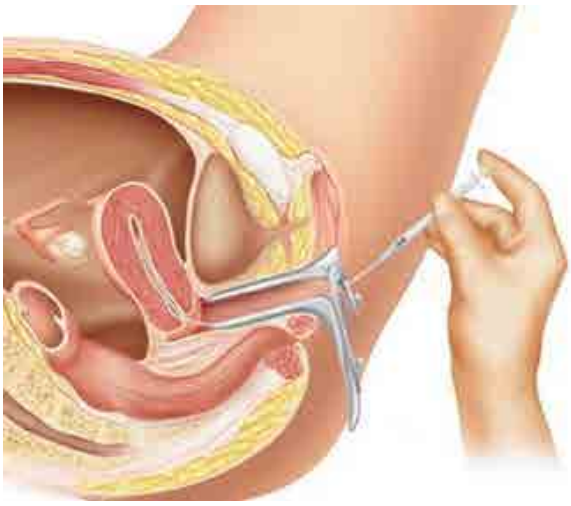

Figure 1.1
Intrauterine insemination procedure
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What is the future of IUI? Although research efforts predominantly focus on improving in vitro fertilization (IVF), due to its less invasiveness complexity and economic affordability, intrauterine insemination rightfully maintains its status as the first-line approach to overcoming infertility. The introduction of legal regulations enabling IUI with donor sperm would significantly facilitate the procedure in cases of severe male infertility and women without partners.

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PREGNANCIES AFTER IVF PROCEDURES – OUTCOME AND DELIVERY

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The use of artificial reproductive techniques is constantly increasing worldwide. In USA 1.6% of all newborns and 18.3% of all newborns from multiple pregnancies are conceived by IVF. The most of pregnancies after IVF are uncomplicated, but IVF pregnancies may be associated with adverse perinatal outcomes, primarily caused by prematurity (most often iatrogenic) and low neonatal birth weight. Multiple pregnancies after IVF contribute significantly to the increase in perinatal morbidity [1].

Etiological factors leading to pregnancy complications after IVF include:

- IVF procedure – used drugs, laboratory conditions during embryo cultivation, medium for culture, or cryopreservation / thawing of embryos;
- maternal conditions related to the cause of infertility or infertility itself; and
- older maternal age. It is often impossible to separate individual factors, because the causes of complications are mostly multifactorial [2].

ESHRE report on IVF in Europe for 2018. on 999,530 cycles finds that at term delivered 83.1% singleton pregnancies, 43.6% of twins and 8.1% of triplets. OHSS was reported in 1719 cases, bleeding in 997, and infection in 139 cases. There were 3 cases of maternal death [3].

The same year, 2018. in USA were reported 306,197 cycles. Out of 3,813,136 children born during 2018. in USA, 74,926 (2.0%) were conceived by ART. 21.4% of ART pregnancies were multiple, while out of all multiple pregnancies 12% were by ART. Out of all small for gestational age neonates, 4.2% were from IVF pregnancies [4].

In order to minimize the risk of preterm birth in pregnancies conceived by ART, FIGO recommendation is to perform single embryo-transfer [5]. However, increased risks for preterm

birth, fetal growth restriction and stillbirth are also associated with a singleton IVF pregnancy. Risks of pregnancy complications are higher in IVF pregnancies compared to spontaneous pregnancies. Risk of preterm delivery after IVF may be the consequence of embryo manipulation (embryo-culture, freezing/thawing, ET), or pathological placentation. Therefore, it is recommended to reduce embryo manipulation to a minimum. Pregnancy complications may be connected with the causes of infertility and, while planning IVF, it is recommendable to discuss the risks with the patient.

Study evaluating pregnancy complications depending on the cause of infertility found that women with tubal factor, PCOS, ovulation problems or endometriosis had pregnancy complications even when they did not have ART. Women with tubal factor, PCOS, ovulation problems or endometriosis had complications even when they did not have ART. Placentation problems significantly higher in ART compared to pregnancies without ART and with the same diagnoses [6]. The other study found lower incidence of Cesarean section and preterm delivery in male induced infertility (ICSI) [7].

Advanced maternal age of the mother is connected to pregnancy complications. Retrospective study from Japan found that the percentage of primiparous women above 40 years who delivered in period 2003. - 2007. and 2013. – 2017. increased from 1.5 to 4.8% due to the increase in the pregnancy conceived by in vitro fertilization (IVF). Advanced maternal age was connected with higher prevalence of postpartum hemorrhage [8]. Study from China on 3325 women report that women of advanced maternal age, IVF-ET pregnancies may result in higher rates of pregnancy complications and adverse birth outcomes, but this is likely to be due to increased rates of multiple pregnancies [9].

AMH and perinatal outcome in ICSI was studied in a multicenter study in China on 13,763 IVF/ICSI cycles, 5657 deliveries and 6797 neonates. Women with elevated AMH had increased risk of having gestational diabetes mellitus and hypertension, but there was no association with poor neonatal outcome [10].

Third stage of labor is complicated by more frequent postpartum hemorrhage, placental retention and need for blood transfusion [11, 12].

Delivery after IVF

Delivery in pregnancies after IVF is controversial and question arises whether Cesarean section or vaginal delivery is preferable. The mode of delivery in cases after infertility treatment, especially after IVF present the great dilemma of the obstetricians, perinatologists, and infertility subspecialists. There is a worldwide significant increase in Cesarean section rate (from 12.1% in 2000 to 21.1% in 2015.), and WHO concluded that frequency of cesarean section over 10% does not reduce maternal and neonatal morbidity [13,14].

In IVF pregnancies, Cesarean section is three times more frequent. Infertile women have more frequent Cesarean section (51.8% vs. 36.1%), lower gestational age at birth and more frequent late preterm delivery [15]. Induction of labor is more likely to be unsuccessful in pregnancies after IVF, or infertility tretatment. [16,17].

Observational study from Spain evaluating the period between 2013. and 2018., found that women who underwent IVF had a higher likelihood to deliver by Cesarean section, both elective (14.4 vs 3.7%); OR - 2.91 and urgent SC (23.3 vs 15.1); OR - 2.27 [18].

A multicenter case–control study from Israel included 80 women aged 17–25 years in singleton pregnancies after IVF and 160 women in a control group matched for maternal age at delivery and parity. The IVF group had a significantly higher rate of induction of labor (48.1% vs. 26.6%,), meconium-stained amniotic fluid (27.6% vs. 14.1%), prolonged second stage of labor (26.0% vs. 7.3%) and operative vaginal delivery (22.5% vs.12.5%). There was no difference in Cesarean section rate, both elective (18.8% vs 15.0%), and urgent (73.3 vs 81.8%) [19].

A population-based cohort study assessed the association between mode of conception and Cesarean section across Robson groups on 921 023 births between 2006–2014. The study reported increased frequency of Cesarean section in women who underwent infertility treatment and IVF, especially in nulliparous women with single term pregnancies [20].

There are lot of meta analyses comparing pregnancy outcome in IVF. Meta analyses that compared singleton pregnancies conceived by simple IVF and ICSI, report higher incidence in pregnancy complications (hypertension, gestational diabetes mellitus, fetal growth restriction, PPROM), and Cesarean section rate (OR - 1.56 / 1.9) in ICSI pregnancies [21,22]. Meta - analysis evaluating pregnancy outcome in dichorionic twins report higher incidence of placenta praevia

(OR / 2.99) and Cesarean section (OR – 1.79) in cases conceived by IVF comparing to spontaneous pregnancies. Meta - analysis comparing FET versus fresh embryo-transfer didn`t find difference in pregnancy complications and perinatal mortality [23]. Pregnancies after oocyte donation have higher incidence of pregnancy complications (hypertension, OR/3.92; fetal growth restriction – OR / 2.71; preterm delivery - OR- 1.34) regardless of maternal age [24].

Management of pregnancies after IVF

Society for Maternal and Fetal Medicine recommended guidelines in management of pregnancies resulting from in vitro fertilization [25]:

- Placentation disorders are more frequent in pregnancies after IVF:

1. pathological placental forms (bilobularis, succenturiata);
2. placenta praevia (OR, 2.72); more often after blastocyst transfer (OR, 2.18);
3. marginal / velamentous insertion of umbilical cord and
4. PAS (3-6 times more often than after spontaneous pregnancy)

- In pregnancies after IVF preterm delivery, fetal growth restriction and stillbirth are more frequent, especially connected to specific IVF techniques and oocyte donation.
- There is no justification for planned delivery at 39 weeks, as it doesn`t reduce the incidence of perinatal morbidity.

IVF pregnancies in Clinic for Gynecology and Obstetrics "Narodni front"

During 2022. in Clinic for Gynecology and Obstetrics "Narodni front" were 7397 deliveries, from what 558 (7.54%) were pregnancies after IVF. Overall Cesarean section rate was 30.5%, while in IVF pregnancies it was 65.59%. 33.51% of women after IVF weere older than 40 years, while 9.86% were older than 45 years.

Conclusion

Pregnancies after IVF are becoming more frequent, especially in older pregnant women. Multiple pregnancies are more common in pregnancies after IVF. In pregnancies after IVF, a higher frequency of preterm birth and placentation disorders are observed. There is no justification to induce labor in uncomplicated pregnancies after IVF without a clear indication before the due date. Uncomplicated pregnancies after IVF in mothers aged less than 40 years are not an indication for Caesarean section, but delivery requires intensive monitoring.

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PRIJEVREMENA OVARIJUMSKA INSUFICIJENCIJA – KONTEKST DUGOROČNIH EFEKATA NA ZDRAVLJE

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Uvod

- Prijevremena ovarijumska insuficijencija (POI), definicija i incidencija

Prijevremena ovarijumska insuficijencija (POI), predstavlja heterogeni poremećaj, multifaktorijalnog porijekla, kojeg čini stanje hipergonadotropinizma (folikulostimulišući hormon veći od 40IJ), hipoestrogenizma (estradiol manji od 50 pmol/L), sa konsekutivnom amenorejom ili oligomenorejom, u žena mlađih od četrdeset godina [1].

POI je kompleksan i relativno slabo rasvijetljen entitet, sa mnoštvom uzročnih faktora koji ga mogu izazvati, ali i multisistemskim posledicama za koje se zna da potiču od preranog nedostatka ovarijumskih polnih steroida [2].

Incidencija POI je oko 1% žena prije četrdesete godine života i približno 0,1% žena prije tridesete godine života. Smatra se rijetkim ali važnim uzročnikom deficita polnih hormona kod žene ali i ženskog infertiliteta [3].

- Etiologija

POI može bit rezultat spektra poremećaja koji podrazumijevaju smanjenu ovarijumsku funkciju, a to su: prijevremeno opadanje inicijalnog broja ovocita tokom razvoja jajnika, ubrzana folikularna destrukcija ili oslabljen odgovor folikula na djelovanje gonadotropina [4].

POI je u 74-90% slučajeva idiopatski poremećaj, mada može biti sa familijarnim pojavljivanjem (4-33%) ili sporadičan [4].

Poznati uzroci POI su: genetske aberacije; autoimune bolesti koje pogađaju ovarijalno tkivo; jatrogeni uzroci–nakon operativnih zahvata na ovarijuma, radioterapijskih i hemioterapijskih procedura; štetni faktori spoljašnje sredine (virusi, toksini, pušenje cigareta); metabolički faktori-galaktozemija, 17-OH deficijencija [4].

Nedovoljno rasvijetljeni uzroci POI su stresori, inflamacijska stanja organizma, skraćenje telomeraze, ubrzanje biološkog sata [5].

Nauka intenzivno radi na rasvjetljavanju etioloških faktora i mogućnostima prevencije a aktuelno ukazuje da je hormonska supstituciona terapija (HST) lijek koji je neophodan za opšte zdravlje ovih pacijentkinja.

- Rani simptomi i znaci

Vazomotorni simptomi (VMS) su najčešće prva obilježja rane ili prijevremene menopauze. Talas vrućine (valung) je iznenadna epizoda vazodilatacije u području lica i vrata,koja traje 1-5 minuta i praćena je profuznim znojenjem. Utvrđeno je da žene koje prijavljuju talase vrućine imaju suženu termoregulacionu zonu i zato suptilne promjene centralne temperature pobuđuju termoregulacione mehanizme što izaziva vazodilataciju, preznojavanje ili drhtavicu.

Opadajući nivoi estrogena i inhibina istovremeno i rastući nivo FSH mogu samo djelimično objasniti poremećenu termoregulaciju u ranoj menopauzi, s druge strane studije pokazaju da

značajan udio u patofiziologiji VMS imaju promjene na nivou neurotransmitera centralnog nervnog sistema i promjene u perifernoj vaskularnoj reaktivnosti [6].

Estrogen ima moćnu vazoaktivnu funkciju, koja se ogleda u povećanom elasticitetu krvnih sudova i modifikaciji odgovora na reaktivnu dilataciju i lokalnu inflamaciju, tako da sami nedostatak estrogena u poznoj perimenopauzi i ranoj menopauzi, koji se klinički manifestuje VMS može predstavljati uvod u razvoj ateroskleroze i buduća kardiovaskularna oboljenja [9].

- Kasne posledice neliječene POI

Nedostatak ovarijalnih estrogena u POI osim vazomotornim simptomima (VMS), koji su najčešće prolaznog karaktera, ispoljava se i trajnim posledicama na cjelokupno zdravlje i to: urogenitalnom atrofijom, seksualnom disfunkcijom, gubitkom koštane mase i metaboličkim promjenama koje kasnije dovode do razvoja kardiovaskularne bolesti (KVB) i dijabetesa (DM) ukoliko se adekvatna estrogena sredina ne uspostavi supstitucionom terapijom [6].

Urogenitalna atrofija uzrokovana efektima hipestrogenemije na spoljašnje ginekološke organe, mokraćnu bešiku i uretru manifestuje se suvoćom i nelagodnošću u predjelu genitalne regije, rekurentnim urogenitalnim infekcijama kao i bolnim i nelagodnim polnim odnosima [5].

Seksualna disfunkcija je 2-8 puta učestalija kod žena sa POI u poređenju sa ženama istog doba koje imaju regularne menstralne cikluse [34].

Osnovni mehanizmi gubitka koštane mase uključuju: slabije dostizanje vrhunca koštane mase, ubrzanu koštanu resorpciju udruženu sa estrogenim deficitom, prisustvo ostalih komorbiditeta koji koji povećavaju rizik od osteoporoze i potecijalno prisustvo patoloških stanja koji su u etiologiji POI a takođe mogu uticati na gubitak koštane mase [18].

Maksimalna koštana masa kod žena, postiže se do tridesete godine života, i estrogen je fundamentalan faktor u ovom procesu. Prolongiran deficit estrogena prije ovog doba rezultira smanjenim dostizanjem maksimalne koštane mase, dok estrogeni deficit nakon dobi od trideset godina, posebno u kontekstu POI, rezultira ranim gubitkom koštane mase [14].

Hipoestrogenizam u POI indukuje produkciju u višku receptora aktivatora nukleusnog faktora kappa liganda (RANKL) od strane osteoblasta, što predstavlja stimulaciju osteoklastogeneze i koštane resorpcije što će vremenom dovesti do osteoporoze.

Terapija estradiolom povećava produkciju osteoprotegerina, sekretovanog od strane osteoblasta, koji je inhibitor RANKL [15-16].

Dugotrajan hipoestrogenizam je faktor rizika za metabolički sindrom, dislipidemiju, endotelijalnu disfunkciju, inflamaciju, kardiovaskularne bolesti, poremećaje autonomnog i centralnog nervnog sistema i mnoge druge bolesti [37].

Nedostatak estrogena promoviše aktivaciju sistema renin-angiotenzin, podiže nivo endotelina – moćnog vazokonstriktora i ometa vazodilataciju posredovanu azot oksidom (NO). Oksidativni stres koji je podržan endotelinom i angiotenzinom II može dodatno doprinijeti razvoju ateroskleroze [36].

Hipoestrogenizam i hiperinsulinizam, nezavisni su faktori rizika za kardiovaskularnu bolest,indukujući centralnu gojaznost i zadržavanje tečnosti. Osim redistribucije tjelesne masti dolazi do promjena samih adipocita koji postaju veći i rezistentni na dejstvo insulina a samim tim oslabljene sposobnosti da održavaju nivoe lipida i glukoze [35].

U skladu sa navedenim patofiziološkim procesima, žene ubrzo nakon menopauze imaju povišen krvni pritisak, kao i evidentnu ili subkliničku vaskularnu bolest [35].

Primarna ovarijumska insuficijencija i rana menopauza konzistentno su povezane sa povišenim rizikom od koronarne bolesti srca, šloga i povišenim mortalitetom od kardiovaskularnih bolesti ukoliko deficitarni estrogeni milje nije adekvatno i na vrijeme nadoknađen supstitucionom terapijom [10].

Promjene u tjelesnim dimenzijama, dobijanje u tjelesnoj težini, urogenitalne i psihološke promjene mogu narušiti osjećaj sopstvene privlačnosti i samopouzdanje [5].

U mnogim studijama koje su obuhvatale žene sa dijagnozom POI ukazano je na slabije psihosocijalno funkcionisanje, slabiji kvalitet života, slabiju vitalnost i češće poremećaje mentalnog zdravlja u poređenju sa grupama žena koje su u menopauzu ulazile u uobičajenim godinama [18].

Kod žena koje su bile podvrgnute hirurškim procedurama prije ulaska u prirodnu menopauzu, bilo da se radilo o bilateralnoj ovarijektomiji ili histerektomiji sa konzervacijom adneksa, češće su dijagnostikovane depresija i anksioznost i to vjerovatno zbog prijevremenog potpunog otkazivanja funkcije jajnika a u uslovima neadekvatne promptne hormonske supstitucije [18].

- Hormonska supstituciona terapija

Pacijentkinje sa POI moraju biti adekvatno informisane o terapijskim mogućnostima. Preporučeno je usvojiti zdrave životne navike, pridržavati se balansiranog dijeteskog režima, fizičke aktivnosti, redovnog spavanja i obustaviti štetne navike kao što je navika pušenja [36].

Hormonska supstituciona terapija (HST) je okosnica liječenja ovih pacijentkinja i zavisno od perioda života ima mnogostruke benefite.

o Omogućava razvoj sekundarnih polnih karakteristika (uključujući i rast uterusa), kada POI nastupi prije puberteta.

o Efikasno ublažava vazomotorne simtome (talase vrućine i preznojavanja) i urogenitalne probleme koji nastaju zbog vulvovaginalne i atrofije mokraćne bešike (vaginalna suvoća, bolnost prilikom polnog odnosa, urgentnost mokrenja i rekurentne infekcije urogenitalnog trakta).

o Ima povoljne efekte na ostale simptome koji smanjuju kvalitet života (promjene raspoloženja, kognitivne poremećaje, smanjenje ukupne energije i vitalnosti, muskuloskeletne probleme i bolove).

o Adekvatno dozirana hormonska supstituciona terapija omogućava šansu za trudnoću ovim pacijentkinjama ili adekvatnu sredinu za razvoj doniranog embriona. 90% pacijentkinja sa dijagnostikovanom POI su nulipare [19]. Vjerovatnoća ostvarivanja spontanog začeća kod ovih žena je manja od 5% [20]. U studiji Dragojević i sar. uz povećanje doze estradiola moguć je i veći broj trudnoća [38].

o Hormonska supstituciona terapija će minimizovati buduće zdravstvene rizike kod žena sa POI a to su obolijevnje od kardiovaskularnih bolesti, osteoporoze, metaboličkog sindroma i DM tip 2 i smanjiti mortalitet.

Cilj primjene HST je postizanje tipičnih vrijednosti nivoa estradiola u serumu od 100pg/ml ili 400pg/ml. Zavisno od puta primjene ekvivalentne doze su: 17B estradiol (2mg/dn); konjugovani ekvini estrogeni(1,25mg/dn); ethynil estradiol (10mcg/dn); ili transdermalni estradiol (75-100mcg/dn). Kombinovani oralni kontraceptivi (KOK) se mogu primjenjivati do perioda očekivane menopauze [5].

Uloga progesterona u terapiji POI veoma često se posmatra isključivo kroz efekte na uterus, sto ima svoja ograničenja. Veoma je važno naglasiti da su progesteronski receptori (A i B) prisutni na krvnim sudovima svih organa i prilikom supstitucije treba održavati balans progesterona sa estrogenom imitirajući prirodan ciklus [5].

Vujovic i sar. ukazuju na značaj OGT testa prije započinjanja HST, prije svega da bi se detektovao hiperinsulinizam sa svojim nepovoljnim proinflamatornim, proaterogenim i protrombotskim efektom na krvne sudove, a zatim se HST uključila samostalno ili uz metformin individualizovanim režimom, što može prevenirati bolesti i omogućiti asimptomatsku tranziciju od reproduktivnog perioda do menopauze, unapređujući kvalitet života [36].

Nepovoljni efekti hipoestrogenizma na insulinsku senzitivnost, a koji indukuju insulinsku rezistenciju, gojaznost, hipertenziju i dijabetes mellitus, mogu biti prevenirani primjenom supstitucione terapije, estradiolom (E2) uz drospirenon (DRSP) [35].

Individualizovani terapijski pristup je neophodan uz preporuku procjene nivoa hormona na godišnjem nivou da bi se održavala optimalna doza [5].

Hormonska terapija nema vremensko ograničenje. Dosadašnje preporuke sugerišu primjenu terapije do 50-55 godine, ali novije studije ukazuju da prestankom terapije dolazi do naglog povećanja incidencije kardiovaskularnog obolijevanja tokom prve godine [5].

Nakon 60 godine života preporučuje se primjena terapije transdermalnim putem [5].

Cilj istraživanja

Ispitati učestalost komorbiditeta kod pacijentkinja sa prijevremenom ovarijumskom insuficijencijom koje nikada nijesu koristile hormonsku supstitucionu terapiju.

Materijal i metode

Analizane su istorija bolesti 30 pacijentkinja koje su zbog različitih stanja ambulantno i hospitalno liječene u Klinici za ginekologiju i akušerstvo Kliničnog centra Crne Gore.

Kriterijumi uključenja u studiju su bili: podatak o poslednjoj menstruaciji prije četrdesete godine života, amenoroični period duži od deset godina. Ispitanicama su analizirane: godine starosti, godine starosti kada je nastupila menopauza, dužina amenoroičnog perioda i indeks tjelesne mase.

Analizirano je prisustvo komorbiditeta: osteoporoza, diabetes mellitus tip 2 i arterijska hipertenzija. Takođe je analizarana učestalost histerektomije sa adneksektomijom kao etiološkog faktora prijevremene menopauze.

Rezultati istraživanja

Starost ispitanica u vrijeme ispitivanja bila je 34-70 godina, sa aritmetičkom sredinom 55,5 godina i medijanom vrijednosti 54 godine. Poslednja menstruacija nastupila je od 24-39 godine, sa aritmetičkoim sredinom 36 godina i medijanom vrijednosti 39 godina. Dužina trajanja menopauze bila je od 10 do 34 godina, sa aritmetičkom sredinom 26 godina i medijanom vrijednosti 20 godina. Indeks tjelesne mase kretao se od 18 do 40 kg/m2, sa aritmetičkom sredinom 27kg/m2 i medijanom vrijednosti 27 kg/m2. Histerektomija sa adneksektomijom kao etiološki faktor prijevremene menopauze,postojala je kod 10 pacijentkinja , tj kod njih 33%. Smanjenu gusinu kosti su imale 22 pacijentkinje, od kojih je čak 10 imalo osteoporozu komplikovanu minimum jednom frakturom (čak 33%). Dijabetes mellitus tip 2 je imalo 15 % ispitivanih pacijentkinja, tj 6 pacijentkinja

od ispitivanih 30. Arterijsku hipertenziju je imalo 24 od ispitivanih 30 pacijentkinja, što predstavlja čak 80 %.

Diskusija

Prijevremena insuficijencija jajnika ako nije adekvatno i na vrijeme liječena hormonskom supstitucionom terapijom, predstavlja svojevrstan teren za razvoj mnogih komorbiditeta.

Gubitak koštane mase, nakon menopauze u prosjeku iznosi 2-3 % godišnje. Efekat deficita estrogena kod žena sa POI jedan je od najprepoznatijih neželjenih efekata ovog stanja [12]. Osteoporoza je jedan od osnovnih problema žena sa POI, sa prevalencijom od 8-27 % [28]. Žene sa POI imaju značajno manju koštanu gustinu i rastući rizik od osteoporoze i njenih komplikacija u poređenju sa ženama koje u menopauzu ulaze u uobičajenim godinama, posebno se ova razlika odnosi na žene mlađe od 70 godina [29].

Hipoestrogenizam i hiperinsulinemija, dovode do porasta tjelesne mase prosječno oko 5 kg i redistribucije masnog tkiva po tipu centralne gojaznosti, čineći put ka razvoju metaboličkog sindroma [5]. Žene sa POI imaju kraći očekivani životni vijek, uglavnom zbog bolesti kardiovaskularnog sistema [12].

Klinički manifestna kardiovaskularna bolest kod žena, manifestuje se prosječno 10 godina kasnije nego kod muškaraca, međutim povezana je sa lošijom prognozom. Rizik od koronarne srčane bolesti i šloga duplira se tokom prve dekade nakon menopauze da bi u kasnijim godinama prevazišla rizik kod osoba muškog pola [11].

Posebno se rizik od mortaliteta odnosi na mortalitet uzrokovan ishemijskom bolesti srca, koji je za oko 80% povišen kod pacijentkinja sa POI u odnosu na kontrolnu grupu žena koje su u menopauzu ušle u razdoblju od 49 do 55 godina života [12].

Zaključak

Pacijentkinje sa prijevremenom ovarijumskom insuficijencijom koje nijesu koristile supstitucionu terapiju hormonima češće i ranije u životu obolijevaju od osteoporoze, hipertenzije, kardiovaskularne bolesti i dijabetes melitusa tip 2.

Pristup pacijentkinji sa prijevremenom ovarijumskom insuficijencijom treba započeti empatičnim informisanjem o dijagnozi, ranim simptomima i kasnijim rizicima ovog stanja kao i terapijskim mogućnostima, pružanjem medicinski potvrđenih i tačnih podataka.

Svim pacijentkinjama sa prijevremenom ovarijumskom insuficijencijom treba obezbijediti informacije o značaju nadoknade estroprogestagenima, koji su lijek neophodan za njihovo opšte zdravlje i uvesti terapiju na vrijeme.

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UROGYNECOLOGY

VAGINALNA HISTEREKTOMIIJA U 10 KORAKA

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Histerektomija je jedna od najčešće izvođenih ginekoloških operacija. Opisano je mnogo različitih tehnika, a tehnika izbora temelji se na hirurškoj indikaciji, karakteristikama pacijenta te vještinama i preferencijama hirurga. Cochrane-ov pregled Charlotte M. Pickett i saradnika o hirurškom pristupu histerektomiji za benigne indikacije navodi da je vaginalna histerektomija postupak s najbržim oporavkom [1, 2]. U prospektivnoj randomiziranoj studiji nije utvrđena razlika između vaginalne histerektomije i LAVH s obzirom na procjenjeni gubitak krvi, komplikacije, boravak u bolnici i period rekonvalescencije [2, 3, 4]. Troškovi LAVH bili su znatno veći.

Vaginalna histerektomija se izvodi od 19. vijeka (Langenbeck 1813. godina) i od tog perioda postoje brojne modifikacije ove operacije. Učinjena je evaluacija modifikacija vaginalne histerektomije s ciljem da se nakon toliko godina prakse i iskustva optimizira i pojednostavi. Definisani su i analizirani zajednički koraci raznih modifikacija, ocijenjeni i isključeni nepotrebni, a ostali su samo preispitani i apsolutno nezamjenjivi koraci [5]. Rezultat je vaginalna histerektomija u deset koraka. Brz oporavak pacijentkinja, niska stopa morbiditeta, kraći boravak u bolnici i manji troškovi su prednosti vaginalne histerektomije nad ostalim histerektomijama [2, 3].

Prikaz operativne tehnike vaginalne histerektomije u 10 koraka:

- Korak 1: prednja kolpotomija

Rez na vaginalnom zidu i preparisanje prednje vaginalne sluznice od podsluzokožnog tkiva. Kod pacijentkinja sa prolapsom rez se izvodi kružno oko grlića, nastavi se prema orificium externum uretre odvajajući vaginalnu sluznicu prema bočno. Joel-Cohen preporučuje preparisanje vaginalne sluznice u obliku kapi i počinje odozgo od orifitium externum uretre prema dolje i bočno, okružujući grlić i vraća se na početak ispod uretre. Povlačeći vrh kapi prema dolje odvaja se vaginalna sluznica od mokraćne bešike [6].

- Korak 2: Odvajanje mokraćne bešike od materice

Identificira se se granica pripoja mokraćne bešike za grlić i oštro makazama presiječe, potom se tupo ispreparira mokraćna bešika do prednje plike. Plika vesicouterina se ne otvara u ovoj fazi operacije.

- Korak 3: Otvaranje stražnjeg peritoneuma

Kružno oko grlića se zareže vaginalna sluznica i prikaže peritonealni pripoj za grlić i oštro se makazama otvori stražnja plika.

