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MEDITERAN

26-28 September 2019

MONTENEGRO

BOOK OF ABSTRACTS

16th INTERNATIONAL CONGRESS

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

UGOSCGRS

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of Serbia, Montenegro and Republic of Srpska
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UGOSCGRS

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Dear Colleagues,

It is our pleasure to invite you to the 16th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska (UGOSCGRS). Congress will be held on September 26 – 28, 2019, in Budva, Montenegro.

Through joint activity of the Association and national societies of Serbia, Montenegro and Republic of Srpska we have organized four well attended and successful meetings in recent years. We can proudly say this event has grown to one of the leading regional meetings in gynecology and obstetrics. Our goal stay the same: continuous and intensive work on improving gynecology and obstetrics as profession.

The faculty counts outstanding regional and international experts from various disciplines covering topics relevant for day-to-day practice, but also giving us the insight into future perspectives in gynecology and obstetrics.

Each invited lecturer has chosen relevant topic regarding personal area of expertise – mainly gynecology and obstetrics, but also neonatology and anesthesiology. In such manner, we hope that the upcoming congress 2019 will be interesting to all participants: from residents, specialists working in primary, secondary and tertiary health care, to experts in different areas of our profession.

Topics will be presented in respected sessions of gynecology, gynecologic oncology, obstetrics, perinatology and assisted reproduction. New will be the sessions organized by the Association of Gynecologic Oncologists of Serbia (UGOS) and Serbian Urogynecologic Association(SUGA), covering the updates and recommendations, personal and instituitional experiences. The versatility of the event will be further strenghtened by the Free comunication session.

During three congress days in a beautiful environment of Montenegrin coast, we believe there will be enough time to learn and renew knowledge, but also to network and exchange ideas and experiences with colleagues.

We will be delighted to welcome you in Budva, Montenegro in September 2019.

With best wishes,

President of Association of Gynecologists and Obstericians of Serbia, Montenegro and Republic of Srpska
Prof. Dr. Aleksandar Stefanović

Dear colleagues and respected guests,

We are honored to be your hosts in Montenegro, Budva for the upcoming 16th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska (UGOSCGRS).

Association UGOSCGRS is a professional organization of gynecologists and obstetricians of Serbia, Montenegro and Republic of Srpska. It is the successor of the previously existing Association of gynecologists and obstetricians of Yugoslavia (UGOJ), founded in 1956. Association has held, in its previous history, 15 international congresses and 19 international symposiums.

Congress will be held in the Hotel Mediteran Congress center, Bečići, Budva, from 26th till 28th of September, 2019. We are expecting good attendance and a significant number of lecturers from the region and abroad. Considering that, we are sure that the upcoming event will be one of the largest and most significant regional meetings.

Our meeting and exchange of opinions on actual issues in gynecology and obstetrics will hopefully be fulfilled with good weather and a prolonged summer atmosphere, which will be an additional benefit for all participants.

We invite you to join us, refresh your knowledge and feel a breath of the Mediterranean.

President of the Association of Gynecologist and Obstetricians of Montenegro
Prim. Dr. Vojislav Miketić

CONFIRMED INVITED SPEAKERS:

- **Igor Aluloski,** North Macedonia
- **Sonja Babović,** Montenegro
- **Nikola Badžakov,** North Macedonia
- **György Bartfai,** Hungary
- **Zion Ben Rafael,** Israel
- **George Creatsas,** Greece
- **Snežana Crnogorac,** Montenegro
- **Branko Cvjetičanin,** Slovenia
- **Omer Devaja,** United Kingdom
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- **Ivana Likić Lađević,** Serbia
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- **Saša Ljuština,** Serbia
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- **Branka Nikolić,** Serbia
- **Tatjana Nikolić,** Serbia
- **Jackie Nizard,** France
- **Sveto Pantović,** Serbia
- **Ljubomir Petričević,** Austria
- **Miloš Petronijević,** Serbia

CONFIRMED INVITED SPEAKERS:

- **Vladimir Petrović,** Serbia
- **Danica Plemić Gubić,** Republic of Srpska
- **Denis Querley,** France
- **Miloš Radović,** Serbia
- **Dragan Rakanović,** Republic of Srpska
- **Snežana Rakić,** Serbia
- **Goran Relić,** Serbia
- **Katarina Sedlecky,** Serbia
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- **Iztok Takač,** Slovenia
- **Tihomir Vejnović,** Serbia
- **Snežana Vidaković,** Serbia
- **Svetlana Vrzić Petronijević,** Serbia
- **Joško Zekan,** Croatia
- **Radomir Živadinović,** Serbia

ACCREDITATION:

Congress is accredited by the decision of the Health Council of Montenegro No. 464/4 as International Congress with 20 points for invited lecturers, 15 points for oral presentation, 8 points for co-authors, 4 points for poster presentation and 3 points for passive participants.

26th of September, 2019

11:00-12:00 **Registration**

12:00-12:10 **Words of Welcome**

LECTURE HALL A

FERTILITY-SPARING IN GYNECOLOGIC ONCOLOGY

Chairs: Aleksandar Stefanović, Ivan Đukić, Borut Kobal

12:10-12:30 **Cryopreservation & transplantation of ovarian tissue among other fertility preservation techniques (KEYNOTE LECTURE)**
Meirow Dror

12:30-12:45 **Laparoscopic restaging as a fertility sparing procedures in early epithelial ovarian cancer: oncologic and reproductive outcomes from UMC Ljubljana**
Borut Kobal

12:45-13:00 **Fertility preservation in patients with brest cancer**
Snežana Vidaković

13:00-13:15 **Conservative treatment of endometrial cancer**
Katarina Stefanović

13:15-13:30 **Discussion**

13:30-13:45 **Commercial Lecture – BeoLab**
Welcome to the future - world of digital pathology
Miljan Krstić

13:45-14:00 **Commercial Lecture – Farmont**
Roidakal – novel therapy for prevention of preterm birth and miscarriage
Azis Haliti

14:00-14:45 **Lunch Break**

14:45-15:15 **Vaginal aplasia. Creatsas vaginoplasty 30 year experience (KEYNOTE LECTURE)**
George Creatsas

OBSTETRICS

Chairs: Vojislav Miketić, Vesna Ećim Zlojutro, Željko Miković, Tihomir Vejnović, Dragica Draganović

15:15-15:30 **Stop the medicalization of childbirth**
Vojislav Miketić

15:30-15:45 **Delayed delivery of the second twin**
Željko Miković

15:45-16:00 **Cesarean Section – Modification Vejnović; 3d Animation of uterus suturing**
Tihomir Vejnović

16:00-16:15 **Cesarean section - where are we today?**
Danica Plemić Gubić

16:15-16:30 **Hypertensive disorders in pregnancy – management of delivery and intrapartal surveillance**
Snežana Rakić

16:30-16:45 **Adolescent childbirth and risky sexual behavior in the north of Kosovo**
Goran Relić

16:45-17:00 **Cesarean section and anesthesia in pregnant women with coronary syndrome**
Tatjana Ilić Mostić

17:00-17:15 **Discussion**

LECTURE HALL 2

UROGYNECOLOGY AND RECONSTRUCTIVE SURGERY

Chairs: Adolf Lukanovič, Damir Hodzić, Sveto Pantović

15:15-15:30 **Do meshes have a future in urogynecology?**
Adolf Lukanovič

15:30-15:45 **Pelvic health and minimal invasive gynecological surgery**
Rajko Fureš

15:45-16:00 **Combined minimally invasive treatment for chronic urinary disorders in women**
Damir Hodžić

UROGYNECOLOGY

16:00-16:15 **The role of plastic surgery in gynaecology**
Jelena Jeremić

16:15-16:30 **Vaginal mesh - the controversy**
Sveto Pantović

16:30-16:45 **Apical prolapse - sacrospinal fixation**
Miloš Radović

16:45-17:00 **Transobturator suburethral sling procedure in the management of stress urinary incontinence - our results**
Saša Ljuština

17:00-17:15 **Discussion**

OPENING CEREMONY

18:00-19:00 **OPENING CEREMONY (Hotel Mediteran)**

19:00-21:00 **WELCOME COCKTAIL (Hotel Splendid)**

27th of September, 2019

LECTURE HALL A

HPV SESSION

Chairs: Vesna Ećim Zlojutro, Goran Dimitrov, Radomir Živadinović, Iztok Takač

09:00-09:15	**The value of condyloma treatment for maintaining reproductive health** Vesna Ećim Zlojutro
09:15-09:30	**Contemporary aspects of the prevention of sexually transmitted diseases** Miloš Petronijević
09:30-09:45	**HPV vaccination in Slovenia** Iztok Takač
09:45-10:00	**Treatment of cervical dysplasia** Branko Cvjetičanin
10:00-10:15	**The influence of socio-demographic factors and social relations on the quality of life in women treated with cervical dysplasia caused by human papilloma virus** Viktorija Jovanovska
10:15-10:30	**The role of prophylactic HPV vaccine in prevention of cervical cancer the myth or evidence-based medicine** Vladimir Petrović
10:30-10:45	**Discussion**
10:45-11:15	**Commercial lecture – MSD** **HPV immunisation in the region** Aleksandar Stefanović, Joško Zekan
11:15-11:35	**Commercial lecture – Sanofi Pasteur** **Modern immunization of women during pregnancy** Vladimir Petrović
11:35-11:45	**Coffee Break**

IVF SESSION

IVF SESSION

Chairs: Nebojša Radunović, Snežana Vidaković, Sanja Sibinčić, Elijana Garalejić, Tatjana Motrenko

11:45-12:15 **Repeated implantation failure – Does it exist? (KEYNOTE LECTURE)**
Zion Ben Rafael

12:15-12:30 **Fertility preservation - where we are today**
Tatjana Motrenko

12:30-12:45 **Social freezing: advantages and disadvantages**
Sanja Sibinčić

12:45-13:00 **Impact of female partner smoking on in vitro fertilization outcome**
Elijana Garalejić

13:00-13:15 **Role of mitochondria in the process of oocyte aging and sperm quality**
Ana Mitrović

13:15-13:30 **Thyroid hormones and outcomes of assisted reproduction**
Svetlana Spremović Rađenović

13:30-13:45 **Diagnosis of tubal factor infertility**
Aida Šahmanović

13:45-14:00 **Discussion**

14:00-15:00 **Lunch break**

15:00-15:15 **Commercial lecture – Astra Zeneca**
Lymparza (olaparib) - individual approach for significantly better results
Katarina Stefanović

GYNECOLOGICAL ONCOLOGY

GYNECOLOGICAL ONCOLOGY

Chairs: Aleksandar Stefanović, Joško Zekan, Ivan Đukić, Yulia Dobrohotova

15:15-15:45 **Update on the classification and management of cervical cancer (KEYNOTE LECTURE)**
Denis Querley

15:45-16:00 **Gestational trophoblastic neoplasia – our experiences**
Saša Kadija

16:00-16:15 **Cervical cancer in the last three years in Montenegro**
Ivan Đukić

16:15-16:30 **Surgical management of cervical cancer**
Joško Zekan

16:30-16:45 **Cervical cancer and pregnancy**
Yulia Dobrohotova

16:45-17:00 **Diagnostic-therapeutic options and significance of minimally invasive surgery in malignant gestational trophoblastic diseases**
Branka Nikolić

17:00-17:15 **PARP inhibitors in ovarian cancer therapy - the healing path**
Ivana Likić Lađević

17:15-17:30 **Discussion**

LECTURE HALL B

GYNECOLOGY

Chairs: Gyorgy Bartfai, Ana Mitrović, Katarina Sedlecky

09:00-09:15 **How can we decrease the failure rate in hormonal contraception use?**
Gyorgy Bartfai

09:15-09:30 **Contraception tailored to the needs of adolescents**
Katarina Sedlecky

09:30-09:45 **Recurrent vulvovaginal candidiasis**
Ljubomir Petričević

09:45-10:00 **Prevention of thromboembolic complications in gynecology practice**
Lapina Irene

10:00-10:15 **Minimally invasive approach in the surgical treatment of uterine myoma**
Rastko Maglić

10:15-10:30	**Adolecent pregnancy and contraception (KEYNOTE LECTURE)** George Creatsas
10:30-10:45	**Discussion**

SESSION OF ASSOCIATION OF GYNECOLOGIC ONCOLOGY OF SERBIA

SESSION OF ASSOCIATION OF GYNECOLOGIC ONCOLOGY OF SERBIA

12:15-12:30	**Laparoscopy in the treatment of cervical cancer as part of a conservative surgery treatment and laparoscopic radical hysterectomy. Is there a future? LACC study review.** Omer Devaja
12:30-12:45	**Borderline ovarian tumors** Goran Malenković
12:45-13:00	**Role of sentinel lymph node detection in cervical and endometrial cancer. Time for a standard approach.** Lazar Nejković
13:00-13:15	**Neoangiogenesis inhibitors in cervical cancer therapy** Aljoša Mandić
13:15-13:30	**Discussion**

NEONATOLOGY

NEONATOLOGY

Chairs: Tatjana Nikolić, Vesna Mandić Marković, Mirjana Marković

15:45-16:00	**Newborn from pregnancy complicated by maternal hypertension disease** Tatjana Nikolić
16:00-16:15	**Newborn of diabetic mother** Mirjana Marković
16:15-16:30	**Preeclampsia – neonatal risks** Sonja Babović
16:30-16:45	**Discussion**

28th of September, 2019

LECTURE HALL A

PERINATOLOGY

Chairs: Miroslava Gojnić Dugalić, Vojislav Miketić, Vesna Ećim Zlojutro, Snežana Rakić, Branka Čančarević Đajić

09:00-09:30 **Challenges in maternal cardiac diseases in pregnancy (KEYNOTE LECTURE)**
Jackie Nizard

09:30-09:45 **"In utero" fetal therapy as an overview and Romanian single center experience**
Nicolae Suciu

09:45-10:00 **Hypoxia and offspring disability - the role of perinatologists in fetal programming**
Miroslava Gojnić Dugalić

10:00-10:15 **Pregnancy and malignant disease**
Snežana Crnogorac

10:15-10:30 **Advantages and limitations of prenatal diagnostics of congenital heart defects**
Svetlana Vrzić Petronijević

10:30-10:45 **Can we recognize the signs of fetal heart failure on time?**
Jelena Dukanac Stamenković

10:45-11:00 **Discussion**

KEYNOTE LECTURES

Chairs: Aleksandar Stefanović, Miroslava Gojnić Dugalić

11:00-11:20 **Folate containing oral birth control pills-a new concept for prevention of birth defects (KEYNOTE LECTURE)**
Wolfgang Holzgreve

11:20-11:40 **Training in Europe: the new curriculum in obstetrics and gynaecology for all of us (KEYNOTE LECTURE)**
Jackie Nizard

11:40-11:55	**Commercial lecture – Roche diagnostics** **The value of biomarkers in diagnosis of preeclampsia - sFlt-1 i PLGF** Miroslava Gojnić Dugalić, Azis Haliti, Najdana Gligorović Barhanović
11:55-12:15	**Coffee break**

PERINATOLOGY

Chairs: Miloš Petronijević, Danko Natalić, Goran Relić, Danica Plemić Gubić

12:15-12:30	**Current recommendations for screening and diagnosis of chromosomal anomalies** Danko Natalić
12:30-12:45	**Immune factors of placental dysfunction - diagnostic and therapeutic dilemmas** Vesna Mandić Marković
12:45-13:00	**Immunomodulatory effect of progesterone-induced blocking factor (PIBF) in pregnancy** Igor Hudić
13:00-13:15	**Impact of epidural analgesia on birth dynamics, complications and neonatal outcome** Dragan Rakanović
13:15-13:30	**Volume ultrasound of fetal anomalies** Mesud Šehić
13:30-13:45	**Modern diagnostics of preeclampsia** Nataša Karadžov Orlić
13:45-14:00	**Discussion**

LECTURE HALL B

GYNECOLOGICAL ONCOLOGY

Chairs: Saša Kadija, Ivan Đukić, Goran Dimitrov, Aljoša Mandić

09:00-09:15	**Aborted radical hysterectomy - when and why?** Goran Dimitrov

09:15-09:30 **Survival of advanced stage high-grade serous ovarian cancer patients: challenges for the future**
Igor Aluloski

09:30-09:45 **Specifications of cervical adenocarcinoma in relation to squamous cell carcinoma**
Radomir Živadinović

09:45-10:00 **Our experience with "fertility sparing" radical vaginal trachelectomy and laparoscopic lymphadenectomy in early invasive cervical carcinoma**
Nikola Badžakov

10:00-10:15 **The implementation of LAST guidelines for p16 use in routine practice**
Snježana Frković Gracio

10:15-10:30 **Discussion**

12:15-14:00 **FREE COMMUNICATIONS (7 minutes per presentation)**

Chairs: Svetlana Vrzić Petronijević, Ivana Likić Lađević, Vesna Mandić Marković, Igor Hudić, Zoran Vilendečić, Igor Pilić

- **Dexamethasone effect on Doppler blood flow in women at risk of the preterm delivery**
  Janković S.
- **Management of inherited thrombophilia in pregnant women, with or without therapy with low molecular weight heparin - prospective analytical study**
  Dugalić S, Petronijević M, Stefanović A, Stefanović K, Vrzić Petronijević S, Stanisavljević D, Mitrović M, Dotlić J, Perišić Mitrović M, Radojević M, Mostić Stanišić D, Milošević B, Božić D, Jovanović I.
- **Perioperative and early postoperative complication analysis in patients with uterine myomas: laparotomy vs. laparoscopic approach**
  Ilić M, Lacković M, Stojanović M, Veselinović A, Mitić N, Mihajlović S
- **Urethral bulking agents in treatment of urinary stress incontinence**
- **Prevalence and antibiotic susceptibility of genital mycoplasma hominis and ureaplasma urealiticum in a university hospital in Macedonia**
  Gjorgievska Nikolovska E, Atanasova Boshku A.