- Korak 4: Disekcija donjeg dijela uterusa

Klemanje, presijecanje i podvezivanje ligg. sacrouterina zajedno sa paracervikalnim tkivom. Ligature se ostavljaju za kasniju fiksaciju za vaginalni zid i međusobno se povezuju.

- Korak 5: Klemanje, presijecanje i podvezivanje vasa uterina
- Korak 6: Otvaranje prednjeg peritoneuma

Kroz stražnju kolpotomiju se izvuče uterus i operater iza fundusa ulazi prstima i elevira prednji peritoneum koji potom oštro otvara makazama.

- Korak 7: Disekcija gornjeg dijela uterusa

Klemanje, presijecanje i podvezivanje ligg. rotunda, ligg. ovarii proprium i tubae i odstrani uterus (HP). Ligature se ostavljaju za kasnije međusobno vezivanje sa drugom stranom.

- Korak 8: Ne šivati peritoneum

Godine 1980. Harold Elis je pokazao da nije potrebno zatvarati peritoneum. Britanski kraljevski koledž za akušerstvo i ginekologiju u svojoj smjernici 2002. g. preporučuje ostavljanje peritoneuma otvorenim sa nivoom dokaza Ib [7]. Michael Starck i grupa autora ne preporučuju zatvaranje peritoneuma [5].

Peritoneum je tanak, za razliku od kože i vaskularni mostovi na mjestu šavova su fokus za ishemiju i adhezije. Kad ostane otvoren peritoneum, ćelije same stvaraju novi peritoneum. Druga prednost otvorenog peritoneuma je slobodna drenaža u peritonealnu šupljinu gdje se krv i limfa mogu resorbovati.

- Korak 9: Rekonstrukcija karličnog dna

Fiksiranje ligg. sacrouterina s paracervikalnim tkivom za vaginalni zid i međusobno povezivanje adneksalnih ligamenata.

- Korak 10: Zatvaranje vaginalnog zida

Produžni resorptivni šav. Otvor između prednjeg i zadnjeg zida vagine se šije transverzalno.

Cilj: Prikazati operativno liječenje prolapsa genitalnih organa žena vaginalnom histerektomijom u deset koraka.

Materijal i metode: Retrospektivna analiza vaginalnih histerektomija u periodu od 2015. do 2022. g. na Ginekološkom odjeljenju u Prijedoru. Indikacija za izvođenje vaginalne histerektomije na našem odjeljenju je totalni i subtotalni prolaps uterusa.

Rezultati: U posmatranom periodu urađeno je 157 vaginalnih histerektomija. Prosječna starost pacijentkinja je 65 godina. Rutinski je provođena antibiotska profilaksa (Cefazolin 1–2g) i tromboembolijska profilaksa niskomolekularnim heparinom.

Učestalost intraoperativnih komplikacija kod vaginalne histerektomije: povreda mokraćne bešike 1,2%, rizik za povredu crijeva je 0,4%, povreda uretera oko 0,5%, obilnije krvarenje – najčešće mjesto krvarenja su vasa uterine, konverzija u laparotomiju. U posmatranom periodu kod 2 pacijentkinje je evidentirano obilnije krvarenje sa potrebom transfundiranja.

Postoperativne komplikacije kod vaginalne histerektomije su: ileus, infekcije vaginalnog zida i apsces, dehiscencija vaginalnog zida, fistule (vezikovaginalne, ureterovaginalne i rektovaginalne) i tromboembolijske komplikacije. U posmatranom periodu na našem odjeljenju nije evidentirana ni jedna od navedenih komplikacija.

Postoperativni tretman pacijentkinja: ustajanje prvog postoperativnog dana i per oralna ishrana.

U periodu od 2015. do 2018. g. kateter je vađen četvrtog postoperativnog dana i uspostavljana spontana mikcija, hospitalizacija je trajala 5 dana. Od 2019. g. kateter je vađen drugog postoperativnog dana i hospitalizacija je trajala 3 do 4 dana.

Zaključak: U posmatranom periodu nije bilo intraoperativnih i postoperativnih komplikacija.

Vaginalna histerektomija je jednostavna procedura za izvođenje sa malom incidencom komplikacija.

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COMPLICATIONS OF UROGYNECOLOGICAL OPERATIONS

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Pelvic organ prolapse (POP) is a benign condition in women, with a prevalence of up to 50% in women who have given birth. In many women, it manifests itself as a decline of the vaginal walls and/or uterus with pressure, urinary dysfunction, defecation dysfunction, and sexual dysfunction, all of which negatively affect the quality of life. The lifetime risk of having one of the urogynecological operations during their lifetime in the general population of women is about 13%. Although POP can occur in younger women, the highest frequency of POP symptoms is in women aged 70 to 79 years. Considering the general aging of the population in developed countries, it is expected that by 2050, the number of women with POP will increase by approximately 50%.

The average frequency of urogynecological operations is 1.5 to 1.8 operations per 1000 women per year. Approximately 300,000 of these surgeries are performed annually in the United States alone. At our clinic, on average, about 700 vaginal surgeries are performed per year (250 anterior plastic surgery, 120 posterior plastic surgery, 150 vaginal hysterectomy, etc., 70 slings...)

One of the frequent complications is relapse. Older studies showed that women who underwent primary POP surgery had approximately a 30% to 50% chance of needing a second prolapse surgery. More recent studies show a lower reoperation rate of approximately 6% to 30%. This lower reoperation rate may reflect improvements in surgical technique as well as stratification of urinary incontinence as a distinct risk in outcome data. Risk factors for recurrent prolapse include age younger than 60 years, obesity, and preoperative stage III or IV prolapse.

The most common complications after urogynecological operations are bleeding, infection (usually urinary tract), urinary dysfunction (which is usually transient). Less common complications include rectovaginal or vesicovaginal fistula, ureteral injury, shortened vagina, or restriction of vaginal caliber. Changes in vaginal anatomy can lead to both dyspareunia and pelvic pain and pain during intercourse.

There are also unique complications associated with the use of mesh in urogynecological surgery. This includes contracture of the mesh, erosion of the vagina, urethra, bladder and rectum. Considering the use of a large number of different terms and the imprecise definition of postoperative classifications, in 2012 the International Association of Urogynecologists (ICS) created a classification of postoperative complications based on category (C), time (T) and location (S) of complications, which should include all possible complications of vaginal surgery. Referral to a gynecologist with appropriate training and experience in the field of urogynecology is absolutely recommended for management of complications of vaginal surgery.

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APPLICATION OF SUBURETHRAL SLING: 10-YEAR EXPERIENCE IN SINGLE TERTIARY REFERRAL CENTRE

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Introduction: Midurethral sling (MUS) implantation is the gold standard treatment for stress urinary incontinence in women after failure of conservative therapy. Both retropubic and transobturator suburethral slings can be used with good results. Suburethral sling placement is a safe procedure with a low rate of readmissions, reoperations, and complications. The global prevalence of stress urinary incontinence after age 18 years in Europe is 31% and the prevalence increases continuously with age. The most common complications are urinary tract infections, in about 2,7% of patients and surgical site infection in 1%. Reoperation for mesh revision or removal is low (1.1% at 9 years). The most common indication for reoperation is urinary retention (about 25%) followed by bleeding complications (about 5-15%). The incidence of pelvic pain after placement of a suburethral sling for incontinence ranges between 0% and 30%. It has been shown previously that revision of MUS for pelvic or perineal pain could lead to 50% reduction of pain in 63.3% of cases at 2 months post-operatively, but was associated with a 51% risk of recurrent SUI. Other studies have reported similar recurrence rates of SUI, ranging from 50% to 71%, after laparoscopic removal of a retropubic MUS and 36% to 42% after vaginal removal. The continence rate after repeat surgery for SUI was 70% and this increased to 85% after a second repeat surgery.

Methods: We retrospectively reviewed medical records for all women who underwent placement or reoperation of MUS between January 2011 and December 2022 in a single tertiary referral center. Suscesfull outcome was defined as absence of clinical symptoms and no urine leaking during Valsava maneuver. All patients who had removal of suburethral tape were previously unsuccessfully conservative treated. TOT slings were removed via the transvaginal approach.

Results: Median follow-up was 60 months (18–144). We had total 209 patients. Efficiency of treatment was recorded in 202 patients (96%). Urinary Infections occurred in 9 patients (4.3%), without surgical site infections. Reoperations were performed in 10 patients (4.8%), two cases of hematoma and MUS was removed in 8 patients (4.5%). Median time of sling removal was 6 months. SUI recurrence occurred in 3 of 8 cases (37.5%) who underwent total removal of sling.

Conclusion: Suburethral sling placement is safe procedure with good outcome in resolving urinary tract symptoms and continence rate with low risk of complications and need for explantation. Literature date showed low incidence for MUS removal of around 2%. Our data also reported 4% of MUS removal. After MUS revision for chronic pelvic pain, post-operative stress urinary incontinence may occur in 35-40% of patients. These patients can be managed with replacement of suburethral sling or conservative measures only.

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VAGINALNI PESARI – NOVA ILI STARA METODA

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Vaginalni pesari su mekani ulošci, načinjeni od silikona ili gume, koji se plasiraju u vaginu i služe u terapiji prolapsa pelvičnih organa (cystocele, enterocele, rectocele, prolapsa vaginalnog zida, prolapsa materice) i stress inkontinencije. Koriste se kao nehirurška terapija slabosti karličnog dna, koje najčešće nastaje kao posledica višestrukih i/ili teških porođaja, hroničnog zatvora, hroničnog kašlja i teškog fizičkog rada. Hirurško lečenje je sigurno definitivno rešenja, ali nošenje pesara predstavlja konzervativnu terapiju. Naročito je značajna aplikacija pesara kod starije populacije, kod koje se može uspešno i dugotrajno nositi. Smatra se da 24-49% žena odustane od terapije pesarom u periodu od 12-24 meseca zbog nelagode, bola ili obilnog neprijatnog iscedka. Hirurško lečenje problema prolapsa peličnih organa je udruženo sa komplikacijama i smatra se da se kod 2 od 10 žena problem prolapsa javi ponovo nakon hirurške intervencije.

U lečenju spada ginekoloških organa prvo treba savetovati plasiranje vaginalnog pesara, naročito kod starijih pacijentkinja kod kojih postoje kontraindikacije za operativno lečenje. Najčešće su načinjeni od silikona, ređe od gume, u različitim oblicimai i veličinama. Komplikacije prilikom nošenja su svedene na minimum ukoliko se pravilno odabere veličina i redovno održava higijena.

Neophodno je što preciznije izmeriti obim vagine, koristeći probne pesare radi određivanja oblika i veličine koji je za pacijentkinju najbolji, obzirom da će ispadati ukoliko je mali, a žuljati i dovesti do dekubitusa ukoliko je prevelik.

Pesari mogu biti različitih oblika:

- Prsten
- Prsten sa pojačanjem za plasiranje ispod uretre
- U oblik (gehrung)
- Oblika zamke (hodge)
- Disk sa držačem na sredini (gelihorn)
- Kocka

Spad materice prvog i drugog stepena obično se leči aplikacijom vaginalnog pesara oblika prstena ili krofne. Ukoliko postoji i cistocela, koristi se prsten sa pojačanjem. Za terapiju prolapsa uterusa trećeg stepena, koristi se kocka, kod koje se mora češće raditi toaleta jer nema sposobnost drenaže. Pesari oblika krofnei i diska sa držačem na sredini se koriste kod lečenja prolapsa trećeg stepena. Pesari U oblika su se pokazali veoma dobri ukoliko sa prolapsom uterusa trećeg stepena postoji udružena cistocela i rektocela, ali su nešto teži za plasiranje.

Kod pacijentkinja sa malom cistocelom, koristi se disk sa ojačanjem ili zamka sa ojačanjem. Veći prolaps prednjeg vaginalnog zida leči se plasiranjem diska sa ojačanjem ili pesara u obliku kocke.

Pesari sa ojačanjem ili specijalno dizajnirane proteze se mogu koristiti veoma uspešno kod stress urinarne inkontinencije.

Kontraindikacije za plasiranje pesara su: infekcije vagine I male karlice, PID I akutne maligne bolesti genitalnih organa.

Pre aplikacije pesara neophodno je:

- Utvrditi stepen atrofije vaginalne sluzokože
- Isprazniti bešiku
- Odabrati najveći pesar koji je pacijentkinji udoban za nošenje, ne žulja i ne oseća neudobnosti i sa kojim može normalno da mokri.

Neophodna je redovna toaleta pesara, tako što se savetuju dolasci kod ginekologa na 2 do 3 meseca uz redovnu higijenu. Ponekad se pacijentkinja može obučiti kao da sama vrši toaletu pesara i pravilno ga ponovo aplikuje. Takođe, pacijentkinje se obuče i savetuju da redovno rade vežbe za jačanje mišića karličnog dna. Ukoliko nošenje pesara ne dovede do pozitivnih rezultata i poboljšanja stanja pacijentkinje, iz bilo kog razloga, ukoliko su tegobe izražene, može se pristupiti lečenjun različitim operativnim tehnikama.

Komplikacije su retke, ali moguće obzirom na postojanje stranog tela u vagini. Ozbiljne komplikacije su izuzetno retke, opisano je samo 36 od 1964. do 2019.godine. Postojanje vaginalnog iscedka i neprijatnog mirisa se izbegava redovnom higijenom i korišćenjem vaginaleta. Ponekad se pesari teško vade ukoliko su zapušteni i mogu dovesti do inflamacije . U izuzetno retkim slučajevima mora se učiniti hirurško uklanjanje.

Iako se pesari retko koriste u našoj populaciji važno je da se podsetimo o njihovoj važnosti i benefitima koje nose. Finansijski su isplativi, poboljšavanju kvalitet života pacijentkinja koje izbegavaju operativno lečenje smanjujući tegobe.

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SHORT COMMUNICATIONS

NEONATAL OUTCOME IN PREMATURE BIRTH DEPENDING ON THE MODE OF DELIVERY IN UNCOMPLICATED PREGNANCIES

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Spontaneous preterm birth accounts for almost half of all preterm births. There is an increasing tendency in the number of premature births. When premature births occur, the biggest question is: C-section or vaginal birth? This decision has many controversies.

Our study included 1035 women with singleton uncomplicate pregnancy delivered at Ginecology and obstetrics Clinic Narodni Front, between 22 and <37 weeks of gestation, in the interval from 2019. to 2022. year. We assessed associations between mode of delivery and pregnancy outcomes in singleton preterm pregnancies. We analyzed maternal age, gestational age, weight, length, duration of labor, CRP, pH, pO2, pCO2, lactates, BE, glycemia, MV hours, O2 hours, NICU days and ApS-5. Average age at delivery was about 31 years, average gestation was about 34ng, with an average infant weight of 2450g, and the median duration of labor was 3.5h. Late premature and moderate premature pregnancies were ended vaginaly. Delivery before 32 NGs was predominantly completed by CS. Neonatal IVH was statistically significantly higher after vaginal delivery in pregnancies before 32 NG (χ^2=8,310, df=2, p=***0,015***). An interesting fact is that the male sex is more common among premature babies.

In pregnant women with preterm delivery, it is obvious that the most common time for preterm delivery is in the interval after 34ng. For moderate and late preterm deliveries, it is recommendable that they end by vaginal delivery. Caesarean section remains a more frequent way of ending pregnancies before 32 ng. In addition to the baseline excess, which is lower after vaginal delivery, there are no significant difference in the postpartum state of the newborn in relation to the mode of delivery.

PRIMENA FMF ALGORITMA U PREDIKCIJI PREEKLAMPSIJE

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Preeklampsija je kompleksan progresivni multisistemski poremećaj u trudnoći, koji komplikuje 2-8% svih trudnoća [1]. Iako je nepoznate etiologije, uzrok bi se mogao tražiti u poremećaju remodelovanja spiralnih arterija [2]. Preeklampsija je odgovorna za preko 70.000 smrti trudnica i preko 500.000 fetalnih smrti godišnje [3]. Terapijski režimi imaju brojna ograničenja, medikamentozna prevencija minimalno je efikasna, a porođaj se smatra jedinom efikasnom terapijom [4].

Postoji više klasifikacija preeklampsije, od kojih se najčešće koriste dve - prema vremenu porođaja (rano nastala, kasno nastala, preterminska i terminska) i prema težini bolesti (blaga do umerena i teška) [5-8].

Smatra se da prolazi kroz dva stadijuma. Prvi stadijum nastaje početkom prvog trimestra usled poremećaja placentacije i drugi ,,maternalni sindrom”) u drugom i trećem trimestru koji se karakteriše ekscesivnim oslobađanjem antiangiogenih faktora. Iako je nepoznat tačan mehanizam kako dolazi do poremećaja placentacije, pretpostavlja se da uteroplacentna ishemija pokreće hipertenzivni, multiorganski odgovor (drugi stadijum, „maternalni sindrom“) [3].

Problem je što ne postoji pouzdan test kojim bi se u ranoj trudnoći predvideo razvoj preeklampsije. Pažnja se usmerava na ranu kliničku detekciju, odnosno praćenje pojave simptoma i znakova preeklampsije. Pouzdana predikcija i detekcija preeklampsije ne postoji pre nego što postane simptomatska. Identifikacija trudnica sa faktorima rizika za preeklampsiju povećava mogućnost pravovremenog postavljanja dijagnoze. Rano postavljanje dijagnoze može poboljšati maternalni i perinatalni ishod obezbeđivanjem adekvatne terapije (npr. kortikosteroidi u cilju maturacije fetalnih pluća, terapija hipertenzije i porođaj).

Od izuzetne važnosti je evaluacija i identifikacija visokorizičnih trudnica u ranoj trudnoći na osnovu faktora rizika. Određivanje faktora rizika na osnovu različitih kliničkih i demografskih faktora daje mogućnost individualne procene rizika, neophodnost intenzivnijeg praćenja ili uvođenje profilaktičkih mera (npr. niske doze aspirina) [2].

Najznačajniji faktori rizika predstavljeni su od strane „American College of Obstetricians and Gynecologists“ (ACOG), ,,International Federation of Gynecology and Obstetrics” (FIGO), „National Institute for Health and Care Excellence“ (NICE) i „Fetal Medicine Foundation“ (FMF) [5-8]. Iako postoje preklapanja, postoje i razlike, kako u samim faktorima rizika između preporuka, tako i po tome što, npr. preporuke ACOG i FIGO, sve faktore rizika smatraju podjednako važnim, dok se po preporukama FMF i NICE ti faktori dele na faktore visokog i faktore umerenog rizika. Ipak, u svim preporukama zajedničko je stanovište - što je više faktora rizika, verovatnije je da će težina bolesti, kao i sam ishod biti teži.

Hronična hipertenzija, pregestacijski dijabetes melitus, indeks telesne mase (BMI) >30 kg/m2, antifosfolipidni sindrom, pozitivna anamneza preeklampsije i višeplodne trudnoće, najznačajniji su faktori rizika za preeklampsiju. Neki autori kao značajan faktor rizika pominju i upotrebu asistiranih reproduktivnih tehnologija [2].

U ranoj trudnoći određivanje gestacijske starosti, praćenje vrednosti krvnog pritiska i rezultata osnovnih laboratorijskih analiza, uključujući broj trombocita, koncentraciju kreatinina, testova

za procenu funkcije jetre i proteina u 24h urinu, može biti od pomoći kasnije tokom trudnoće u razlikovanju preeklampsije od drugih oboljenja, koja mogu biti udružena sa sličnim kliničkim znacima ili laboratorijskim nalazima.

Predloženi i razvijeni su brojni prediktivni modeli. Prediktivni modeli, kao onaj predložen od stane ACOG, kod koga se svaki faktor rizika smatra podjednako značajnim, može detektovati 35-40% preeklampsija uz stopu lažno pozitivnih od 10% [9]. Prediktivni model za predikciju preeklampsije u prvom trimestru, predstavljen od strane FMF, a podržan od strane FIGO, koji u kalkulaciji rizika koristi više faktora rizika i kombinuje ih sa vrednostima krvnog pritiska, doplerskim indeksima uteroplacentne cirkulacije, biohemijskim i/ili angiogenim markerima, povećava stopu detekcije na 75% uz stopu lažno pozitivnih od 10% [10]. Ovaj model, predstavljen od strane FMF, procenjuje rizik za razvoj preeklampsije korišćenjem Bajesove teoreme i pokazao se kao superiorniji u odnosu na tradicionalni model koji se oslanja samo na pojedinačne faktore rizika [10]. U skorije vreme, FMF predstavio je algoritme za procenu faktora rizika u drugom i trećem trimestru, ali još uvek nedostaje eksterna validacija tih algoritama.

Na osnovu faktora rizika dobijenih iz anamneze, može se predvideti samo oko 30% trudnica kod kojih će se razviti preeklampsija [2]. Iz tog razloga, neprestano se ispituju različiti laboratorijski, ultrazvučni i drugi testovi kojima bi se, uz faktore rizika dobijene iz anamneze, povećala stopa detekcije žena kod koji će se razviti preeklampsija. Do sada je predstavljen 21 algoritam, koji u prvom trimestru za procenu rizika koriste različite biohemijske markere i kombinuju ih sa maternalnim karakteristikama i do sada poznatim faktorima rizika. U najvećem broju studija za razvoj algoritama korišćena je logistička regresiona analiza. U proceni rizika, najčešće se koriste serumske vrednosti β-hCG, srednji arterijski pritisak (MAP), srednja vrednost pulzatilnog indeksa uterinih arterija (Mean UtA-PI), placentni faktor rasta (PlGF) i plazma proteina-A vezan za trudnoću (PAPP-A) u različitim međusobnim kombinacijama [11].

U modelima za procenu rizika koriste se specifične karakteristike trudnice, različiti anamnestički podaci, doplerska ispitivanja i biomarkeri u serumu. Najčešće se koriste u pomenutim preporukama - demografski podaci, podaci iz lične, porodične i opstetričke anamneze, vrednosti BMI, visine srednjeg arterijskog pritiska, doplerski indeksi uterinih arterija i biomarkeri (npr. PAPP-A, PlGF, Solubilna fms-slična tirozin kinaza 1 (sFlt-1) i dr). Većina istraživača koristi različite varijable u logističkoj regresionoj analizi za procenu najboljeg modela za određivanje individualnog rizika za razvoj preeklampsije u ranoj trudnoći. Senzitivnost ovih modela generalno je viša nego kada se koriste pojedinačni faktori rizika [2]. Pojedini kliničari, kod visokorizičnih pacijentkinja, profilaktički uvode u terapiju niske doze apirina krajem prvog trimestra.

Ne savetuje se skrining zasnovan samo na karakteristikama majke, jer se na taj način može predvideti oko 23% kasnih i 19% ranih preeklampsija, sa stopom lažno pozitivnih od 10% [12].

Prema preporukama NICE, u skriningu za razvoj preeklampsije pre 37. nedelje gestacije senzitivnost (DR) je 42%, a stopa pozitivnih na testu (SPR) 11,5%, a posle 37. nedelje DR 31,6%, a SPR 11,5%. Prema preporukama ACOG, u skriningu za preeklampsiju pre 37. nedelje gestacije DR je 89,2%, a SPR 66,1%, a posle 37. nedelje DR 90,1%, sa SPR 66,1% [13].

U studijama koje su sprovođene od strane FMF, korišćene su različite granične vrednosti. Ukoliko su u skrining uključene samo maternalne karakteristike (demografski parametri i podaci iz anamneze), prema algoritmu FMF, pri graničnoj vrednosti 1:62, za razvoj preeklampsije pre 37. nedelje DR je 44,8%, a SPR 10%, a za razvoj preeklampsije posle 37. nedelje DR iznosi 33,5%, uz SPR od 10%. Ukoliko je granična vrednost 1:70 za razvoj preeklampsije pre 37. nedelje DR je 48,3%, stopa

lažno pozitivnih (FPR) 11,5%, uz SPR 11,8%, a posle 37. nedelje DR iznosi 36,8%, FPR 11,2%, uz SPR od 11,8%. Kod granične vrednosti 1:100 za razvoj preeklampsije pre 37. nedelje DR je 59,4%, FPR 18,8%, uz SPR 19,1%, a posle 37. nedelje DR iznosi 48,5%, FPR 18,5%, uz SPR od 19,1% [6, 13].

Ukoliko se u skrining, prema preporukama FMF, pored maternalnih karakteristika uključe MAP, Mean UtA-PI i serumske vrednosti PlGF i PAPP-A, pri graničnoj vrednosti 1:66, za razvoj preeklampsije pre 37. nedelje DR je 74,8% uz SPR 10%, a za razvoj preeklampsije posle 37. nedelje DR iznosi 41,3% uz SPR od 10%. Ukoliko je granična vrednost 1:70 za razvoj preeklampsije pre 37. nedelje DR je 76,1%, FPR 10%, uz SPR 10,6%, a posle 37. nedelje DR iznosi 42,4%, FPR 9,9% uz SPR od 10,6%. Kod granične vrednosti 1:100 za razvoj preeklampsije pre 37. nedelje DR je 80,7%, FPR 14,1%, uz SPR 14,7%, a posle 37. nedelje DR iznosi 51,0% uz SPR od 14,7% i FPR 13,9% [6, 13].

Algoritmi za skrining preeklampsije koji u prvom trimestru kombinuju maternalne karakteristike, pulzatilni indeks uterinih arterija, srednji arterijski pritisak i angiogene markere nametnuli su se kao značajno bolji prediktori preeklampsije i bolje je njih koristiti, nego pojedinačne markere koji su se pokazali kao nedovoljno precizni. Od trenutno postojećih algoritama, kao najprecizniji je algoritam FMF, koji u proceni rizika u prvom trimestru koristi demografske karakteristike majke, postojeća medicinska stanja, srednji arterijski pritisak, srednju vrednost pulzatilnog indeksa uterinih arterija i placentni faktor rasta, te se sa velikom pouzdanošću može koristiti u kliničkoj praksi [14]. Važna napomena je da nijedan od postojećih algoritama za predikciju preeklampsije nije savršen, te bi reevaluacija postojećih markera, kao i pronalaženje novih, uz razvoj odgovarajućeg algoritma, mogli povećati stopu detekcije preeklampsije, pa samim tim smanjiti stopu morbiditeta i mortaliteta majki i plodova.

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TREATMENT OF MALIGNANCES IN PREGNANCIES

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Introduction: Cancer complicating pregnancy is rare but potentially life-threatening condition for both the mother and her child. More and more women are deciding to postpone pregnancy until later in life, mostly in order to complete their education and start a career. As, on the other hand, the frequency of malignant diseases moves towards a younger age, cancer associated with pregnancy becomes an increasing problem. The frequency of cancer in pregnant women is similar to that in the population of other women of the same age. The risk that the pregnancy will be associated with a malignant disease is 0.07% to 0.1% (about 1 case in every 1000 births). According to the results of one of the largest studies of malignant tumors in pregnancy, which included almost a thousand cases, breast and cervical cancers are the most common in pregnancy, followed by melanoma, lymphomas and leukemias, stomach and rectal cancers, and bone and soft tissue sarcomas. Cancer treatment during pregnancy is particularly delicate, because the patient has to choose or has the feeling that she has to choose between her own life and the life of her unborn child. Both diagnostic and therapeutic interventions must be performed carefully, bearing in mind the associated risk factors for both the pregnant woman and the fetus. Malignant disease in pregnancy complicates the procedure with both cancer and pregnancy. One of the main problems caused by malignant disease in pregnancy is late diagnosis. The diagnostic methods that can be safely used during pregnancy are limited. Some diagnostic methods are unreliable, such as mammograms or tumor markers, and some, such as computed tomography (CT), radioisotope tests or conization, can be harmful or even dangerous. Proper assessment of the expediency of continuing or terminating pregnancy in each individual clinical situation, as well as determining an adequate treatment method, is based more on adapting to each individual case, rather than on the application of standard schemes and approaches. Over recent years there has been an evolution in the concept of treatment of malignant disease in pregnancy, from complete neglect of pregnancy and frequent immediate terminations of pregnancy to a much more serious approach aimed at reducing the risk of death or injury to both.

During pregnancy, it is possible to apply all modalities of oncological treatment, but only under certain conditions that primarily depend on the gestational age and possible harmful effects on the fetus. In doing so, the health of the woman should be in the first place, and then the possibilities of a favorable outcome of the pregnancy must be taken into account. Physiological hemodynamic changes in pregnancy affect both the perioperative procedure and the possible application of cytotoxic agents. Surgical intervention is possible in all trimesters, but it is preferable to perform it in the (early) second trimester when the risk of miscarriage is the lowest and when the size of the uterus still allows a certain degree of access to the organs of the abdomen and pelvis. Laparoscopy during pregnancy is feasible, but it depends on the gestational age, the experience of the surgeon, the type of tumor and the type of procedure that is planned. Chemotherapy is contraindicated in the first trimester of pregnancy to avoid impact on organogenesis, as early

fetal exposure to chemotherapeutics is associated with a 10-20% risk of major malformations after 14 weeks of gestation, the use of a number of chemotherapy drugs is feasible, including taxanes, platinum agents

Material and Methods: The study included pregnant women diagnosed with malignant tumor during pregnancy from 2001 to 2022. The pregnancy course and outcome as well as parameters that could influence the condition of mothers and children were evaluated. Mothers and children were followed-up for one year after delivery to assess survival and condition.