FREE COMMUNICATIONS

- **Rational antibiotic use in small gynecological interventions**
  Stojanović M, Veselinović A, Ilić M, Lacković M, Mitić N, Mihajlović S
- **Incidence of early neonatal sepsis caused by β-hemolytic Streptococcus**
  Veselinović A, Ilić M, Stojanović M, Lacković M, Mitić N, Mihajlović S
- **Benign multicystic peritoneal mesothelioma – case report**
  Stamatović A, Crnogorac S, Vukmirović F, Filipović Z.
- **Appendectomy and anaesthesia during pregnancy**
  Ilić-Mostić T, Gunjić J, Mostić Stanišić D, Milenković D, Dugalić S.
- **Cervical carcinoma with bilateral ovarian metastases and reccurent vaginal bleeding induced by oral anticoagulant use**
  Lacković M, Stojanović M, Ilić M, Veselinović A, Mitić N, Mihajlović S.
- **Discussion**

CLOSING REMARKS

14:15 **CLOSING REMARKS**

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FERTILITY-SPARING IN GYNECOLOGIC ONCOLOGY

OUR EXPERIENCE WITH "FERTILITY SPARING" RADICAL VAGINAL TRACHELECTOMY AND LAPAROSCOPIC LYMPHADENECTOMY IN EARLY INVASIVE CERVICAL CARINOMA

Nikola Badzakov et al.

Clinical Hospital "Acibadem Sistina", Department of Obstetrics and Gynecology,

"Mala Bogorodica", Skopje, North Macedonia

Aim of the study: vaginal radical trachelectomy (VRT) was developed by Dargent as alternative surgical treatment for cervical cancer. The technique is performed by laparoscopic approach and vaginal route, only the tissue surrounding the cervix and the upper part of the vagina are removed with the cervix with pelvic lymphadenectomy**.**

Methods: 9 patients with cervical carcinoma stage from I A1 to I B1 were selected for VRT who desired fertility-sparing management. To be eligible, patients had to have a lesion that appeared confirm to the exocervix. All patients were counseled that this procedure was not standard therapy at the time. We did routinely employ preoperative only US assess of the cervix to detect measurement of the tumor. A VRT was performed using the laparoscopic-vaginal approach. The procedure started with laparoscopic pelvic lymphadenectomy, the radical trachelectomy was carried out transvaginally: the parametria and cervix were removed with amputation of the cervix approximately 1 cm below the cervical-uterine isthmus. The cervical/vaginal branches of the uterine vessels were ligated without disturbing the vascular supply to the uterus. Once the radical trachelectomy was performed, the specimen was submitted to pathology for document clearance of the cancer at the margins. Postoperatively, patients were carefully followed up 1, 3, 6, 12, 24 months with clinical examination, PAP smears and routine ultrasound assessment. As a complete clinical cytological, ultrasound remission was confirmed to one year after surgery, we accepted that the patient try to become pregnant.

Results: the mean age of patients was 29 years (range 24-50), 8 were nulligravid and one after delivery with section. Eight (89%) were squamous cell cancer, 1 (11%) were adenocarcinoma. The mean tumor size was 1.7 cm (range 0.6 – 2.2 cm). There was no conversion form laparoscopy to laparotomy or radical hysterectomy. Bladder function was assessed objectively after 2nd day with removal of catheter by performing measurement ultrasound post-voiding residual urine and patient were in the hospital 3 days. All patients remain without evidence of disease at follow up to 24 months. There were 4 (44%) pregnancies spontaneously become pregnant, 2 (22%) pregnancies with IVF program. Two deliveries with section > 37 gw, three < 37 gw.

Conclusion: in early stage cervical carcinoma, the most important prognostic factors are tumor size and presence of lympho-vascular space invasion. VRT is an oncologically safe procedure in well-selected patients with early stage disease. The morbidity of the procedure is low and it allows fertility preservation.

LAPAROSCOPIC RESTAGING AS A FERTILITY SPARING PROCEDURES IN EARLY EPITHELIAL OVARIAN CANCER: ONCOLOGIC AND REPRODUCTIVE OUTCOMES FROM UMC LJUBLJANA

Kobal Borut, Cvjetičanin Branko, Jakimovska Stefanovska Marina, Puma L.

University Medical Centre Ljubljana, Department of Obstetrics and Gynecology, Ljubljana, Slovenia

Ovarian cancer is counted to be the eighth most common cancer in women worldwide. In developed countries, FIGO stage I ovarian cancer (limited to the ovaries) is diagnosed in 20% to 33% of cases.

Early stage ovarian cancer have a good prognosis with an 5-year overall survival (OS) 85-95% and the most important prognostic indicators are considered to be the degree of differentiation (grade), stage and histotype.

The standard surgical approach in early-stage ovarian cancer is based on removal of both ovaries, peritoneal washing, peritoneal biopsies (pelvic peritoneum, paracolic gutters, diaphragm) and omentectomy (at least infracolic), bilateral pelvic and para-aortic lymphadenectomy.

According to ESMO ESGO, open surgery represents The standard approach and the minimally invasive techniques can be considered for restaging surgery in cases when the initial ovarian tumor has been removed.

However minimally invasive approach, carried out by trained surgeons in expert centres, represents a safe and adequate procedure to treat and stage early epithelial ovarian cancer and some previous studies confirm that surgical treatment of FIGO stage I ovarian cancer by laparoscopy and laparotomy have comparable oncologic outcome in terms of rate of recurrence, disease-free survival (DFS), and overall survival (OS).

Indeed, advantages of laparoscopic surgery over laparotomy are well established, including superior intraoperative visualization, smaller incisions, reduced blood loss, decreased postoperative complications such as wound infections and small bowel ileus, shorter hospitalization time, and faster recovery.

To date, fertility preservation plays an important role in in managing ESOC in premenopausal women because of the increasing trend toward late childbearing.

Fertility-sparing surgery is based on unilateral salpingo-oophorectomy, pelvic washing, pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal and diaphragmatic biopsies, appendectomy, biopsy assessment of the contralateral ovary, and endometrial biopsy. This management seems to be safe in patients with low-grade stage IA (serous, endometrioid or mucinous expansile subtype) and allows an high rate of upstaging. FSS is acceptable for stage IC1 tumors, with half of these recurrences being isolated on the remaining ovary and therefore able to be rescued by subsequent surgery. However, the recurrence rates are higher in stage IC2, IC3 and grade 3 disease, although mainly in extraovarian sites and are, therefore, not clearly correlated with the fertility-sparing approach. Adequate counselling is, therefore, needed in this situation.

Our purpose is to verify the oncologic and reproductive outcomes in patients who underwent to surgical staging for I stage ovarian epithelial cancer with a fertility sparing surgery, in our Centre, Division of Gynecology and Obstetrics UMCL, Ljubljana, from 2009 till 2018.

We retrospectively collect our data, searching for all that women that underwent to fertility sparing surgery for I stage ovarian epithelial cancer. We registered data about their age at diagnosis, the surgical approach (laparoscopic or laparotomic), histologic features of the tumor, the requirement of adjuvant therapy, the eventual relapse of the tumor and the overall survival. Besides the oncologic outcome, we

evaluated if these patients give births after surgery.

During a 9 years period, we collect a total amount of 11 patients. Median age of these patients was 32 years old. 5 of them had a FIGO I A stage tumor and 6 of them had a FIGO I C stage tumor. All of them underwent to a complete surgical staging; none of them reported complications after surgery. 7 patients had a laparoscopic procedure and 4 patients a laparotomic one. From histologic point of view, 6 cases had a low risk histologic type tumor (mucinous G1, endometrioid G1-G2, serous low grade) and 5 cases had high risk cancers (clear cell). These last 5 patients underwent to adjuvant platinum based chemotherapy. Only one patient had a relapse, she underwent to surgical laparotomic staging in 2011 for a clear cell FIGO stage I C ovarian tumor and she presented with ascites and advanced stage cancer after 7 years of follow up. We don't register any death among these patients.

Among these patients, 4 of them give birth after surgery; 3 conceived spontaneously and one gave birth to twins after IVF, all of them had a laparoscopic surgical fertility sparing staging procedure, the women conceived with IVF received also platinum based CT. There were no serious adverse in obstetric and neonatal outcomes among women with live births.

In our experience laparoscopic fertility sparing approach in patients with FIGO I stage ovarian tumor is a safe procedure with oncological outcomes comparable, or even if better, than laparotomic approach. In the context of a fertility-sparing program, the advantages provided by laparoscopy, particularly a lower likelihood of adhesions, pelvic inflammation, and functional anomalies potentially impairing fertility, are of great importance. Low risk early stage ovarian cancer are managed safely either by laparoscopy or laparotomy.

High risk ovarian cancers remain challenging; in our data we found only one case of relapse and it was a clear cell tumor. By notice, the patient had the first surgery in a first level hospital and staging with fertility sparing in our Centre after the histologic finding of malignancy. The two surgical procedures were done by laparotomy. It's well known that the surgical management of these pathologies should be referred to specialized centers, if there is a suspicious of malignancy. On the other hand, the worse oncologic outcome observed in high risk ovarian cancers, is almost related to the natural history of the disease and not specifically to the use of a conservative treatment.

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CONSERVATIVE TREATMENT OF ENDOMETRIAL CANCER

KONZERVATIVNO LEČENJE KARCINOMA ENDOMETRIJUMA

Katarina Stefanović

Klinika za ginekologiju i akušerstvo Kliničkog Centra Srbije, Medicinski fakultet u Beogradu

Karcinom endometrijuma je najčešći ginekološki karcinom u Sjedinjenim Državama sa oko 61 380 novih slučajeva u 2017. godini, što predstavlja skoro 7% svih novih karcinoma otkrivenih kod žena [1]. Iako se generalno dijagnostifikuje kod žena u postmenopauzi, karcinom endometrijuma se sve češće javlja i kod mlađih žena [2–4]. Od svih žena u 2017. godini u Sjedinjenim državama sa karcinomom endometrijuma dijagnostifikovano je 7,1% žena u dobi između 20 i 44 godine [1]. Uprkos činjenici da učestalost u ovoj starosnoj grupi je mala u poređenju sa sa ženama u postmenopauzi očekuje se da se nastavi porast s obzirom na sve veću pojavu gojaznosti i dijabetesa u ovoj starosnoj grupi. Među najčešće identifikovanim faktorima rizika kod mladih žena kojima je dijagnostikovan karcinom endometrijuma je gojaznost povezana je sa perifernom konverzijom estrogena aromatizacijom u masnom tkivu [5]. Kancelarijski način života je takođe smatran faktorom rizika o čemu svedoči nedavna metaanaliza koja je pokazala smanjenje rizika za karcinom endometrijuma za 20% kod žena koje se bave visokim nivoom fizičke aktivnosti [6]. Dosadašnje studije nedvosmisleno ukazuju da su hiperinsulinemija i dijabetes tipa 2 glavni učesnici stimulacije proliferacije ćelija raka endometrijuma [7–9]. Pored toga, studije su pokazale da su ti faktori rizika značajni i među ženama koji su genetski predisponirani za rak endometrijuma, kao u slučaju onih sa Linch sindromom kada je rizik značajno veći kada istovremeno postoje dijabetes i hiperholesterolemija koja nije zavisna od insulina [10]. Ostali potencijalni faktori rizika, kao što su hipertenzija, nuliparnost, rana menarha i anovulatorna stanja, poput sindroma policističnih jajnika, takođe doprinose razvoju raka endometrijuma kod mladih žena [11]. Značajan broj žena reproduktivne dobi danas odgađa rađanje dece iz socioekonomskih razloga, a to je dovelo do sve većeg broja žena koje nisu ostvarile potomstvo u trenutku postavljanja dijagnoze. Dakle, neophodno im je obezbediti očuvanje fertiliteta, omogućiti im priliku da zatrudne a istovremeno im pružiti adekvatan tretman raka. Pored toga, pokazalo se da pacijenti sa karcinomom endometrijuma mlađi od 45 godina mogu imati povoljniju prognozu od starijih pacijenata. To je rezultat većeg udela dobro diferenciranih tumora i ograničenih invazija miometrijuma u ovoj mlađoj starosnoj grupi [12–15]. Rutinski kandidati za konzervativno lečenje uključuju one pacijente sa dijagnozom složene atipična hiperplazije endometrijuma ili ranog karcinoma endometrijuma. Terapija uključuje histeroskopski vođenu resekciju karcinoma endometrijuma praćenu hormonskom terapijom ili upotrebom intrauterinih uređaja sa hormonskom aktivnošću (IUDs) uz redovno histeroskopsko praćenje..

Na Klinici za ginekologiju i akušerstvo u poslednjih nekoliko godina kroz rad Konzilijuma za Karcinom i Humanu reprodukciju primenjivan pristup konzervativnog tretmana karcinoma endometrijuma i dve pacijentkinje su rodile živu i zdravu novorođančad.

Treba naglasiti da je velika većina literature vezana za ovu problematiku napisana iz retrospektivnih serija ili recenziranih članaka sa malim brojem pacijenata, stoga postoji nedostatak podataka o potencijalnim ispitivanjima. Zato do sada možemo zaključiti da konzervativni tretman upotrebom hormonske terapije sa ili bez histeroskopske resekcije lezije treba razmotriti kod odabranih mladih pacijenata sa I stepenom endometrijalnog karcinoma gradusa tumora 1 koji žele da sačuvaju plodnost. Ovi pacijenti bi trebalo da budu podvrgnuti sveobuhvatnom redovnom praćenju nakon postizanja potpunog odgovora (CR). Treba napomenuti da uprkos visokim stopama CR-a, postoje i pacijenti kod kojih naknadno dolazi do pojave recidiva ili čak progresije bolesti (PD). Po postizanju kompletnog odgovara pacijentkinje bi takođe trebale što pre pokušati da ostvare trudnoću, spontano ili putem ART-a, kako bi umanjile rizik od recidiva. Na kraju nakon postizanja trudnoće ili nakon neuspeha u ART-u, pacijentima treba ponuditi standardnu operaciju.

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OBSTETRICS

DELAYED DELIVERY OF THE SECOND TWIN

ODLOŽENI POROĐAJ DRUGOG BLIZANCA

Željko Miković

Ginekološko-akušerska klinika „Narodni front“, Beograd

Odloženi porođaj drugog blizanca može biti jedini pristup koji omogućava preživljavanje bar jednog deteta u multiplim trudnoćama. Situacije u kojima ovaj pristup predstavlja opciju, kao što su preterminsko prsnuće plodovih ovojaka prvog fetusa ili započet porođaj prvog fetusa, javljaju se iznenada i predstavljaju izazov za perinatologa.

Cilj rada je da prikaže iskustva u odloženom porođaju drugog blizanca na Ginekološko-akušersoj klinici „Narodni front“.

Metodologija: Prikazani su podaci o multiplim trudnoćama sa odloženim porođajem drugog blizanca. U petogodišnjem intervalu bilo je 11 slučajeva odloženog porođaja kod multiplih trudnoća, od čega je deset bilo gemelarnih, a jedna trigemina trudnoća.