Results: Most malignancies were gynecological (31%) and hematological (23.8%), diagnosed and surgically treated in the second trimester. Most children were in good state throughout pregnancy, but were delivered by Caesarean Section before term. Adjuvant therapy during pregnancy caused mostly transitory deterioration of children conditions. Deliveries in average occurred during the 33.01+/-6.16 gestational week (range 20 to 40) and mostly by Caesarean Section (76.2%). For mothers, pregnancy survival rate was 95.2% and after one year it was 87.5%. Still, 37.5% of women were still ill one year postpartum. Majority of fetuses were of good condition with adequate growth and development (69%) throughout pregnancy. Pregnancy survival rate for children was 94% while one-year survival rate was 76.2%. Regression analysis showed that predictors of good maternal outcome were surgery during pregnancy as chosen therapy, no progression of the malignancy during pregnancy, stable condition of the fetus during pregnancy and delivery at later gestational week. Predictors of good outcome of children were lower histopathological grade of malignancy, surgery as therapy for malignancy, no progression of the malignancy during pregnancy, higher birth-weight and Apgar score.

Conclusions: If the tumor is not progressing, pregnancy should be continued as long as possible to obtain adequate birth-weight of the child. The optimal management for pregnant women with cancer should be selected by the medical team (Ob/Gyn/perinatologist, neonatologist, oncologist), the patient and her family, depending on the gestational age, type and stage of cancer, therapeutic options and the patient's wishes. Surgical therapy and chemotherapy are feasible in pregnancy but in highly defined cases.

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STRATEGIES FOR CERVICAL CANCER SCREENING

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Cervical cancer is the fourth most common cancer among women worldwide, with incidence and mortality rates that are up to 10 times higher in Serbia than in developed countries. In comparison to other common cancers cervical cancer is highly preventable. Two prevention levels have led to significant decrease in newly detetected cervical cancers cases, but limited to developed countries. First level is HPV vaccination, whose roots extend back to 2006. Access to HPV vaccination in Serbia is no longer limited, since it has been free of charge for girls and boys aged 9 to 19 from 2022. The second level, organized screening programme, is the national, official and continuos screening of defined group of women. Finland, England, Germany, Netherlands, Norway, Denmark, Sweden are some of the countries that have been conducting organized screening for almost two decades with astonishing results. Unfortunately, this kind of prevention in Serbia is still to be established. The only way to screen population in Serbia is via opportunistic screening during their regular gynecology check-up, leading to low screening participation. The reasons for postponing the implementation of organized screening lie in limited availability of modern technologies for screening and treatment, the lack of sustainable funding and national capacities to implement nationwide programmes for elimination of cervical cancer. In November 2020, WHO launched the Global strategy to accelerate the elimination of cervical cancer, including the following targets for each of the three pillars for 2030: 90% human papillomavirus (HPV) vaccination coverage of eligible girls, 70% screening coverage with a high-performance test and 90% of women with a positive screening test or a cervical lesion managed appropriately. Therefore, in 2021, WHO published guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. WHO recommends starting regular cervical cancer screening by using HPV DNA detection rather than cytology at the age of 30 years among the general population of women. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals, which is every 5 to 10 years. In Serbia, we still rely on cytology screening, which has not been as successful in low- and middle-income countries, but reduced cancers for 70% in developed countries. It would be reasonable to consider HPV DNA detection as a primary screening tool, as it showed better sensitivity and specificity. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial.

Strategies that will be crucial for implementing organized screening programme in Serbia are provision of management, operational and human resources, required equipment, sending screening invitations, appropriate population informing and education, and establishing strong links between the multiple levels of the health service (primary, secondary and tertiary care) and individual patients.

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HUMAN BIOMONITORING OF ESSENTIAL, NONESSENTIAL, RARE EARTH, AND NOBLE ELEMENTS IN PLACENTAL TISSUES

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Exposure to certain metals has been recognized as a risk factor for numerous complications in vulnerable population groups, particularly pregnant women. This investigation evaluated the levels of essential (Cr, Mn, Co, Cu, Zn, Se, Mo) and nonessential trace metals with recognized toxicity (Be, Al, Ti, V, Ni, Ga, As, Rb, Sr, Cd, Sb, Ba, Tl, Hg, Pb, Bi, Th, U), together with rare earth elements (Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Yb, Lu), and noble metals (Ru, Rh, Pd, Re, Os, Ir, Pt, Au, Ag) in the placental tissues of healthy pregnant women (n = 105). The selection of participants was undertaken with special reference to specific confounding factors that could influence the trace element profiles. Among trace elements, Zn was the most abundant and Lu was the least abundant. Cd and Os placental levels show a tendency to increase with women's age. Compared with literature data, high levels of Ni were found. This is the first study that provides the composition levels of essential and toxic trace elements, rare earth elements, and noble metals in human placental tissues. Also, for the first time, normal (reference) ranges for 50 (ultra)trace elements in placental tissues are proposed. Reference ranges are especially important in biomonitoring studies, which nowadays give increasing importance to the analysis of solid tissues instead of body fluids. Overall, the information provided in this study can serve as a starting point for further clinical trials and/or prediction of potential risks to pregnancy.

CONTEMPORARY PERINATOLOGY – PREVENTING GESTATIONAL DIABETES IN BOTH WOMEN AND NEWBORN CHILDREN

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We analysed the trends in diabetes in pregnancy in Belgrade, Serbia for the period of the past decade and forecast the number of women with pre-gestational diabetes for the years 2030 and 2050. The study included the data on all pregnant women with diabetes from the registry of the deliveries in Belgrade, by the City Institute of Public Health of Belgrade, Serbia for the period between 2010 and 2020 and the published data on the deliveries on the territory of Belgrade. During the examined period the total number of live births in Belgrade was 196 987, and the prevalence of diabetes in pregnancy was 3.4%, with the total prevalence of pre-gestational diabetes of 0.7% and overall prevalence of GDM of 2.7%. The average age of women in our study was significantly lower in 2010 compared to 2020. The forecasted prevalence of pre-gestational diabetes among all pregnant women for 2030 is 2% and 4% for 2050 in our cohort. Our study showed that the prevalence of pre-gestational diabetes has increased both among all pregnant women and among women with diabetes in pregnancy in the past decade in Belgrade, Serbia and that it is expected to increase further in the next decades and to further double by 2050. Our study showed that the prevalence of pre-gestational diabetes has increased both among all pregnant women and among women with diabetes in pregnancy in the past decade in Belgrade, Serbia and that it is expected to increase further in the next decades to 2% in 2030 and to further double by 2050 to 4%. As all types of hyperglycaemia in pregnancy have significant intergenerational effect, expecting to influence the global prevalence of diabetes, as well, the forecasted increase in the prevalence of pre-gestational diabetes places high responsibility on the clinicians working with the women with diabetes in pregnancy as the adequate glycaemic control not only influences the proximal outcomes related directly to the pregnancy and the childbirth, but also distal outcomes relating mostly to the risk for the diabetic complications in the women with pre-gestational diabetes.

DELIVERY OF THE LOW BIRTH WEIGHT SINGLETON FETUS WITH CEPHALIC PRESENTATION

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Preterm birth is the major cause of neonatal mortality in the developed countries. Babies born too small are often born too soon. Low birthweight (LBW) defined as less than 2500 g occurs in 30-60% of infants delivered preterm and has been associated with increased risk of mortality, short and long term morbidity and economic burden [1]. The prognosis for survival and long term outcomes of low birth weight neonates is significantly improved by admimnistration of antenatal corticosteroides, liberal use of cesaren delivery for fetal indications, use of magnesium sulfat for neuroprotection and use of surfactant therapy [2].

Optimal route delivery of these fetuses is controversial in obstetric and neonatal community. The method of delivery is dependent of a variety factors. There is a little evidence from controlled studies on which to base of the management of preterm birth [3].

Preterm labor per se does not dictate one way or the other. Cesarean birth is associated with known risks for the mother and no proven benefits for the LBW neonate in cephalic presentation who is tolerating labor [4]. Pregnant woman with LBW fetuses should undergo a trial of labor in absence of a standard indication for planned cesarean birth (placenta previa, previous cesaran section).

Most evidences from studies have not demonstrated significant improvement in perinatal morbidity or mortality for the cephalic fetus delivered by cesarean, particulary when the primary indication for operative birth was LBW and even at very early gestational ages.

This places the mother at increased risk of serious complications, such as placenta accreta spectrum and uterine rupture in next pregnancies.

Vaginal delivery can be associated with increased risk of IVH in very low birth weight infants, but no difference in the neonatal outcome and future neuorodisability has been shown in most of the studies when compared to cesarean section [5].

Head compression by maternal soft tissues in the vertex LBW fetus is not a major determinant of IVH. For this reason avoiding prophylactic episiotomy and forceps is recommended [6].

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FETAL SURVEILLANCE IN PREGNANCIES WITH ASYMMETRIC GROWTH RESTRICTION

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Fetal growth restriction (FGR) complicate about 3-7% of all pregnancies and asymmetric FGR affects about 70% to 80% of all FGR cases. The overall incidence of fetal hypoxia varies widely among European hospitals, ranging from 0.06 to 2.8%.

Fetal growth restriction (FGR) is final result of chronic deprivation of oxygen and nutrients to the fetus and it is a physiologically appropriate response to this pathophysiology event.

A fetus exposed to prolonged hypoxemia will not achieve the genetic potential for growth, and will activate compensatory mechanisms in suboptimal intrauterine conditions. This leads to growth restriction, redistribution of oxygen and blood to vital organs, reduction in the amount of amniotic fluid, reduction in the number of movements and compensatory fetal tachycardia. Chronic utero-placental insufficiency leads to progressive fetal hypoxemia, fetal decompensation and acidosis.

The focus of prenatal care in pregnancies with FGR is to identify those fetuses that are at greatest risk of perinatal death and therefore may have benefit from early delivery. Differentiating a constitutionally small fetus from a fetus with pathological growth can help avoid unnecessary interventions and jatrogenic prematurity and can establish appropriate follow-up of these pregnancies and timing of delivery. Causes of fetal hypoxemia can be maternal, placental and fetal. Maternal causes are: chronic lung disease, anemia, smoking, toxicomania, malabsorption, exposure to toxins.Fetal causes are: genetic disorders, structural anomalies, congenital infections and exposure to teratogens. The most important cause of assymetric IUGR is placental insuffitienty, followed also by chronic abruption, chronic villitis, placental mosaicism, placental infarcts, umbilical cord anomalies.

Risk factors for the development of FGR are: older maternal age, chronic hypertension, preeclampsia, chronic kidney disease, systemic lupus erythematosus, antiphospholipid syndrome and diabetes mellitus type I.

Currently, there is no screening test in routine clinical use that is a good predictor of FGR. In clinical practice, a combination of biochemical parameters of the first trimester, mean arterial pressure of the pregnant woman, Doppler measurements at the level of the uterine artery and umbilical artery, as well as other biochemical factors /PlGF and sFlt-1/ are used to predict hypoxemia and growth restriction.

Early fetal growth restriction has a prevalence of 0.5% to 1%, it is more often associated with pathological findings of fetoplacental and uteroplacental circulation parameters. The underlying pathophysiological mechanism is hypoperfusion of the placenta.

The most important parameters for fetal monitoring are:estimated fetal weight (EFW), Doppler ultrasound and fetal behavior parameters :biophysical profile score -BPP and cardiotocography CTG.

Cardiovascular (Doppler) and behavioral (BPP and NST) manifestations of fetal deterioration in asymmetric FGR can occur independently of each other. For example, abnormal BPP may occur

before late Doppler changes (reverse umbilical artery Doppler flow in umbilical artery, ductus venosus wave abnormalities) . This is the reason for fetal monitoring with multiple modalities. Observational data suggest that adoption of FGR detection and follow-up protocols can reduce stillbirths.

The type and frequency of Doppler ultrasound examination for fetal surveillance in FGR are not standardized. For example, the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), and the American Institute for Ultrasound in Medicine (AIUM) suggest not using Doppler assessment of the ductus venosus (DV) and middle cerebral artery (MCA) for routine clinical management of FGR, while the International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) supports their use.

The time and method of delivery of a fetus with FGR and chronic hypoxemia is one of the most serious dilemmas in perinatology due to the etiological diversity.

The growth restricted fetus will compensate condition through hematologic and hemodynamic responses. There is an increase in erythropoesis, nucleated red blood cells, and hematocrit related to the degree of in utero hypoxia. In FGR, immune dysfunction occurs, platelet counts decrease, and abnormal villous vasculature may increase. This is correlated with the severity of placental insufficiency together with platelet activation/aggregation. Immune dysfunction manifests as a decrease in the number of fetal white blood cells, neutrophils, monocytes and lymphocytes.

Hemodynamic responses to hypoxic stress involve the redistribution of cardiac output to critical organs for survival. Blood flow in the hypoxic fetus is reduced to the brain, myocardium, and upper body and away from the kidneys, gastrointestinal tract, and lower extremities. Vasoconstriction of the lower extremities increases right ventricular afterload.

At the same time, cerebral vasodilation protects against hypoxic brain injury and reduces left ventricular afterload. If hypoxia persists, fetal distress occurs as hemodynamic changes eventually become inadequate to maintain adequate oxygenation. Fetal hypoxia negatively affects neurodevelopment.

FGR is a leading cause of stillbirth and neonatal morbidity and mortality.

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LONGITUDINAL CHANGES IN HDL METABOLISM IN HIGH-RISK PREGNANCIES

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Pregnancy is physiologically associated with metabolic changes (including insulin resistance, hyperinsulinemia, and mild dyslipidemia), low-grade inflammation, and oxidative stress, which develop during the adaptation of maternal metabolism with an aim to ensure an adequate growth of the fetus [1].

Physiological changes in lipid metabolism are essential for fetal growth and development. They are manifested by an increase in serum levels of total cholesterol and triglycerides, induced by estrogen, progesterone, and lactogen from the placenta, and by a substantial rise in insulin secretion due to pancreatic β-cell hyperplasia [2]. Although low density lipoprotein cholesterol (LDL-C) concentrations moderately increase, a specific feature of dyslipidemia in physiological pregnancy is a concomitant increase of high-density lipoprotein cholesterol (HDL-C) level. HDL-C reaches a peak in mid-gestation and tends to slightly decline toward the end of pregnancy, but higher levels persist even after delivery [3]. Hypertriglyceridemia and lower HDL-C concentration before pregnancy and during the first trimester also as insufficient increase in HDL-C concentration during the 1st and 2nd trimester have been connected with metabolic pregnancy complication development such gestational diabetes, gestational hypertension, preeclampsia [4,5]. Recently, our research team found that the atherogenic index of plasma (AIP), calculated as base ten logarithm of plasma TG to HDL-C ratio, was associated with high-risk pregnancies and we suggested this biomarker for the risk assessment of preeclampsia [6]. However, it is now clear that the role of HDL particles goes far beyond the reverse cholesterol transport manifested through HDL-C concentrations. HDL particles have extraordinary composition that includes more than 100 different proteins, cholesterol, non-cholesterol sterols (NCSs), glycerophospholipids, triglycerides and other lipid compounds, indicates many distinctive physiological functions [7]. However, structural and functional changes of HDL particles are seldom investigated in pregnancy, whereas the associations of HDL modificationsduring pregnancy with the pregnancy outcome are almost completely unexplored.

Our team is conducting a study where we analyzed gynecological, specific biochemical and genetic factors which underlie key HDL particles modifications during pregnancy. In order to investigate a new insight into molecular mechanisms involved in structural and functional modifications of HDL particles during pregnancy we will analyse candidate genes expressions. We will use peripheral blood mononuclear cell (PBMC) obtained from venous blood samples of the study participants as a source of genetic material since these cells represent adequate biological samples for analysis of transcriptome in pregnancy complications. Moreover, PBMC were demonstrated to be reliable surrogate indicators of hepatic regulations of lipid metabolism. Polymerase chain reaction (PCR) will be used for genotyping and the assessment of gene expression levels.

In this study, expressions of the following genes will be quantified: ABCA1 gene which codes synthesis of transport protein responsible for cholesterol efflux to apoA-1 [8], ABCG1 gene which is confined to synthesis of a transporter that enables cholesterol efflux to HDL 2 and 3 particles [9], SCARB1 gene responsible for synthesis of scavenger receptor class B member, which is involved

in cholesterol transport to and from HDL [10] and PLTP gene for phospholipid transfer protein which participates in the assembly of HDL particles [11].

This study is conceived as longitudinal observational study. Initially, 241 pregnant women were included in the study but 131 were followed from the beginning of gestation until term. We recruited women at their first antenatal check-up at the Gynecology and Obstetrics Clinic Narodni Front" (Belgrade, Serbia). Blood was sampled toward the end of the 1st, 2nd and 3rd trimester. Apart from the collection of laboratory analyzes for biochemical and genetic testing, the hormonal status in the first trimester (PAPP-A and BhCG) was also measured. Fetal biometric data during pregnancy monitoring, uteroplacental and fetoplacental flow, cervicometry, as well as all complications and conditions that occurred during monitoring of pregnant women (IUGR, gestational hypertension, preeclampsia, gestational diabetes mellitus, cholestasis etc.).

We are planning to form two groups based on pregnancy outcome – group A which will include women with normal pregnancies and group B which will include high risk pregnancies, and compare results between the groups.

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AKUTNI APENDICITIS U TRUDNOĆI – PRIKAZ SLUČAJA

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Uvod: Učestalost neakušerskih hirurških procedura tokom trudnoće kreće se od 0,3% do 2%. Najčešća operacija je apendektomija, sa učestalošću od 0,2% do 1,5%. Dijagnoza apendicitisa u trudnoći, naročito u 2. i 3. trimestru (kada se najčešće i javlja) komplikovana je fiziološkim i anatomskim promenama u trudnoći. To može odložiti pravovremeno postavljanje dijagnoze, a neadekvatan pristup i odloženo hirurško lečenje povećava maternalni i fetalni morbiditet i mortalitet. Učestalost perforacije inflamiranog apendiksa veća je kod trudnica nego kod negravidnih žena. Glavni simptom je bol u trbuhu. Početni bol se oseća u predelu umbilikusa sa kasnijom tipičnom lokalizacijom u donjem desnom kvadrantu, s tim sto je kod trudnica bol lokalizovan na nešto višem nivou od uobičajene tačke palpacije izvan trudnoće. Ostali simptomi, kao sto su mučnina, povraćanje, opstipacija, dijareja i duzurične tegobe, česti su i kod zdravih trudnica. Ukoliko su ovi simptomi naglo nastali, ili su udruženi sa bolom u trbuhu, postavlja se sumnja na akutni apendicitis. Diferencijalno dijagnostički u obzir dolaze ciste jajnika (naročito torzija ciste), holecistitis i holelitajaza, pankreatitis, opstrukcija creva, ulkus duodenuma, akutni pijelonefritis, urolitijaza. Takođe, može biti prisutan HELLP sindrom, abrupcija placente, ruptura uterusa i horiomnionitis. Odluka o hirurškom lečenju zasniva se na anamnezi, fizikalnom pregledu i imidžing metodama. Najkritičniji period za operativno lečenje u trudnoći je period organogeneze. U 1. i 2. trimestru trudnoće operacija se može izvesti i laparoskopski. Preporučuje se održavanje niskih pritisaka pneumoperitoneuma, od 10 do 15 mmHg, jer pneumoperitoneum može kompromitovati venski dotok krvi u srce, sa posledičnim smanjenjem minutnog volumena srca. CO2 može biti apsorbovan preko peritoneuma i tako izazvati fetalnu acidozu. U perioperativnom periodu trebalo bi izbeći nesteroidne antiinflamatorne lekove, naročito posle 32. nedelje gestacije, jer mogu dovesti do prevremenog zatvaranja duktusa arteriozusa. Spontani pobačaji i prevremeni porođaji su najznačajnije komplikacije operacije majke tokom trudnoće. Najmanji je rizik tokom 2. trimestra. Uprava za hranu i lekove SAD-a (FDA) je ustanovila sistem klasifikacije rizika za lekove koji se koriste tokom trudnoće, kako bi se napravio bolji odabir medikamenata u tretmanu gravidnih pacijentkinja.

Prikaz slučaja: Pacijentkinja starosti 32 godine, trećerotka, primljena na Kliniku u 18. nedelji trudnoće, koja je komplikovana bolovima u trbuhu, praćenim febrilnošću i povraćanjem. Po prijemu pacijentkinja je kompletno klinički, laboratorijski i ultrazvučno ispitana (ultrazvučno verifikovana vitalna trudnoća kao i eutrofičan rast ploda). Započeta je empirijska antibiotska terapija, uz inicijalnu nadoknadu tečnosti infuzionim rastvorima i simptomatsku terapiju. U laboratorijskim analizama markeri infekcije (C-reaktivni protein, prokalcitonin i presepsin) u porastu. Urađen ultrazvični pregled abdomena gde se ne vizuelizuju patološke promene. Postavljena sumnja na akutni apendicitis, a nakon obavljene konsultacije abdominalnog hirurga pacijentkinja prevedena na odeljenje hirurgije Urgentnog centra, gde je učinjena laparoskopska apendektomija. Drugog postoperativnog dana, pacijentkinja prevedena na Kliniku za ginekologiju i akušerstvo. Konstatovana vitalna trudnoća, ponovljeni markeri infekcije u trendu pada. Sedmog postoperativnog dana, pacijentkinja je otpuštena sa Klinike urednih laboratorijskih analiza i dobrog opšteg stanja, vitalne trudnoće. Porođena u terminu, rođeno živo muško dete, telesne težine 3200 grama, Apgar 9.

Zaključak: Multidisciplinarni pristup u lečenju i preoperativnoj pripremi trudnice zahteva angažovanje ginekologa, hirurga i anesteziologa.

Poželjno je smanjiti izloženost fetusa medikamentima, naročito u periodu organogeneze. Tokom operacije u trudnoći važno je održavanje intrauterine fiziološke sredine. Ukoliko se postigne dobra oksigenacija majke i perfuzija uterusa, fetus će dobro podneti i operaciju i anesteziju.

INDEKS MALIGNOSTI U DIFERENCIJALNOJ DIJAGNOZI BENINGNIH I MALIGNIH TUMORA JAJNIKA

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Uvod: Karcinom jajnika je vodeći uzrok smrtnosti u grupi ginekoloških maligniteta. Rezultati epidemioloških studija ukazuju da više od 70% slučajeva karcinoma jajnika se dijagnostikuje u uznapredovalom stadijumu bolesti. Asimptomatičnost i nedovoljna efikasnost dijagnostičkih metoda glavni su uzrok visoke stope smrtnosti od karcinom jajnika. Rano dijagnostikovanje ovarijalnih neoplazmi je u direktnoj vezi sa dužinom postoperativnog preživljavanja. Napredak u cilju bolje diferencijacije benignih od malignih tumora jajnika, napravljen je razvijanjem indeksa malignosti, kao što su RMI i ROMA. Iako su RMI i ROMA važne metode u preoperativnom razlikovanju pacijentkinja sa adneksalnim masama, neophodna je dalja validacija ovih metoda.

Cilj: Utvrditi validnost RMI i ROMA u diferencijalnoj dijagnozi benignih od malignih tumora jajnika kod pacijentkinja u premenopauzi i postmenopauzi, kao i validnost pojedinačnih komponenti predikcionih testova u zavisnosti od menopauzalnog statusa pacijentkinja.

Metode: U ovoj studiji preseka bile su uključene 153 pacijentkinje koje su podvrgnute operativnom lečenju (laparotomija, laparoskopija) tumora adneksalnih masa, u Ginekološko akušerskoj klinici „Narodni front". Svim pacijentkinjama preoperativno je urađen transvaginalni ultrasonografski pregled i određene su koncentracije CA-125 i HE4 u serumu i izračunavani su RMI i ROMA. U cilju postavljanja konačne dijagnoze i određivanja stadijuma bolesti odstranjeni adneksalni tumori su analizirani histopatološki.

Rezultati: Histopatološka analiza je pokazala da je 116 (75,8%) pacijentkinja imalo benigne tumore, dok je 37 (24,2%) pacijentkinja imalo maligne tumore jajnika. Pacijentkinje sa malignim tumorima jajnika su imale značajno veće koncentracije CA-125 ($p<0,001$) i HE4 ($p<0,001$) u serumu i značajno veće vrednosti RMI ($p<0,001$) i ROMA ($p<0,001$) u poređenju sa pacijentkinjama koje su imale benigne tumore jajnika. Najbolju prediktivnu vrednost u razlikovanju benignih od malignih tumora jajnika imala je granična vrednost RMI od 200. RMI je pokazao dobru prediktivnu vrednost i pravilno klasifikovao 85% pacijentkinja u celokupnom uzorku, 90,1% premenopauzalnih i 77,4% postmenopauzalnih pacijentkinja. Senzitivnost RMI, CA-125, HE4 i ROMA kod premenopauzalnih pacijentkinja je iznosila 73,7/66,4/63,3 i 71,7, dok je kod postmenopauzalnih pacijentkinja iznosila 77,6/62,5/66,7 i 78,1. Specifičnost RMI, CA-125, HE4 i ROMA kod premenopauzalnih pacijentkinja je iznosila 86,5/61,0/72,3 i 63,0, dok je kod postmenopauzalnih pacijentkinja iznosila 88,9/73,3/85,0 i 90,9.

Zaključak: U ovoj studiji je pokazano da RMI ima bolju senzitivnost i specifičnost za preoperativnu identifikaciju benignih i malignih adneksalnih masa u celokupnom uzorku, kao i kod premenopauzalnih pacijentkinja, dok ROMA ima bolju prediktivnu vrednost kod postmenopauzalnih pacijetkinja. Takođe, optimalna granična vrednost RMI od 200 za preoperativnu trijažu adneksalnih masa obezbeđuje visoku osetljivost i specifičnost.

ATIPIČNA KLINIČKA SLIKA DERMOIDNIH CISTI

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Dermoidna cista, ili zreli cistični teratom jajnika jedan je od najčešćih tumora jajnika. Čini 10-20% svih tumora jajnika, i 60% svih benignih tumora jajnika, i najčešća je neoplazma jajnika kod žena mlađih od 20 godina. Sreće se kod pacijentkinja svih starosnih grupa, sa najvećom učestalošću kod žena između 30 i 40 godina. Bilateralni zreli cistični teratomi sreću se u 10-17% slučajeva.

Zreli teratom može sadržati više tipova ćelija, koje potiču iz jednog ili više klicinih listova – ektoderma, mezoderma i endoderma. Ektodermalni derivati, koji uključuju keratinizirajući epiderm, lojne i znojne žlezde, folikule dlake i neuroektodermalna tkiva, često su najistaknutiji. Mezodermalni derivati se sastoje od mišića, kostiju, hrskavice, masti i povremeno zuba, dok su derivati endoderma tkivo štitne žlezde, pljuvačne žlezde, respiratorno i gastrointestinalno tkivo.

Većina dermoidnih cisti je asimptomatska, i često se dijagnostikuje slučajno pri rutinskom ultrazvučnom pregledu. Ukoliko postoje, simptomi i znaci obično uključuju bol i distenziju trbuha, konstipaciju, učestalo mokrenje i palpabilni tumor u maloj karlici ili abdomenu. Ukoliko dođe do razvoja komplikacija – torzije jajnika, što se sreće u 6-16% slučajeva, ili rupture ciste, koja se javlja kod 0,3–4% pacijentkinja, može doći do razvoja kliničke slike akutnog abdomena. Retko, kod ovih pacijentkinja može doći do razvoja hroničnog granulomatoznog peritonitisa i opsežnih priraslica.

Lečenje podrazumeva hiruršku eksciziju tumora. Ekspektativno lečenje može biti opcija za pacijentkinje sa malom dermoidnom cistom, ali kako ova vrsta tumora jajnika pokazuje tendenciju rasta tokom vremena, većina pacijentkinja biće na kraju podvrgnuta hirurškom zahvatu. Kod većine pacijentkinja sa zrelim cističnim teratomom predlaže se cistektomija jajnika, u cilju postavljanja definitivne dijagnoze, očuvanja tkiva jajnika i izbegavanja potencijalnih komplikacija – torzije, rupture ili razvoja malignih komponenti. Kod pacijentkinja koje su završile rađanje, adneksektomija je adekvatna terapija. Zreli cistični teratomi mogu se ukloniti bilo laparoskopijom ili laparotomijom. Iako je poželjno uklanjanje u celosti, može doći do rupture ciste, kada abdomen treba obilno isprati kako bi se prevenirao hemijski peritonitis zbog prisustva lojnog sadržaja.

Anti-NMDA receptor encefalitis

Anti-N-metil-D-aspartat (NMDA) receptorski encefalitis je poremećaj koji obično pogađa mlade odrasle osobe i decu, predominantno ženskog pola kod mladih odraslih osoba, i manje izraženom razlikom među polovima kod dece i pacijenata starijih od 45 godina. Poremećaj je povezan sa predvidljivim skupom simptoma koji se kombinuju i čine karakterističan sindrom.

Mnogi pacijenti se javljaju sa prodromalnom glavoboljom, groznicom ili kliničkom slikom virusne infekcije, nakon čega za nekoliko dana sledi višestepena progresija simptoma koji uključuju:

- Izražene psihijatrijske manifestacije (anksioznost, uznemirenost, bizarno ponašanje, halucinacije, deluzije, dezorganizovano mišljenje, psihoze). U veoma retkim slučajevima bolest može biti monosimptomatska (npr. manifestovati se kao izolovana psihoza);
- Poremećaji spavanja, uključujući smanjenje sna na početku bolesti i hipersomniju tokom oporavka;
- Amnezija;
- Epileptički napadi;

- Smanjenje nivoa svesti, stupor sa katatonijom;
- Česte diskinezije: orofacijalni, horeoidni pokreti, distonija, rigidnost, opistotonični položaji;
- Nestabilnost autonomnog nervnog sistema: hipertermija, fluktuacije krvnog pritiska, tahikardija, bradikardija, aritmije, a ponekad i hipoventilacija koja zahteva mehaničku ventilaciju;
- Jezička disfunkcija: smanjen govor, mutizam, eholalija.

Anti-NMDAR encefalitis čini oko 80% svih autoimunih encefalitisa. U oko 40% slučajeva on je paraneoplastična manifestacija tumora – 94% teratoma jajnika, 2% ekstraovarijalnih teratoma i 1% drugih tumora; kod oko 45% pacijentkinja starijih od 18 godina anti-NMDAR encefalitisi istovremeno postoje ovarijalni teratomi.

Dijagnoza anti-NMDA receptor encefalitisa potvrđuje se detekcijom IgG antitela na GluN1 (poznate i kao NR1) subjedinice NMDA receptora u likvoru.

Prognoza u velikoj meri zavisi od blagovremene dijagnoze i terapije. Stopa smrtnosti je između 3 i 9,5%. Savremeni protokoli lečenja podrazumevaju primenu visokih doza kortikosteroida, eventualno u kombinaciji sa IVIG i plazmafereozom, pored simptomatske terapije antipsihoticima i antiepilepticima. Kod pacijentkinja sa teratomom jajnika, izuzetno je važna rana hirurška ekscizija tumora.

Maligna transformacija dermoidnih cisti

Zreli teratomi su skoro uvek benigni. Prema literaturnim podacima, razvoj maligne (somatske) neoplazme javlja se u 0,2-2% zrelih cističnih teratoma i čini ukupno 2,9 % svih malignih tumora germinativnih ćelija jajnika. Iako bilo koja od komponenti zrelog cističnog teratoma može maligno alterisati, karcinom skvamoznih ćelija koji nastaje iz ektoderma je najčešća sekundarna neoplazma. Druge moguće maligne neoplazme uključuju (ali nisu ograničene na) bazocelularni karcinom, melanom, mucinozni karcinom, adenokarcinom respiratornog trepljastog epitela, karcinoid, karcinom štitne žlezde, karcinom lojnih žlezda, oligodendrogliom i sarkom. Izuzetna je pojava različitih ili mešovitih vrsta maligniteta.

Preoperativna detekcija malignite transformacije je veoma teška. Većina pacijentkinja nema specifične simptome i znakove. Senzitivnost i specifičnost dijagnostičkih metoda – ultrazvuka, magnetne rezonance i kompjuterizovane tomografije su niske. Malignitet se obično dijagnostikuje postoperativno, na osnovu histopatološkog nalaza.

Lečenje zavisi od histološkog tipa i gradusa maligne komponente, kao i stadijuma bolesti.

Faktori rizika za prisustvo maligne komponente kod zrelog cističnog teratoma uključuju starost preko 45 godina (prosečna starost 50 godina, naspram 33 godine za benigne cistične teratome), prečnik tumora >10 cm, brz rast i karakteristične nalaze ultrazvuka, magnetne rezonance ili kompjuterizovane tomografije (npr. protok niske rezitencije intratumorske cirkulacije na Dopleru). Kako se u većini slučajeva prisustvo maligniteta otkrije tek postoperativno, neophodno je ove faktore rizika imati na umu pri donošenju odluke o lečenju pacijentkinja sa suspektnom dermoidnom cistom.

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NOVEL BIOMARKERS TO DISTINCT UTERINE LEIOMYOSARCOMAS FROM UTERINE LEIOMYOMAS – A BIOINFORMATICS APPROACH

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Introduction

Despite comprising just 3-9% of all uterine malignancies, uterine leiomyosarcomas (uLMS) exhibit aggressive characteristics, a bleak prognosis, resistance to conventional treatment approaches, and a significant likelihood of disease recurrence [1,2]. Currently, there is a lack of imaging methods or laboratory tests that can effectively distinguish uterine uLMS prior to surgical intervention with a satisfactory level of assurance [1,3]. The primary diagnostic issue lies in distinguishing uLMS from uterine leiomyomas (ULM), which are benign tumors of the uterine smooth muscle that exhibit comparable clinical and radiological characteristics. Given that the typical technique for treating uterine leiomyoma involves conservative or minimally invasive methods, the misidentification of these conditions could lead to a notable rise in morbidity and fatality rates [4,5]. The field of bioinformatics has emerged as a crucial component in the investigation of rare cancers, addressing the challenge of insufficient sample sizes for comprehensive investigations [6,7]. This study aimed to investigate the driving genes, key pathways, and potential novel biomarkers for distinguishing uLMS and ULM using an integrated bioinformatics approach.

Methodology

We used advanced search query to obtain datasets from Gene Expression Omnibus (GEO) [8] that include information about gene expression from uLMS, and ULM. We included the following datasets for further analysis: GSE764 and GSE64763. The University of California, Santa Cruz (UCSC) Xena [9] is an online freely available tool for visualizing and analysis of large public repositories and datasets, including TCGA. The RNA sequencing (RNA-Seq) data, clinical data, and probe annotation files of 33 uLMS patients in TCGA-SARC were downloaded and analyzed by the UCSC Xena. We used GEO2R to detect differentially expressed genes (DEGs) between uLMS and ULM samples. The screening of DEGS was carried out using a threshold of $|\log2\ FC| \geq 1$ and $p < 0.05$. We used an online tool InteractiVenn to plot Venn diagrams of the DEGs of datasets [10]. A comprehensive set of functional annotation tools is available in the Database for Annotation, Visualization and Integrated Discovery (DAVID) to assist investigators in understanding the biological meaning behind large lists of genes. Using DAVID [11] Gene as the foundation, these tools assemble functional annotations from multiple sources using the DAVID Knowledgebase. All DEGs were uploaded, separately analyzed, and visualized through DAVID software with a cut-off p-value < 0.05. The STRING database [12] is an online resource for the investigation of organism-wide protein association and interaction. We used STRING version 11.5 with a cut-off confidence score > 0.4 for the construction of PPI between overlapped DEGs betwwen uLMS and ULM. We uploaded and visualized the PPI network to Cytoscape version 3.9.1 software [13]. We also used The Molecular Complex Detection (MCODE) a Cytoscape plug-in to contemplate the most significant nodes with degree cutoff = 2, K-Core = 2, and Node Score Cutoff = 0.2. Another Cytoscape plug-in, CytoHubba, was used to find the top genes with the Degree method.

Results

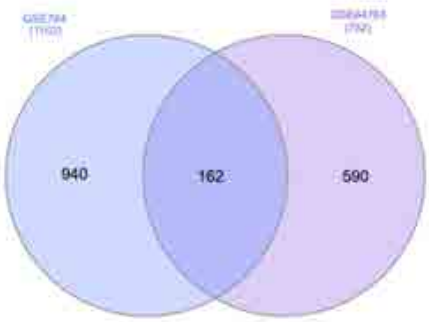

Figure 1 Overlapping DEGs between uLMS and uterine leiomyomas from GSE764 and GSE64763 datasets

Table 1. GO and KEGG pathway enrichment of DEGs between uLMS and ULM

Category	Term	Count	*p*-Value
GOTERM_BP_DIRECT	GO:0008284~positive regulation of cell proliferation	26	2×10^{-4}
GOTERM_BP_DIRECT	GO:0010628~positive regulation of gene expression	21	6×10^{-6}
GOTERM_BP_DIRECT	GO:0007568~aging	12	4×10^{-7}
GOTERM_BP_DIRECT	GO:0045944~positive regulation of transcription from RNA polymerase II promoter	28	1×10^{-10}
GOTERM_BP_DIRECT	GO:0007179~transforming growth factor beta receptor signaling pathway	9	1×10^{-10}
GOTERM_CC_DIRECT	GO:0005615~extracellular space	40	1.98×10^{-7}
GOTERM_CC_DIRECT	GO:0005576~extracellular region	38	1.55×10^{-10}
GOTERM_CC_DIRECT	GO:0005737~cytoplasm	72	2.06×10^{-10}
GOTERM_CC_DIRECT	GO:0031093~platelet alpha granule lumen	7	1.31×10^{-11}
GOTERM_CC_DIRECT	GO:0042383~sarcolemma	8	1.53×10^{-11}
GOTERM_MF_DIRECT	GO:0005515~protein binding	134	1.19×10^{-10}
GOTERM_MF_DIRECT	GO:0005158~insulin receptor binding	5	3.76×10^{-10}
GOTERM_MF_DIRECT	GO:0005178~integrin binding	9	5.80×10^{-10}
GOTERM_MF_DIRECT	GO:0005509~calcium ion binding	19	6.29×10^{-10}
GOTERM_MF_DIRECT	GO:0005114~type II transforming growth factor beta receptor binding	4	6.70×10^{-10}
KEGG_PATHWAY	hsa05205:Proteoglycans in cancer	15	5.27×10^{-8}
KEGG_PATHWAY	hsa05200:Pathways in cancer	23	1.60×10^{-10}
KEGG_PATHWAY	hsa05202:Transcriptional misregulation in cancer	14	1.62×10^{-10}
KEGG_PATHWAY	hsa05206:MicroRNAs in cancer	15	6.25×10^{-10}
KEGG_PATHWAY	hsa05218:Melanoma	7	3.86×10^{-12}

Figure 2. PPI network constructed in STRING with overlapping DEGs between uLMS and ULM

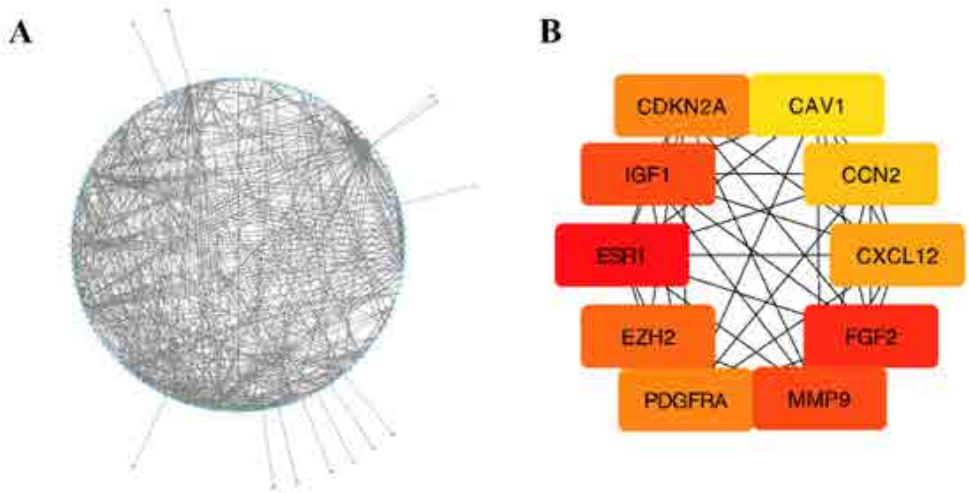

Figure 3 A PPI network constructed by Cytoscape B Cytohubba MCC module ranked the hub genes from the following network (the color correlates with the rank: red rectangles present the highest rank, followed by orange and yellow).

Table 2. Hub genes ranked by Degree method from Cytohubba plug-in, with the full gene names, regulation (downregulated/upregulated) and Degree score.

Gene symbol	Gene name	Regulation	Score
ESR1	estrogen receptor 1	downregulated	36
FGF2	fibroblast growth factor 2	downregulated	34
MMP9	matrix metallopeptidase 9	upregulated	33
IGF1	insulin like growth factor 1	downregulated	33
EZH2	**enhancer of zeste homolog 2**	**upregulated**	**31**
CDKN2A	**cyclin-dependent kinase inhibitor 2A**	**upregulated**	**29**
PDGFRA	**platelet-derived growth factor receptor A**	**downregulated**	**29**
CXCL12	**C-X-C motif chemokine 12**	**downregulated**	**28**
CCND2	**G1/S-specific cyclin-D2**	**downregulated**	**27**
CAV1	**caveolin-1**	**downregulated**	**25**

Discussion

Estrogen and progesterone receptors are considered biomarkers of prognosis in uLMS patients [14,15]. In correlation with rather high hormonal receptors expression in uLMS, there is evidence that uLMS shows a good response to aromatase inhibitors as an adjuvant therapy in newly-diagnosed patients with grade I uLMS, as well as those with recurrent, unresectable, and metastatic disease [16,18]. To date, only one clinical study showed that longer progression-free survival correlated with higher expression of the mentioned hormonal receptors which is in line with our result of the significant downregulation of ESR1 in uLMS patients [18].

As a result of ECM and basement membrane degradation, it is believed that MMP9 is involved in tumor migration, invasion, metastasis, and angiogenesis [19,20]. One study suggested the change in MMP9 expression and cell motility as a part of the decidualization process, could be estrogen-dependent and mediated by E2–ESR1–FOSL1 signaling pathway [21]. More studies should further investigate the relationship between ESR1 and MMP9 in the pathogenesis of uLMS, but it is possible that these two genes, alone or combined, have an influence on tumor behavior.

Dysregulated EZH2 expression may cause dysfunction of critical genes related to the G2/M transition [22]. Given that EZH2 expression is increased in tumors and associated endothelial cells, this protein is considered an important candidate for targeted therapy in several malignancies, along with endometrial cancer [23]. One study showed that a subset of undifferentiated uterine sarcomas is characterized by loss of SMARCA4 expression and that these tumors may be responsive to the EZH2 inhibitor tazemetostat (25). Moreover, a study by Omran et al. on uLMS cell lines showed that Entinostat (HDAC1 and HDAC3 inhibitor), combined with tazemetostat may provide a promising treatment option for uLMS treatment [26].

By immunohistochemistry it was found that CAV1 expression was high in fibroblasts, smooth muscle cells, adipocytes and endothelial cells with a fine granular membranous and a diffuse cytoplasmic staining pattern [22]. Moreover, levels of CAV1, comparable to normal mesenchymal cells, were retained in all benign mesenchymal tumors, including 5 of 5 fibromatoses, 7 of 7 leiomyomas, 4 of 4 lipomas, and 6 of 6 hemangiomas. CAV1 expression was found to be absent or strongly reduced in 3 of 3 fibrosarcomas, 17 of 20 leiomyosarcomas, 5 of 8 angiosarcomas, 15 of 18 malignant fibrous histiocytomas, and 8 of 8 synovial sarcomas. Therefore it was concluded that CAV1 could be a candidate tumor suppressor gene in sarcomas [27].

There are several limitations to our study. Firstly, the conducted research via bioinformatic analysis does provide valuable results and novel insights into uLMS pathogenesis and prognosis, but these results require validation in the clinical setting. Furthermore, the expression of DEGs and hub genes should be verified via immunohistochemistry or even genetic studies and correlated with the clinical features of the uLMS patients.

Conclusion

Through our comprehensive bioinformatic research, we have successfully discovered several central genes and signaling pathways that are closely linked to uLMS. It is of utmost importance to conduct further investigation on a panel comprising these hub genes as potential biomarkers for studying the pathogenesis, prognosis, and differentiation of uLMS in comparison to other benign and malignant uterine tumors, particularly ULM. In light of the aggressive nature and unfavorable prognosis associated with uLMS, compounded by the absence of established therapy protocols, our findings present compelling evidence to warrant additional investigation into the underlying

molecular mechanisms driving the development of uLMS. Moreover, our findings hold potential implications for enhancing the diagnostic capabilities of this rare malignancy.

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3D/4D ULTRASOUND AND ULTRASOUND COMPUTED TOMOGRAPHY IN THE ASSESSMENT OF THE NATURE OF THE LESION IN THE BREAST

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Classification of breast lesions is based on BIRADS. Sonographic findings of all breast lesions are classified into 5 categories. Crucial elements of classification are doctor's experience and training as well as appropriate US equipment.

Breast ultrasound was performed in 2000 patients between 2017 and 2022 at our unit. We used ultrasound machine with broadband linear probe L 12-5 MHz and 17-5 MHz. Sonographic findings were scored using criteria for breast ultrasound. Crucial sonographic markers are (ehogenicity of lesions and surrounding, mass shape, orientation, posterior acoustic features, lesion boundary, position of SF fascia superfitialis /T sign and „+" sign, microcalcification, Doppler effects, sonomorphology and vascularization of regional lymphatic nodes.

We examined 2000 patients aged 14 to 81 years. Normal breast ultrasound belonging to Category 1 was found in 995 (49,75%). Simple cysts and fibroadenomas classified as Category 2 were observed in 677 (33,85%). In 288 (14,40%) patients, apparently benign solid masses (Category 3) were found. Suspicious masses were observed in 28 (1,40%) women and masses highly suggestive of malignancy were found in 12 (0,60%) patients (Categories 4 and 5, respectively). In the 4-th category of 28 patients underwent FNB, of which 3 cases the findings were benign. In 25 cases, findings indicated malignancy. In all 12 cases of patients in 5-th category histopathological findings were malignant.

Ultrasound examination and categorization of breast lesions and recurrent information of HP verification allows malignant solid masses to be distinguished from benign ones with high accuracy.

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THE NOVEL POSSIBLE BIOMARKERS OF FOLLICULAR FLUID AS IDICATORS OF GOOD QUALITY OOCYTES AND EMBRYONS IN IN VITRO FERTILIZATION

Jovana Radaković Ćosić

GAK Narodni front

Folikularna tečnost (FT) kao okruženje oocite značajno utiče na sazrevanje i kvalitet jajnih ćelija. [1] FT ispunjava unutrašnjost folikula, a nastaje sekrecijom stromalnih ćelija folikula i eksudacijom plazme. [2] Izučavanje sastava FT i njenih komponenti može pokazati da postoje idikatori koji unapred mogu ukazati na adekvatnu zrelost i kvalitet jajnih ćelija, a samim tim i kvalitet embriona. Promene u sastavu plazme kao i sekrecije granuloznih i tekalnih ćelija se reflektuju i na sastav FT. [3] U sastavu FT se nalaze hormoni, faktori rasta, interleukini, produkti oksidativnog stresa, proteini, peptidi i aminokiseline, azot-monoksid, fosfolipidi i slobodne masne kiseline. [4] Kontrolisana ovarijalna stimulacija (KOS) kao prva od faza procesa vantelesne oplodnje (VTO) utiče na promene kako u serumu, tako i FT pacijentkinje. Samim tim ispitivanja povezana sa sastavom folikularne tečnosti mogu ukazati na određene biomarkere koji bi mogli ukazati na povećanje uspeha procesa vantelesne oplodnje. [5]

Proces VTO je asistirana reproduktivna tehnika (ART) koja omogućava lečenje neplodonosti i kod koje se u uslovima izvan organizma žene spajaju najkvalitetniji spermatozoid i kvalitetna jajna ćeija, te nakon procene kvaliteta embriona se oni vraćaju u matericu pacijentkinje. [6] VTO se sastoji iz nekoliko faza: 1) Priprema pacijenata za sam proces VTO 2) KOS – primena hormona 3) Trigger ovulacije 4) Punkcija folikula i aspiracija jajnih ćelija 5) Sakupljanje i priprema sperme 6) In vitro fertilizacija (IVF) ili Intracitoplazmatska injekcija spermatozoida (ICSI) 7) Embriotransfer 8) Podrška lutealne faze progesteronima 9) Zamrzavanje embriona 10) Test trudnoće. [7, 8]

Za uspešnost procesa VTO od presudnog značaja je kvalitet dobijenih jajnih ćelija, kvalitet spermatozoida i samim tim i kvalitet embriona. Morfološki kriterijumi za procenu kvaliteta jajne ćelije obuhvataju nekoliko karakteristika kumulus-oocita kompleksa, citoplazme oocita, polarnog tela, zone pellucide, perivitelinskog prostora i mejotičkog vretena. S obzirom da morfološka procena nije dovoljna fokus današnjih ispitivanja su pre svega biomarkeri koji se nalaze u FT, ali i serumu pacijentkina u procesu vantelesne oplodnje. [9,10]

Azot-monoksid (NO) je neorganski slobodni radikal koji učestvuje u različitim fiziološkim i patološkim procesima u skoro svim organskih sistema današnjih organizama. [11] NO utiče na većinu procesa kako u ženskom, tako i u muškom reproduktivnom sistemu. Studije pokazuju da NO utiče na procese steroidogeneze, folikulogeneze i ovulacije, kao i na proces spermatogeneze i pokretljivosti spermatozoida, a zatim i na razvoj placente u trudnoći, glatke mišiće, samu trudnoću i porođaj. [12] KOS u procesu VTO ima uticaj na koncentracije NO u folikularnoj tečnosti i serumu pacijentkinja. Niži nivo NO u serumu pacijentkinja može imati pozitivan uticaj na folikulogenezu, dok povišen nivo NO može imati štetan uticaj jer dovodi do atrezije folikula tj. apoptoze granuloznih ćelija folikula. [13] Tokom procesa VTO, tačnije tokom KOS dešava se intenzivan transport NO između krvi i folikularne tečnosti. Takođe na sintezu NO u organizmu utiču i vrednosti estrogena koji se tokom KOS-a povećavaju. [14]

Fosfolipidi su gradivni elementi svih ćelijskih menbrana i u svom sastavu imaju lanac slobodnih masnih kiselina. U reproduktivnim procesima fosfolipidi imaju veoma bitnu ulogu. Promena

lipidnog sastava u serumu žena, a samim tim i FT utiče na sazrevanje i morfologiju jajnih ćelija. U procesu VTO, a već tokom KOS zbog promene koncentracije polnih hormona, kako u serumu, tako i u FT se menja i lipidni status tj nivo fosfolipida. Dokazano je da estrogeni utiču na razgradnju lipida u adipocitima, pa samim tim dolazi do porasta konsentracije slobodnih masnih kiselina u serumu žena. [15, 16]

Slobodne masne kiseline nastaju hidrolizom triglicerida pod dejstvom enzima, mogu biti zasićene i nezasićene i razlikuju se u broju ugljenikovih atoma. Esencijalne nezasićene masne kiseline su strukturalni delovi fosfolipida. [17]

Tokom procesa VTO, tačnije tokom faze KOS dolazi do promena u sastavu FT. Komponentne FT, kao i seruma mogu biti mogući indikatori uspešnosti samog procesa VTO. [18]

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PERSISTENT LOW LEVEL OF ELEVATED HCG

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Human chorionic gonadotropin (hCG) is a hormone primarily produced in syncytiotrophoblast cells during pregnancy. Smaller amounts of this hormone are also produced by the pituitary gland, liver and colon. Detection of hCG in blood and urine is a standard test to prove pregnancy. The role of this hormone is to stimulate corpus luteum to produce progesterone in order to maintain the pregnancy. In early pregnancy, the most important thing is that hCG has a proper growth, as well as to ultrasonographally prove pregnancy in the uterine cavity, in order to exclude ectopic pregnancy. Persistent low level of elevated hCG is empirically defined as a value of less than 250 IU/L more than three months. There are those conditions when the use of standard tests prove the positivity of hCG, and the patient is not pregnant. Such conditions can be divided into benign, premalignant and malignant. Benign conditions would be: heterophilic antibodies, pituitary hCG, familial hCG syndrome, exogenous hCG, Munchausen syndrome. Premalignant and malignant conditions would be: active gestational trophoblastic disease, “quiescent” gestational trophoblastic disease and non-trophoblastic malignancy. A positive hCG in the absence of pregnancy represents a challenge for clinicians, because of the diagnosis and the decision on further treatment. Adequate history, gynecological and ultrasound examination, radiological diagnostics (computerized tomography-CT or magnetic resonance-MR of the abdomen and pelvis), laboratory tests (serial monitoring of hCG levels in the blood) are key steps in establishing the right diagnosis, because decision whether it is a benign or malignant condition cannot be based only on the monitoring of hCG values. According to literature data, approximately 7.6% of patients with a persistently low level elevated hCG have active malignancy, which is why is very important to diagnose when this condition is associated with it. The treatment of patients with persistently low elevated hCG is controversial.

According to analysis of 99 patients at the hCG Reference Service Center in the United States of America, chemotherapy is unnecessary and ineffective in the early stage of persistently low hCG elevation because of the possibility of spontaneous healing. However, if there is a mass proven radiologically, then treatment is recommended, although there are no specific guidelines on the type of treatment; surgical or chemotherapy. Considering all the above, when it comes to therapy, chemotherapy should be first choice. A positive response to chemotherapy is more associated with a benign condition than with malignancy.

One condition associated with persistently low hCG elevation is trophoblastic implant in the abdominal cavity, which is a rare finding after treatment of ectopic or intrauterine pregnancy. In most cases, it occurs at the original site of the ectopic pregnancy after salpingoneostomy or salpingectomy. It can also be found in different places on the peritoneum. Most cases of trophoblastic implantation after ectopic pregnancy are treated surgically.

It is important to monitor the hCG after termination of pregnancy. For patients with elevated hCG in combination with a hypervascular mass in the small pelvis, consider trophoblast implant diagnosis and also methotrexate treatment.

ISTHMOCELE DIAGNOSIS AND MANAGEMENT: A REVIEW OF THE LITERATURE WITH A CASE REPORT

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Abstract. Uterine niche is one of the increasingly encountered complications of cesarean section. With rising cesarean rates, complications are also on the rise [1]. Uterine niche, also described as uterine isthmocele, is a cesarean scar defect in the myometrium at the site of a previous cesarean scar due to defective tissue healing and it occurs in up to 70% of women with a previous cesarean [2]. Only 30% of women are symptomatic and they may have varied symptoms- abnormal uterine bleeding, post-menstrual spotting, and infertility, though most women remain asymptomatic and diagnosed incidentally [3]. Diagnosis is made radiologically by transvaginal sonography, saline instillation sonohysterography, or magnetic resonance imaging [3-6]. The occurrence of niche may be prevented by using the correct surgical technique during a cesarean [5]. Patients may be managed medically-hormonal therapy, however, subfertility and persistent symptoms may require surgical correction either by hysteroscopic resection or transabdominal or transvaginal repair [7].

We report on a 37-year-old patient who had a cesarean section in 2018 and came for a check-up in December of 2021 after infertility and intermenstrual bleeding. She had regular gynecological check-ups in some private clinics and the reported findings were normal every time. However, our ultrasound examination showed a niche measuring 7x4 mm. After our recommendation, the patient then underwent an NMR of the pelvis, where a postoperative defect measuring 7x21 mm was described, which involved the entire thickness of the myometrium midsagittally and parasagittally on the right, with a bottom bordered by a lined zone 1-2 mm thick, which corresponds to an intact serosa with hemorrhagic content - very suspicious dehiscence of the uterus, while the rest of the myometrium was preserved. Considering that the patient wanted pregnancy, after reviewing the literature and all possibilities, we have decided to perform surgery - laparotomy, excision of the previous scar, and suture of the uterine wall. After the surgical treatment, the patient came for check-ups, and in two months we found out that she was pregnant. She was delivered by cesarean section at term.

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MOLECULAR FEATURES AND HISTOLOGY IMPACTING NEW FIGO STAGING OF ENDOMETRIAL CANCER

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Endometrial cancer is the second most common gynecological cancer worldwide, and therefore carries significant global health burden (1). FIGO staging system has been the main instrument in treatment decision-making protocol, as well as the main prognostic predictor for endometrial cancer. It has been initially introduced in 1988 as an entirely clinical system and underwent revision in 2009.

Since 2009, huge progress in understanding biological behavior and outcomes of diverse histological and molecular varieties of endometrial cancer has been made. The molecular endometrial cancer classification first described by The Cancer Genome Atlas (TCGA) resulted in switch from a morphology-based classification towards an integrated model based on molecular and histologic features (2). The new 2023 FIGO staging system of endometrial cancer (Table 1) is developed to embrace those evidences and aid clinicians with determining treatment options, defining prognostic groups and improve oncological outcomes (3).

Impact of histological findings

Histopathological findings are the central figures in the new 2023 FIGO endometrial cancer staging system. Endometrial cancers are traditionally divided into main histological groups: endometrial endometrioid carcinomas and non-endometrioid carcinomas, where the first group occurs in approximately 80% cases and generally has better prognosis. The second group accounts for 20% of cases and includes all other subtypes which most commonly have poor prognosis and show more aggressive behavior (5).

The 2023 FIGO staging system discriminates all histological types of endometrial cancer into two groups based on their behavior: non-aggressive and aggressive category. Non-aggressive types include low-grade (grade 1 and 2) endometrioid endometrial cancer, while aggressive types are high-grade (grade 3) endometrioid carcinomas and non-endometrioid carcinomas: serous carcinomas, clear cell carcinomas, mixed carcinomas, undifferentiated carcinomas, carcinosarcomas, unusual types like mesonephric-like carcinomas, and gastrointestinal mucinous type carcinomas (3). However, significant finding is that grade 3 endometrioid endometrial cancer is prognostically, clinically, and molecularly heterogenous disease, and therefore molecular classification is essential in assessment of their behavior (3,6). This low-grade and high-grade binary grading system allows easier clinical decision-making and has improved reproducibility, but it is important to emphasize that the three-tiered system is still significant in fertility-preserving treatment strategies (3).