Rezultati: Prosečna životna dob majke iznosila je 32.4 godina (29 -45). Prosečna gestacijska dob prilikom rađanja prvog blizanca bila je 21+6 ng (17+3-25+0 ng), a živorođena su 3 blizanca (27.3%) sa 5’Apgar skorom 3.7 i prosečnom telesnom masom 474g (160 – 710g). Prosečna gestacijska dob prilikom rađanja drugog blizancabila je 28+3 ng (20+6 – 31+6 ng),živorođeno je 10 blizanaca (90.9%) sa5’Apgar skorom 6.4 (5-8) i prosečnom telesnom masom 1172.7g (410 – 1880g). Prosečan interval između porođaja prvog i drugog blizanca iznosio je 45.73 dana (3-96 dana). Ni u jednom slučaju nije zabeležen značajan morbiditet majke ni nakon porođaja prvog, ni nakon porođaja drugog blizanca.

Zaključak: Odloženi porođaj drugog blizanca predstavlja siguran i efektivan pristup u tretmanu multiplih trudnoća i rezultuje u značajnom preživljavanju preostalog/preostalih fetusa uz mali maternalni rizik. Imajući u vidu da se radi o relativno novoj proceduri koja će, s obzirom na sve veći broj multiplih trudnoća, postati aktuelnija, neophodno je uspostaviti standard i formirati protokol.

CESAREAN SECTION AND ANESTHESIA IN PREGNANT WOMEN WITH CORONARY SYNDROME

CARSKI REZ I ANESTEZIJA KOD TRUDNICA SA KORONARNIM SINDROMOM

Tatjana Ilić-Mostić

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije

Uvod: Učestalost ishemije miokarda i razvoj koronarnog sindroma tokom trudnoće može da nastane usled vazospazma, aneurizme, disekcije i hematoma koronarnih arterija, ateroskleroze, teške hipertenzije i hipotenzije, takikardije, anemije i hipoksemije.

Ishemiju miokarda karakteriše povišena metabolička potrošnja kiseonika koji prevazilazi snabdevanje kiseonikom. Koronarni protok krvi normalno se menja paralelno sa potrebom miokarda za kiseonikom. Trudnoća rezultira povećanjem minutnog volumena srca, napetosti I kontraktilnost zida miokarda, ubrzanjem bazalnog metabolizma i potrebom tkiva za kiseonikom. Elektivni carski rez ne eliminiše uticaj stresa na kardiovaskularni sistem: minutni volumen se povećava čak 50% tokom i nakon operacije. Potrošnja kiseonika ostaje povećana za 25% i u neposrednom postpartalnom periodu. Zdrave trudnice mogu tolerisati kardiovaskularne promene tokom trudnoće i porođaja. Međutim, ove promene mogu izazvati ishemiju miokarda kod žena sa oboljenjem koronarnih arterija ili drugih srčanih bolesti. Dijagnoza miokardne ishemije se postavlja detaljnim uzimanjem anamneze, fizikalnim pregledom i analizom EKG. Među pacijentima najznačajniji simptomi uključuju: bol u grudima, dispneju, preznojavanje, slabu toleranciju napora i sinkope. Međutim, svi ovi simptomi se mogu javiti i kod zdravih osoba. Dijagnozu akutnog infarkta miokarda može potvrditi određivanje kardiospecifičnih enzima iz seruma. Optimalno praćenje trudnica sa koronarnom bolešću zahteva kontrolu potreba majke i fetusa. Potrebno je lečiti bolesti i stanja (npr. anemija, tireotoksikoza, hipertenzija, infekcija, zloupotreba supstanci) koje mogu negativno uticati na potrebe miokarda za kiseonikom. Lečenje ishemije miokarda poboljšava srčanu funkciju, što bi trebalo da poveća i uteroplacentalnu perfuziju. Nasuprot tome, preterano agresivna terapija može negativno da utiče na fetus.

Akutni infarkt miokarda (AIM) tokom trudnoće je još uvek ozbiljan problem sa kojim se lekari u akušerstvu suočavaju. Vreme nastanka infarkta miokarda i razvoj koronarnog sindroma utiče na ishod. Infarkt miokarda tokom trećeg trimestra rezultira stopom smrtnosti majki od oko 45%, a tokom prvog ili drugog tromesečja stopa smrtnosti majki je između 23-25%. Među ženama koje su porođene u roku od 2 nedelje od infarkta, mortaliet iznosi oko 50%. Nasuprot tome, primećeno je da nema značajnog porasta mortaliteta žena koje su porođene vise od 2 nedelje nakon nastanka akutnog infarkta miokarda. Većina autora preporučuje da, kada je to moguće, porođaj bude odložen najmanje 2 nedelje posle AIM.

Takođe, kod pacijenata postoji povećan rizik od rekurentnog, perioperacionog infarkta miokarda tokom prvih 6 meseci posle AIM, ali invazivno hemodinamsko praćenje, održavanje normalnog intravaskularnog volumena i agresivno farmakološkolečenje I shemije može da smanji taj rizik. Elektivni carski rez dozvoljava akušeru da kontroliše vreme završavanja trudnoće, a izbegavaju se hemodinamski poremećaji tokom faze ekspulzije. Nedostaci carskog reza uključuju: povećan rizik od gubitka krvi, povećan rizik od infekcije i povećan rizik od plućnih komplikacija postpartalno. Relativno je bezbedno intravensko davanje razblaženog rastvora sintetičkog oksitocina za postizanje kontraktilnosti uterusa kod žena sa oboljenjem koronarnih arterija. Međutim, produžena infuzija velikih doza oksitocina može rezultirati hiponatrijemijom i kongestivnom srčanom insuficijencijom. Ne postoje tačno utvrđene preporuke o načinu završavanja trudnoće, tako da je pristup individualan u zavisnosti od stanja pacijenta. Optimalno praćenje zahteva multidisciplinarni pristup. Potrebno je obezbediti kontinuirani invazivni hemodinamski monitoring, bez obzira na način završavanja trudnoće i izbor anesteziološke tehnike.

Spinalna anestezija dovodi do brze simpatektomije, što može povećati rizik od pojave teške hipotenzije. Kontinuirana epiduralna anestezija je poželjnija tehnika za operativno završavanje. Ako je potrebna opšta anestezija, sprovode se opšte mere održavanja vrednosti pulsa i krvnog pritiska tokom laringoskopije i intubacije. Treba napomenuti da je pacijent pod velikim kardiovaskularnim rizikom i postpartalno, a najčešća komplikacija je razvoj kardiogenog plućnog edema. Invazivni hemodinamski monitoring je neophodan minimum 24 h posle porođaja ili carskog reza (nadzor u Jedinicama intenzivnog lečenja), kao I konsultacije kardiologa.

CESAREAN SECTION - WHERE ARE WE TODAY?

CARSKI REZ PO MISGAV LADACH-U – DESETOGODIŠNJA KLINIČKA ISKUSTVA U PRIJEDORU

Danica Gubić Plemić

JZU Bolnica „Dr Mladen Stojanović“ Prijedor

Carski rez je najčešća akušerska operacija. Trenutne stope carskog reza razlikuju se među društvenim i demografskim grupama, pa tako u subsaharskom području Afrike variraju između 1 i 2%, sve do 50% u Egiptu, Turskoj i Brazilu. U Evropi se kreću između 15% u Skandinaviji i 35% u Portugalu, Rumuniji i Italiji.

Povećana primjena carskih rezova je povezana sa većom stopom maternalnog morbiditeta i mortaliteta uz značajno veće ekonomske troškove u odnosu na vaginalni porođaj. S obzirom da se operacija često izvodi nameće se potreba za unapređenjem operativnih tehnika kako bi zahvati bili sigurniji za porodilje i novorođenčad uz istovremeno smanjenje troškova liječenja.

WHO je provela više randomiziranih studija, gdje su poređene operativne tehnike i na osnovu dobijenih rezultata preporuka *WHO* evidence based za carski rez je: laparotomija po *Joel Cohen*, uterotomija poprečnim rezom u istmičnom dijelu uterusa, nakon vađenja ploda i posteljice, eksterioziranje uterusa i šivanje u jednom sloju, antibiotska profilaksa nakon klemanja pupčanika i izvođenje operativnog zahvata u regionalnoj anesteziji. Kod *SC* po *Misgav Ladach* su ispoštovani navedeni kriteriji. *SC Misgav Ladah* je modifikacija zasnovana na minimalno oštrom preparisanju i tupom razmicanju tkiva prstima uz poštovanje arhitekture tkiva.Uterus se šije u jednom sloju, visceralni i parijetalni peritoneum, mišići i potkoža se ne ušivaju, čime se skraćuje vrijeme operacije, utrošak anestetika i konca za šivanje.

U prijedorskoj bolnici se *Misgav Ladach* operativna tehnika primjenjuje od 2009. god. Desetogodišnje kliničko iskustvo je zasnovano na 1234 carska reza urađena ovom operativnom tehnikom, stopa *SC* u posmatranom periodu se kretala od 16% do 22%. Prosječna gestacijska dob je 39 nedelja, hitnih *SC* je urađeno 719 (58,26%). Najčešće indikacije su prethodni carski rez 372 (30,14%) , disproporcija 194 (15,7%), distocija u porođaju 181(14,7%), karlična prezentacija 134 (10,86%). Maternalni morbiditet: obilnije intraoperativno krvarenje i atonije uterusa su evidentirane kod 34 porodilje (2,5%) i kod 2 porodilje su urađene supracervikalne histerektomije a kod 1 uspješno plasiran „*B Lynch* šav“. Učestalost postoperativnih adhezija kod iterativnih *SC* iznosi 4%, dok je kod 21 porodilje evidentirana ruptura uteri imminens (5,6%). Nije bilo komplikacija digestivog sistema, povreda mokraćne bešike, tromboembolijskih komplikacija. Postoperativni tok uglavnom uredan , prosječna hospitalizacija 5 dana. Perinatalni ishod prema Apgar scor u 1 min je evidentiran kod 1160 (91,5%) novorođenčadi.

SC Misgav Ladach postaje standardna tehnika u savremenom akušerstvu zbog jednostavnosti i brzine izvođenja, uz malu stopu maternalnih komplikacija i dobar perinatalni ishod uz smanjenje troškova liječenja.

HYPERTENSIVE DISORDERS IN PREGNANCY – MANAGEMENT OF DELIVERY AND INTRAPARTAL SURVEILLANCE

HIPERTENZIVNI SINDROM U TRUDNOĆI- NAČIN ZAVRŠAVANJA POROĐAJA I INTRAPARTALNI NADZOR

Snežana Rakić

Ginekološko-akušerska klinika „Narodni front“, Beograd

Porođaj predstavlja najcelovitiju terapiju hiperenzivnog sindroma u trudnoći. Intrapartalni nadzor fetusa i majke zavisi: Od gestacijskestarosti, težine hipertenzivnogsindroma i opšteg stanja porodilje. Ukoliko je opšte stanje trudnice i ploda stabilno trudnoća se može voditi do 38. nedelje gestacije. Pre samog završavanja porođaja mora se utvrditi fetalna plućna zrelost.

Kada se govori o načinu završavanja porođaja u odnosu na opšte stanje porodilje porođaj se uvek prevashodno završava u interesu majke. Kod trudnoća gestacijske starosti od 24.-28.nedelje gestacije, deca male telesne mase, porođaj se završava operativnim putem. Neophodna je arteficijalna maturacija fetalnih pluća. Posle 28. nedelje gestacije potrebno je uraditi maturaciju fetalnihpluća. Način porođaja zavisi od opšteg stanja pacijentkinje, zrelosti grlića materice (*Bishop score*), položaja ploda i njegove vitalnosti. Potrebno je primarno planirati vaginalni porođaj, uz striktan monitoring trudnice i ploda. Kod vaginalnog porođaja poželjan je porođaj u epiduralnoj analgeziji. Kod fetusa u period gestacijske starosti 28. – 33. nedelje gestacije, treba izbegavati maturaciju grlića prostaglandinima i sintocinonom. Ukoliko nije moguće obezbediti relativno siguran porođaj *per vias naturalis* potrebno ga je završiti operativnim putem.

Kada se govori o fazi ekspulzije, nekada opšte stanje porodilje nedozvoljava napinjanje porodilje, pa se tada pod uslovom da postoje akušerski uslovi (prokinut vodenjak, kompletna diltacija i glavica ploda angazovana) porođaj može završiti primenom instrumenta. Kada se govori o prevremnom porođaju kod hipertenzivnog sindroma instrument izbora bi bio forceps.

Porođaj kod fetusa gestacijske starosti 35. -37. nedelja gestacije i nakon 37. Nedelje gestacije treba voditi prema akušerskim indikacijama, osim ukoliko postoji IUGR . Kod fetusa sa IUGR potrebno je pre odluke o načinu završavanja porođaja proceniti stanje fetalne kondicije – bilo upotrebom *Color Doppler*-a, bilo upotrebom stress testa uz neposredni *kardiotokografski monitoring*.

Tokom svake eklamptične episode koja izgleda dramatično, kod fetusa dolazi do pojave bradikardije. Ova bradikardija obično prođe za nekoliko minuta, pa je momentalni porođaj nepotreban. Ukoliko fetalna bradikardija trajedužeod 10 minuta moguć jenastanak abrupcije posteljice. *PIH* je jedan od glavnih etioloških faktora za nastanak abrupcije posteljice. Ukoliko dođe do abrupcije posteljice porođaj se završava hitnim carskim rezom u interesu majke, a i ploda.

Porođaj je osnovna terapija kod pacijentkinja sa preeklampsijom, eklampsijom i *HELLP* sindromom. Ove pacijentkinje se zbrinjavaju u jedinicama intenzivne nege. Pre svakog porođaja neophodno je da stanje trudnice bude stabilno: pritisak se mora stbilizovati i mora postojati balans tečnosti. Potrebno je predupreditи eklamptičke napade.

Izbor anestezije u ovim porođajima je regionalna anestezija (epiduralna, spinalna ili kombinovana spinal - epidural) kao i OETA. Opšta endotrahealna anestezija je značajna u stanjima kod kojih je ugrožen život trudnice. Postojanje HELLP sindroma i trombocitopenija, kao stanja koja prate tešku preeklampsiju, mogu biti kontraindikacije za regonalnu anesteziju.

Intrapartalna terapija trudnica sa vrednostima krvnog pritiska 160/100 *mmHg* iziskuje terapiju *Magnezijum sulfatom* u infuziji. Daje se 20% rastvor *Magnezijum sulfata* u rastvoru *NaCl* u infuziji 8*mE/l*.

U okviruvođenja porođaja i prevođenja u anesteziju neophodnoje proveriti laboratorijske analize zbog brze dinamike njihoveizmene. Ukoliko su trombociti > 75x10/L potrebno je uraditi tromboelastografsku analizu radi primene epiduralne ili spinalneanestezije. Broj tromobocita ispod navedene vrednosti kod ovih pacijentkinja predstavlja kontraindikaciju za regionalnu anesteziju. Pad vrednosti arterijskog pritiska kod trudnice izraženiji je u slučajevima spinalne anestezije. Kod upotrebe spinalne anestezije javlja se u 51% trudnica, dok kod epiduralne anestezije taj pad pritiska iznosi 23%. Pad vrednosti krvnog pritiska u ovim slučajevima može biti i do 30%.

Svaka pacijentkinja koja je u vaginalnom porođaju mora imati: vensku liniju, šok listu prema kojoj se arterijski krvni pritisak meri na svakih 15 min. Kod fetusa je neophodan kontinuirani kardiotokografski monitoring. Ukoliko se radi o težim slučajevima preeklampsije i hipertenzivnog sindroma poželjnoje da pacijentknje budu na kontinuiranom monitoring što se tiče osnovnih vitalnih parametara. Pre porođaja se moraju izvaditi kompletne laboratorijske analize sa posebnim osvrtom na transaminaze, broj trombocita, LDH, ureu, kreatinin, kao i faktore koagulacije. Unos tečnosti kod ovih pacijentkinja mora biti izbalansiran da bi se izbegla pojava plućnog edema.

Terapija *HELLP sindroma*

Potrebno je naglasiti da se bol u gornjem delu trbuha i ispod rebarnog luka mora smatrati *HELLP* sindromom dok se ne dokaže suprotno. *HELLP sindrom* se može isključiti određivanjem broja trombocita. Ukoliko se potvrdi da seradi o trombocitopeniji onda se može govoriti o *HELLP sindromu*.

Terapija preeklampsije podrazumeva prijem ovih pacijentkinja u jedinicu intezivne akušerske nege u tercijarnim ustanovama. U terapiji se koristi davanje *MgSO4* u infuziji radi odražavanja krvnog pritiska ispod 160/105 *mmHg*. Magnezijum sulfat se daje sa inicijalnom dozom od 4g a potom davanje doze održavanja. U zavisnosti od gestacijske staroti fetusa počinje se sa arteficijalnom maturacijom ploda davanjem preparata kortikosteroida i to: *Deksametazona* 2/3 x10 *mg* dnevno ili davanja *metilprednisolona* (*Urbason* 32 *mg*/ dan dnevno), po potrebi više dana. *Metilprednisolon* ograničeno prolazi kroz placenta tako da je potrebna dodatna terapija za sazrevanje fetalnih pluća.