The depth of myometrial invasion has already been recognized as an important risk factor, and new staging system recognizes three categories of myometrial invasion: none, less than 50% and

more than 50% (3). Likewise, LVSI is known risk factor for lymph node metastasis, recurrence and shorter survival in endometrial cancer (7).

Studies have now reported on the clinical relevance of assessing the extent of LVSI, independent of other clinicopathological features (7). For that reason, it is necessary to to discriminate "substantial" or "extensive" LVSI from "focal" or "no" LVSI (3,8), and for staging purposes recommendation by WHO 2020 is adopted (9).

Table 1. 2023 FIGO staging of cancer of the endometrium (4).

Stage	Description
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium or non-aggressive histological type (ie, low-grade endometroid) with invasion of less than half of myometrium with no or focal LVSI or good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp or confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension or with substantial LVSI or aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)
	IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria
	IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIIC1ii Macrometastasis
	IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Accurate appraisal of adnexal involvement remains challenging issue. It was considered necessary to distinguish between endometrial carcinoma with ovarian metastasis and synchronous primary tumors ovary. In the case of high-grade tumors, ovarian involvement is almost always categorized as metastatic and traditionally, low-grade tumors have been considered as dual primary carcinomas, associated with a favorable prognosis. However, studies have shown that

there is a clonal relationship between the endometrial and ovarian tumor in the majority of cases, suggesting that the tumor arises in the endometrium and secondarily extends to the ovary (10). These tumors are considered to have excellent prognosis, and the European Society of Gynecological Oncology (ESGO)/European Society for Therapeutic Radiology and Oncology (ESTRO)/ European Society of Pathology (ESP) suggest conservative treatment for patients with simultaneous low-grade carcinomas of the endometrium and the ovary if specific criteria are present (3,11). The 2023 FIGO staging system incorporated this approach by introducing stage IA3 in low-grade endometrial cancer which fulfill these criteria: no more than superficial myometrial invasion is present (<50%); the absence of substantial LVSI; the absence of additional metastases; the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/breach. If any of these criteria is not fulfilled, such cases remain as stage IIIA1 (3).

Impact of molecular findings

Molecular profiling has been one of main breakthroughs in diagnosis, treatment and prognosis assessment of endometrial cancers in past decade and has now been incorporated in new FIGO staging system. Classification that has been proposed is the simplified surrogate of the one presented by The Cancer Genome Atlas (TGCA), which classifies endometrial carcinomas into four categories: POLE-ultramutated (POLEmut), which has excellent prognosis irrespective of tumor grade; mismatch repair deficient (MMRd), No Specific Molecular Subgroup (NSMP), both of which have intermediate prognosis and p53-abnormal (p53abn), which has poor prognosis (3,5).

Evaluation of molecular subtype is particularly important in high-grade endometrioid endometrial tumors, in which it can discriminate an excellent prognosis subtype from an unfavorable prognosis subtype, POLEmut and p53abn groups respectively. Therefore, for these tumors decisions on treatment of choice should be made according to their molecular subtype.

The performance of complete molecular classification (POLEmut, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial carcinoma for prognostic risk-group stratification and as potential influencing factors for adjuvant or systemic treatment decisions (3).

Thence, in the new 2023 FIGO staging system presence of POLEmut or p53abn status results in upstaging or downstaging in early stages of disease (stage I and II), whereas intermediate risk groups (MMRd and NSMP) do not alter the stage (Table 2).

Table 2. FIGO endometrial cancer stage with molecular classification. (12)

Stage designation	Molecular findings in patients with early endometrial cancer (Stage I and II after surgical staging)
Stage IAmPOLEmu	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICmp53abn	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Conclusion

Recent discoveries in heterogenous biological behavior and outcomes in different histological and molecular subtypes of endometrial cancer called for revision of staging system. The 2023 FIGO staging system presents histological and molecular findings as main features, thus its implementation in clinical practice requires closer collaboration between clinicians and pathologists. Evaluation of main goals of new staging system, such as better prognostic precision and more appropriate treatment decisions, remains the subject of further investigations.

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ONKOLOŠKI ISHOD PACIJENTKINJA SA KARCINOMOM GRLIĆA MATERICE STADIJUMA IB1-IB2 NAKON RADIKALNE HISTEREKTOMIJE BEZ ADJUVANTNE TERAPIJE

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Uvod

Karcinom grlića materice je četvrti najčešći malignitet kod žena. Trenutno postoje dva preporučena pristupa lečenju prema FIGO 2018 kriterijumima za karcinom grlića materice stadijuma IB1-IB2, i to su: primarna operacija koja se sastoji od radikalne histerektomije sa bilateralnom disekcijom karličnih limfnih čvorova ili kombinovana karlična eksterna radioterapija i brahiterapija sa ili bez istovremene hemioterapije. Cilj rada bio je da se utvrditi petogodišnje preživljavanje (ukupno i bez recidiva) pacijentkinja sa skvamocelularnim karcinomom grlića materice, FIGO stadijuma IB1-IB2, koje prema GOG skor sistemu nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije.

Materijal i Metode

Istraživanje je sprovedeno u GAK Narodni Front kod 50 pacijentkinja kod kojih je rađena radikalna histerektomija zbog prethodno dijagnostikovanog karcinoma grlića materice, skvamocelularnog patohistološkog tipa, u periodu od 2011-2015 godine koje su praćene 5 godina nakon operacije. Pacijentkinje su klasifikovane u stadijum IB1 na osnovu FIGO klasifikacije iz 2014.godine (22), u kojoj je granična vrednost karcinoma grlića materice iznosila 4cm.

Rezultati

Većina pacijentkinja nije imala postoperativne komplikacije (87,1%). Probleme sa mokrenjem prijavilo je 12,9%, infekcije 10,0% pacijentkinja, 10% prijavilo je stres inkontinenciju, 4,5% urgentnu inkontinenciju, 3,3% pacijentkinja prijavilo je limfedem donjih ekstremiteta, dok je 2,5% pacijentkinja uključenih u istraživanje prijavilo dizuriju kao postoperativnu komplikaciju. Najveći broj pacijentkinja (93,1%) u petogodišnjem praćenju nije imalo seksualnu disfunkciju. Dve pacijentkinje su imale recidiv bolesti (6,9%). Četrdeset pacijentkinja (93,0%) imalo je pozitivan ishod, dok je 3 pacijentkinje imalo exitus letalis (7,0%). Uzrok smrti kod jedne pacijentkinje bio je karcinom pluća koji je bio nezavistan od osnovne bolesti (de novo), dok uzrok smrti kod dve pacijentkinje bio osnovna bolest.

Diskusija i zaključak. Petogodišnje preživljavanje bez recidiva bolesti kod pacijentkinja sa skvamocelularnim karcinomom grlića materice, FIGO stadijuma IB1-IB2, koje prema GOG skor sistemu nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije je 93,0%, što ukazuje na adekvatnu selekciju pacijentkinja kojima nije data adjuvantna radioterapija.

Uvod

Karcinom grlića materice je četvrti najčešći malignitet kod žena [1,2]. Prema podacima Svetske zdravstvene organizacije (SZO), u 2020. godini u svetu je zabeleženo 604.127 novodijagnostikovanih slučajeva, karcinom grlića materice je bio uzrok smrti 341.831 žene [3-5]. Većina slučajeva karcinoma grlića materice (oko 80%) otkriva se u manje razvijenim regionima sveta, gde prosečna standardizovana stopa incidencije iznosi 17.7 na 100,000 žena, što je skoro dvostruko više nego u razvijenijim regionima u kojima ova stopa iznosi 9.1 na 100,000 žena. Slično oboljevanju, najveći broj

smrtnih slučajeva od karcinoma grlića materice dešava se u manje razvijenim regionima, u kojima su uzrasno-standardizovane stope mortaliteta 2.8 puta više (9.7 na 100,000) nego u razvijenim delovima sveta (2.7 na 100,000). Srbija je 2002. godine imala najveću incidenciju karcinoma grlića materice u Evropi koja je iznosila 27.3 na 100,000 žena. Prema poslednjim podacima Globocan-a, Srbija je sada na petom mestu po incidenciji (24.1 na 100,000 žena) posle Rumunije, Makedonije, Bugarske i Litvanije. Ipak, ova incidencija je dvostruko veća od prosečne stope incidencije u Evropi koja iznosi 10.6 na 100,000 [6].

Već dugi niz godina Papanicolaou (Papa) test predstavlja standardnu metodu za skrining karcinoma grlića materice, smanjujući incidenciju karcinoma grlića materice u populaciji za 60%-90% i stopu smrtnosti za 90%. Međutim, ograničenja ovog testa zasnovanog na citologiji su njegova niska osetljivost (~50%) i značajan udeo neadekvatnih uzoraka. U novije vreme, HPV test je uveden kao test za skrining jer je pokazao je veću osetljivost na prisustvo intraepitelne neoplazije grlića visokog stepena od one postignute citologijom.

Prema SZO klasifikaciji ginekoloških tumora iz 2020-te godine svi tumori grlića materice podeljeni su na: HPV zavisne i HPV nezavisne [7]. Do nove podele tumora grlića materice došlo je usled prepoznatih agresivnijih formi karcinoma grlića koji nisu bili povezani sa HPV infekcijom. Iako se način lečenja i HPV zavisnih i HPV nezavisnih tumora ne razlikuje, nova klasifikacija omogućava jasniju procenu uspešnosti i efikasnosti testiranja za HPV infekciju, skrining programa, ali i procenu uspešnosti i efikasnosti HPV vakcinacije. Pacijentkinje sa karcinomom grlića materice se klasifikuju prema TNM klasifikaciji I FIGO klasifikaciji, koja se zasniva na nalazima različitih modaliteta (uključujući fizikalni pregled, imidžing i patološki nalaz), nakon diskusije multidisciplinarnog tima. Metode koje se koriste za određivanje statusa tumora (T); statusa limfnih čvorova (N); i sistemskog statusa (M), tj. kliničke (c), imidžing (i) i / ili patološke (p) metode na kojima je dijagnoza zasnovana bi trebalo da budu evidentirane. Metastaze u limfnim čvorovima se klasifikuju prema TNM klasifikaciji. Internacionalno udruženje za ginekologiju i akušerstvo (FIGO) ažuriralo je 2018. godine svoje kriterijume za određivanje stadijuma karcinoma grlića materice. Jedna od glavnih promena u odnosu na FIGO kriterijume iz 2014. je podela IB stadijuma karcinoma grlića materice u tri podgrupe uključujući dodatni presek na 2 cm: stadijum IB1 (<2 cm), stadijum IB2 (≥2 cm do <4 cm) i stadijum IB3 (≥4 cm). Još jedna velika promena u ažuriranim FIGO kriterijumima za postavljanje stadijuma je uključivanje radioloških slika i patoloških nalaza.

Cilj lečenja je izbeći primenu istovremeno radikalne histerektomije i radioterapije zbog visoke učestalosti komorbiditeta. Intraoperatvno određivanje zahvaćenosti limfnih čvrorova je prvi korak u hirurškom pristupu. Svaki sumnjiv čvor šalje se na patohistološku analizu i po odgovoru patologa, sa operacijom se nastavlja ili se obustavlja i pacijetnkinja se prevodi na definitivnu hemioraditerapiju. Prezervacija jajnika kod premenopauzalnih žena u slučaju skvamocelularnog i HPV zavisnog adenokarcinoma smatra se bezbednom [8].

Prema prognostičkim faktorima kao što su veličina tumora, prisustvo limfovaskularne invazije i dubina stromalne invazije, tumori su svrstani u tri grupe (niskog, srednjeg i visokog rizika) na osnovu kojih se opredeljuje za tip radikalne histerektomije prema Querleu-Morrow klasifikaciji kao i uključivanje adjuvantne terapije [8].

Adjuvantna terapija se preporučuje kod hirurški lečenih pacijentkinja koje imaju patološke faktore visokog rizika, uključujući pozitivne limfne čvorove, pozitivne hirurške ivice i zahvaćenost parametrijuma [9]. Osim toga, velika veličina tumora, duboka stromalna invazija i invazija limfovaskularnog prostora smatraju se faktorima srednjeg rizika za recidiv karcinoma grlića materice. Ove pacijentkinje su kandidati za postoperativnu adjuvantnu terapiju [9-11]. Međutim,

uloga adjuvantne radioterapije u lečenju ranog stadijuma obolelih od karcinoma grlića materice i dalje ostaje otvoreno pitanje. Adjuvantni tretman u prisustvu faktora srednjeg rizika bio je takođe predmet čestih diskusija [12,13].

Poznato je da postoperativna radioterapija dovodi do značajnog povećanja incidencije neželjenih događaja, kao što su limfedem, ileus, opstrukcija uretera, fistula, i drugih neželjenih događaja, koji utiču na kvalitet života pacijentkinja sa karcinomom grlića materice. Zbog toga se trenutno u naučnoj zajednici vodi žučna rasprava o ulozi adjuvantne terapije u prisustvu faktora srednjeg rizika kod ovih pacijentkinja, do koje je došlo zbog promena u hirurškim tehnikama i tehnikama radioterapije, boljih dijagnostičkih metoda i uključivanja patoloških i radioloških merenja veličine tumora u aktuelnu FIGO klasifikaciju karcinoma glića materice. Zbog toga je u ovoj retrospektivnoj studiji, evaluirana dugoročna prognoza pacijentkinja sa skvamocelularnim karcinomom srednjeg rizika, stadijuma IB1i IB2, koje nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije.

Cilj rada

Cilj rada bio je da se utvrditi petogodišnje preživljavanje (ukupno i bez recidiva) pacijentkinja sa skvamocelularnim karcinomom grlića materice, FIGO stadijuma IB1-IB2, koje prema GOG skor sistemu nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije.

Materijal i metode

U istraživanje je uključeno 50 pacijentkinja kod kojih je rađena radikalna histerektomija zbog prethodno dijagnostikovanog karcinoma grlića materice, skvamocelularnog patohistološkog tipa, FIGO stadijuma IB1i IB2, kod kojih osnovu GOG skor sistema nije primenjena dodatna zračna terapija nakon operacije. Istraživanje je sprovedeno u GAK " Narodni Front " kod pacijentkinja koje su operisane u periodu od 2011-2015 godine i praćene 5 godina nakon operacije. Pacijentkinje su klasifikovane u stadijum IB1 na osnovu FIGO klasifikacije iz 2014. godine [22], u kojoj je granična vrednost karcinoma grlića materice iznosila 4cm. Prema GOG skoru, rizik se kategoriše kao: nizak rizik (<40), srednji rizik (40-120) i visok rizik (>120). U ovu studiju uključene su pacijentkinje sa skorom ≤120, kod kojih nije primenjena adjuvantna radioterapija. GOG skor je računat na osnovu rada Delgada i saradnika [19] podrazumeva množenje relativnih rizika za dubinu stromalne inavzije, veličinu tumora i limfovaskulanu invaziju.

Za sve pacijentkinje prikupljeni su osnovni demografski i klinički podaci: starost, status pušenja, stepen obrazovanja, prisustvo komorbiditeta. Zabeležene su najčešće postoperativne komplikacije: poremećaj mokrenja, dizurija, stress ili urgentna inkontinencija, vezikovaginalna i uretrovaginalna fistula, limfocista, limfedem donjih ekstemiteta, infekcije, duboka venska tromboza i embolija, rektalna disfunkcija i dr. U petogodišnjem praćenju, prikupljeni su podaci o redovnim ginekološkim pregledima, prisustvu seksualne disfunkcije i problema sa mokrenjem, u cilju ispitivanja uticaja bolesti na kvalitet života. Ispitivano je i prisustvo recidiva, kao i ukupno preživljavanje u petogodišnjem vremenskom periodu.

U radu su korišćene metode deskriptivne i inferencijalne statistike. Od metoda deskriptivne statistike korišćene su mere: centralne tendencije (aritmetička sredina i medijana), mere varijabiliteta (standardna devijacija i interkvartalni opseg) i relativni brojevi. Krive preživljavanja definisane su korišćenjem Kaplan-Meier metoda, a značajnost razlike utvrđena je Long rank testom. Statistička analiza urađena je korišćenjem softvera IBM SPSS Statistics 21.

Rezultati

U istraživanje je uključeno ukupno 50 žena, prosečne starosti 54,72±11,60 godina. Najmlađa pacijentkinja imala je 32 godine, dok je najstarija pacijentkinja imala 75 godina. Što se tiče stepena obrazovanja ispitivane populacije više od polovine pacijentkinja uključenih u studiju imalo je srednje obrazovanje (60,6%), 18,2% pacijentkinja bilo je fakultetski obrazovano, dok je 15,2% pacijentkinja imalo završenu osnovnu školu. Višu školu imalo je 6,1% pacijentkinja.

Skoro polovina pacijentkinja (44,8%) izjavilo je da trenutno puši, dok je nepušača bilo 37,9% pacijentkinja. Bivših pušača bilo je 17,2%.

Više od jedne trećine pacijentkinja (35,9%) imalo je komorbiditete (povišen pritisak, šećerna bolest, srčana i plućna oboljenja, poremećaj rada štitne žlezde, autoimuna oboljenja), dok 64,1% pacijentkinja uključenih u studiju nije imalo komorbiditete.

Ispitivanjem postoperativnih karakteristika utvrđeno je da većina pacijentkinja nije imala postoperativne komplikacije (87,1%), dok je 12,9% pacijentkinja prijavilo postojanje postoperativnih komplikacija. Probleme sa mokrenjem prijavilo je 12,9% pacijentkinja uključenih u istraživanje, infekcije je prijavilo 10,0% pacijentkinja, 10% prijavilo je stres inkontinenciju, 4,5% urgentnu inkontinenciju, 3,3% pacijentkinja prijavilo je limfedem donjih ekstremiteta, dok je 2,5% pacijentkinja uključenih u istraživanje prijavilo dizuriju kao postoperativnu komplikaciju. Nijedna pacijentkinja nije prijavila: vezikovaginalnu fistula, uretrovaginalnu fistula, limfocistu, duboku vensku trombozu, emboliju niti rektalnu disfunkciju kao postoperativnu komplikaciju (0,0%).

Većina pacijentkinja (86,2%) išla je na redovne kontrole, dok je četiri pacijentkinje 13,8% prijavilo da nije išlo na redovne kontrole. Skoro polovina pacijentkinja bila je fizički aktivna (46,4%), 21,4% pacijentkinja imalo je umerenu fizičku aktivnost, dok je 32,1% pacijentkinja bilo slabo fizički aktivno. Najveći broj pacijentkinja (93,1%) u petogodišnjem praćenju (27/29) nije imalo seksualnu disfunkciju, dok je samo dve pacijentkinje prijavilo postojanje seksualne disfunkcije (6,9%). Jedna pacijentkinja (16,7%) prijavila je probleme sa mokrenjem.

Što se tiče ishoda bolesti dve pacijentkinje su imale recidiv bolesti (6,9%). Četrdeset pacijentkinja (93,0%) imalo je pozitivan ishod, dok je 3 pacijentkinje imalo exitus letalis (7,0%). Uzrok smrti kod jedne pacijentkinje bio je karcinom pluća koji je bio nezavistan od osnovne bolesti (de novo), dok uzrok smrti kod dve pacijentkinje bio osnovna bolest.

Petogodišnje preživljavanje bez recidiva bolesti kod pacijentkinja sa skvamocelularnim karcinomom grlića materice, FIGO stadijuma IB1i IB2, koje prema GOG skor sistemu nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije je 93,0%, što ukazuje na adekvatnu selekciju pacijentkinja kojima nije data adjuvantna radioterapija.

Diskusija

Grlić materice je bila prva lokalizacija koja je 1958. godine uvrštena u FIGO klinički sistem za procenu stadijuma karcinoma, pri čemu je patološki stadijum (TNM) korišćen za opis limfnih nodusa i metastatske bolesti. Klasifikacija je zatim pretrpela brojne modifikacije u poslednjih nekoliko decenija [16]. Do 1994. godine široko definisan IB stadijum podeljen je na dva stadijuma na osnovu veličine tumora: IB1 (≤4 cm) i IB2 (>4 cm), u cilju uspostavljanja specifičnih strategija lečenja, u skladu sa različitom prognozom ova dva podstadijuma [18]. FIGO klasifikacija je zatim ponovo ažurirana kako bi se omogućila upotreba novijih kliničkih, radioloških ili patoloških nalaza u klasifikaciji radi unapređenja protokola lečenja za karcinom grlića materice [16]. Uzevši u obzir da su stope recidiva niže kod tumora stadijuma IB <2 cm veličine u poređenju sa tumorima

veličine 2–4 cm, u stadijum IB je uvedena nova dodatna granica na 2 cm, čime su uspostavljene tri subkategorije: IB1, IB2 i IB3 [18].

Usled preklapanja terapijskih protokola u klasifikaciji unutar IB stadijuma i izmena u samoj klasifikaciji FIGO, usledila su mnogobrojna istraživanja koja su imala za cilj da odgovore na pitanja o definisanju adekvatnih terapijskih protokola. Pitanje koje je od ključnog značaja za terapijski protokol za karcinome grlića materice unutar IB stadijuma do 4 cm veličine, je da li adjuvatna radioterapija poboljšava stopu preživljavanja i da li sprečava pojavu recidiva, uzimajući u obzir odnos koristi i rizika radioterapije.

Kohortna studija sprovedena od strane Cibula i saradnika [19] obuhvatila je 231 pacijentkinju sa karcinomom grlića materice, srednjeg nivoa rizika. Kod 127 pacijentkinja, rađena je radikalna histerektomija bez adjuvantne radioterapije, dok je kod 104 pacijentkinje radikalna hirurgija bila praćena adjuvantnom radioterapijom. Rezultati studije pokazali su da je ukupno petogodišnje preživljavanje (OS) u grupi pacijentkinja kod kojih je rađena je radikalna histerektomija bez adjuvantne radioterapije iznosilo 95%, dok je u kontrolnoj grupi ukupno petogodišnje preživljavanje iznosilo 91%. Takođe, ukupno desetogodišnje preživljavanje u istoj kohorti pacijentkinja iznosilo je 89% naspram 84%. Kod samo dve od 127 pacijentkinja uključenih u studiju, kod kojih je rađena radikalna histerektomija bez adjuvantne radioterapije, pokazan je recidiv u karlici. Totalna stopa relapsa, stopa smrtnosti, ukupno preživljavanje ili preživljavanje specifično za bolest, nije se razlikovala kod pacijentkinja kod kojih je rađena radikalna histerektomija bez adjuvantne radioterapije u odnosu na kontrolnu grupu pacijenatkinja koje su primile adjuvantnu radioterapiju nakon radikalne operacije.

U studiju Cao-a i saradnika koja je objavljena 2020-te godine, uključene su pacijentkinje podvrgnute radikalnoj histerektomiji i disekciji karličnih limfnih čvorova zbog potvrđenog karcinoma skvamoznih ćelija grlića materice stadijuma IB1–IIA2, prema FIGO klasifikaciji. Od ukupno 861 pacijentkinje uključene u studiju, 85 nije podvrgnuto adjuvantnom tretmanu, 283 bilo je podvrgnuto adjuvantnoj radioterapiji karlice, dok je 493 pacijentkinja bilo podvrgnuto istovremenoj hemoradioterapiji [20]. Rezultati studije pokazuju da je stopa petogodišnjeg preživljavanja iznosila 87,1% bez pojave recidiva za pacijentkinje koje nisu bile podvrgnute adjuvantnom tretmanu. Takođe, pokazano je da je invazija limfovaskularnog prostora predstavljala jedini nezavisni prognostički faktor i za preživljavanje bez recidiva i za ukupno preživljavanje. Slični rezultati dobijeni su i u studiji sprovedenoj 2021. godine od strane Haesen-a i saradnika [21], koja pokazuje da je stopa recidiva kod pacijentkinja sa karcinomom grlića materice FIGO stadijum IB ≤ 4 cm lečenih radikalnom histerektomijom, bez primene adjuvantne terapije, bila niska i iznosila je 10%, kao i da nije bilo razlike u ukupnom preživljavanju i preživljavanju bez progresije bolesti kod pacijentkinja sa ili bez srednjih faktora rizika. Invazija limfovaskularnog prostora predstavljala je jedini faktor rizika koji je uticao na ishod preživljavanja bez progresije bolesti.

Studija iz 2020-te godine, sprovedena od strane Yahate i saradnika [22] pokazala je da pacijentkinje koje nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije imaju dobru prognozu. Od ukupno 82 pacijentkinja praćenih 84 meseci (1-206 meseci), šest pacijentkinja (7%) imalo je recidiv bolesti tokom srednjeg intervala (opseg) praćenja bez bolesti od 24,5 (6–56) meseci. Petogodišnja stopa preživljavanja kod pacijentkinja kojima nije davana adjuvantna radioterapija iznosila 92,6%, dok je ukupna petogodišnja stopa preživljavanja iznosila 96,3%. Slični rezultati dobijeni su u našoj studiji, u kojoj je četrdeset pacijentkinja (93,0%) imalo pozitivan ishod, dok je 3 pacijentkinje imalo exitus letalis (7,0%).

Urinarni sistem potvrđen je kao dominantno mesto komplikacija nakon radikalne operacije sa ili bez davanja adjuvantne radioterapije pacijentkinjama. Rezultati istraživanja sprovedenog u Kini (23) koje je obuhvatalo 21,026 pacijentkinja lečenih radikalnom histerektomijom zbog potvrđenog karcinoma grlića materice, pokazali su učestalost uroloških komplikacija od 1,54%. Najčešća urološka komplikacija kod pacijentkinja uključenih u studiju (223/21,026) bila je pojava genitourinarnih fistula. Kompikacije koje su se razvile nakon povrede uretera potvrđene su kod 83 (0,39%) pacijentkinje, 17 (0,08%) pacijentkinja imalo je komplikacije nakon povrede mokraćne bešike, dok je jedna (0,005%) pacijentkinja dobila komplikaciju nakon kombinovane povrede uretera i mokraćne bešike [24]. Rezultati našeg istraživanja pokazuju da je probleme sa mokrenjem prijavilo 12,9% pacijentkinja, infekcije 10,0% pacijentkinja, 10% pacijentkinja prijavilo je stres inkontinenciju, 4,5% urgentnu inkontinenciju, 3,3% pacijentkinja prijavilo je limfedem donjih ekstremiteta, dok je 2,5% pacijentkinja uključenih u istraživanje prijavilo dizuriju kao postoperativnu komplikaciju. Rezultati prethodno publikovanih studija omogućili su bolje razumevanje dugoročne prognoze pacijentkinja sa cervikalnim karcinomom srednjeg rizika, stadijuma IB1i IB2, koje nisu primile adjuvantnu radioterapiju nakon radikalne histerektomije. Pokazano je da adjuvantna radioterapija značajno smanjuje rizik od nastanka lokalnog recidiva. Međutim, ukupno preživljavanje nije značajno poboljšano, a uočen je negativan efekat na kvalitet života. Na osnovu rezultata našeg istraživanja može se reći da pacijentkinje sa cervikalnim karcinomom srednjeg rizika, stadijuma IB1i IB2, koje nisu primile adjuvantnu radioterapiju imaju visok procenat petogodišnjeg preživljavanja. Ova saznanja mogla bi biti osnov za reviziju dosadašnjih protokola lečenja karcinoma grlića materice, sa ciljem da se sa što manjim morbiditetom postignu što bolji rezultati lečenja.

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AWARENESS, NETWORK AND ADVOCACY IN ONCOFERTILITY

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By 2030, WHO estimates that 1.4 million reproductive-aged women will be diagnosed with cancer annually. Fortunately, cancer is no longer considered an incurable disease in many cases. From 2008–2014, 85% of women under the age of 45 years diagnosed with cancer survived. This increase in survival rate has shifted attention from focusing exclusively on preserving life to focusing on preserving quality of life after treatment. Advances in cancer treatment include surgery, chemotherapy, and radiotherapy, which have proven to be lifesaving; however, they result in gonadal toxicity or in some cases removal.

Oncofertility is an interdisciplinary field comprising the development of methods to restore reproductive function and expand fertility options for young patients with cancer. Advancements in both reproductive and oncology disciplines are needed to solve fertility-related issues and create awareness to cope with the social, ethical, and legal issues that arise with the development of new reproductive interventions. Oncofertility also involves reproductive issues after cancer treatment, such as family planning, complex contraception, hormonal management throughout survivorship, and surrogacy. Aim is to addresses the complex health care and quality-of-life issues that concern young cancer patients whose fertility may be threatened by their disease or its treatment.

In addition to these patients who have onset of malignant disease before fertility is achieved, there is a growing number of patients who have malignant diseases that is detected during pregnancy. All these patients are extremely difficult and complex and require treatment by several highly specialized experts in different fields of medicine using personalized approach for each patient individually and yet within the framework of all the latest knowledge and clinical practice guidelines.

Modern gynecological practice has led to the development of conservative treatment (sparing surgery – and fertility preservation surgery), in the initial stages of malignant diseases of the gynecological organs – which enables the preservation of reproductive function under strictly defined conditions.

Given that oncologists are the first physicians that oncofertility patients will interact with, it is important for them to be involved in fertility preservation care. One of the largest barriers in accessing fertility preservation services is that oncologists do not feel that they are knowledgeable enough to discuss fertility options with their cancer patients. Almost half of oncologists in one study reported not being aware of fertility preservation options for female patients.

In addition, need to spread awareness led to the creation of organizations like:

- The International Network on Cancer, Infertility and Pregnancy (INCIP) established an international registry on cancer during pregnancy and FP during cancer treatment and promotes research aiming to increase knowledge among healthcare workers and the public.

- European Society of Gynecological Oncology (ESGO) Fertility Preservation
- The European Society of Human Reproduction and Embryology (ESHRE) established in early 2017 a Special Interest Group focusing on fertility preservation
- German-Austrian-Swiss network FertiPROTEKT, representing a centralized as well as decentralized network in a large country.
- Oncofertility Consortium (OC) representing a decentralized, nationwide, interdisciplinary, and interprofessional network of medical specialists, scientists, and scholars who are exploring the relationships between health, disease, survivorship, and fertility preservation in cancer patients.

The aim was to inform health professionals and the public about the oncofertility field and to establish best oncofertility practices

Also, in accordance with current trends in the world, at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Serbia, where the reference National Center for Oncofertility is grounded, the Serbian Society for Fertility Preservation and Oncofertility was formed with aim to connect all experts from the country and abroad, create national register and support patients and their families.

With all said, global collaborations benefit the scientific community by accelerating the pace of discovery and decreasing the time to clinical application. Cultivating a collaborative environment with a multidisciplinary team is essential to the success of this process. Furthermore, research has shown that the trend toward international collaboration and network building attracts attention to issues and leads to a greater number of publications and greater support for basic research and clinical studies.

Patient advocacy organizations play a critical role in increasing public awareness of a specific cancer and in demanding improvement in approaches to treatment. These organizations are supporting those living with cancer, raising awareness about cancer and related issues, advancing cancer research, improving the quality of cancer care, addressing legislative and regulatory issues affecting cancer care and research as also can increase participation in clinical trials and help raise funds for research.

Engaging patients in research can increase its quality, and as health care providers integrate it into care, the quality of care will increase. Engagement enables mutual learning, and the building of new skills, knowledge, and skills by patients increased understanding of basic science research and the broadening of researchers' perspectives, including an understanding of what is important to patients.

The term oncofertility was created when few options were available and now provides terminology for a medical field at the intersection of many iatrogenic causes of infertility. It is clear, that both oncologists and fertility specialists recognize the importance of oncofertility care. Unfortunately, there are currently no unified protocol and clinical care guidelines for fertility preservation for these patients, therefore, it is necessary to insist on these concepts and take a step further.

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ONCOFERTILITY UNLOCKED: CONSERVATIVE TREATMENT OF EARLY STAGE ENDOMETRIAL CANCER – A CASE REPORT

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According to World Health Organization data endometrial cancer is the sixth most commonly diagnosed cancer among women of all age and eighth most commonly diagnosed cancer among women under the age of 45 (1). More than 35 thousand women worldwide under the age of 45 are diagnosed with endometrial cancer every year, and more than 3 thousand die (2).

Standard treatment for endometrial cancer is surgical - total hysterectomy with bilateral salpingo-oophorectomy. This means loss of fertility which is in particular important for women who did not finish their childbearing (3). Since the oncological outcomes for early stage endometrial cancer are proved to be safe, conservative treatment could be proposed to women of reproductive age who wish to preserve their fertility.

The importance of fertility sparing treatment in early stage endometrial cancer is mirrored in the fact that in current year the joint guidelines of leading world gynecological societies has been published. The European Society of Gynecological Oncology (ESGO), the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for or Gynaecological Endoscopy (ESGE) has released the guidelines for fertility preservation treatment of patients with endometrial carcinoma (4). The goal of this multidisciplinary approach was to help clinicians to improve quality of care and to improve quality of life for this patients.

Also, in current year International Federation of Gynecology and Obstetrics (FIGO) Committee on Women's health updated the staging system of endometrial cancer after 14 years (5). The new classification is based on histological type and molecular testing which both better define oncological outcome (5). Advancements in genetic and immunohistochemical markers in clinical trials resulted in modifications in the FIGO classification. Importance of molecular classification is to better select patients who are candidates for conservative treatment and to enable clinicians to better predict the outcome and response to hormonal treatment (6). As well there could be markers associated with better reproductive outcomes.

Molecular profiling of endometrial cancer categorize endometrial cancer into four groups: POLE ultramutated (POLEmut), MMR deficient (MMRd), non-specific molecular profile (NSMP), and p53 abnormal (p53abn). POLE mutations represent favorable prognosis while p53abn represent poor prognosis. Intermediate risk groups are MMRd and NSMP. Interestingly, FIGO stage could be rather upstaged or downstaged according to molecular status, precisely based on POLEmut (downstaging) and p53abn (upstaging).

Since conservative treatment is not standard method of care, patients who are candidates for fertility sparing treatment must be thoroughly evaluated and treated under strict conditions. This kind of treatment is offered for patients with endometrial carcinoma grade I, stage IA without myometrial invasion. Pathological diagnosis is made after hysteroscopic-guided

endometrial biopsy and uterine curettage and is revised twice by expert pathologist as second opinion. Myometrial invasion is best assessed using MRI. Patients are carefully selected and their reproductive potential and risk factors are taken into consideration. Ovarian function is assessed by age, Anti-Mullerian hormone (AMH), hormonal status and body mass index (BMI). Hysteroscopy is important for diagnosis but as well as treatment of early stage endometrial cancer. Treatment consists of hysteroscopic tumor resection in the first place and oral progestins or levonorgestrel intra-uterine device (LNG-IUD) afterwards. According to latest guideline, therapy is maintained for 6 to 12 months, and must not exceed 15 months. During follow up pelvic ultrasound is made every 3 months and histological assessment is made every 3-6 months.

At Clinic for Gynecology and Obstetrics University Clinical Center of Serbia the Board for Cancer and Human reproduction deals with oncological patients who wish to preserve their fertility. Considering the new staging system and importance of molecular classification of endometrial cancer for predicting response to therapy, we here present a case of a patient with early stage endometrial cancer with favorable prognosis according to molecular testing.

A patient aged 40 years old, with no previous pregnancies, had exploratory curettage because of irregular bleeding and pathological finding indicated endometrioid endometrial cancer, grade 2. The patient was presented to our Clinical Board with wish to preserve fertility and was carefully evaluated. Firstly, the expert pathologist's revision from our Institution was done confirming endometrioid endometrial cancer, but grade 1. The standard evaluation protocol at our Institution consists of personal and family medical history, reproductive history, tumor markers, PAP smear and colposcopy, chest X ray, breast ultrasound, gynecological exam and pelvic ultrasound, MRI of pelvis, as well as evaluation of ovarian reserve with antral follicular count and hormonal status. All patients presented to the Board are informed about risks and possible unfavorable outcomes of conservative treatment and informed consent is obtained for each patient.

Patient's family history was positive for ovarian cancer, but her personal medical history was not remarkable. PAP smear, colposcopy, tumor markers, chest X ray and breast ultrasound were all within normal range. Pelvic ultrasound and MRI both described endometrial polyp, minor intramural myoma on the anterior uterine wall and follicular cysts on both ovaries. Invasion of the myometrium was excluded by MRI. After evaluation, the Board decision was to perform hysteroscopy with polypectomy and uterine curettage and diagnostic laparoscopy. The final histopathological result was endometrioid endometrial cancer, grade 1 within polyp. The Board decision was to insert LNG-IUD with GnRH analogous for six months. Molecular testing was done. POLEmut was detected, while MSI and p53abn were absent, meaning favorable prognosis was expected. Ultrasound evaluation was done after 3 months and hysteroscopy was performed after six months. After six months of therapy with LNG-IUD and GnRH analougs, the hysthopathological finding after hysteroscopy revealed no carcinoma. The good response to therapy was in concordance with molecular results.

In conclusion, molecular testing is encouraged, but there is still need for further investigations. Detailed evaluation of patients with endometrial cancer with genetic and immunohistochemical testing could give clinicians better perspective of treatment response, oncological and reproductive outcomes, but also could give hope for patients at the beginning of treatment.

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IMMUNOLOGICAL FACTOR AS A CAUSE OF RECURRENT IMPLANTATION FAILURE AND HABITUAL ABORTIONS

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Despite serious developments in the field of reproductive medicine, Reproductive Implantation Problems (RIF) remain a common problem. Apart from RIF after IVF, Recurrent Pregnancy Loss (RPL) has been recognized as a potentially similar problem, and many authors consider them together.

"Recurrent implantation failure" (RIF) is used to describe the failure to achieve a clinical pregnancy after the transfer of at least four embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years.

"Recurrent pregnancy loss" (RPL) implies two or more successive pregnancy losses before 20 weeks (American Society of Reproductive Medicine; ACOG).

The etiology of RIFs and RPLs can be broadly classified into modifiable and non-modifiable, and further attributed to maternal, paternal, or embryonic factors. The commonest cause of implantation failure and miscarriage relates to chromosomal abnormalities of the embryo. Some of the potential maternal factors include anatomical uterine anomalies; hematological conditions associated with thrombophilia; and metabolic disturbances such as hyperinsulinemia, diabetes mellitus, or thyroid disorders. Paternal factors have also been recognized to be important. However, in over 50% of cases of RIF and RPL, the causes are not identified and are classified as idiopathic. In this case, if all findings are normal immunological factors may be considered as a potential etiological factor and specific testing may be performed.

During implantation, fetal-maternal immune tolerance is achieved. Embryo expresses paternal antigens which are foreign to the mother and are viewed as allograft. During implantation and entire pregnancy entire maternal immune system is switched to tolerogenic functional state, which is a prerequisite for the successful maintenance of pregnancy. It is achieved by: 1. The atypical expression of major histocompatibility complex (MHC); 2. The specific roles of some hormones and cytokines; 3. The temporal and spatial distributions of the uterine natural killer (uNK) cells.

Idiopathic RIF/RPL may be caused by immunological factors. Failure to establish maternal immune tolerance for successful implantation and acceptance of semi-allograft fetus may be the consequence of the imbalances within T-helper lymphocytes (Th1, Th2, Th17, Treg) or alterations in peripheral and uterine NK cells (pNK and uNK).

T helper (Th) cells are mononuclear cells within peripheral blood defined by their cytokines production profile. The 1 is responsible for cell-mediated immunity and production of interleukins (IL) - IL2, interferon-γ (IFNγ), and tumor necrosis factor - TNF-α7. Th2 is responsible for antibody-mediated immunity and the production of IL4, IL5, IL6, IL10, and IL13. TREG cells induce immune tolerance, while Th 17 autoimmunity.

In early pregnancy establishment of an appropriate cytokine milieu is critical for embryo implantation and angiogenesis. It is achieved by an increase in pro-inflammatory cytokines and Treg cells in peripheral blood in the uterus. For normal implantation and successful pregnancy shift

from Th1 to Th2 positive status is needed. During physiological pregnancy, there is predominant Th2 type immunity and Th2 cytokines (IL4, IL6, IL10) are increased. Recently normal values for specific Th1/Th2 cytokines are established - TNFα/IL10 being 30.6 and IFNγ/IL10 20.5.

In RPL Th1-type cytokine responses are augmented and there is a dominance of Th1 cytokines (IL2, IFNγ, THFα). Peripheral blood ratios of Th1/Th2 are increased.

In RIF IL1β (pro-inflammatory cytokine) is increased while TGFβ1 is decreased with increased ratios of Th1/Th2. Th1/Th2 ratio may affect outcomes in IVF.

Other cytokines may also be altered. In some RPL cases, Th17 which produces pro-inflammatory cytokines may be elevated. Treg cells (CD4+CD25+Foxp3*) which suppress Th1 and Th17 and regulate maternal immune tolerance to the fetus may be decreased in RPL. In placental tissue from successful pregnancies determination of Th1 and Th17 cytokines are decreased.

Possible biomarkers of immunogenic and tolerogenic states in early pregnancy may be: Th1 cytokines, Th2 cytokines, Th17 cytokines, and Treg cells.

As multiple cytokine pathways have been implicated in RPL and RIF, testing restricted sets of cytokines may be insufficient during initial studies.

NK cells are part of the internal immune system and they present 5-10% of peripheral lymphocytes (pNK) and 70-90% of uterine lymphocytes (uNK). There are two subgroups according to surface density: a) CD56bright – immune regulatory cytokines and b) CD56dim – higher cytotoxicity.

pNK cell differs from uNK cell by phenotype and function. 90% of pNK are CD56dim, while 80% of uNK are CD56bright. This is essential for the success and maintenance of pregnancy.

Phenotype and functional differences in NK cells differ in phenotype and have different functions. pNK show strong cytotoxicity with antiviral and antineoplastic effect, while uNK have poor cytotoxicity. Also, there are different profiles of secreted cytokines and REC-gene expression.

Uterine NK (uNK) cells share some phenotypic traits with both CD56bright and CD56dim NK cells. These traits include expression of high levels of killer cell immunoglobulin-like receptors that are responsible for self-tolerance. However, uNKs have a poor response to target cell stimulation despite having similar levels of granzyme A and B to the CD56dim NK cells. Furthermore, uNK cells have distinct messenger ribonucleic acid (mRNA) and microRNA profiles as well as the expression of CD49a, CD103, and CD9.

Embryo implantation takes place in the luteal phase of the menstrual cycle as a response to progesterone and IL15 production, which leads to an increase in uNK cell proliferation.

As these cells are present at the implantation site, they play a major role in this early stage of pregnancy through endothelial cell-modulating factors such as vascular endothelial growth factor, which results in vascular remodeling, control of trophoblast remodeling as well as cytokine secretion in the uterus.

Endometrium in early pregnancy changes. The number of CD56+ NK becomes higher in decidual tissue in women after spontaneous abortion compared to artificial abortion. Pilot studies conducted on a limited number of patients show differences in mid-secretory endometrium NK cells in women with infertility or RPL.

There is a controversy regarding the significance of pNK and reproductive outcomes. Several studies report higher levels of specific types of NK cells in risk groups.

To date, there is no standardization for either pNK or uNK cell enumeration and functional testing strategies related to reproductive immunity, especially regarding how well pNK cell characteristics mimic tissue resident uNK cell types and function like them. Testing strategies involving the enumeration of pNK or uNK cells are also problematic. Firstly, there is a large variation in the numbers of pNK cells in healthy subjects, and these numbers may overlap with those described for women with RIF or RPL. Secondly, the number of NK cells does not represent their function which may be relevant in the context of RIF and RPL. uNK cells in studies have been evaluated in the situation of RIF and RPL in the mid-luteal phase and measured predominantly as a percentage of total stromal cells rather than numbers per magnification. Due to the hormonal variation in the population of uNK cells, as well as the invasive nature of the test, which requires an endometrial biopsy, a consensus on the number or percentage of stromal cells in normal pregnancy from a healthy control group is yet to be reached. There is a striking inconsistency between sources in the cutoff value of pNK cells that is considered "elevated" and in the methodology for measuring NK cells. Normal values of the absolute number and percentage of NK cells in women are considered to be 10%. The best option for measuring NK cells is a question. uNK cells seemed to be the best choice, as they are measured directly in the uterus.

There is a variation in the techniques used to measure NK cells – pNK and uNK . Also, there are inconsistencies between pNK and uNK measurements. That is why one method is not a reliable substitute for the other. A study from 2014. Shows that women with RPL have higher pNK cell numbers and percentages, while there is no difference in uNK cells. Also, uNK cells are difficult to measure and there is a fluctuation throughout the menstrual cycle and stress. Also, there is no convincing evidence that uNK cells pose a threat to the invading trophoblast.

Possibilities of immunological testing include immunophenotype, cytokines levels, and determination of uNK obtained by endometrial biopsy.

Prenatal immunology testing is based on currently available tests, and there is no consensus concerning the role of cytokine testing in the context of Th1/Th2 cytokine ratios and NK cell subsets analysis in women with RIF and RPL. Testing outcomes may be influenced by maternal concurrent illness, infection, or underlying atopy. Further studies of the crosstalk between immunology and reproductive biology are likely to provide the "fertile groundwork" required to improve the clinical care of women with RIF and RPL. Further testing of immune changes in normal pregnancy and pregnancies with RIF/RPL is necessary.

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VAGINALNI POROĐAJ NAKON CARSKOG REZA

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Porođaj carskim rezom (CD) je jedna od najčešćih operacija širom sveta, sa sve većom učestalošću (1). Učestalost carskog reza u svetu dostiže i preko 60% a najviša je u Dominikanskoj Republici, Brazilu i Egiptu. U Evropi, najveću stopu carskih rezova ima Rumunija dok u našoj zemlji iznosi oko 29%. Žena sa prethodnim carskim rezom ima dve opcije za završavanje sledeće trudnoće: probni porođaj nakon carskog reza (TOLAC) ili elektivni ponovljeni porođaj carskim rezom (ERCD), sa svim prednostima i nedostacima vezanih za oba entiteta. (3)

Da li je Cragenova maksima „Jednom carski rez, uvek carski rez" još uvek validna?

Od 1988. godine prema preporukama American College of Obstetricians and Gynecologists ACOG, uz ispunjavanje odgovarajućih uslova savetuje se da se pokuša sa vaginalnim završavanjem porođaja kod žena sa prethodnim urađenim niskim transverzalnim carskim rezom (4).

Prema definiciji Royal College of Obstetricians and Gynaecologist RCOG-a, vaginalni porođaj nakon carskog reza VBAC se može ponuditi većini žena sa jednoplodnom trudnoćom, cefalične prezentacije u 37+0 nedelja ili kasnije koje su imale jedan porođaj carskim rezom na donjem segmentu sa transverzalnim rezom, sa ili bez istorije prethodnog vaginalnog porođaja. (5)

Prema preporukama ACOG-a, ukoliko se planira TOLAC, osnovni uslovi koji moraju biti ispunjeni su: ne više od jednog carskog reza sa niskim transverzalnim rezom, klinički adekvatna karlica, bez drugih ožiljaka i bez prethodnih ruptura uterusa kao i dostupnost lekara, monitoringa porođaja, dostupnost anestezije i mogućnost hitnog carskog reza. (6)

Verovatnoća uspeha vaginalnog porođaja nakon carskog reza (VBAC) varira u odnosu na različite demografske i opstetričke parametre. Na primer, žene kojima je obavljen prvi porođaj carskim rezom zbog distocije porođaja manje je verovatno da će VBAC uspeti, dok će kod onih čiji je prvi carski rez rađen zbog karlične prezentacije, biti veća šansa da će isti biti uspešan. (7) Takođe, kod žena čiji je prvi porođaj indukovan ili stimulisan, manja je verovatnoća da će VBAC biti uspešan u odnosu na pacijentkinje koje su imale spontani porođaj. Ostali faktori koji negativno utiču na uspešnost VBAC-a uključuju starost majke (što je veća starost niži je procenat uspešnosti VBAC-a), visok indeks telesne mase (BMI), gestaciona starost pri porođaju veća od 40. nedelje gestacije. Kratak vremenski period između dva porođaja (manje od 19 meseci) i prisustvo preeklampsije na prvom porođaju takođe smanjuju šansu za uspešnost VBAC-a.

Obavezno je antenatalno savetovanje o prednostima uspešnosti VBAC (kraći boravak u bolnici, manje bolan postpartalni period, brži oporavak) ali i rizicima od uterine rupture (manje od 1%) (8-11).

Najšire korišćeni kalkulator, VBAC kalkulator koji je patentirao National Institute of Child Health and Human Development Eunice Kennedy Shriver (NICHD), objavljen je 2007. godine i identifikovao je starost, indeks telesne mase, istoriju vaginalnog porođaja, indikacije za prethodni carski rez, istoriju VBAC i hipertenziju kao prediktore uspešnosti VBAC-a. (12)

Prednosti VBAC-a su te što se izbegava abdominalna operacija, postoji niži procenat gubitka krvi, tromboembolija, infekcija kao i kraći oporavak nakon porođaja. Pored toga, VBAC može smanjiti rizik od stanja koja su povezana sa sa višestrukim porođajima carskim rezom (npr. histerektomija,

povreda creva ili bešike, transfuzija, infekcija i abnormalna placentacija kao npr. placenta previa i placenta accreta spectrum syndrom) (13,14).

Važno je napomenuti da je epiduralna analgezija bezbedna tokom TOLAC-a (15)

Najznačajnija komplikacija TOLAC-a i VBAC-a jeste ruptura ili dehiscencija ožiljka na materici. Ovi entiteti su u najvećoj meri povezani sa morbiditetom i mortalitetom majke i novorođenčeta. Ipak, ova stopa je jako niska i iznosi oko 0,5 % (16).

Rizik od rupture uterusa zavisi od nekoliko faktora i to:

1. broja prethodnih carskih rezova (ne više od 1)
2. pravca ožiljka na uterusu (žene sa niskim transverzalnim ožiljkom imaju niži rizik od rupture u poređenju sa klasičnom incizijom koja dolazi do fundusa- istorijski značaj) (6)
3. zatvaranja uterusa po slojevima – smatra se da je dehiscencija ožiljka od carskog reza češća kada je rekonstrukcija izvršena u jednom sloju (17)
4. indukcije ili stimulacije porođaja – smatra se da su indukcija i stimulacija porođaja oksitocinom kao i inicijacija porođaja prostaglandinima povezani sa povećanim rizikom od rupture uterusa (18, 19)
5. vremenskog intervala od prethodnog carskog reza (< 18meseci povećan rizik od rupture uterusa) (20)
6. životne dobi (> 30 godina)
7. makrozomija ploda (21)

Ruptura uterusa može biti:

- Kompletna ruptura – svi slojevi uterusa su razdvojeni
- Inkompletna ruptura – uterini mišić razdvojen sa intaktnim visceralnim peritoneumom

Smatra se da je samo oko 30% ruptura otkriveno u ranom postpartumu te određeni autori preporučuju sprovođenje rutinske revizije kavuma uterusa dok drugi smatraju da je revizija potrebna samo kod simpomatskih ruptura. Znaci rupture uterusa mogu biti kasne deceleracije, fetalna bradikardija i smanjena varijabilnog na kardiotografskom zapisu, krvarenje, bol, maternalna hipovolemija sa znacima hemoragičnog šoka, atonija uterusa, hematurija, nema ruptura asimptomatska ruptura. Ukoliko se pojave ovi znaci i posumnja se na rupturu uterusa, dalji plan lečenja jeste hitna laparotomija i carski rez. Ukoliko se sumnja na intraabdominalno krvarenje, preporučuje se medijalna laparotomija. Nakon ekstrakcije ploda, ukoliko je pacijentkinja hemodinamski nestabilna, savetuje se histerektomija. U ostalim slučajevima, kod manjih gubitaka krvi i manjih ruptura, moguća je reparacija mesta rupture i rekonstrukcija zida uterusa. Prema podacima, 1 od 3 žene sa rupturom uterusa zahteva histerektomiju. (22-24).

Na kraju svega izloženog možemo zaključiti da ukoliko imamo zdravu trudnicu, u 37+0 nedelji gestacije, sa manje od 40 godina starosti, bez hipertenzije, sa normalnim BMI koja nije imala prethodne operacije na materici osim carskog reza koji je učinjen iz određenih indikacija (a da pritom imamo potpunu dokumentaciju vezanu za prvi porođaj), da su adekvatne karlične mere, povoljan akušerski nalaz, uredan kardiotokografski zapis i da je sa njom obavljeno antenatalno savetovanje i da imamo prisutnu adekvatnu opremu i salu za eventualni hitni carski rez, možemo svesti rizik na minimum i pokušati TOLAC.

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ANALYSIS OF ESSENTIAL, TOXIC, RARE EARTH, AND NOBLE ELEMENTS IN MATERNAL AND UMBILICAL CORD BLOOD

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Progressive industrialization in recent decades has contributed to the increase of metal levels in the environment, which has a dangerous impact on human health, primarily pregnant women. In this study, we aimed to compare levels of various elements in maternal and umbilical cord (UC) plasma samples collected from 125 healthy pregnant women, conduct correlation analysis among paired plasma samples, and compare our data with other populations worldwide. The study design included the following elements: essential (Mn, Co, Cu, Zn, Se, Mo), non-essential (Be, Al, Ni, As, Rb, Sr, Cd, Sb, Pb, U), rare earth (La, Pr, Ce, Nd, Sm, Eu, Gd, Dy, Ho, Er), and noble metals (Ru, Rh, Re, Pt). Levels of 30 elements were higher in maternal plasma than in UC plasma samples. However, no disparities at the statistically significant level were found for Be, Zn, Rb, Cd, Ce, and Ho. Correlation analysis among paired plasma samples revealed only positive/synergistic correlations of different strengths between most elements. Compared to other countries across the globe, our participants had considerably lower plasma levels of Zn and higher levels of Co, Ni, and As. This study provides not only a new and deeper comprehension, but also the first insight into the levels, correlation, distribution, and potential transplacental transfer of 30 elements.

FREE COMMUNICATIONS

GENETIČKE ALTERACIJE TUMOR SUPRESOR GENA I PROTOONKOGENA U SPORADIČNIM EPITELNIM KARCINOMIMA OVARIJUMA

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Uvod: Karcinom ovarijuma nastaje kao rezultat niza genetičkih promena koje uključuju protoonkogene i tumor supresor gene, koji imaju ključnu ulogu u regulaciji ćelijskog rasta. Promene c-erbB-2 i c-Myc protoonkogena i p53 i BRCA1 tumor supresorskih gena, često su primećene kod sporadičnih karcinoma ovarijuma.

Cilj: Cilj ovog rada bio je da se ispita učestalost gubitka heterozigotnosti (LOH) u regionima gena p53 i BRCA1, kao i učestalost amplifikacije onkogena c-Myc i c-erbB-2 u sporadičnim epitelnim karcinomima ovarijuma, i povezanost ovih promena sa stadijumom i prognozom bolesti.

Metode: Analizirali smo genetičke alteracije kod 15 pacijentkinja sa potvrđenom dijagnozom sporadičnog epitelnog karcinoma ovarijuma. DNK svake pacijentkinje je izolovana iz tumorskog tkiva i iz krvi, koja je predstavljala negativnu kontrolu. Mikrosatelitski markeri regiona gena p53 i BRCA1 amplifikovani su PCR metodom. Određivanje alelnog statusa mikrosatelita i detekcija LOH-a izvršena je nakon PAA gel elektroforeze. Amplifikacije c-Myc i c-erbB-2 detektovane su diferencijalnom PCR. Nivo uvećanog broja kopija gena je meren korišćenjem Scion softvera za slike.

Rezultati: LOH u regionu gena p53 detektovan je u 33,3% uzoraka karcinoma ovarijuma, od kojih su svi bili u FIGO IIIc stadijumu. U regionu gena BRCA1, LOH je otkriven u 40% uzoraka ovarijalnih karcinoma. Prema FIGO klasifikaciji, 60% ovih karcinoma je bilo u stadijumu IIIc. LOH u oba analizirana regiona detektovan je u 13,3% uzoraka, u fazi FIGO IIIc.

Amplifikacija c-Myc i c-erbB-2 onkogena nađena je u po 27% analiziranih uzoraka, u rasponu od 50% do 250%. Delecija erb je detektovana u četiri uzorka (27%). U jednom od uzoraka su istovremeno nađene amplifikacije i Myc i erb gena (6,6%). Većina karcinoma ovarijuma (60%) sa promenama u c-Myc i c-erbB-2 pripadala je uznapredovalim FIGO stadijumima (IIIc).

Zaključak: Oba tipa genetičkih promena, LOH u genima p53 i BRCA1 i amplifikacija onkogena c-Myc i c-erbB-2, najverovatnije su kasni događaji u patogenezi sporadičnih epitelnih karcinoma ovarijuma, koji su u korelaciji sa uznapredovalim stadijumom bolesti, i smatraju se nepovoljnim prognostičkim parametrom.

Ključne reči: genetičke alteracije, karcinom ovarijuma

PRIKAZ SLUČAJA EKTOPIČNE TRUDNOĆE NEUBEDLJIVE KLINIČKE SLIKE

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Uvod: Iako je poslednjih godina došlo do velikog pomaka u dijagnostici u ginekologiji i akušerstvu, ektopična trudnoća i dalje zadaje poteškoće u pravovremenom otkrivanju i daljem lečenju, kako zbog pogrešne subjektivne procene ginekologa tako i neubedljive kliničke slike, nespecifičnih simptoma ili njihovog izostanka.

Prikaz slučaja: Pacijentkinja stara 34 godine upućena je iz Doma zdravlja zbog suspektnog spontanog pobačaja u 7. nedelji gestacije. Subjektivno se dobro oseća, urednih vitalnih parametara, hemodinamski stabilna, od tegoba navodi samo oskudno krvarenje braonkaste boje. Osim jednog vaginalnog porođaja i prethodna tri spontana pobačaja njena ginekološka anamneza je bez posebnosti. Pod spekulumom krvari oskudno tamnom krvlju. Pri ginekološkom pregledu nalaz ginekoloških organa je uredan, uočava se diskretna palpatorno bolna osetljivost sa leve strane. Abdomen je mek, u ravni grudnog koša, bez peritonealnog nadražaja. Pri TVUZ vizualizuje se prazan kavum uterusa sa decidualo izmenjenim endometrijumom. Levi jajnik je uvećan, sa jasno vidljivim gestacijskim meškom implantiranim u levi ampularni deo jajovoda. U gestacijskom mešku prisutna je žumančana kesa dimenzija 2,9 mm, sa plodom veličine 5 mm i jasnom, ritmičnom srčanom radnjom. U Duglasovom prostoru nalazi se manja količina slobodne tečnosti. Uzeta je analiza krvi koja je pokazuje nivo beta-hCG od 5598,0 IU/L.