U slučaju pojave *HELLP sindroma* neophodno je porođaj sprovesti što ranije. Način porođaja je direktno zavistan od opšteg stanja porodilje kao i gestacijske starosti , kao i zrelosti grlića materice. Kod stabilnog fetalnog i maternalnog stanja treba težiti vaginalnom porođaju. Nema iskustava sa indukcijom porođaja u ovim slučajevima u literaturi.

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ADOLESCENT CHILDBIRTH AND RISKY SEXUAL BEHAVIOR IN THE NORTH OF KOSOVO

ADOLESCENTNI POROĐAJI I RIZIČNO SEKSUALNO MLADIH NA SEVERU KOSOVA

Goran Relić, Milijana Relić, Aleksandra Ilić

Medicinski Fakultet Priština, Kosovska Mitrovica

Uvod. Adolescentni predstavljaju veoma vulnerabilnu grupu podložnu prihvatanju raznih oblika rizičnog ponašanja, koje podrazumeva mogućnost negativnog ishoda seksualnog kontakta, kao što su: neželjena trudnoća, polno prenosive bolesti, nekorišćenje kontracepcijskih sredstava te konzumaciju alkohola i droga pre polnog odnosa.

Cilj rada. Utvrditi: broj adolescentnih trudnoća u odnosu na ukupan broj porođaja, godine života, način porađanja, paritet i starost trudnoće maloletnih majki, dužinu, težinu i vitalnost (*AS*) njihove novorođenčadi, stepen informisanosti adolescenata o rizičnom seksualnom ponašanju.

Materijal i metode rada. Retrospektivno ispitano je ukupno 398 porođaja adolescentkinja (do navršenih 19 godina) tokom 2000-2009.g. na ginekološko-akušerskom odelenju Z.C.K. Mitrovica. U istom vremenskom periodu anonimno su anketirani učenici završnih razreda srednjih škola (od 17-19 godina) u K. Mitrovici, Zvečanu i Leposaviću. Statistički je obrađeno 433 kompletno popunjenih upitnika.

Rezultati. Od ukupno 6335 porođaja, bilo je (6,3%) adolescentnih trudnica od 12 do 19 godina života. Najviše je bilo prvorotki (81,1%), drugorotki (15,6%) i trećerotki (3,3%). Blizanačku trudnoću imalo je (1,1%) adolescentnih porodilja. Carskim rezom završeno je (15,5%) porođaja. Vaginalnim putem porođeno je (84,5%) adolescentkinja. Prevremeni porođaj bio je (7,5%) adolescentnih porodilja, od toga je (40%) adolescentkinja porođeno carskim rezom i (60%) adolescentkinja vaginalnim putem. Kod (10%) adolescentnih porodilja urađena je *Revisio cavi uteri manualis*. *Apgar Scorom* između 7 do 10 u prvoj minuti ocenjeno je (76,3%) novorođenčadi adolescentnih majki. *Apgar score* 4- 6 imalo je (20,4%) dece, dok je ≤ 3 imalo samo (3,2%) dece.

Anonimnom anketom obuhvaćeno je 433 ispitanika, 63% učenica i 37% učenika muškog pola. Približno svaka treća ispitana učenica (33%) bila je seksualno aktivna i 40,6% učenika muškog pola. 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% ispitanika. Kondom koristi 51% seksualno-aktivnih dečaka. 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 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.

CESAREAN SECTION – MODIFICATION VEJNOVIĆ 3D ANIMATION OF UTERUS SUTURING

Tihomir Vejnovic

University of Novi Sad, Faculty of Medicine, Department of Gynecology and Obstetrics

Vejnović modification of cesarean section represents an improvement of previous operative techniques. Vejnović introduced a new perspective on cesarean section as an imitation of vaginal delivery. This point of view induced changes in each step of the operation (opening of the anterior abdominal wall, opening of the uterus, delivering the baby and placenta, revision of the uterine cavity and dilation of the cervix, uterus suturing, closing of the anterior abdominal wall), which reduced the traumatization of the tissue, and supported healing and physiological postpartum processes.

According to that, three basic principles of Vejnović modification were defined:

1. Minimal tissue trauma 2. Minimal operation time 3. Imitation of vaginal delivery.

The principle of imitation of vaginal delivery involves the creation of a new birth canal, which is tailored for an individual fetus. It means that the opening of the abdominal wall and the uterus should be the smallest possible for the baby to pass through, using the same mechanism as in vaginal delivery. In this way, pressure is achieved on the head and chest of a newborn, which helps to squeeze out fetal lung fluid, thus providing better transition to air breathing.

The most significant contribution of the modified technique is a new way of uterus suturing. It is also based on the principle of imitation of natural processes, especially of the uterus involution after delivery. According to Vejnović modification, uterus suturing is performed in four steps. By a particular order of placing the stitches and tightening the knots, the length of the uterus incision already intraoperatively gets twice shorter. Centripetally directed vectors of the force within the scar, contribute to its further reduction in the postoperative period and preserving the thickness of the uterine wall. Everything above-mentioned provides faster and better healing of the uterus and reduces the risk of acute complications (bleeding and infection), as well as chronic complications of caesarean section in future pregnancies (rupture of the uterus and placenta accreta) which may cause much greater morbidity and potentially fatal consequences.

It has been scientifically confirmed that this modified technique leads to a significant reduction in blood loss, the length of the operation and stay in hospital, as well to the reduction in suture material consumption and use of instruments. Likewise, patients operated with Vejnović modification experienced less postoperative pain, used fewer painkillers, and had less surgical wounds complications.

A retrospective study showed that among the 15.000 patients operated only by using Vejnović modification, there was no case of placenta accreta, which is considered to be the most serious complication of cesarean section.

This operative technique was presented in over fifteen health centers in the world. In several clinics in Europe (Serbia, Romania, Germany, Austria, Hungary), Vejnović modification is adopted and applied regularly.

In 2017, the Ministry of Health of the Republic of Serbia approved the implementation of the **Modification of cesarean section operative technique by Vejnović** as scientifically proven and tested new health technology.

In order to provide a precise explanation of the modified technique and a better quality of education for surgeons, 3D animation of modified uterus suturing by Vejnović was made and educational coursesare regularly organized.

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UROGYNECOLOGY AND RECONSTRUCTIVE SURGERY

PELVIC HEALTH AND MINIMUM INVASIVE GYNECOLOGICAL SURGERY

Rajko Fureš 1-4, Damir Hodžić 1,3,5, Tonći Visković 1,2, Ivica Balagović 1,6, Nikša Knezović 2, Mario Fučkar 1,7, Jadranka Šanjug 2-4, Martin Gredičak 1-3, Bruno Grabušić 2, Sanja Malinac Malojčić 2,3, Mladen Krajcar 2, Vesna Borgudan 2, Nikolina Sokalić 2,7, Žana Stanić 1,2

1 Croatian Society for Pelviperineology – CSP.

2 Department of Gynecology and Obstetrics. Zabok General Hospital and Croatian Veterans Hospital, Croatia.

3 Faculty of Dental Medicine and Health Osijek. University of Josip Juraj Strossmayer – Osijek, Croatia.

4 Faculty of Medicine Osijek. University of Josip Juraj Strossmayer – Osijek, Croatia.

5 Clinic Hospital "Merkur", Clinic for Gynecology and Obstetrics, Zagreb, Republic of Croatia.

6 Department of Surgery - Urological Service. Zabok General Hospital and Croatian Veterans Hospital, Croatia.

7 Special Hospital for Medical Rehabilitation Krapinske Toplice, Croatia.

Introduction and aim: Pelvic health and minimally invasive gynecologic surgery are highly correlated. The introduction of new minimally invasive diagnostic and therapeutic procedures has made very significant strides in the treatment of gynecological patients. Today, the work of modern gynecologists today is unthinkable without the daily application of minimally invasive gynecological surgery and the latest technological advances.

Material and methods: The minimally invasive endoscopic approach in gynecologic surgery has no alternative today. Modern gynecologic endoscopists have already acquired, during their specialization, recent theoretical and practical insights into the field of minimally invasive gynecological surgery. Minimally invasive gynecological surgery plays a significant role in the diagnosis and treatment of many pelvic health entities, and is certainly the method of choice today and into the future.

Results: It is certain that the minimally invasive approach in gynecological surgery has brought great benefits to many patients. The most important benefits are in the area of prevention and preservation of health, and the elimination of diseases and complications related to conventional approaches in the treatment of gynecological diseases. Minimally invasive pelvic surgery provides the best access for the benefit of our patients and their pelvic health. The aforementioned approach is aimed at numerous beneficial effects for our patients, but it is also useful for doctors, who have received the highest quality tool for the treatment of gynecological diseases while serving pelvic health. The revolutionary progress of minimally invasive gynecological surgery has been traced to the parallel development of gynecological endoscopy since the early 1990s, in the developed world. The development of minimally invasive surgery in the territory of the Republic of Croatia and Southeastern Europe can be traced intensively in the past two and a half decades.

Conclusions: With the concept of integrative pelviperineology, minimally invasive gynecological surgery is gaining importance in the field of pelvic health. The most significant steps have been taken in the field of alternatives to hysterectomy, so today laparoscopic hysterectomy is indeed standard, but it is not always the method of choice. Increasingly, the approach of prevention of organ removal in this case of the uterus is being considered, combined with a multidisciplinary approach involving physicians specializing in a variety of profiles, aiming at patient well-being.

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COMBINED MINIMALLY INVASIVE TREATMENT FOR CHRONIC URINARY DISORDERS IN WOMEN

Damir Hodžić [1, 2], Višnja Latin [2], Josip Valetić[1]

[1] University Hospital "Merkur", Department of Gynecology and Obstetrics, Zagreb, Croatia

[2] Polyclinic "Vili" for Gynecology, Obstetrics, Internal Medicine and Radiology, Zagreb, Croatia

Combined minimally invasive treatment for chronic urinary disorders in women, e.g. urinary incontinence, pelvic organ prolapse (POP), chronic or interstitial cystitis, lower urinary tract symptoms (LUTS), etc. includes contemporary synergistic individually tailored approach using vaginal laser thermotherapy, pelvic functional magnetic stimulation (FMS) and intravesical instillation of hyaluronic acid (HA).

Stress urinary incontinence (SUI) occurs as a common problem, especially in postmenopausal women, often related with POP. Totally 91 women has been treated with Er:YAG laser (Smooth XS Dynamis, Fotona, Slovenia). Mean number of the sessions was 3.0±1.6 (1-10) and mean follow-up was 21.0±13.9 (1-44) months. In 84 (92.3 %) patients was occurred initial satisfaction. According to voiding diary, there was noticed reduction of incontinency episodes ≥93%, voiding frequency ≥82% and nocturia ≥74%. Also was occurred clinical regression of POP stage for 1-2 grades. Four (4.4%) patients initially referred a quite slight improvement, but their treatments are continuing by the standard protocol. Treatment failed in 3 (3.3%) patients with severe SUI quitted after 4 sessions and required paraurethral bulking injection. Nine patients (9.9%) required maintaining 1-6 treatments within 12-36 months after finishing initial laser therapy.

FMS is convenient, non-invasive therapy method for urinary incontinence based on extracorporeal treatment of pelvic floor with powerful magnetic field. Totally 110 women has been treated for stress, urgent (UUI) or mixed urinary incontinence (MUI) using the modern FMS device (Magneto Stym, Iskra Medical, Slovenia**)** with magnetic field power of 2 Tesla and frequency range of 1-80 Hz. Treatments lasted 20 minutes each, repeated twice or three times a week, up to 16 sessions totally, using the treatment protocol adequate for the type of urinary incontinence.

Out of the totally 110 women, 26 (23.6%) suffered from SUI, 17 (15.4%) from UUI and 67 (61.0%) from MUI. Eleven (10.0%) patients were previously treated with laser therapy for SUI/MUI or POP ≤ 3 stage. In patients suffering from UUI, 59% were completely dry, 29% showed significant improvement and 12% did not show any improvement after the treatment. In patients suffering from SUI, 81% were completely dry after the therapy, 15% showed significant improvement and 4% did not show any improvement. In patients suffering from MUI, 72% were completely dry, 25% showed significant improvement and 3% did not show any improvement. The frequency of leakage in patient with SUI and UUI decreased from 5.9 to 3.2 and 7.8 to 4.5 episodes per day. In MUI group reduction from 6.3 to 2.9 episodes per day was noted. Significant reduction in nocturia episodes for all types of incontinence was occurred as well.

The occurrence of acute cystitis in women is 0.5-0,7 episodes yearly, but 28% recur for another 18 months. Totally 33 women with chronic cystitis and LUTS were treated with Instylan (Yuria-Pharm, Ukraine), sterile 50 ml 0,16% solution based on HA for intravesical irrigation (80 mg sodium hyaluronate). Mean number of instillations was 3.6±1.8 (1-9) and mean follow-up was 7.7.±7.5 months (1-24). Initially, 30 (90.9%) patients were moderately or strongly satisfied with effectiveness of the treatment. All of them reported reduction in symptoms of cystitis, overactive bladder, bladder pain syndrome, incontinency, etc. and improvement of the QoL as well. The remaining 3 (9.1%) patients referred a slight initial improvement, but they just started treatment which continuing by the standard protocol.

TRANSOBTURATOR SUBURETHRAL SLING PROCEDURE IN THE MANAGEMENT OF STRESS URINARY INCONTINENCE-OUR RESULTS

Saša Ljuština

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

Introduction: Implantation of a synthetic midurethral sling (SMUS) has become the gold standard in treatment of stress urinary incontinence (SUI). The reported success rate is up to 85% five years after the procedure. The outcome of sling surgery is assessed both via objective and subjective measures – cough stress test, transperineal/introital ultrasound being the most commonly employed objective and the patient satisfaction and quality of life questionnaires subjective outcome measures.

Surgical treatment of SIU with the implantation of SMUS at the Clinic for Gynecology and Obstetrics, Clinical center of Serbia has begun more than 10 years ago, with around 120 procedures performed at the Clinic annually.

Aim: To assess the success and complication rate of the suburethral sling procedure done at the Clinic for Gynecology and Obstetrics, Clinical center of Serbia.

Materials and methods: We have retrospectively reviewed hospital data on patients who underwent SMUS implantation as well as the data regarding surgical complications of the procedure. We have also interviewed and examined patients who had surgical correction of SIU in the last one to five years. All the patients underwent stress test and transperineal/introital ultrasound and filled in the validated Australian pelvic floor questionnaire as well as Patient global impression of improvement (PGI-I) scale.

Results: The rate of SIU complications in our case series is up to 10%, which corresponds to the literature data. The results of the scores both on the Australian pelvic floor questionnaire and PGI-I scale showed significant subjective improvement of symptoms after the treatment. The subjective outcome measures are in line with the results of the stress test and ultrasound imaging postoperatively.

Conclusion: Transurethral sling implantation procedure is an effective and safe modality of treatment of stress urinary incontinence with low complication rate and high degree of postoperative patient satisfaction.

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DO MESHES HAVE A FUTURE IN UROGYNECOLOGY?

Adolf Lukanović, David Lukanović

Departement of Obstetrics and Gynecology, Univeristy Medical Center Ljubljana

Medical faculty, University of Ljubljana

Quality of life, namely micturition, defecation and sexuality, all three functions of the pelvic floor that may be improved or impaired during reconstructive pelvic surgery were matter of attention since past. Given the enormous diversity of anatomy, techniques, instrumentation and skill, it is unlikely that variations of these parameters will ever be studied in adequate detail to determine what is related to each parameter. Therefore it is esential and appropriate to regard the pelvic floor as a unique anatomical and functional unit. An integrated multidisciplinary approach to the evaluation and treatment of pelvic floor disorders is therefore required. This multidisciplinary approach is best summarised in the statement of famous Turner Warwich: The best person to treat incontinence and prolapse is not the urologist, the gynaecologist nor the colorectal surgen-it is the person who has been trained to do this. The reconstructive surgery has several golden standards which are appropriate choice of surgical procedure, appopriate choice of sutture materials, appropriate dissection technique, exact method of haemostasis and importance of surgeons learning curve and surgeons skillfullness.