Obzirom na ultrazvučni nalaz i nivo hormona u krvi indikovano je hitno operativno lečenje. Tokom laparoskopije uočen je levi jajovod sa proširenim, gravidno izmenjenim ampularnim delom sa manjom rupturom zida iz koje oskudno krvari. Učinjena je salpingektomija i materijal je poslat na histopatološku analizu. Postoperativni period protiče uredno, sa kontrolnim beta-hCG od 3062,3 IU/L dan nakon operacije, a beta-hCG 300 IU/L sedam dana nakon. Histopatološki nalaz potvrdio je dijagnozu tubarne trudnoće.

Zaključak: Ovaj prikaz slučaja nas podseća na sposobnost ektopične trudnoće da se razvija asimptomatski, odnosno sa neubedljivim kliničkim znacima koje mlade i inače zdrave pacijentkinje dobro kompenzuju. Zbog toga su visok nivo prenatalne nege i adekvatno zbrinjavanje pacijentkinje neophodni za uspešno lečenje. Laparoskopija i dalje predstavlja zlatni standard kako u verifikovanju ektopične trudnoće tako i u njenom lečenju.

EVALUATION OF PERIOPERATIVE COMPLICATIONS IN PATIENTS AFTER MYOMECTOMY

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Introduction Fibroids are benign tumors of the uterus that occur in about 20 - 25% of women of reproductive age. Myomas are asymptomatic in 50% of cases, and can cause symptoms such as prolonged heavy menstrual bleeding, infertility, or compressive symptoms. The modern myoma therapy approach involves drug therapy and a surgery. Surgery, apart from hysterectomy, includes myomectomy which can be performed by classical laparotomy or laparoscopic techniques in cases where there is no suspicion of malignant alteration. In recent years, the laparoscopic approach is considered more favorable than classic laparotomy due to fewer complications.

The aim of our study was to compare the indications for surgery in patients with uterine myomas and intraoperative and postoperative complications between classic laparotomy and laparoscopic myomectomy.

Methods Study included 100 patients who underwent classical abdominal myomectomy by laparotomy (AM) and 30 patients who underwent myomectomy by laparoscopy (LM). All patients were younger than 40 years, without comorbidities, without previous suppressive therapy, with BMI < 28. We registered: demographic characteristics, clinical symptoms and indications for surgery, duration of surgery, intraoperative blood loss, intraoperative and postoperative complications, blood transfusion and time to hospital discharge.

Results LM patients were younger than AM (34.8 ± 4.5 vs 37.7 ± 4.8). there was no difference in parity, BMI, previous surgeries and number of myomas. In LM group infertility was predominant indication for surgery (70% vs 57%). In AM prolonged bleeding and rapid myoma growth were more often seen. There was no difference in duration of surgery, but estimated blood loss was less in LM than in AM (246 ± 161 vs 351 ± 219ml). No intraoperative complications, nor the need for radicalization of the operative procedure, i.e. conversion in the case of LM, were registered in any operative course, neither AM nor LM. In the postoperative course, there was a statistically significantly greater drop in hemoglobin in AM than in LM (10.3 ± 7.4 vs 8.9 ± 6.8). In LM, the frequency of anemia (13.33% vs 21%), the need for blood transfusion (6.67% vs 14%), and febrility (3.33% vs 7%) were significantly lower than in AM. In LM, bowel mobilization is significantly faster (25.4 ± 4.74 vs 39.4 ± 5.32 hours). In the LM, the duration of hospitalization was significantly shorter than in AM (1.3 ± 0.4 vs 4.7 ± 1.2 days).

Conclusion Laparoscopic myomectomy is more often chosen by younger women with infertility problems. The duration of surgery does not differ between the two operative techniques. After laparoscopic myomectomy, the frequency of anemia and the need for blood transfusion is lower, fever in the postoperative course is less common, bowel mobilization occurs faster and hospital dicharge is faster compared to abdominal myomectomy. Those facts may indicate the advantages of laparoscopic myomectomy in terms of a lower percentage of perioperative complications and length of hospitalization.

NOVOOTKRIVENI KARCINOM DOJKE KOD TRUDNICE U TREĆEM TRIMESTRU TRUDNOĆE – PRIKAZ SLUČAJA

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Uvod: Uticaj trudnoće na rak dojke posmatra se sa tri aspekta. Prvi, trudnoća kao faktor rizika za nastanak karcinoma dojke. Drugi, dijagnoza raka dojke kod trudnice, kada postoje posebne procedure za dijagnostiku i liječenje bolesti. Treći, trudnoća kod žene koja je u remisiji bolesti Ca dojke.

Prikaz slučaja: Pacijentkinja, 28-godišnja iz Banja Luke, drugorotka, hospitalizovana na KGA UKC RS (16.10.2022), u 35 n.g. zbog povišenih vrijednosti krvnog pritiska, otežanog hoda - uz pomoć štaka i bolova u lijevoj lumbalnoj loži. U prilogu nalaz neurologa iz avgusta 2022. sa dijagnozom "Lumboishialgia l. sin". Od strane hematologa uvedena profilaksa LMWH. Ponovo konsultovan neurolog koji ordinira analgetike i indikuje MR, LS kičme nakon poroda. Sedam dana poslije, otežano diše, navodi suvi kašalj i zamaranje pri najmanjem naporu s02 94%. Traži se RTG toraksa. Na RTG-u toraksa (25.10.2022) uočena bilateralna pleuralna efuzija, sumnja na plućnu emboliju. Urađena pleuralna punkcija pod kontrolom UZV, dobije se 500 ml žućkaste tečnosti.

Dana 26.10.2022. pacijentkinja je prezentovana Konzilijumu za nemaligne bolesti gdje je indikovan CT po programu za PTE. CT nalaz (26.10.2022) opisuje multiple sekundarne depozite u plućnom parenhimu i izraženu medijastinalnu limfadenopatiju, te multiple metastaze u kostima: sternum, rebra, skapule. U nivou Th 6 pršljenskog tijela–patološka fraktura sa migracijom frakturnih fragmenata intraspinalno. Suspektan tumefakt veličine 3,6 cm sa znacima retrakcije kože, te embolizacija segmentnih arterija. Trudnoća završena hitnim carskim rezom (26.10.2022), rođeno živo, nedoneseno, muško novorođenče 2650 g/48 cm, Ap 7/8, koje se premjesti na Odjel Intezivne njege. Torakalni hirurg indikuje uraditi CNB CT verifikovane promjene na desnoj dojci (27.10.2022) u cilju patohistološke verifikacije a nakon porođaja indikovana scintigrafija skeleta, CT abdomena, pregled od strane onkologa i prikaz Konzilijumu za maligne bolesti dojke. Dana 28.10.2022. pacijentkinja se premješta na Kliniku za plućne bolesti uz terapiju u dobrom opštem stanju. Po prispjeću PH nalaza (28.10.2022) CNB tumora desne dojke postavi se konačna dijagnoza "Ca glandulae mammae dex", CK I spoj LK, Ct4Cn2M1.Nakon tretmana u Klinici za plućne bolesti pacijentkinja se premješta u Kliniku za onkologiju zbog dalje dijagnostike verifikovanih promjena u desnoj dojci i metastatskih promjena na plućima, kostima i specifičnog onkološkog liječenja. Pacijentkinja u više navrata prezentovana Konzilijumu za maligna oboljenja.

- 01.11.2022. plasiran torkalni dren od strane torakalnog hirurga
- 08.11.2022. po odluci Konzilijuma indikovana je hitna palijativna radioterapija torakalnog šestog pršljena u hospitalnim uslovima te uključiti bifosfonate u mjesečnim intervalima

- 10.11.2022. po odluci Konzilijuma indikovana je HT po protokolu Docetaxel uz Trastuzumab/ Pertuzumab uz nastavak bifosfonata. Od novembra 2022. godine do avgusta 2023. godine sprovedena biološka terapija, palijativna radioterapija te hemioterapija po protokolu za Ca dojke

Zaključak

Redovno i pravilno provođenje skrining programa, kao i multidisciplinarni pristup je istovremeno i najbolja prevencija za klinički oblik bolesti. Ono što predstavlja problem kod mlađih žena koje žele trudnoću, a kojima predstoji liječenje adjuvantnom hemioterapijom jeste uticaj terapije na fertilnu funkciju jajnika.

DIFERENCIJALNO DIJAGNOSTIČKE DILEME I POSTUPAK KOD KRVARENJA U PERIMENOPAUZI – PRIKAZ SLUČAJA

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Uvod: Rak grlića materice je najčešći ginekološki karcinom u svetu i nalazi se na 4. mestu svih karcinoma kod žena. Incidencija ove bolesti, kao i smrtnost su veći u zemljama u razvoju, što čini da se oko 85% slučajeva te bolesti godišnje beleži upravo tamo. U poređenju sa drugim ginekološkim karcinomima rak grlića materice se javlja u ranijoj životnoj dobi, a srednja dob kada se postavlja dijagnoza u proseku je 49 godina. Infekcija HPV-om (najčešće genotipovi 16 i 18) se smatra primarnim uzrokom ove bolesti. Pušenje, veći broj porođaja ili pobačaja, dugotrajno korišćenje kombinovane oralne hormonske kontracepcije, loša polna higijena samo su neki od faktora rizika. Rani karcinomi grlića materice uglavnom su asimptomatski. Dijagnostika obuhvata kompletne laboratorijske analize, detaljan klinički pregled, kolposkopiju i Papanikolau test. Ipak, biopsija grlića materice osnovna je metoda postavljanja dijagnoze ovog karcinoma, a katkad je i konizacija metoda izbora.

Prikaz slučaja: Pacijentkinja stara 46 godina javila se na pregled zbog produženog krvarenja u perimenopauzi komplikovanog sekundarnom anemijom. Daje anamnestički podatak da unazad tri godine zna za postojanje dva mioma (intramuralni i submukozni), koje redovno kontroliše. Takođe, daje podatak o urednom kolposkopskom nalazu i PAPA testu, koji su rađeni mesec dana ranije u odnosu na hospitalizaciju. Protokolarno je urađena eksplorativna kiretaža materice, a histopatološki nalaz je pokazao da je reč o fragmentu suspektnog displastičnog tkiva. Sledeći korak u dijagnostici bila je biopsija grlića materice. Rezultat je pokazao da je reč o HSIL (CIN III) promeni. Doneta je odluka da se uradi konizacija grlića materice. Tokom perioda čekanja rezultata histopatološke analize biopsije grlića, submukozni miom je krenuo da se rađa, te je odlučeno da se operativnim putem završi kompletna ekstirpacija, a dobijeni materijal poslat je na histopatološku analizu, gde je potvrđeno da je reč o miomu. Histopatološki nalaz konizacije pokazao je da je u pitanju planocelularni infiltrativni karcinom grlića, srednje diferentovan, FIGO stadijum Ib. Pacijentkinja je zatim upućena na onkološki konzilijum, gde je doneta odluka da se sprovede radikalna histerektomija po Wertheim - Meigs, što je u našoj ustanovi i urađeno. Od radikalnog hirurškog lečenja prošlo je više od četiri meseca. Pacijentkinja se javlja na redovne ginekološke kontrole, dobrog je opšteg stanja i urednog ginekološkog nalaza.

Zaključak: Krvarenja u perimenopauzi, posebno kod pacijentkinja sa prisutnim miomima mogu predstavljati pravi izazov za ginekologe u vidu dijagnostikovanja i samog zbrinjavanja ovih stanja. Propusti u vidu fokusa isključivo na praćenje i eventualno lečenje mioma, mogu dovesti do nepovoljnog ishoda za same pacijente. Stoga je u ovakvim situacijama od suštinskog značaja multimodalan pristup koji obuhvata dobro uzete anamnestičke podatke, detaljan ginekološki pregled, korišćenje više dijagnostičkih metoda, kao i sagledavanje šire slike. Pravovremena i adekvatno postavljena dijagnoza, procena rizika, kao i preduzimanje odgovarajućih metoda lečenja ključni su u optimizaciji ishoda za pacijentkinju.

CONGENITAL AFIBRINOGENEMIA PATIENT'S PREGNANCY OUTCOME: A CASE REPORT FROM THE ANESTHESIOLOGY PERSPECTIVE

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Introduction: Congenital afribrinogenemia is a rare autosomal recessive genetic condition defined by a deficiency in blood coagulation factor I, which results in bleeding, thrombosis and obstetric complications. Studies have shown that this condition affects one person in a million. If not treated multidisciplinary and patient-centered, it might lead to unfavorable pregnancy outcomes.

Case report: The Clinic for Gynecology and Obstetrics of the University Center of Serbia provided care for a 35-year-old pregnant woman with congenital afibrinogenemia. She gave birth to a healthy baby boy with an Apgar score of 9 and no surgery or anesthesia complications despite all peripartal risks to herself and the child. Throughout the entire pregnancy, we closely monitored her clinical and laboratory results, spoke with many specialists, and prescribed medications in accordance with the results. Her medical history revealed that she was allergic to cryoprecipitate and acetylsalicylic acid. She experienced hemorrhagic cerebrovascular insult four years prior to being pregnant as a result of congenital afibrinogenemia, and yellow body cyst rupture for the same reason. She also had insulin resistance, Hashimoto thyroiditis, and Rh incompatibility while pregnant.

She had been admitted to the hospital in the sixth week of her pregnancy. The patient had two grams of Fybriga every other week before getting pregnant. A hematologist modified the dosage of the replacement fibrinogen for the entire hospitalization of the pregnant patient in accordance with laboratory and clinical results. Two hours prior to delivery, the patient took 3 g of Fybriga, and an urgent assessment revealed that her fibrinogen level was 2.5 g/l. The patient was under general balanced anesthesia. She got no blood volume compensation during surgery and was hemodynamically stable. She was only given 1 l of fluids. Tranexamic acid and Oxytocin injection were both part of the 65-minute anesthetic session. She also received 1 g of tranexamic acid immediately following a cesarean section. Patient was given 2 g of Fybriga, 1 g of Tranexamic acid, and 0.3 ml of Fraxiparine intravenously over the course of 12 hours on the second postoperative day. On the third day, in addition to previous therapy, she received vitamin K1 in a dose of 5 mg. She had laboratory tests done every day and hematologist was present in the operating room among other specialists.

Conclusion: The main component of treating pregnant women with this disease and preventing bad outcomes is replacement therapy with figrinogen concentrate, and some publications recommend values greater than 2 g/L. Although fibrinogen replacement prevents bleeding issues, it can eventually result in trombotic consequences. There is currently a lack of information about the best delivery method for women with congenital afibrinogenemia. According to research, vaginal delivery may increase the risk of cranial bleeding, making cesarean sections more suitable than vaginal deliveries. Anesthesiologists face challenges while managing pregnant patients

since being pregnant is by itself a altered health condition. Close laboratory monitoring and an interdisciplinary approach led by numerous specialists in compliance with the anesthesiologist are essential for managing this uncommon disease and ensuring a positive outcome for our pregnant patients.

ODREĐIVANJE PODKLASE IMUNOGLOBULINA G U PROCENI RIZIKA ZA RAZVOJ HEMOLITIČKE BOLESTI NOVOROĐENČETA – PRIKAZ SLUČAJA

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Uvod: Dugi niz godina kod RhD negativnih trudnica praćen je nivo antitela i nivo bilirubina u amnionskoj tečnosti. Stepen ugroženosti ploda procenjivan je na osnovu Lajlijeve krive (Liley) I titra antieritrocitnih antitela. Određivanje titra antitela i dalje predstavlja dragocen dijagnostički parametar koji uz ultrazvučni nalaz (UZ) čini standardni protokol za procenu fetalne anemije I stepena hemoličke bolesti fetusa/novorođenčeta (HBFN).

Prikaz slučaja: U Kliniku za ginekologiju i akušerstvo javila se trudnica starosti 24 godine, ORhD-, u petom mesecu prve, spontano nastale trudnoće. Trudnoća je prethodno kontrolisana u Domu zdravlja i bila je urednog toka. Pacijentkinja je negirala prethodnu primenu transfuzije, pobačaje, hronična oboljenja, operacije i primenu RhD profilakse. Preležala je COVID infekciju u prvom trimestru. Vakcinisana je sa 2 doze Pfizer vakcine pre trudnoće. Antieritrocitna antitela su prvi put detektovana u 32. nedelji gestacije i to: anti-D+C u IgM i IgG klasi, a enzimski su detektovana antitela čija se specifičnost nije mogla utvrditi. Titar anti-D antitela je bio 8. Antitela su u u daljem toku trudnoće kontrolisana na dve nedelje. Nakon mesec dana identifikovano je anti-Jka antitelo. Finalni nalaz antitela je Anti-D+C+Jka, gde je titar anti-D antitela iznosio je 16. Ultrazvučni nalaz fetusa tokom cele trudnoće bio je uredan, placenta uredne morfologije, cirkulacija i dinamika ploda uredni, bez znakova anemije ploda. Trudnica je negirala bolove, krvarenje, oticanje plodove vode i druge tegobe tokom trudnoće. Poslednji utvrđen titar anti-D antitela iznosio je 64. Imajući u vidu visok titar antitela, pristupilo se određivanju podklasa IgG kako bi se utvrdila potencijalna potreba za eksangvino transfuzijom (EST). Podklase IgG1 i IgG3 su bile negativne. Porođaj je završen carskim rezom. Rođeno je terminsko žensko dete sa Apgar skorom 8/9 telesne mase 3470g, krvne grupe O RhD+ uz pozitivan nalaz DAT 3+. Podklase IgG1 i IgG3 su i kod deteta bile negativne. Elucijom eritrocita deteta ustanovili smo Anti-D+C+Jka. U prvom času nakon rođenja bilirubin je iznosio 37 umol/L, dok je hemoglobin bio 145 g/l, tako da nije bilo potrebe za transfuzijom i EST. Majka i dete su otpušteni u dobrom opštem stanju.

Zaključak: Određivanje antitela IgG1 i IgG3 podklase se u ovom slučaju pokazalo kao dobar dijanostički parameter, koji bi mogao imati ulogu u planiranju EST, što je od značaja za pravovremenu pripremu krvi za EST od strane ovlašćene transfuziološke ustanove. Saradnja ginekologa-akušera, pedijatra i transfuziologa je od esencijalnog značaja za uspešno zbrinjavanje HBFN.

TERAPIJSKI PRISTUP I ISHOD TRUDNOĆE KOD NOVOOTKRIVENE TUBERKULOZE U DRUGOM TRIMESTRU TRUDNOĆE – PRIKAZ SLUČAJA

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Procjenjuje se da je 1,7 milijardi ljudi zaraženo bacilom tuberkuloze i stoga su u opasnosti za razvoj tuberkuloze. Na globalnom nivou do pandemije izazvane Sars-CoV-2 virusom, tuberkuloza je bila najčešći uzrok smrti povezane sa zaraznim bolestima. Za žene inficirane sa Mycobacterium tuberculosis trudnoća je povezana sa povećanim rizikom za razvoj ili pogoršanje tuberkuloze. U nekim endemskim područjima tuberkuloza je važan uzrok mortaliteta i morbiditeta majki i povezana je sa većom stopom prijevremenog porođaja, rađanja djece niske porođajne težine i fetalne smrti. U pojedinim studijama mrtvorođenost i neonatalna smrt su bile češće kod pacijentkinja sa latentnom tuberkolozom u odnosu na neinficirane pacijentkinje, ali nije dokazana statisktički značajna razlika. Od ranije je poznato da neliječena tuberkuloza predstavlja daleko veću opasnost za trudnicu i fetus nego liječenje bolesti, tako da je rano otkrivanje i liječenje tuberkuloze u trudnoći od ključne važnosti za smanjenje navedenih rizika.

Prikazan je slučaj dvadesetčetvorogodišnje trudnice (primigravida) koja je u 20. nedelji trudnoće hospitalizovana na GAK zbog prolongiralnog febrilnog stanja i suvog kašlja. Zbog povišenih parametara upale incijalno pacijentkinja liječena antibiotskom terapijom, te uz konsultaciju sa infektologom i pulmologom korigovana antibiotska terapija u dva navrata. Tokom hospitalizacije javljaju se bolovi u desnoj polovini grudnog koša uz izraženiji suvi nadražajni kašalj. Četrnaestog dana hospitalizacije pacijentkinja premještena na Kliniku za infektivne bolesti gdje je urađena šira dijagnostička obrada uz konsultativne preglede. Sputum na BK je bio negativan, Quantiferon test negativan, hemokultura, urinokultura, serološki testovi i brisevi uredni, PCR test na Covid-19 negativan, a sputum na Lowenstein u radu. Naknadno pacijentkinja navela da je sestra prije pet godina liječena od tuberkuloze. Niskodozni CT grudnog koša je opisao bilateralnu infiltraciju pluća i desnostranu pleuralnu efuziju uz subpleuralne noduse. Ponovo korigovana antibiotska terapija, uz ulkus i tromboprofilaksu, te ordinirana kortikosteroidna terapija i derivati krvi zbog anemijskog sindroma. Dvadeset petog dana hospitalizacije zbog ponovnog porasta upalnih parametara i progresije desnostrane pleuralne efuzije od strane torakalnog hirurga indikovana operativna intervencija VATS debridman, te se intraoperativno verifikuju brojne adhezije i sitnozrnaste promjene po parijetanoj pleuri desno. Na patohistološku analizu se pošalju dijelovi pleure i definitivna HP analiza potvrdi da se radi o hroničnoj granulomatoznoj inflamaciji tipa tuberkuloze. Zbog navedene HP verifikacije započne se liječenje antituberkuloznim lijekovima (Izoniazid 300 mg, Rifampicin 600 mg i Etambutol 1200 mg) u 24. nedelji trudnoće. Na primjenjenu terapiju došlo je do kliničkog, laboratorijskog i radiološkog poboljšanja, te je pacijentkinja u 45. danu otpuštena kući respiratorno i hemodinamski stabilna uz uredan sonografski nalaz fetusa. U 32. nedelji trudnoće pacijentkinja se javila na pregled zbog subjektivnog osjećaja da slabije osjeti pokrete ploda i ultrazvučno se verifikuje intrauterina smrt ploda. Trudnoća završena indukovanim porođajem i rađanjem mrtvog ženskog ploda težine 1560 g. Pacijentkinja nastavila dalje liječenje antituberkuloznim lijekovima i redovnim kontrolama pulmologa.

PERINATAL OUTCOME IN PRETERM GROWTH RESTRICTED FETUSES WITH BRAIN SPARING EFFECT BASED ON VENOUS BLOOD FLOW

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Hypoxemic brain damage presents a substantial cause of perinatal mortality and morbidity. The risk of hypoxemia is the highest in preterm growth-restricted fetuses. The brain-sparing effect results from blood redistribution towards the brain. It is a sign of fetal vulnerability and is connected with moderate academia at birth. Disturbed blood flow in venous circulation is a sign of severe fetal vulnerability. Pathological venous flow is connected with severe academia.

The aim of our study is to evaluate perinatal outcomes in preterm growth-restricted fetuses with brain-sparing effects based on venous blood flow.

Methods We evaluated 72 preterm growth-restricted fetuses of placental etiology and diagnosed brain sparing effect (cerebral/umbilical ratio <1). All the fetuses were divided based on the venous blood flow (ductus venosus (DV) and umbilical vein (UV)) into: a) 40 fetuses with normal venous blood flow and b) 32 fetuses with pathological venous circulation (DV Pi ≤ 95th percentile, or absent/reversed A wave, and/or pulsatile blood flow in UV). We compared: biophysical profile score (BPS), Doppler blood flow in the umbilical artery (UA), median cerebral artery (MCA), DV and UV, CTG, and delivery data (gestational age, neonatal body weight, umbilical artery pH and BE, neonatal mortality and morbidity).

Results The group with abnormal venous blood flow had lower gestational age at birth (30.35 ± 2.69 vs 34.2 ± 2.19 wg), BPS (5.55 ± 1.19 vs 6.07±1.03), umbilical artery Pi (1.91 ± 0.21 vs 1.71 ± 0.43), higher incidence of decelerations on CTG (84.38% vs 62.5%), lower neonatal body weight (1084.50 ± 314.4g vs 1852.67 ± 478.35g), Apgar score (5.9 ± 2.13 vs 7.67 ± 1.72), umbilical artery pH (7.14 ± 0.17 vs 7.22. ± 0.09), higher BE (6.39 ± 4.25 vs 5.69 ± 2.39) and higher incidence of neonatal morbidity (90 : 85%) and mortality (6 : 0). We observed an inverse correlation between umbilical artery PI and umbilical artery pH.

Conclusion Doppler evaluation of fetal blood flow is a key method in diagnosing and predicting perinatal asphyxia. Along with arterial blood flow, pathological venous blood flow is the most important predictor of adverse perinatal outcomes. The delivery in growth-restricted fetuses should be planned based on the venous blood flow, if possible before the appearance of ductus venosus reversed A flow and umbilical vein pulsations.

ISKUSTVA U TRETMANU VANMATERIČNE TRUDNOĆE METROTREKSATOM

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SAŽETAK – Cilj ovog istraživanja bio je retrospektivno analizirati sigurnost i stopu uspješnosti protokola s tri doze metotreksata (MTX) za liječenje hemodinamski stabilnih slučajeva vanmaternične trudnoće u Službi za ginekologiju i akušerstvo JZU Bolnica „Sveti apostol Luka“ Doboj tokom četvorogodišnjeg razdoblja. Studija je procijenila efikasnost liječenja MTX-om u 46 žena s vanmaterničnom trudnoćom u odnosu na početne nivoe ljudskog horionskog gonadotropina (hCG) , kao i u odnosu na četverogodišnji period prije uvođenja MTX. Uspješno liječenje zabilježeno je u 13/46 žena, dok je 27/46 pacijentica podvrgnuto operativnom liječenju.

Ključne riječi: Ektopična trudnoća – liječenje; Jednokratna i višestruka doza metotreksata – učinkovitost;

Prevalencija vanmaternične trudnoće (EP) nastavlja rasti zbog sve veće učestalosti činioca rizika i boljih dijagnostičkih alata.Nedavno je ukupna stopa EP-a među ženama u dobi od 15 do 44 godine bila 0,64% i nije pronađen trend povećanja ili pada. Incidenca EP raste sa uzrastom, od 0.3 % među ženama u dobi od 15 do 18 godina na 1% među ženama dobi od 35 do 42 godine. Dostupnost odgovarajućeg testa humanog horionskog gonadotropina (hCg) u serumu omogućava ranu dijagnostiku EP. Uvođenje transvaginalnih sondi visoke rezolucije dovelo je do revolucionarnih promjena prema konzervativnim strategijama tretmana EP. Transvaginalni ultrazvuk i pregled cijele male karlice, čak i u prisustvu intrauterine trudnoće, predstavlja važnu pomoć u dijagnozi heterotopne trudnoće 4 .

Hirurško liječenje EP-a glavni je oslonac liječenja, a laparoskopska hirurgija trenutno je ‘zlatni standard’ zbog veće naknadne intrauterine trudnoće nakon salpingotomije u usporedbi sa salpingektomijom.

Medicinsko liječenje s nekoliko supstanci uključujući metotreksat (MTX), hiperosmolarnu glukozu, kalijev hlorid, prostaglandin F2 alfa, estradiol i trihosantin bilo je predmetom brojnih ispitivanja.

Sve ovo svakako ima potvrđeno mjesto u liječenju manjeg nerupturiranog EP-a, gdje je cjelovitost jajovoda obično očuvana, a čini se da je u odabranih pacijentkinja jednako efikasan kao i hirurški zahvat. Jasno je, međutim, da mnoge žene s EP-om nisu prikladne za medikamentoznu terapiju i nedavne studije su istraživale moguće načine poboljšanja efikasnosti medikamentozne terapije i boljeg predviđanja slučajeva u kojima će medikamentozno liječenje biti uspješno. MTX je antagonist folne kiseline koji se veže na enzim dihidrofolat reduktazu, koji je uključen u sintezu purinskih nukleotida. Idealno je prikladan za inhibiciju brzo rastućih ćelija kao što je trofoblast. MTX se obično koristi kao lijek prve linije u liječenju novodijagnostikovane EP-a, jer je najtemeljitije proučen i potvrđen za kliničku upotrebu. MTX se može primijeniti sistemski (intramuskularne i intravenske injekcije), oralno ili lokalnom injekcijom pod ultrazvučnim ili laparoskopskim vodstvom.

U zena sa EP koje su hemodinamski stabilne i žele očuvati svoj fertilitet, liječenje jednom dozom MTX-a ima tendenciju da bude jednako liječenju laparoskopskom operacijom u pogledu stope

uspješnosti, komplikacija i naknadne plodnosti. Čini se da je to održiva alternativa laparoskopskoj salpingotomiji za odabranu skupinu pacijenata s EP.

Cilj ovog istraživanja bio je procijeniti efikasnost liječenja MTX-om u ponovljenim dozama u odabranim slučajevima EP-a.