The introduction of new syntetic materials in reconstructive surgery brought new dilemas. Can these procedure be performed more efficiently and effectively with various new products and will they bring better outcomes because conventional repairs are inadequate regarding long term successes. Introduction of meshes in everyday clinical practis revealed that surgeons are not aware of several new problems concerning its use, all possible complications, such as mesh retraction, infection and consequently rigid vagina, sveral kinds of visceral erosions, urinary problems and dispareunia. Before medical authorities gave any explanation to these trends in a public health notification issued in 2002, the American Food and Drug administartion (FDA) reported more than 1000 unexpected and severe adverse events, mostly associated with transvaginal placement of surgical mesh to treat pelvic organ prolapse and stress urinary incontinence. In july 2011, a second FDA warning has been amended on the basis of 2874 newly identified Medical Device Reports; 1503 associated with pelvic organ prolapse repairs and 1371 associated with stress urinary incontinence. In addition, lawyers have publicly advertised their services, targeting women with transvaginal mesh placed both for pelvic organ prolapse and stress urinary incontinence, and the media has reported on the pelvic organ prolapse mesh litigation. Undoubtedly this multimedia attention has resulted in confusion, fear and an unbalanced negative perception regarding the midurethral sling as a treatment modality for female stress urinary incontinence. This negative perception of the midurethral slings is not shared by the medical community and the overwhelming majority of women who have been satisfied with their midurethral sling. The midurethral sling was not the subject of the 2011 FDA Safety Communication, »Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse«. In this document, it is explicitly stated: »The FDA continues to evaluate the effects of using surgical mesh for the treatment of stress urinary incontinence and will report about that usage at a later date. Soon in 2013, the FDA webside stated that »The safety and effectiveness of slings is well established in clinical trials that followed patients for up to one year.«

Since the publication of numerous level one randomized comparative trials, the slings has become the most common surgical procedure for the treatment of female stress urinary incontinence allaround the world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the midurethral sling is associated with less pain,shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. In our study in 1999 we estimated that the costs of Burch colposuspension is more than 40% more expensive that MUS. Full-lenght midurethralslings, both retropubic and transobturator, have been extensively studied, are safe, and effective relative to other treatment options and remain the lea-

ding treatment option and current gold standard for SUI surgery. Over 3 million have been placed worldwide and a recent survey indicates that these procedures are used by 99 % of clinicians members of American Advancing Female Pelvic Medicine Association. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a sustantial percent of incontinent women to live without treatment. One of the unintended consequenses of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of stakeholders engagement which are dedicated to improving the quality of lives of females with SUI.

The disconnect between evidence based medicine and the medico-legal system is well documented. Despite the consistent differentiation between tapes/slings for SUI and transvaginal mesh for prolapse by FDA and other international scientific associations, litigation and plaintiff lawyers, and probably the general public, do not make a distinction between these two significantly different products, placed in a different anatomical location to treat different pelvic floor problems.

Despite firm position statements from several specialty colleagues and societes stating evidence based support for the midurethralsling, some government jurisdictions are moving towards severe restrictions or a ban for these tapes. It is not only a retrograde step; it would also mean resorting to more traditional operations that have less efficacy, more voiding dysfunction or postoperative overactive bladder symptoms. It could significantly limit access to an efficious treatment for a common, burdensome and costly condition for women.

In the haste for some countries to severely restrict or abandon the use of tapes for SUI, authorities should be cognizant that they are leaving their incontinence sufferers and the clinicians who treat them with overall inferior surgical treatment options. The experience of many clinicians with any of these alternate options might be little or none. The inherent danger to patients with surgeons returning to these options would be far greater than leaving in use, tapes of proven efficacy and safety.

This kind of surgery should be performed by experienced surgeons in referal centers with a sufficient number of patients. We advise to use mesh in pelvic floor reconstructive surgery only when indicated such as for severe prolapse, defective pelvic tissues and recurrence. Respecting the standard surgical principles the better is the outcome.

Instead of conclusion:

- The choice of mesh is of paramouth importance. The evidence currently favours Type 1 monofilament mesh with large pore size.
- Careful handling of the mesh
- Use minimal mesh material, avoid folding
- Laying the mesh loosely
- Avoid use of multifilament anchoring sutures
- Use of antibiotics perioperatively
- Wound irrigation
- Avoid and detect intra-operative viscus perforation
- Adequate closure of overlying walls with minimal gap between may reduce mesh erosion
- Secure haemostasis

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VAGINAL MESH – THE CONTROVERSY

Sveto Pantović

Clinic for Gynecology and obstetrics, Clinical Centre of Serbia

Pelvic organ prolapse is a condition that can cause significant symptoms that affect a woman's quality of life. It is the result of defects in the supporting structures of the vagina and, depending on the location and size, can alter the functions of the organs contained within the female pelvis. Approximately 11% of women will undergo surgical intervention for their prolapse or for incontinence in their lifetime. Unfortunately, one third of these will require reoperation for failed procedures. Pelvic floor surgeons have sought to improve these outcomes. Based largely on the success of midurethral slings (MUS), transvaginal mesh has been implanted, and commercial kits developed with the intent of improving these outcomes. In 2008, the Food and Drug Administration (FDA) issued a Public Health Notification in response to possible increased adverse events associated with the use of mesh compared to traditional repairs. The 2011 update required that further study be conducted for the use of transvaginal mesh.

In light of these issues, surgeons (and patients) are asking the question "does vaginal mesh have a place in vaginal prolapse repairs?". In reviewing this issue, the answers are not clear. It does seem clear that routine mesh placement in all patients is probably not necessary, and not good practice. Additionally, the lack of data does not support mesh placement in the posterior compartment. But, what about in the middle and anterior compartments? Is there a role for mesh in patients who have recurred or are at risk for recurrence? When trying to answer these important questions it becomes imminently clear that our current methods of accumulating data and answering these important questions are woefully inadequate. Hopefully, the FDA studies and registries in development will help us answer these important questions.

However, there are legitimate sequelae that are unique complications of transvaginal mesh procedures. NICE recommendations said that symptoms could include pain or sensory change in the back, abdomen, vagina, pelvis, leg, groin or perineum that is, either unprovoked, or provoked by movement or sexual activity and either generalised, or in the distribution of a specific nerve, such as the obturator nerve, vaginal problems including discharge, bleeding, painful sexual intercourse, or penile trauma or pain in sexual partners, urinary problems including recurrent infection, incontinence, retention, or difficulty or pain during voiding, bowel problems including difficulty or pain on defaecation, faecal incontinence, rectal bleeding or passage of mucus, symptoms of infection, either alone or in combination with any of the symptoms outlined above.

As in most of our quality of life procedures, patient communication and informed consent are of paramount importance when considering transvaginal mesh procedures. Patients should be told why mesh may be better for them and that there are non-mesh alternatives available. Patients should be informed of the complications that may occur following prolapse repairs, in general, and those that are unique to mesh. They should be informed that mesh is permanent and that more than one operation may be required to correct the complication, should it occur. After this discussion, it is inevitable that many women will choose not to have a transvaginal mesh procedure. However, a woman who has had a recurrent pelvic organ prolapse or is at risk of recurrence, may choose to do so—and there is no definitive or controlled data to suggest that she shouldn't. Randomized and controlled trials such as PROSPECT will hopefully allow women to make a more informed choice in future.

APICAL PROLAPSE-SACROSPINAL FIXATION

Miloš Radovic

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia

Introduction: Vaginal sacrospinal fixation-colpopexy sec. Nickols is surgical procedure resolving POP pathology with prevention of recurent postoperative apical prolapse. There are aprox. 20 diferent types/ modifications of colpopexies all arround the world.

Aim and Methods: 15 years of patient clinical folow up in combined retrospective and prospective study. Including 463 mesh and sling SUI procedure and 551 vaginal colposuspension! Investigating wich is the best and safest way to perform a colpopexy? With detailed description of Nickols/Richter surgical technik performed on KGA KCS. Determining is there a necessity of involving histeropexy at the end of every routine vaginal histerectomy procedure?

Results: Statistic data in our study has shown that Colpopexy singnificantly decreases the risk of recurent postoperative apical prolaps! Burch Tanago and other ventero/ligamento fixation procedures with abdominal approach are most invasive.Laparoscopic mesh sacrocolphysteropexy is moderatly invasive. But it is time consuming, most expensive and associated with several serious postoperative complications. Gilliam-Bere procedure, Moskowitz, Mac Call culdoplasty, 11 ligamentopexies and colpocleisis rest in history.

Conclusion: Vaginal approach is of course minimally invasive, shortest, simple to perform, with best cost/benefit ratio and with lowest percent of intra/post-operative complications! Sacrospinal Colpopexy is the safest surgical POP procedure associated with prevention of recurent postoperative apical/ vaginal prolapse. It is an operative method of choice for apex fixation and should be always included as obligatory part of every vaginal histetrectomy!! Therefore as the most frequently performed surgical procedure it has become inseparable part of every vaginal histerectomy performed for central vaginal defect on our clinic (KGA KCS) in last 12 years!! Also billateral colpopexy has become a surgical metod of choice for eversion of vagina and some types of enterocella!!

HPV SESSION

TREATMENT OF CERVICAL DYSPLASIA

LIJEČENJE PREKANCEROZA CERVIKSA UTERUSA

Branko Cvjetićanin, Borut Kobal

Division of Gynaecology and Obstetrics, University Medical Center, Ljubljana, Slovenia

Uvod: Prekanceroze cerviksa uterusa nastaju kao posljedice dugotrajne infekcije sa visokorizičnim podtipovima HPV virusa (16, 18, 45,…). Danas je opšte prihvaćeno mišljenje, da perzistentna infekcija sa HPV virusima preko visokorizičnih prekanceroza može prouzrokovati invazivni rak cerviksa uterusa. Klasfikacija prekanceroza se je vremenom mijenjala od blage/umjerene/težke displazije i karcinoma insitu, preko cervikalnih intraepitelijskih neoplazija (CIN 1,2,3 i AIS), do trenutno važeće klasifikacije SZO iz 2014 godine koja prekanceroze dijeli na nisko i visoko rizične skvamozne lezije (PIL-NS ili LG-SIL, PIL- VS ili HG- SIL) i adenokarcinom insitu (AIS). U velikoj većini primjera HPV infekcije dolazi do samoizlječenja. Isto tako u slučajevima prisutnosti LG-SIL, većinom lezija spontano regredira, odnosno dođe do samoizlječenja. U oko 15% slučajeva LG-SIL napreduje u HG-SIL a u oko 20% slučajeva nelječeni HG-SIL napreduje u invazivni karcinom cerviksa uterusa. Danas još uvijek ne poznajemo terapiju za liječenje HPV infekcije, zato svu pažnju posvećujemo preventivi-diagnostici- lječenju i kontroli prekanceroza cerviksa uterusa.

Diagnostika i liječenje prekanceroza: U diagnostici prekanceroza cerviksa uterusa koristimo citološki (PAP) bris, HPV bris i kolposkopiju sa po potrebi ciljanom biopsijom. U Sloveniji smo sa uvođenjem aktivnog skrininga (program ZORA) cjepljenja HPV i aktivnim liječenjem prekanceroza cerviksa incidenciju smanjili sa više od 20/100000 na manje od 10/100000 žena. LG-SIL u većini primjerja samo kontrolišemo do samoizlječenja, a u slučaju perzistiranja duže od dvije godine i liječimo. Liječiti možemo i pacientice koje ne možemo iz bilo kojeg razloga kvalitetno kontrolisati, te one koje i po iscrpnom informisanju to ipak žele. LG-SIL uglavnom liječimo sa destruktivnim metodama (LV). Pacijentice sa HG-SIL uvijek liječimo. Liječenje prekanceroza cerviksa je hirurško i uglavnom sa ekscizijskim metodama. Hirurške tehnike prekanceroza cerviksa uterusa dijelimo na destrukcijske i ekscizijske. Destrukcijske tehnike su krioterapija, diatermija sa elektrokoagulacijom i laserska vaporizacija. Većinom ih koristimo u liječenju LG-SIL, a rijetko i u liječenju HG-SIL kod mlađih žena kada je lezija kolposkopski dobro vidljiva i ograničena. Ekscizijske tehnike liječenja prekanceroza su LETZ, konizacija sa laserom ili harmoničkim skalpelom, klasična konizacija i histerektomija.

Najstarije metode hirurškog liječenja prekanceroza cerviksa su klasična konizacija i histerektomija. Za histerektomiju se odlučujemo rijetko, uglavnom kod pacientica u menopavzi, onih sa pridruženim bolestima reproduktivnih organa i onih kod kojih se prekanceroza ponavlja, odnosno sa manje invazivnim hirurškim postupcima nismo bili uspiješni. Savjetuje se vaginalni hirurški pristup (vaginalna histerektomija ili LAVH).

Klasičnu konizaciju sa hladnim nožem sve rijeđe koristimo, a većinom u slučajevima mikroinvazivnog karcinoma cerviksa uterusa (FIGO stadij 1A), AIS, CA insitu i velikih lezija HG-SIL, koje sežu duboko u cervikalni kanal. Konizaciju je moguće napraviti i laserski ili harmoničkim skalpelom. . Veliku većinu HG-SIL možemo uspiješno izliječiti sa LETZ (ekscizija transformacijske zone sa električnom omčicom). Različite veličine električnih omčica nam omogućuju, da se prilagodimo veličini lezije te obliku i veličini cerviksa uterusa. Danas je LETZ kao mikroinvazivan zahvat u širokoj upotrebi i u većini slučajeva zamjenjuje potrebu po klasičnoj konizaciji. Prednosti LETZ zahvata su u manjem defektu cerviksa uterusa, te u izvođenju postupka u lokalnoj anesteziji i ambulantno, odnosno u dnevnoj bolnici, a i manji je rizik za prijevremeni porod. U do 10% slučajeva može doći do odloženom pooperativnog krvarenja i potrebe po reviziji. Slabost je i teža ocijena ekscizijskih rubova od strane patologa zbog termičkog oštećenja. Veći je i rizik da promijena ne bude izrezana u zdravo, odnosno, da je prisutna u ekscizijskom rubu. Ocijenjuju,

da je riziko za ponavljanje bolesti po LETZ do 5%. U više od 90% slučajeva po LETZ više ne nalazimo prisutnosti HPV virusa. Incidencija HG-SIL je u Sloveniji oko 90/100000 žena. LETZ postupak napravimo godišnje u oko 1200 slučajeva, od toga oko 600 LETZ postupaka na ginekološkoj klinici u Ljubljani.

Zaključak: Visoko rizične prekanceroze cerviksa uterusa (HG-SIL) je potrebno hirurški liječiti. Danas je najčešće upotrebljena LETZ metoda, čije prednosti su ambulantno izvođenje u lokalnoj anesteziji, manja lezija cerviksa uterusa i manji riziko prijevremenog poroda. Za smanjenje invazivnog karcinoma cerviksa uterusa najznačajnija je prevencija HPV infekcije (cjepljenje), aktivni skrining (PAP i HPV bris), te pravovremena diagnostika visokorizičnih prekanceroza cerviksa uterusa (kolposkopija – ciljana biopsija) sa adekvatnom terapijom. Po hirurškom liječenju prekanceroza cerviksa uterusa su potrebne adekvatne i skrbne kontrole koje u Sloveniji izvodimo po usvojenim smijernicama.

THE VALUE OF CONDYLOMA TREATMENT FOR MAINTAINING REPRODUCTIVE HEALTH

ZNAČAJ LIJEČENJA KONDILOMA U OČUVANJU REPRODUKTIVNOG ZDRAVLJA

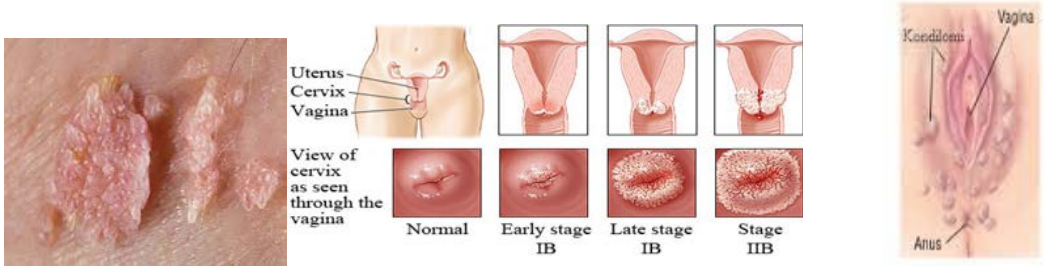
Vesna Ećim-Zlojutro

Klinika za ginekologiju i akušerstvo Banja Luka, UKC Republike Srpske

Kondilomi (genitalne bradavice) su uzrokovani nisko rizičnim tipovima *HPV*-a (6,11, 41,43). Zarazni su i prenose se polnim kontaktom. Kao faktori rizika se navode rani seksualni odnosi, promiskuitet, stres i promjena imunološkog sistema što dovodi do aktivacije virusa u organizmu. Ova bolest postala je svjetska epidemija i brzo postaje polno prenosiva bolest br.1 u svijetu po broju zaraženih. U SAD je 20 miliona ljudi zaraženo ovim virusima. Procjenjuje se da je oko 80% seksualno aktivnih ljudi zaraženo nekom vrstom ovog virusa. Podaci iz Hrvatske govore da je ovim virusom inficirano 60% seksualno aktivnih žena i muškaraca. Najčešće zaraženi su oni od 20 do 24 godine, dok je kod žena starijih od 40 smanjen broj inficiranih. U Srbiji se procjenjuje da su kondilomi verifikovani kod 1,2 miliona pacijenata.

Klinička slika

Simptomi *HPV* infekcije se javljaju u naredna 3 mjeseca nakon seksualnog kontakta sa oboljelom osobom i ako se nekad mogu pojaviti i nakon par godina. Zbog anatomskih i fizioloških razloga *HPV* virus ima mnogo povoljnije uslove za razvijanje infekcije kod žena.



Slika1. Izgled kondiloma

Kondilomi su izrasline na koži u genitalnoj regiji i oko anusa, mekane na dodir. Njihova površina može da bude ravna, šiljata, kao karfiol, bijela, blijeda ili roze boje. Mogu izazvati peckanje i svrab. Mogu se javiti pojedinačno ili kao grupice izraslina koje daju karfiolast izgled. Najčešće se javljaju na ulazu u vaginu, na vaginalnoj sluzokoži, grliću, anusu i međici. U vremenu kada se prvi seksualni odnosi dešavaju već u 13. i 14. godini, mnogo je faktora koji kasnije mogu da utiču na sposobnost začeća (reproduktivnu sposobnost) mladih devojaka.

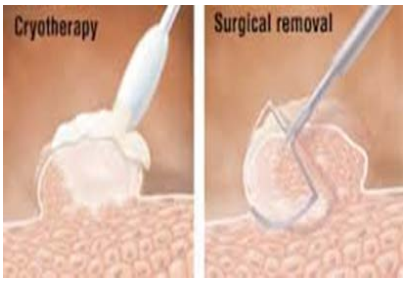
Dijagnoza kondiloma

Dijagnostikovanje kondiloma kod muškaraca prije pojavljivanja prvih simptoma je gotovo nemoguće, tako da se oni najčešće dijagnostikuju kada se pojave prvi simptomi. Kod žena se dijagnoza postavlja pri kliničkom pregledu, a definitivna potvrda je patohistološka dijagnoza i HPV tipizacija. Redovni pregledi, uzimanje Papa nalaza, kolposkopija i biopsija su neizostavni dio dijagnostike.

U prevenciji najveću ulogu ima zdravstveno prosvjećivanje, upoznavanje naročito mladih, ali i njihovih roditelja sa infekcijama sa *HPV*, način prevencije i liječenja. Upoznati sa značajem korištenja kondoma kao i naglasiti značaj redovnih ginekoloških pregleda. Upoznati sa značajem vakcinacije koja je u nekim zemljama već obavezna.

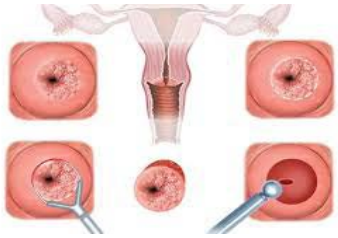
Liječenje kondiloma

Liječenje kondiloma je individualno. Može biti iscrpljujuće i dugotrajno, često uključuje hiruršku intervenciju, a može biti i kratko i bezazleno. Uklanjanje kondiloma se radi na višenačina: - krioterapija (smrzavanje)



Slika 2. Krioterapija

-elektrokauterizacija (spaljivanje kondiloma) - LOOP, lasersko uklanjanje




Laser LOOP

-uklanjanje kondiloma radio talasima

-hemijska terapija (*Podofilox, Aldara, 5-FU, Interferon alfa*)

Materijal i metode

Analizirali smo patohistološke dijagnoze u kojima je poslije intervencije potvrđeno prisustvo kondiloma u 2018.godini. Pacijentkinje smo podijelili u grupe po starosnoj dobi, intervenciji koja je urađena i PH dijagnozi.

Rezultati

Tabela br 1. Intervencije na grliću sa dijagnozom kondiloma

Starosna dob	LOOP	Conisatio	Cervicitis	Ukupno
20-29	15	22	18	55
30-39	57	39	43	139
40-49	63	29	58	150
50-59	47	0	0	47
➢ 60	7	0	0	0
Ukupno	189	90	119	*398*

Grafikon1. PH nalazi u u odnosu na starosnu dob

Zaključak

Podaci iz literature govore o epidemijskim razmjerama infekcije sa *HPV*. Iako virus koji izaziva kondilome spade u nisko rizične neliječena infekcija može dovesti do posljedica za reproduktivno zdravlje zbog **širenja** infekcije kao i intervencija koje se sprovode u cilju dijagnostike i liječenja. Analizirajući naše podatke vidi se da je najveći broj pacijentkinja sa patološkim PH bio je u grupi od 30-39 i 40 -49 godina. Samo saznanje da sa prvim seksualnim kontaktom dolazi do prenosa HPV, i da to izaziva ozbiljne probleme – polne bradavice (kondilome) i prekanceroze na grliću materice je dovoljno traumatično za mladu devojku. Razočaranje koje tada nastupa može u velikoj meri uticati na kasniji seksualni **život. Ako se na to nadovežu** greške u dijagnostici i terapiji to će otežati psihičko stanje, ali sa druge strane dovesti do fizičkih promena na genitoanalnoj regiji. Uvođenje nacionalnih skrininga, zdravstveno prosvjećivanje i vakcinacija su imperative u prevenciji oboljenja sa *HPV*.

THE IMPACT OF SOCIODEMOGRAPHIC FACTORS AND SOCIAL COMMUNICATIONS ON THE QUALITY OF LIFE IN WOMEN CURVED FROM CERVICAL DISPLACATION CAUSED BY HUMAN PAPILOMA VIRUS

Viktorija Jovanovska

University Clinic for gynecology and obstetrics, Skopje, North Macedonia

Quality of life (QoL) can be defined in different ways, therefore its measurement and incorporation in clinical studies is difficult. As the disease and its treatment affect psychological, social and economic well-being, it also affects the biological integrity of an individual. Accordingly, any definition of quality of life should be comprehensive, allowing individual components of quality of life to be comprehensive. The studies describe questionnaires that measure one component - unidimensional and questionnaires that measure multiple components - multidimensional questionnaires. When using a multidimensional questionnaire, it is a good thing that each of the scales within the questionnaire is displayed as one-dimensional, which means that it is possible to analyze individually the specific components of the quality of life related to health (HRQoL)

When using the JOCA-2015 questionnaire, in 200 patients treated with cervical dysplasia caused by Human Papilloma Virus (HPV) at the University Clinic of Gynecology and Obstetrics, Skopje, Macedonia, the influence of socio-demographic factors such as residence, ethnicity, degree of education, age, occupation, permanent partner, on the quality of life of these patients. Also the correlation between the emotional state of the patient and the social ties is investigated.

In our research, for $R = -0.07$ and ($p > 0.05$), it was found that with the rise in age, the quality of life is insignificantly declining, which is in accordance with the data from the world literature. In the investigated relationship between the sexual age of the patient and the quality of life for $R = 0.04$ and ($p > 0.05$), a lot of poor correlation was established, with the increase in the sexual age of the patients, the quality of life is insignificantly increasing. The spread of higher cervical lesions increases with age, reaching peak in a 45-49 year old woman. The presence of HPV infection significantly affects the psychological state of life and the quality of life of women in urban middle age, which is proven by the better life of women living in the village, which correlates with the results in previous published studies. Regarding the ethnicity of women in Macedonia, there was no significant difference in the quality of life of patients ($p > 0.05$). The results showed that patients with an irregular partner have insignificant ($p > 0.05$) higher level ($P = 87.47$) quality of life compared with the participants with a permanent partner ($P = 85.92$), which is contrary to the results published in certain studies from the world literature, where women with a permanent partner have a better quality of life, as a result of physical, emotional and psychological support from the same. Regarding the level of education, patients with higher education have a better quality of life, and according to the occupation, it has been proved that high school students, students and the unemployed have a higher quality of life than employed and retired patients.

The increase in the value of social cohesion at the time of use of JOCA 2015 leads to a significant increase in the quality of life, which confirms the general thesis that the support from the partner, family, friends, and the wider trust level in the doctor arising from adequate information that gives them to the patient and the belief in treatment, positively reflect the impression of life. The correlation showed that the increase in the unit value of sexual activity, the satisfaction of treatment, the general impressions, leads to a significant increase in social ties.

CONTEMPORARY ASPECTS OF THE PREVENTION OF SEXUALLY TRANSMITTED DISEASES

Miloš Petronijević

Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia

Sexually transmitted infections (STIs) are a rising problem worldwide, threatening the physical, mental, reproductive and sexual health of women everywhere. Women are more vulnerable to STIs than men, and obstetricians have great responsibility in supporting informed, safe and responsible sexual health. Today, 37 million people live with HIV, more than 500 million are estimated to carry herpes simplex virus (HSV), and 300 million women have a human papillomavirus (HPV) infection; every day more than 1 million people acquire an STI, over 30,000 people are affected by syphilis, 250,000 people are infected by chlamydia, 170,000 people are diagnosed with gonorrhea.STIs are common and preventable causes of morbidity and serious complications. Untreated chlamydial and gonococcal infection may result in pelvic inflammatory disease, which can lead to infertility, ectopic pregnancy, and chronic pelvic pain in 10-20% of cases. STIs can also result in adverse outcomes in pregnancy, including spontaneous abortion, still birth, premature birth, and congenital infection. The presence of STIs can facilitate HIV transmission, so primary prevention is of high priority.The comprehensive approach to STI prevention is based on five major strategies: 1) Accurate risk assessment, with education and counseling of at-risk individuals on ways to avoid STIs, 2) Pre-exposure vaccination of individuals at risk for vaccine-preventable STIs, 3) Identification of both asymptomatic and symptomatic individuals with STIs, 4) Effective diagnosis, treatment, counseling, and follow-up of infected individuals, and 5) Evaluation, treatment, and counseling of sex partners of infected individuals. Risk assessment through routine sexual histories is critical to allow targeted STI screening and prevention counseling . Behavioral risk factors include new or multiple sex partners, sex partners with recent STI, no or inconsistent condom use outside a monogamous sexual partnership, trading sex for money or drugs, and sexual contact with sex workers. Adolescents, pregnant women, HIV-infected individuals, men who have sex with men, transgender individuals and lesbians warrant specific considerations for screening and counseling because of the high rate of STIs among these populations. Vaccination is an important strategy to prevent several infections that are sexually transmitted or associated with sexual activity (Hepatitis A vaccine, Hepatitis B vaccine, Human papillomavirus (HPV) vaccine, meningococcal vaccine.STI prevention efforts should also include the use of barrier methods, including male and female condoms. Use of male condoms has been associated with a decreased risk of transmission of HIV, chlamydia, gonorrhea, herpes simplex virus, and HPV. Effective antimicrobial-based preventive strategies include antiretroviral treatment as prevention, pre-exposure prophylaxis, and post-exposure prophylaxis to prevent HIV infection as well as suppressive antiviral therapy of individuals with genital herpes simplex virus (HSV) to prevent transmission. These issues are discussed in detail elsewhere. Male circumcision can reduce HIV acquisition among heterosexual men and decrease the risk of infection with HSV and HPV.

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HPV VACCINATION IN SLOVENIA

Milena Mikluš, Barbara Nerat, Kaja Takač Kašan, Maruša Esih, Veronika Vogrin, Iztok Takač

Clinic for Gynaecology and Obstetrics, University Medical Center Maribor, Slovenia

Cervical cancer is the fourth most common gynaecological cancer. In 2018, 120 women were diagnosed with cervical cancer in Slovenia. Persistent viral infection with high-risk HPV genotypes causes virtually all cancers of the cervix, therefore vaccines have been developed to protect against acquisition of HPV infection and development of subsequent HPV-associated diseases. Most HPV infections, however, are transient and spontaneously cleared by the immune system of the host, except in susceptible individuals and in immunocompromised, when they persist and lead to preinvasive and invasive lesions of the genital tract. The vaccination against human papillomavirus (HPV) has been included in the national vaccination program in Sloveniasince 2009. Included in the program are girls aged 12 to 13 years (attending school year 6). The vaccination is voluntary although parents are asked to sign a consent form. The vaccine has been proven to be very effective and safe; however, the HPV vaccinationrate in Slovenia is still too low – under 50%. There are three different vaccines, which vary in the number of HPV types they contain and target. These are quadrivalent HPV vaccine (Gardasil), which targets HPV types 6, 11, 16 and 18; 9-valent vaccine (Gardasil 9), which targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 and bivalent vaccine (Cervarix), which targets HPV types 16 and 18. Successful national vaccination programs data worldwide confirm that the vaccine against HPV is effective and extremely safe. Countries with high prevalence rates have recorded a significant decline in the prevalence of HPV, genital warts and pre-cancerous changes in the cervix. One additional challenge is the introduction of HPV vaccination for boys. In Slovenia,the HPV vaccine can be given to boys at 9 years of age and above; however, they are not included in the national vaccination program. Over the recent years, some regions have decided to finance the vaccination program of boys and the immunization rate reached 25–69%. In Slovenia, the goal of the vaccination program is to achieve high vaccination rates and reduce distrust ofvaccines. If we manage to achievehigher vaccination rates and improve responsiveness of the screening programs, we will be able to diagnose and treat these patients more successfully.

GYNECOLOGY

HOW CAN WE DECREASE THE FAILURE RATE IN HORMONAL CONTRACEPTION USE?

György Bártfai

Department of Obstetrics and Gynecology, University of Szeged, Szeged, Hungary

Nowadays there is a reach arsenal of reliable contraceptive methods. Among them one of the most reliable methods to avoid unintended pregnancy is the hormonal contraception. There is a considerable difference between the failure rate of the typical and the perfect use. It is mainly true for the oral hormonal contraceptives. This difference is much smaller while using long-acting reversible contraceptive methods (LARC). Using LNG-IUS, there is no difference at all in the percentage of women experiencing an unintended pregnancy during the first year of use, which is 0.1% either in typical or in perfect use. One significant source of the failure is the patient error and the adherence. One of the major reasons of the failure is the myth and misconception regarding unfavourable side-effects of hormonal contraceptives, like fear of weight gain, skin problems, or mood depression, which can negatively change the adherence to treatment. Nowadays, using programmes which send warning message to mobile phone can be substantially decreases the error of forget to take the pill. The other reason for the possible hormonal contraceptive failure is that there are certain enzyme-inductors drugs, which can modify the metabolism of the sexual steroid content of the contraceptive in the liver. Therefore, the practitioners has to be careful when prescribing the hormonal contraceptives or administering other types of hormonal contraceptives for women with epilepsy or patients who are taking anti-HIV or anti-fungal medication and there are a few antibiotics which can also change the effectiveness of them. There are some diseases like inflammatory bowel disease (IBD) which could impair the absorption of the pill. Smoking and alcohol consumption also interferes with the effect of the hormonal contraceptives. It is paramount of importance the proper counselling of the patients, in particular the teenagers. To select the most suitable contraceptives for the patient should be tailored by the gynaecologist to the woman's wish, her health status and other kind of medications, and her habits should also be considered.

MINIMALLY INVASIVE APPROACH IN THE SURGICAL TREATMENT OF UTERINE MYOMA.

MINIMALNO INVAZIVNI PRISTUP U OPERATIVNOM LEČENJU MIOMA MATERICE.

Rastko Maglić

GAK "Narodni front", Beograd, Srbija

Miomi materice predstavljaju najčešće benigne tumore kod žena. Poznati su još od antičkih vremena i opisivani kao "kameni materice". Danas oni predstavljaju jedan od najčešćih uzroka kako abnormalnih uterinih krvavljenja iz materice, tako i infertiliteta. Miomi tip 1,2 i 3 su danas najčešći uzroci opisanih tegoba.

U operativnom lečenju mioma trend lečenja sve više se prenosi na minimalno invazivne metode i postupke, koji ne samo da povlače kraći ostanak u bolnici i manji morbiditet, već i daju bolje i dugotrajnije rešenje problema. Pre svega se koristi histeroskopska resekcija mioma (miomektomija) sve do veličina mioma od 4-5 cm a preko te veličine laparoskopska ekstirpacija sa višeslojnim suturnim zbrinjavanjem nastalog defekta.