Ispitanice i Metode

Slučajevi pacijentkinja sa EP retrospektivno su identifikovani u Službi za ginekologiju i akušerstvo JZU Bolnica „Sveti apostol Luka“ Doboj tokom osmogodišnjeg perioda (2015 – 2023). Bolnički i ambulantni kartoni pacijentkinja detaljno su pregledani kako bi se identifikovali pacijenti. Ep je dijagnostikovan nelaparoskopskim algoritmom koji kombinuje kvantitativne nivoe beta hCg, transvaginalni sonogram i kiretnu dob.. Ukupne serumske koncentracije beta hCg određene su hemiluminiscentnim imunometrijskim testovima. Sa primjenom MTX početo je 2019 godine.

Kriterijumi isključenja su bili nivo beta hCg >5 000 IU/l, potvrđena intrauterina trudnoća, adneksalna masa>4cm u najvećoj dimenziji, poremećaj funkcije jetre (nivo aspartat aminotransferaze više nego dvostruko veći od normalnog nivoa) ili bubrega(vrijednost serumskog kreatinina > 1.5 mg/dl), leukopenija (<2000/cm3), trombocitopenija (<100 ooo/cm3), te nesposobnost pacijentkinja da se pridržavaju protokola liječenja.

Liječenje se sastojalo u primjeni 100 mg MTX ubrizganog intramuskularno nakon pristanka pacijentkinje. Druga i treća doza MTX od 50 mg primijenjena je drugog i šestog dana. Pacijentkinje sa povoljnim rezultatima praćeni su ponavljanjem kliničkih, laboratorijskih i ultrazvučnih pregleda do isčeznuća beta hCG odnosno pojave nuspojava.

Hirurško liječenje indikovano je ako se nivo beta hGG nije dovoljno smanjila do četrnaestog dana (<15% nivoa od sedmog dana), ili je počela rasti bilo kada, ili u slučaju pojave boli u karlici koja se ne može kontrolisati neopiodnim analgeticima ili pojavom znakova unutrašnjeg krvarenja.

Rezultati

Ukupno je identifikovano 46 ektopičnih trudnoća u četverogodišnjem periodu od kada je počela primjena MTX.(Tabela 1.) Od ovog broja MTX je uspješno primijenjen u 28,26% slučajeva (13 od 46). Hirurški je zbrinuto 54,34% slučajeva (25 od 46), dok je 17,39% (8 od 46) samo praćeno klinički, laboratorijski i ultrazvučno do isčeznuća beta hCG bez primjena bilo hirurškog, bilo medikamentoznog liječenja.

Tabela 1. Primena MTX od 2019. do 2022. godine

Godina	Broj EP	Ekspektativno	MTX	Operativno	
				Lap.	LPSC
2019	6	0	2	2	2
2020	11	2	2	4	3
2021	11	2	3	4	2
2022	18	4	6	5	3
Ukupno	46	8	13	15	10

U četvorogodišnjem periodu prije početka primjene MTX (2015-2018 godina) ukupno je identifikovano 36 ektopičnih trudnoća.(Tabela 2.) Hirurški je zbrinuto 80,55% (29 od 36) dok je 19,44% (7 od 36) praćeno klinički, laboratorijski i ultrazvučno od isčeznuća beta hCg

Tabela 2. Primena MTX od 2015. do 2018. godine

Godina	Broj EP	Ekspektativno	MTX	Operativno	
				Lap.	LPSC
2015	12	3	0	9	0
2016	9	1	0	8	0
2017	7	2	0	5	0
2018	8	1	0	7	0
Ukupno	36	7	0	29	0

Rasprava

Medicinski tretman MTX vanmateričnih trudnoća na početku se koristio u slučajevima abdominalne trudnoće .Brzo propadanje posteljice uzrokovano primjenom MTX može dovesti do razriješenja bez posledica, dok hirurška manipulacija posteljicom rezultuje, u pravilu, obilnim krvarenjem. Slična ispitivanja preduzeta za cervikalne i intersticijalne trudnoće pokazala su slične rezultate. Obrazloženje za upotrebu MTX u ovim slučajevima sastojalo se u očekivanju da će doći do trenutne destrukcije trofoblastne aktivnosti posteljice, što bi trebalo dovesti do smanjenja vaskularnosti posteljice i ograničenja potencijalnih hemoragijskih komplikacija zadržavanja posteljice. Terapija MTX za tubarne trudnoće temelji se na očekivanju sličnih učinaka. Erozivno djelovanje trofoblasta i odvajanje jajne ćelije od zida jajovoda mogu biti odgovorni za krvarenje u jajovode iz fimbričnog otvora, koji može biti ispunjen ugruščima.

Vjerovatno je da takvo krvarenje u jajovod uzrokuje ili peritubarne priraslice ili opstrukciju.. To sugeriše da bi sa primjenom MTX treba započeti što ranije, prije pojave krvarenja u jajovodu.

Najvažnija prediktivna varijabla za uspjeh liječenja EP je beta hCg. Uspješno liječenje EP MTX-om obrnuto je povezano sa nivoom beta hCg. MTX ne bi trebalo koristi u liječenju EP kada je početni nivo beta hCg>500 iU/l. Treba biti oprezan u korištenju MTX kada pacijentkinja ima krvarenje ili bol bez osjetljivosti.

Rezultati podupiru značajan rast neuspjeha medikamentoznog liječenja jednom dozom MTX kada je početni hCg iznad 5000 iU/l.U retrospektivnoj studiji pacijentkinja koje su bile liječene terapijom jednom dozom MTX procijenjeno je da su se nivoi hCG nakon liječenja smanjile između 0. I 4. dana u 40% slučajeva, a 100% tih slučajeva imalo je uspjeh u liječenju.

Čini se da je smanjenje nivoa beta hCg vrlo prediktivno za uspjeh liječenja. Varijabla razlike beta hCg pouzdan je prediktor uspjeha u slučajevima sa rastućim nivoima beta hCG nakon terapije MTX. . Studija pacijentkinja koje su primale MTX za EP definisan je kao klinički stabilna pacijentkinja čiji se nivo beta hCg sedmog dana smanjila za >= 50% u poređenju za beta hCg-om nultog dana.

Rezultati ukazuju da primjena MTX , u indikovanim slučajevima, dovode do značajnog smanjenja operativnog rješavanja EP, što svakako ima dugoročan uticaj, kao na fertilitet pacijentkinja, tako i na opšti mortalitet i morbiditet.

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POVIŠENA VREDNOST KREATININA U TRUDNOĆI I NJEGOVA ULOGA U DIJAGNOSTICI RETKOG SINDROMA – PRIKAZ SLUČAJA

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UVOD:

Townes Brocks sindom je redak genetički poremećaj, koji se javlja sa prevalencijom od oko 1:250000 živorođenih. Izazvan je mutacijom u SALL1 genu na hromozomu 16, koja se nasleđuje autozomno dominantno. Najupečatljivije odlike Townes Brocks sindroma su imperforirani anus na rođenju, malformacije šake, naročito palca, poremećena fukcija bubrega, malformacije uha i spoljašnjeg ušnog kanala. Ređe se javljaju srčani poremećaji, a retko je opisana i mentalna retardacija. Sve navedene osobine se javljaju sa varijabilnom ekspresivnošću, od vrlo blagih, kada se dijagnoza može postaviti kasnije u životu ili se uopšte ne prepozna, do vrlo upečaljivih obeležja po kojima se rano može posumnjati i potom tragati za dijagnozom.

Dijagnoza Townes Brocks sindroma se postavlja ukoliko kod pojedinca postoje dve od tri karakteristike:

1. Anorektalne malformacije (imperforirani anus, analna stenoza, ektopični anus)
2. Malformacije šake (polidaktilija, palac sa tri falange, duplikacija palca)
3. Malformacije uha (mikrotija, preaurikularni apendiks ili sinus, satyr ear, lop ear) uz senzoneuralni gubitak sluha
4. Član porodice sa dijagnozom ovog sindroma

U prepoznavanju Townes Brocks sindroma se koristi i akronim REAL (renal-ear-anal-radial).

U literaturi se u sklopu sindroma opisuje i poremećena fukcija bubrega koja može biti poslednica kako strukturalnih (hipoplazija, unilateralna agenezija, multicistični bubrezi), tako i izolovanih funkcionalnih ispada u radu bubrega.

PRIKAZ SLUČAJA:

Pacijentkinja stara 33 godine se javila na prvi pregled u bolnici u 36. nedelji gestacije, do tada redovno kontrolisana u privatnoj ordinaciji. Trudnoća je spontano nastala, urednog toka, bez komplikacija. Lična anamneza nije sadržala informacije od značaja. Fenotip pacijentkinje je bio neupadljiv, sa diskretnom malformacijom ušnih školjki u vidu naglašenog presavijenog heliksa. U laboratorijskim analizama su uočene nešto više vrednosti kreatitina u serumu (kreatinin 127, referentni opseg laboratorije 44-88), te je pacijentkinja upućena na konsultativni pregled kod nefrologa. U ponovljenim laboratorijskim analizama su dobijene slične vrednosti (kreatinin 116, eGFR 46.4). Naknadno dobijeni anamnestički podaci su naveli na sumnju da se radi o naslednom oboljenju, s obzirom da je otkriveno da je otac pacijentkinje u terminalnom stadijumu bubrežne insuficijencije, na dijaliznoj terapiji, kao i da rođena sestra i sestrin sin imaju već potvđenu dijagnozu Townes Brocks sindroma. Pacijentkinja je takođe naknadno dala podatak da je u prvim mesecima života operisana zbog urođene malformacije prstiju. Kod pacijentkinje tokom trudnoće nije postavljena definitivna dijagnoza, s obziom da se tek u trećem trimestru postavila sumnja na pomenuti sindrom, kao i na vrlo blage i nespecifične fenotipske karakteristike. Trudnoća je izneta

bez komplikacija, porođaj završen carskim rezom zbog karlične prezentacije ploda. Po rođenju, novorođenče je bilo morfološki bez ispada, upućeno na dalje genetičko ispitivanje.

ZAKLJUČAK:

Dijagnoza Townes Brocks sindroma se u većini slučajeva ne postavlja brzo i često nije očigledna. Postoji značajno preklapanje kriterijuma za više sličnih sindroma. Stepen ekspresije mutiranog SALL1 gena diktira koliko će se pojedine morfološke karakteristike ispoljiti. REAL sindrom ne utiče na dužinu života, i u najvećem procentu nije povezan sa lošijim kvalitetom života kod njegovih nosioca. U odraslom dobu dijagnoza se postavlja uglavnom u tridesetim godinama, ispoljavanjem bubrežne insuficijencije različitog stepena, dok u krajnjem stadijumu može dovesti i do potrebe za transplantacijom kao jedinom mogućom metodom lečenja.

VALUES OF SERUM ESTRADIOL ON THE FIFTH DAY OF THE STIMULATED CYCLE IN THE PREDICTION OF IVF SUCCESS IN POOR RESPONDER

Dejan M. Pavlović

Vasiljević Mladenko, Vujović Maja, Mitrović Jelena, Sretenović Dragutin, Subotić Draško, Mandić Milica

Clinic for Gynecology and Obstetrics "Narodni front", Belgrade

Introduction: Patients with poor ovarian response (POR) usually have elevated FSH, lower AMH, and low numbers of oocytes retrieved. Since the follicular reserve is reduced, during ovarian hyperstimulation these patients usually receive high doses of gonadotropins and have longer periods of stimulation. They achieve a smaller number of poor-quality follicles and a lower increase in estradiol.

The aim of our study was to examine the level of estradiol on the fifth day of the stimulated cycle in patients with poor ovarian reserve compared to patients with normal ovarian reserve and examine the predictive value of the serum estradiol level on the fifth day of the stimulated cycle for the success of IVF in poor responder.

Methods: We evaluated 50 patients with POR and 50 patients with normal ovarian reserve. All patients were stimulated with gonadotropins in short protocols using a gonadotropin-releasing hormone antagonist. Stimulation started with gonadotropins according to the protocol for POR or the protocol for normal ovarian reserve. We registered: the second-day number of antral follicles, E2, LH, and progesterone; levels of E2 and endometrial thickness on the fifth day and by the end of stimulation; duration of stimulation; the number of retrieved oocytes, number of M2 oocytes, fertilization rate, number of embryos, day od ET, number of transferred embryos, rate of biochemical and clinical pregnancies.

Results: POR had a significantly lower number of antral follicles (3.88 ± 1.43 vs 8.41±3.22) and lower E2 values (126.22 ± 41.29 vs 157.96 ± 45.66 pmol/l) with higher LH values (3.89 ± 3.43 vs 2.65 ± 2.74 IU/L) on the second day, while progesterone values did not differ significantly. On the fifth day, POR had a lower level of E2 (687.34 ± 188.55 vs 1056.49 ± 443.9 pmol/l), smaller endometrial thickness (5.14 ± 0.79 vs 7.11 ±1.03 mm). The number of follicles > 17 mm on the day of chorionic gonadotrophin administration was significantly lower in patients with POR (1.89 ± 1.78 vs 9.78± 4.65). No difference was observed in the number of days of stimulation, nor the total dose of gonadotropins used. The control group had a higher number of retrieved oocytes and mature oocytes, a higher fertilization rate (72.7% vs 83.4%), and a higher total number of embryos. There was no significant difference in the day of ET and the number of transferred embryos. Control group had higher rates of biochemical (24.58% vs 40.12%) and clinical (17.93% vs 31.28%) pregnancy. A positive correlation was found between the serum level of E2 on the fifth day of the cycle with the total number of follicles, the number of oocytes, the number of mature oocytes M2, and the number of embryos.

Conclusion: A higher level of serum E2 on the fifth day of ovarian hyperstimulation reflects a potentially higher number of oocytes that can be obtained. The detection of serum concentrations of E2 on the fifth day of stimulation of ovulation with gonadotropins, in poor responder patients can enable an early assessment of the ovarian response to ovarian hyperstimulation.

TERMINALNA FAZA KARCINOMA GRLIĆA MATERICE KOD VIŠEROTKE U PUERPERIJUMU – PRIKAZ SLUČAJA

Tamara Bezbradica

Arnela Cerić Banićević, Andrija Banićević, Đurđina Momić, Ognjenka Čančar

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Uvod: Karcinom grlića materice je najčešće dijagnostifikovan tumor u trudnoći, čija je učestalost od 0,01% do 0,9%. Simptomatologija je oskudna i simptomi su identični onima van trudnoće. Dijagnoza se postavlja biopsijom grlića materice.

Prikaz slučaja: Pacijentkinja u 37. godini života, porođena vaginalno u februaru mjesecu 2023. sa šestim djetetom u OB Doboj. Pacijentkinja je 19.4.2023. biopsijom grlića materice dijagnostikovan invazivni karcinom grlića. Dana 17.5.2023. pacijentkinja je predstavljena Ginekološko-onkološkom konzilijumu. Od tegoba navodi vaginalno krvarenje i bol u abdomenu. Od dijagnostike prilaže CT abdomena i male karlice koji opisuje neoplastičnu promjenu cerviksa sa infiltracijom, zadebljanje zida duodenuma sa slobodnom tečnošću oko duodenuma, sekundarne depozite u oba plućna krila i cističnu promjenu lijevog jajnika. Odlukom konzilijuma tražen je CT toraksa, pulmološka obrada, pregled abdominalnog hirurga te laboratorijski nalazi. Po prikupljanju nalaza pacijentkinja ponovo prikazana na konzilijumu 24.5.2023. gdje su na CT grudnog koša dijagnostikovani sekundarni depoziti plućnog parenhima i promjene na prednjem trbušnom zidu u medijalnoj liniji. Odlukom konzilijuma indikovana je palijativna RT u hospitalnim uslovima, te po završetku RT razmotriti HT po protokolu Cisplatina/Taxol. Sprovedena RT na KGA UKC RS. Zbog pogoršanja opšteg stanja pregledana od strane infektologa, pulmologa i onkologa. Obrađena serološki, radiološki – MR abdomena i male karlice. Zbog hematemeze abdominalni hirurg indikuje premještaj na KOAH. Zbog ponovnog pogoršanja opšteg stanja pacijentkinja se premjesti na JIL. Uradi se EGDS, uoči se krvarenje u gastroduodenumu i postavi se indikacija za hitan hiruški tretman. Hiruškom eksploracijom uočeno mjesto perforacije ulkusa na prednjem zidu bulbusa duodenuma i krvarnje tumorske promjene na zadnjem zidu duodenuma, koje se hirurški zbrine. Nakon stabilizacije opšteg stanja pacijentkinja se premjesti sa JIL u KOAH. Dalje tretirana konzervativno prema protokolu uz primjenu transfuzije odgovarajuće krve grupe. Zbog daljeg pogoršanja opšteg stanja dolazi do kardiorespiratorne insuficijencije te do letalnog ishoda 18.6.2023.

Zaključak: Obzirom da se radi o pacijentkinji koja je porođena šesti put, treba naglasiti bitnost pravilnog i pravovremenog sprovođenja skrining programa, te multidisciplinarnog pristupa kako u trudnoći tako i između trudnoća, kako bi se dijagnoza maligne bolesti postavila u ranom stadijumu i izbjegla pojava kliničkih oblika bolesti i letalnog ishoda.

PRIKAZ SLUČAJA DUBOKE PELVIČNE ENDOMETRIOZE

Milana Radovanović[1]

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Uvod: Duboka infiltrativna endometrioza je oblik endometrioze koja prodire duboko ispod površine peritoneuma i uzrokuje bol i neplodnost. Može zahvatiti celu karlicu, narušiti anatomiju i funkcionalnost vitalnih organa, sa negativnim uticajem na pacijentkinjin stil života.

Dijagnoza duboke infiltrativne endometrioze zasnovana je na kliničkom i fizikalnom pregledu, ginekološkom pregledu, a ukoliko je neophodna operacija, identifikacija i biopsija lezija. Terapijski pristup često ume da bude izazovan. Duboka infiltrativna endometrioza je najagresivnija forma, koja zahvata 20% žena koje imaju endometriozu.

Prikaz slučaja: Pacijentkinja A.L. 28 godina, javilja se inicijalno hirurgu zbog rektalnog krvarenja koje je povremeno praćeno difuznim bolom u stomaku. Mokrenje učestalo, stolica neredovna.

Njena LA i PA su uredne. Prilaže analize (Leu 9, CRP 5, urin b.o). Pregledana od strane hirurga, čiji nalaz je bio uredan, uz savet da potraži misljenje proktologa, uradi test na okultno krvarenje i eventualno ginekološki pregled. Pacijentkinja postupa kako je rečeno i na sledeći kontrolni pregled donosi test na okultno krvarenje: negativan; i uredan nalaz koloproktologa. Rektoskopski pregled u prilogu : nema defekta na sluznici kao i makromorfoloških promena. Savetuje se promena režima ishrane i dalje praćenje. Par meseci kasnije pacijentkinja se javlja u našu ambulantu radi daljeg lečenja i dijagnostike, sa i dalje prisutnim rektalnim krvarenjem. Uzimanjem detaljnih anamnestičkih podataka otkriveno da se rektalno krvarenje javlja uvek u vreme menstrualnog ciklusa , tj. da zapravo pacijentkinja menstruira rektalno, kao i da poseduje nalaz MR karlice star 2 godine na kome su opisane ciste oba jajnika. Prilaže pomenuti magnet male karlice: Desno adneksalno prisustvo hemoragične ciste veličine 60x47x52mm; Levo adneksalno cista veličine do 8mm ispunjena hemoragičnim sadržajem. U Duglasovom prostoru, od zida rektuma posteriorno i uterusa anteriorno, uočava se mekotkivna promena dimenzija 39x18mm, koja se anteriorno propagira ka desnim adneksama.

UZ TV sondom: U predelu desnih adneksa cista 49x48mm, tkivo jajnika se ne vizualizuje. Levi ovarijum 36x 25mm, sa folikulom 14mm, i nekoliko AF. U c.Douglasi manja količina slobodne tečnosti. CA125 56.6, Dat savet da se opet pregleda od strane hirurga, koloproktologa i da se ponovi MR abdomena i male karlice.

Na kontrolni ginekološki pregled pacijentkinja donosi novi MSCT abdomena i male karlice: MR nalaz odgovara bilateralnoj ovarijalnoj endometriozi sa suspektnim znacima duboke pelvične endometrioze, obliteracije rektouterinog špaga i endometrioze rektuma.

Nakon svega sagledanog, odlučeno je da se pristupi eksplorativnoj laparoskopiji. Intraoperativni nalaz je ukazao na postojanje duboke pelvične endometrioze, prisustvo više endometriotičnih polja na peritoneumu male karlice, adneksalno obostrano. Učinjena je i hromopertubacija koja je ukazala na obstruisan desni jajovod te je učinjena neosalpingostomija. Učinjena cistotomija, cistektomija i preparati su poslati na HP analizu.

Po otpustu iz bolnice pacijentkinji je uključen Dipherelinae po šemi od 3 ciklusa. Nakon završenog lečenje, eliminacije simptoma bolesti i povećanja kvaliteta života pacijentkinja se odlučila da pristupi programu za VTO .

Zaključak: Na osnovu prikazanog slučaja može se zaključiti da su detaljni anamnestički podaci dobijeni od pacijenta nekada glavni putokaz u nejasnim diferencijalno-dijagnostičkim slučajevima, i da za one slučajeve koji obuhvataju hiruršku i ginekološku simptomatologiju, laparoskopija predstavlja najoptimalnije rešenje.

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1. Bonadio RR, et al. Clinics.2018;73(suppl1):e450s

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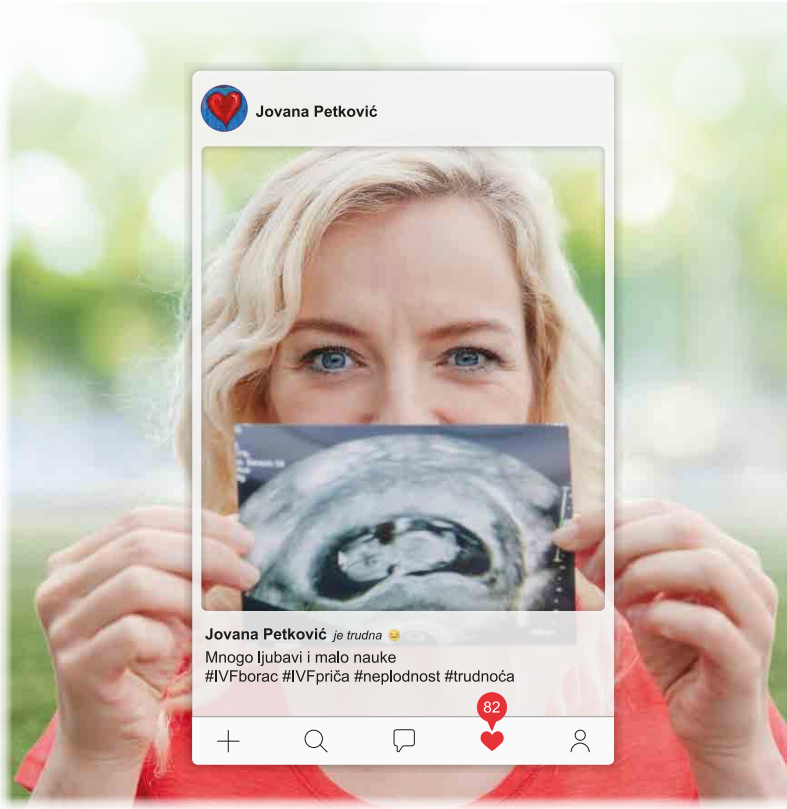

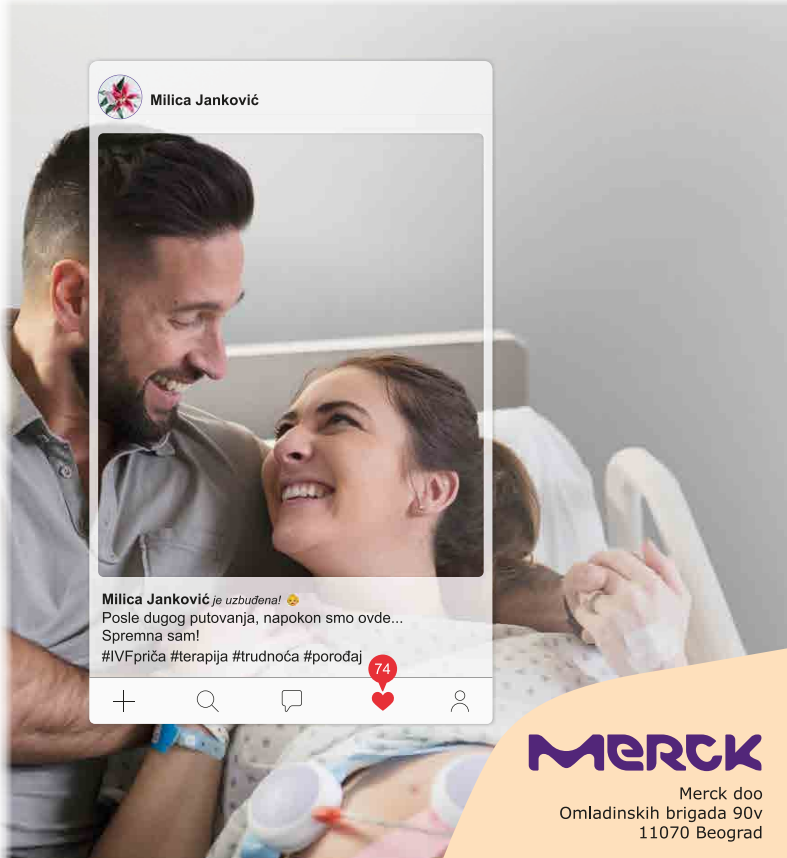

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1. MAT Q4 2021 Nicholas Hall's global CHC sales database, ***DB6***.
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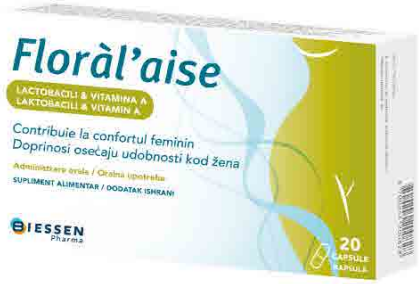

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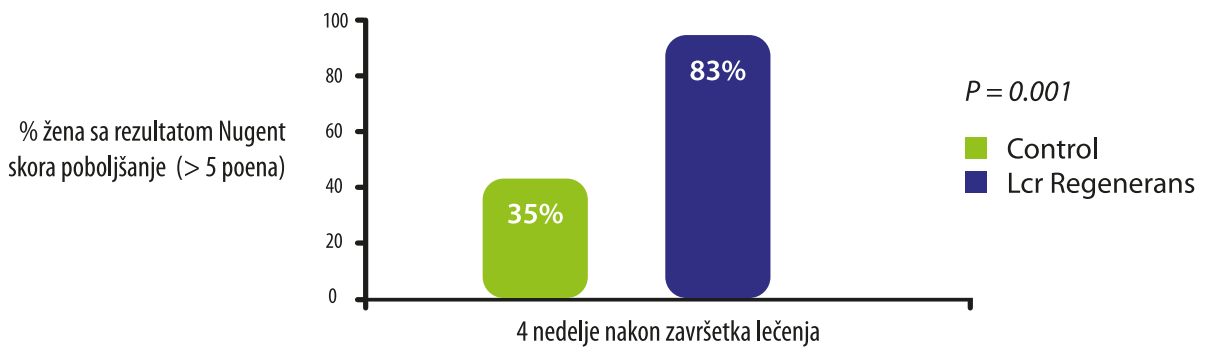

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VIUSID za sistemsku primenu, sa **GLIZIGEN** proizvodima za lokalnu upotrebu, imaju visoku efikasnost u tretmanu **humanog papiloma virusa i genitalog herpesa.**

RASTVOR

Obezbeđuje potrebe za jačanje imunog sistema i negativizaciju virusa.
2X5 ml za decu od 3g.
2x10 ml za decu od 6 g.

PRAŠAK

KESICA od 4g = 30ml rastvora. Rastvoriti kesicu u 150ml vode ili voćnog soka. Terapijska dnevna doza 3x1 kesica, doza održavanja 1x1 kesica.

SPREJ

Kao terapija protiv HPV i HSV.
1-2 sprej doze 3-4 puta dnevno direktno na promene.

INTIMNI GEL

Svakodnevna upotreba po potrebi, kao dnevna profilaksa i kod urogenitalnih infekcija.

AKTIVIRANA GLICIRIZINSKA KISELINA

Glavni aktivni princip u VIUSID i GLIZIGEN proizvodima, dobijen iz korena sladića i podvrgnut MOLEKULSKOJ AKTIVACIJI čime se povećavaju NJENA biološka svojstva.

HPV i HSV

- Veoma efikasni u negativizaciji virusa.
- Odličan anti-inflamatorni i anti-ulkusni efekat.
- Podnošljivi proizvodi čak i pri visokim dozama, bez iritacije ili neželjenih efekata, čak i u trudnoći.
- Veoma efikasni u imunostimilaciji za kontrolu vaginalnih infekcija tokom trudnoće i porođaja.
- Laka i brza primena podstiče pacijente na dužu primenu.

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