Tamo gde miomi ne prave funkcionalne poremećaje postoji stručna dilema da li takve miome treba uopšte operisati ili ih samo pratiti i do koje veličine. Da li ih treba pratiti do perimenopauzalnog perioda, nakon koga je totalna laparoskopska histerektomija optimalni modalitet lečenja, ili koristiti kombinaciju medikamentne terapije (Esmia) i RF ablacije, ili ultrazvučne ablacije nodusa ili embolizaciju uterinih arterija kao metode neoperativnog minimalno invazivnog lečenja. Takođe uvek postoji dilema kod velikih nodusa (preko 10cm dijametra) da li i dalje koristiti minimalno invazivni pristup ili treba izabrati laparotomiju kao optimalnu operativnu metodu. Ovu diskusiju dodatno je iskomplikovao stav američkih ginekologa/onkologa oko morselacije mioma i rasejanja tkiva, zbog objavljenih slučajeva morseiranih leiomiosarkoma (LMS).

Novi pristupi u prezervaciji feriliteta naglašavaju mesto minimalno invazivnih pristupa u lečenju mioma – kako bi se sačuvala materica kao osnovni reproduktivni organ.

U Srbiji su, u današnje vreme, histeroskopija i laparoskopija već potpuno etablirane metode sa granicama operativnog lečenja koje se poklapaju sa svetskim standardima. Ekstremni slučajevi (po lokaciji, veličini i metodama lečenja) rešavanja ovih tumora su prezentovani od strane naših autora na više svetskih kongresa.

U ovom predavanju će biti sistematizovana dijagnostika, metodologija lečenja i prikazani adekvatni primeri lečenja mioma materice u skladu sa njihovom prezentacijom, veličinom i lokacijom. Takođe će biti prikazana distribucija mioma prema lokaciji, broju i načinu operativnog lečenja u zadnje dve godine na GAK "Narodni front" koja je ilustrativna za razvoj minimalno invazivnog pristupa u lečenju mioma materice.

CONTRACEPTION TAILORED TO THE NEEDS OF ADOLESCENTS

KONTRACEPCIJA PRILAGOĐENA POTREBAMA ADOLESCENATA

Katarina Sedlecki, Zoran Stanković, Ilijana Mažibrada, Svetlana Perović

Institut za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“

Uvod: Seksualna aktivnost tokom adolescencije je u porastu. U istraživanju sprovedenom tokom 2011. godine putem Interneta, seksualnu aktivnost do kraja adolescencije u Srbiji ostvari približno 80% devojaka i verovatno još više mladića. Približno četvrtina prvi polni odnos doživi sa 16 i manje godina. Zato, potrebe adolescenata za kontracepcijom ne treba zanemarivati, već im treba omogućiti informisani izbor njima najprihvatljivijeg, a istovremeno bezbednog metoda.

Cilj: Prikazati savremene stavove o izboru kontracepcije u adolescenciji.

Materijal i metod: Za potrebe ovog rada pregledani su radovi na engleskom jeziku, publikovani u poslednjih 10 godina, koji su ispitivali različite aspekte korišćenja kontracepcije u adolescenciji. Članci su identifikovani kroz baze podataka *Medline*, *Science Direct, Google i Popline*, a za dodatnu literaturu je pretražen i spisak referenci tih članaka. Razmotrena su i mišljenja stručnjaka, izneta kroz revijalne radove o ovoj temi.

Rezultati: Da bi potražili savet o kontracepciji, mladima su važni privatnost, poverljivost, prijateljski i neosuđujući pristup, nezavisno od njihovog uzrasta, roda, seksualne orijentacije, kulturnog obrasca, etničke pripadnosti i psiho-fizičkih sposobnosti. Savetovanje adolescenata zahteva više vremena i umeće aktivnog slušanja. Treba podržavati uključivanje roditelja ili partnera u razgovor o kontracepciji, ali i omogućiti mladoj osobi da bude nasamo sa zdravstvenim radnikom.

Poželjno je da se adolescentkinja ili mladi par postupno informišu, od najefikasnijih ka manje efikasnim metodima kontracepcije dok se ne utvrdi onaj koji je najprihvatljiviji. Najefikasniji metodi kontracepcije pripadaju kategoriji A (intrauterina kontracepcija, progestinski implanti i depo-injekcioni preparati), jer ne zahtevaju svakodnevno angažovanje i imaju nisku stopu neuspeha. Metodi kategorije B su efikasni ali zahtevaju doslednu primenu (kombinovana hormonska kontracepcija i progestinske pilule) i imaju značajno višu stopu neuspeha pri uobičajenom načinu korišćenja. Kategoriji C pripadaju metodi koji su manje efikasni, a zahtevaju veliko angažovanje korisnika (kondom, dijafragma, spermicidi, plodni dani i *coitus interruptus*).

Mladi generalno mogu bezbedno da koriste sve reverzibilne metode kontracepcije (tabela 1). Kod njih, međutim, mogu da budu važni rizici povezani sa njihovim pubertetskim razvojem ili vulnerabilnošću prema polno prenosivim infekcijama. Treba proceniti i druge parametre, poput mogućnosti redovne i pravilne upotrebe metoda kontracepcije, postojanja poremećaja ishrane, gojaznosti, porodične situacije i korišćenja alkohola i drugih psihoaktivnih supstanci.

Tabela 1. Bezbednost korišćenja različitih metoda kontracepcije u adolescenciji

Metod kontracepcije	Kategorija Svetske zdravstvene organizacije za procenu bezbednosti metoda kontracepcije u kliničkom radu*
Kombinovana hormonska kontracepcija	1
Progestinska oralna kontracepcija	1
Progestinski implant	1
Progestinske depo-injekcije	< 18 godina – 2 ≥ 18 godina - 1
Barijerni metodi (kondomi, dijafragma, cervikalne kape)	1
Intrauterini uložak sa bakrom	2
Intrauterini uložak sa levonorgestrelom	2

Izvor: *World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: World Health Organization; 2015.*

* Kategorije Svetske zdravstvene organizacije za procenu bezbednosti korišćenje metoda kontracepcije: 1 – nema rizika; 2 – prednosti premašuju pretpostavljene rizike i metod generalno može da se koristi; 3 – relativne kontraindikacije; 4 – apsolutne kontraindikacije

Zaključak: Za adolescentkinje su prikladni svi reverzibilni kontraceptivi, a najefikasniji su dugodelujući metodi. Posebnu pažnju treba posvetiti promociji dvojne zaštite.

IVF SESSION

IMPACT OF FEMALE PARTNER SMOKING ON IN VITRO FERTILIZATION OUTCOME

UTICAJ PUŠENJA ŽENSKOG PARTNERA NA ISHOD VANTELESNOG OPLODJENJA

Eliana Garalejić

Ginekološko Akušerska Klinika "Narodni Front" Beograd, Srbija

Infertilitet danas predstavlja najčešće oboljenje reproduktivnog trakta i nameće se utisak da se poslednjih godina radi o epidemiji infertiliteta u razvijenim zemljama sveta. Brojni su uzroci infertiliteta a u žiži interesovanja je uticaj faktora spoljasnje sredine kako na fertilnost oba partnera, tako i na ishod vantelesnog oplodjenja. Kod pacijentkinja koje su pušači sa jedne strane je smanjena koncentracija cirkulišućih antioksidanasa a sa druge strane je povećan oksidativni stres koji predstavlja jadan od najznačajnih uzročnika ženskog infertiliteta prouzrokujući tubarni infertilitet, endometriozu, sindrom policističnih jajnika i infertilitet neobjašnjenog uzroka. Mnoge studije su pokazale slabije rezultate u ishodima vantelesnog oplodjenja kod pacijenatkinja koje su pušači u odnosu na pacijentkinje koje to nisu. Poznato je da nikotin ima direktan uticaj na smanjenje ovarijalne rezerve tako da su pacijentkinje koje su pušači imale značajno manji broj dobijenih jajnih ćelija aspiracijom folikula. Ustanovljeno je, da je kod pacijentkinja koje puše, smanjena i receptivnost endometrijuma tako da nikotin ima štetan uticaj i na implantaciju embriona. Prisutno je signifikantno smanjenje u procentu postignutih trudnoća koje ide čak do 50% uz istovremeni značajan porast pobačaja i to i do 25%. Takodje, pacijentinje koje puše imaju od 28 do 46% manju šansu da posle procedure vantelesnog oplodjenja rode živo dete u odnosu na pacijentkinje koje ne puše. Ekspozicija fetusa štetnim intrauterinim uslovima i uticajima, zbog pušenja žene tokom intrauterinog razvoja fetusa, može štetno uticati na rast i razvoj samog fetusa, a kasnije može da dovede i do štetnih posledica na postnatalno zdravlje. Stoga u pripremi infertilnog para, veoma važnu ulogu imaju informacije lekara o štetnom uticaju pušenja po zdravlje uopšte, kao i na ishod vantelesnog oplodjenja, kao i njihovi saveti o svim koristima napuštanja ove štetne navike. Preporučen period apstinencije od pušenja je bar 3 do 6 meseci pre započinjanja procedura vantelesnog oplodjenja.

FERTILITY PRESERVATION - WHERE WE ARE TODAY

PREZERVACIJA FERTILNOSTI

Tatjana Motrenko

Razvoj medicine u lečenju infertiliteta otvorio je ranije nezamislive mogućnosti u očuvanju fertilnosti ne samo muškaraca i žena, nego i prepubertalne dece oba pola. Skok incidence malignih bolesti od 300% (region, Evropa) rapidno je povećao broj pacijenata koji će biti lečeni u ranom i reproduktivnom životnom dobu. Pravovremena dijagnostika i efikasna terapija malignih bolesti su povećala šansu za izlečenje i procentat preživljavanja. Pored malignih, određeni broj genetskih (*Turner i Klinefelter syn*) i sistemskih oboljenja (*SLE*, autoimuna oboljenja, *MS*, endometrioza), kao i genetska predispozicija ka *POF*-u, dovode do prevremenog nestanka gameta i iscrpljivanja gonadalne rezerve. Takođe promene u načinu života često uzrokuju odlaganje materinstva, što direktno utiče na smanjenje plodnosti jer su godine žene, tj starenje jajnih ćelija direktno povezani sa reproduktivnim potencijalom, zbog genetskih i metaboličkih promena unutar oocita.

Muškarci

Zamrzavanje sperme je već godinama rutinska metoda i verovatno najjednostavniji način prezervacije fertilnosti kod muškaraca. Ukoliko se radi o malignoj bolesti, pre početka *HR/RT* terapije i u slučajevima urgentnog lečenja, treba savetovati zamrzavanje sperme u većem broju slamica, bez obzira na spermogram koji može biti i jako loš, jer postupak vantelesne oplodnje *ISCI* metodom ne zahteva veliki broj spermatozoida. Iako nakon hemo ili radio terapije spermatogeneza može biti očuvana, pacijenti se moraju upozoriti na oštećenje *DNK* koje se javlja u hromozomima spermatozoida i uticaju na smanjene šanse začeća, kao i eventualne posledice na potomstvo. U slučaju da se radi o dečacima u predpubertalnom dobu kada spermatogeneza nije počela, jedina mogućnost je uzimanje testikularnog tkiva i zamrzavanje sa idejom da se kasnije, po izlečenju, uradi ortotransplantacija odmrznutog tkiva u testise, što je još uvek eksperimentalna metoda i predmet izučavanja. Kod dečaka sa *Klinfelterovim syn*. roditelji moraju biti upozoreni da po ulasku deteta u pubertet može biti uspostavljena spermatogeneza, te da je jedini način očuvanja gameta rana testikularna biopsija sa krioprezervacijom materijala koji će se kasnije iskoristiti za postupak vantelesne oplodnje.

Žene

Vitrifikacija embriona je već dugo rutinska metoda i deo standardnog tretmana infertiliteta, pa se pacijentkinjama koje imaju partnera i kod kojih je to moguće (maligne bolesti kod kojih se ne mora odmah početi tretman ili tumori koji nisu estrogen senzitivni, ili pacijentkinja sa istorijom *POF*-a), treba savetovati stimulacija ovulacije sa konsekutivnim *IVF*-om i zamrzavanjem kvalitetnih embriona koji mogu biti vraćeni mnogo kasnije. Sama stimulacija ovulacije ne mora biti vezana za određene dane ciklusa, već se može početi bilo kada, jer se ne planira embriotransfer. Postoji mogućnost i takozvane dvostruke stimulacije, da se na prvoj punkciji folikula aspiriraju samo veći folikuli koji će dati zrele oocite, potom nastavi stimulacija i nakon desetak dana uradi druga punkcija kojom će se pokupiti preostali folikuli u razvoju i povećati broj jajnih ćelija koje se dobiju. Ukoliko žena nema partnera, druga mogućnost prezervacije fertilnosti je kripoprezervacija oocita, koja je od 2013 godine prestala da bude eksperimentalna metoda i postala deo rutinske prakse u mnogim državama. Ipak, treba naglasiti da su iskustva u vitrifikaciji oocita razvijena u državama koje su imale dobar donorski program zbog dugogodišnje prakse i zahteva *Tissue Directive*, koja brani upotrebu svežih oocita u postupku donacije, te su svi centri morali razviti dobar program vitrifikacije oocita, i imaju veliko iskustvo u toj oblasti. Na našem području, tj regionu *ex YU* zemalja, donorski program nikada nije zaživeo, niti se krioprezervacija oocita rutinski radi sem u pojedinačnim slučajevima lečenja infertiliteta. Ima sporadičnih slučajeva krioprezervacije oocita u postupku rutinskog lečenja infertiliteta i trudnoća iz njih. Ipak to nije dovoljno da se bez dodatne edukacije embriologa, dobre organizacije laboratorije i kontrole kvaliteta rada (stopa preživljavanja oocita, stope fertilizacije, procenat kvalitetnih embriona, % blastocisti), ovaj program ponudi kao standardna praksa, kako pacijentkinjama

u postupku lečenja malignih bolesti, tako i kao program tzv „*Social freezing*“-a. Sve pacijentkinje moraju biti upoznate sa realnim šansama za trudnoću iz ovakvih postupaka – *CPR* (stopa kliničkih trudnoća) po 1 oocitu varira od 4,5% do 12 % u populaciji žena ispod 30 godina starosti, a *LBR* - stopa živorođene dece je 6,5% po jednom oocitu. Veći broj vitrifikovanih oocita znači i veću šansu za trudnoću, a potrebno je minimum 8 – 10 M II oocita za 50% *CPR*. To je jako bitno za žene koje iz socijalnih razloga odlažu rađanje, kako bi imale pravu informaciju o mogućnostima kasnije trudnoće, kao i da time nisu dobile zagarantovano majčinstvo.

Ukoliko se radi o tumoru dojke koji je estrogen senzitivan pa je stimulacija kontraindikovana i treba što pre početi terapiju, kao i kod prepubertalnih devojčica, jedina opcija je krioprezervacija ovarijalnog tkiva, tj korteksa, metodom slow feeezinga, sa kasnijom orto ili xeno transplantacijom. Metoda je u razvoju od 2004.g. kada je J. Donnez u Belgiji izveo prvu uspešnu kriporezervaciju dela ljudskog ovarijuma sa konsekutivnom transplantacijom u hipofizektomisane miševe gde je 1/3 transplanta preživela i dala hormonsku i folikularnu aktivnost. Tehnika se u međuvremenu razvijala, pored Belgije i Danska je razvila program prezervacije fertilnosti ovom metodom, da bi i ostale vodeće zemlje krenule tip putem. Za sada je u većini zemalja ova metoda samo eksperimentalna, ali tamo gde postoji značajno iskustvo kao u Belgiji, od ove godine je zdravstveno osiguranje prihvatilo da pokriva troškove kriprezervacije ovarijalnog tkiva i kasnije transplantacije kod malignih bolesti, u indikovanim slučajevima. Dokumentovano je širom sveta oko 100 rođene dece iz ove metode, dobar deo njih i spontanim začećem u slučaju ortotransplantacije. Kod promene *HT*, jedna od mogućnosti smanjenja toksičnog uticaja citostatika je davanje agonsta *GnRH*, s akcentom da davanje samo umereno smanjuje uticaj na ovarijume, nikako ga ne eliminišući.

Imajući u vidu brojne mogućnosti prezervacije fertilnosti, potrebno je uspostaviti multidisciplinarne timove (onkolog, pedijatar, hirurg, psiholog, endokrinolog, radiolog, genetičar i svakako subspecijalista reproduktivne medicine) koji će pacijentima pružiti pravovremene i realne informacije, kojima je u mnogočemu moguće promeniti ishod kako lečenja tako i mogućnost dobijanja potomstva. Na žalost, nigde u zemlji i okruženju ne postoji koordinisana akcija kojom bi se u 21 veku omogućilo pacijentima da u potpunosti iskoristeopcije koje im pruža medicina i nauka.

DIAGNOSIS OF TUBAL FACTOR INFERTILITY

ISPITIVANJE TUBARNOG FAKTORA INFERTILITETA

Aida Šahmanović

Klinika za ginekologiju i aklušerstvo, Klinički Centar Cne Gore

Uvod: Tubarni faktor infertilita uslovljen okluzijom tuba kao i peritonealnom patologijom koja uzrokuje adhezije se dijagnostikuje u oko 25-35% slučajeva ženskog infertiliteta. Ispitivanje potencijalne tubarne patologije predstavlja esencijalni korak u obradi infertiliteta, ali i izazov u smislu koji od testova primijeniti kod konkretnog neplodnog para.

Cilj rada i metodologija: Cilj ovog članka je sistematski pregled novije ali i klasične literature na temu ispitivanja tubarnog faktora infertiliteta i upoređivanja tačnosti testova za ispitivanje prohodnosti tuba koji su nam danas na raspolaganju. U tu svrhu je sproveden elektronski pregled literature uz korišćenje *PubMed* i *Cochrane Central Register of Controlled Trials* baza i *Google Schoolar* pretraživača.

Rezultati: Laparoskopija sa hromopertubacijom se smatra definitivnim testom za procjenu tubarne bolesti. Histerosalpingografija (HSG) ima umjerenu senzitivnost (65%) ali odličnu specifičnost (83%) u infertilnoj populaciji. Bez obzira na lošiju senzitivnost, HSG je vrijedna, minimalno invazivna metoda ispitivanja tubarne prohodnosti, koja ocrtava i konture uterusne šupljine i lumen Falopijevih tuba. Sonohisterosalpingografija (SHG) je ultrazvučno baziran imidžing modalitet koji omogućava ispitivanje tubarne prohodnosti kao i uterine i ovarijalne patologije. Sprovedena meta-analiza koja je proučavala tačnost HSG, SHG i laparoskopije je pronašla da je SHG superiporan u odnosu na HSG i može se porediti sa laparposkopskom hromopertubacijom. Vizualizacija „*flow*“ efekta ili mjehurića vazduha koji se raspršuju kroz ušća jajovoda („*Parryscope*“ tehnika), ultrazvučno procijenjeno povećanje količine tečnosti u *cul-de-sac*, kao i selektivna kanulacija Falopijevih tuba su obećavajuće histeroskopske tehnike. Indirektni serološki testovi kojima se detektuje imunološki odgovor, odnosno antitijela specifična za hlamidijalne antigene su jednostavan i neinvazivan metod procjene tubalne bolesti. Mol i kolege su sproveli meta-analizu koja je poredila serološki mikroimunofluorescentni test na *C. Trachomatis* sa HSG u dijagnozi tubarne okluzije koristeći laparoskopsku hromopertubaciju kao zlatni standrad. Test mikroimunofluorescencije je imao senzitivnost manju od 75% ali specifičnost veću od 75%.

Zaključak: Laparoskopija sa hromopertubacijom ostaje „zlatni standard“ i test na koji se pacijentkinja sa identifikovanim faktorima rizika odmah upućuje. HSG je u širokoj upotrebi, ali je SHG potpuno komparabilna, ako ne i metoda sa više prednosti. Potrebne su veće prospektivne studije da bi se donijeli definitivni zaključci o izvodljivosti i tačnosti histeroskopskih tehnika. Serološki testovi mogu biti screening testovi da bi se pacijentkinje klasifikovale u nisko-ili visoko-rizičnu grupu za tubarnu bolest i dalje usmjeravale na ispitivanje sa invazivnijim testovima, kao što su HSG, SHG ili laparoskopija.

THYROID HORMONES AND OUTCOMES OF ASSISTED REPRODUCTION

Svetlana Spremovic-Radjenovic

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

Introduction**:** 4,6% children in Europe have been born using assisted reproduction tehnologies (ART). In the aim to create optimal conditions for women included in procedure of in vitro fertilization (IVF), the few therapies are used: low molecullar heparin, corticosteroidies, thyroid hormones, metformin, mioinozitols... Identification of optimal reference range for thyreostimulating hormone (TSH) in patients included in ART procedures is very contradictory item and reason for meny discusion

Aim of this presentation is to show results of metaanalises, own expiriances, recomendations and guidelines for optimal TSH in women included in ART procedures.

Results: The reference values for TSH are not modifyed in general population, no matter in 95% of population TSH is less than 2,5 IU/ml; reference values are changed to 2,5 IU/ml as the upper normal value in 1. and 2. trimester and 3 IU/ml in 3. trimester. If the concentration of TSH before pregnancy in women with infertility problems is between 2,5 i 4 IU/ml, there are two possibilities: monitoring in early pregnancy and if TSH is higher than 4 IU/ml, starting with therapy, or begin with levothyroxine therapy in the aim to diminish TSH concentration to less than 2.5 IU/ml, using the reasoning that therapy with levothyroxine (LT4) is harmless but prevents progresion to clinicaly expressed hypothyreoidisam in first trimester of pregnancy (recomendation numb 18, American Thyroid Association, 2017). \in this way there is enough experiance and conditions to compare results of pregnacy outcomes for ART procedures in women with normal TSH but >2,5 IU/ml in group of women who have taken therapy with thyroid hormones and in group of women who have not. Results in our IVF center in 250 patients did not show any diference in pregnancy rate in patients with TSH concentration in upper normal range. The last metaanalise about preconceptional TSH concentration on pregnancy rate, clinical pregnancy rate i live birth rate from IVF-a /ICSI analysed 18 studies and 14 846 women and accordint to the results if breaking point for TSH is 2,5 IU/ml and analyse is done for range to upper normal reference value, TSH concnetration in that range does not influence on ART porcedure outcome

Conclusion: The newest results refering to optimal TSH in ART-a procedures is necessary to present and include in guidelines and recomendations to diminish confusion and contradictory isues in this field.

REPEATED IMPLANTATION FAILURE – DOES IT EXIST?

Zion Ben - Rafael

Dept of Ob/Gyn Rabin Medical Center and incumbent of the Tarnesby chair of fertility regulation, Tel Aviv University, Israel and IVF unite Laniado, Israel

IVF is a multi-stages procedure with many variables that can each fail. Some variables are inherent in the procedure, some in the patients, and every step and variable can be close to threshold, which decreases but not negate, and hence each cycle can succeed or fail with no real good explanation. The term repeated implantation failure (RIF) is a misnomer, since every failure has probably different or even more than one explanation, not necessarily related to each other. Furthermore, treatments include so many adds-on procedures, that for themselves lack real proofs, was deemed a (Iatrogenic) syndrome only by lamping them together.

Add-ons procedures receive recent negative attention in the lay media and professional societies. Since most of them are offered as a costly (unproven!) "better way" to reach better results after several failures. Repeated failure, is also the point of departure of research studies, be the studies randomized or not, to prove that these add-ons are effective. But what is RIF? Does it exist? And if it is not what are the implications on the studies that are based on them?

Different authors have selected different definition. The more commons published definitions, are failure to achieve an ultrasonographical detectable pregnancy in women less than 40 years with at least 3-4 ET or up to 4-10 good quality embryos, or 4 blastocyst or even after two failed cycles, or after 2 ET. The fact that know society have stepped in to the challenge to define RIF is interesting. The different definitions are usually not explained in the publication. However some used the presumed maximal implantation rate (IR) per embryo in optimal situation like oocyte donation and natural conception that are claimed to reach 40%. However, this basis is challenged. Extrapolation of large data base like the ESHRE registry encompassing all European countries show substantially lower IR. (H.R. 2017 Cahlaz-Jorge ESHRE registry 2013)**,** the pregnancy rate per ET was 23.4% (90,618 preg out of 386,632 ET with a mean of 1.88 embryos per transfer (Number of 1,2,3,4 embryos transferred were 31%, 56%, 11% 1%= 1.88 Embryos) Pregnancy rate divided by the mean number of embryos should give us the mean IR which is less than 15%. Miscarriage will bring the figure even lower, so 3-4 failure should be very common and probably does not require any change in plan in the next cycle, certainly not of untested procedures. Using a mathematical model, Somigliana et al (RBMO, 2017) have shown that assuming 30% implantation rate, the cumulative chances of pregnancy after 3 or 6 cycles was 59% and 79%, respectively, consequently, the false–positive rate of a diagnosis of RIF after 3 or 6 failed cycles is 75% and 51%, respectively attesting to the fact that no change in treatments should be institute.

Undoubtedly, every failure is stressful for the patient and care givers. The majority of failed IVF do not need re-evaluation of their clinical diagnosis and status since they probably had a comprehensive evaluation before they have started. Furthermore, they might not have any real obstacle to success. Patients who are exposed to endless lay-press stories and publication fear that they have been misdiagnosed or mistreated, while physician who are in constant competition in this highly privatized sector fear that the failure will result in drop-out, so both side are ready to grasp in the next cycle, every new procedure or protocols, that might be offered even if not proven. We will discuss all of these common add-ons solutions and will raise the related doubts.

SESSION OF ASSOCIATION OF GYNECOLOGIC ONCOLOGY OF SERBIA

LAPAROSCOPY IN THE TREATMENT OF CERVICAL CANCER AS PART OF A CONSERVATIVE SURGERY TREATMENT AND LAPAROSCOPIC RADICAL HYSTERECTOMY. IS THERE A FUTURE? LACC STUDY REVIEW.

LAPAROSKOPIJA U LEČENJU CERVIKALNOG KARCINOMA U OKVIRU FERTILITI POŠTEDNOG PRISTUPA I LAPAROSKOPSKA RADIKALNA HISTEREKTOMIJA: IMA LI BUDUĆNOST? OSVRT NA LACC STUDIJU.

Omer Devaja

London Bridge Hospital, London, England

The most significant advancement in reducing surgical morbidity in gynaecology over the last two decades has been an increased application of minimal invasive surgical techniques. Minimally invasive surgery has been shown to have better surgical outcomes with equivalent survival rates in patients with endometrial, colorectal, and gastric cancer in previous randomized controlled trials. In March, the results of the Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial were announced at the 2018 Society of Gynecologic Oncology (SGO) annual meeting. It was expected that the same result would be obtained in cervical cancer, but the disease-free survival and overall survival rate of minimally invasive radical hysterectomy (MIS RH) surgery group was significantly lower than that of open radical hysterectomy (ORH) surgery in LACC trial. However, before accepting the results of the LACC trial, we must go through a lot of important things that were not considered and controlled, and thus biased the results in the LACC trial. The first problem is that the survival rate of the open surgery group was too good and much higher than that reported previously. Only 7 of 319 (2.2%) patients in open surgery group had recurrence in the LACC trial. In previous large studies with long term follow-up, the recurrence rate after ORH for stage IA2-IB1 cervical cancer is about 10%.

Second, the high recurrence rate of the MIS group may be due to surgical technique or

carelessness of the operator, not because of the MIS itself. Third problem is the surgeon proficiency for MIS RH in LACC trial. The surgeon proficiency criteria for MIS RH in the LACC trial was only 10 cases. However, to achieve enough radicality and sufficient oncologic outcomes, over 40-50 cases are required for surgical proficiency.

The recurrence rate after LRH was equivalent only for small tumor less than 2 cm.

Fourth problem is that the results of subgroup analysis have not been reported. This analysis should be performed to determine which group has higher recurrence rate after MIS RH. This should include tumor size, stage, histology, surgery type (type II vs. III radical hysterectomy), surgeons' experience, and nationality or ethnicity, etc.

Fifth problem is that the participation in countries where MIS RH has become surgery

of choice has been low. In countries where MIS RH has already been recognized as an

operation that should be selected first, most of the patients assigned to ORH withdrew their participation in the study.

In conclusion, the report of outcomes in this trial is too early, and it should be reevaluated after at least 2 years. The poor survival outcome of the MIS RH group is not a problem of the MIS itself, but is probably due to the inadequate control of the operator and the surgical technique in LACC trial. Therefore, a new study which is controlled for these factors is needed.

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BORDER LINE OVARIAN TUMORS

Goran Malenkovic

Oncology institute of Vojvodina, Sremska Kamenica, Serbia

Borderline tumors, as with other ovarian tumors, are difficult to detect clinically until they are advanced in size or stage. In the United States, borderline tumors make up approximately 15% of all epithelial ovarian tumors. The mean age of occurrence is approximately 10 years younger than that of women with malignant ovarian cancer.

Most common symptoms are abdominal pain, abdominal distention, and abdominal mass. Approximately 30% of patients are asymptomatic.

The two major histologic tumor subtypes are serous and mucinous, with serous being more common.

Comprehensive staging of borderline ovarian tumors is of significant prognostic value and is performed surgically.

Adequate staging in serous borderline ovarian tumor includes detailed inspection of the peritoneum and peritoneal staging biopsies. Appendectomy as a staging procedure is not recommended even in the mucinous borderline ovarian tumor, and on the other side there is no evidence supporting lymphonodal dissection. Peritoneal implants are described as invasive or noninvasive. It is important to note that serous borderline ovarian tumor with invasive implants according to 2014 WHO classification now defined as extraovarian low-grade serous carcinoma. Complete removal of peritoneal implants is necessary for both staging and therapeutic purposes. In the case of serous borderline ovarian tumor with peritoneal implants, residual disease has been reported to be a prognostic factor.

Omission of staging has an impact both on recurrence rate and individual patient prognosis.

Fertility-sparing surgery is defined as the preservation of the uterus and at least a part of one ovary is the standard management of young patients with serous borderline ovarian tumor while bilateral salpingo-oophorectomy with hysterectomy is the standard management of borderline ovarian tumor in menopausal patients. Cystectomy is an acceptable management in serous borderline ovarian tumor to preserve fertility.

Unilateral salpingo-oophorectomy is recommended in case of mucinous borderline ovarian tumor to decrease the risk of invasive recurrence after cystectomy.

Patients with mucinous borderline ovarian tumor relapse less frequently than those with serous disease, but when a relapse occurs, the risk of an invasive recurrence seems to be higher for mucinous borderline ovarian tumor. The risk of recurrence is very low but exists, and is estimated under 1% after fertility-sparing surgery.

According to the available evidence, there is no benefit in adding adjuvant treatment after surgery in patients with serous borderline ovarian tumor with invasive implants.

Patients with borderline tumors have an excellent overall prognosis with 60% chance of having stage I disease when diagnosed.

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NEOANGIOGENESIS INHIBITORS IN CERVICAL CANCER THERAPY

INHIBITOR NEOANGIOGENEZE U TERAPIJI KARCINOMA GRLIĆA MATERICE

Aljoša Mandić

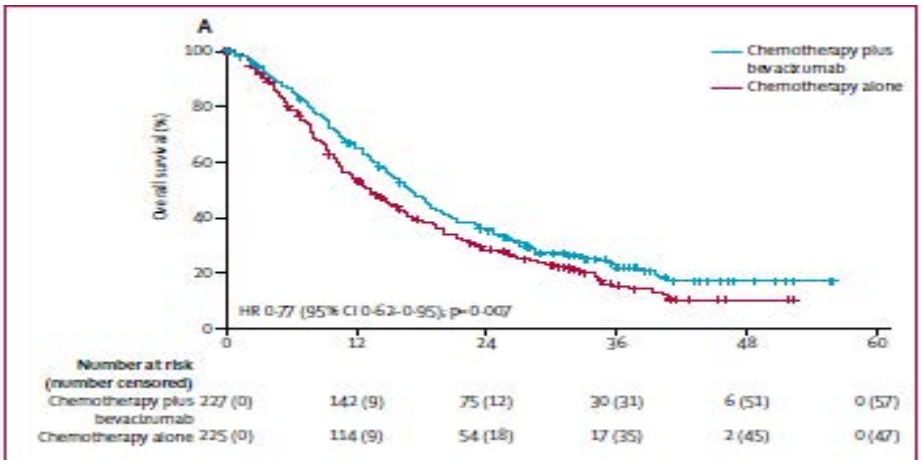
Institut za onkologiju Vojvodine, Sremska Kamenica, Srbija

I pored značajnog napredka u primarnoj i sekundarnoj prevenciji raka grlića materice, on ostaje značajan globani zdravstveni problem, naročito u nerazvijenom delu sveta.. Smrtnost od raka grlića materice je oko 266.000 godišnje što je oko 7,5% u odnosu na karcinomima izazvane smrti kod žena. Glavnina toga oko 87% odpada na nerazvijene zemlje. U Evropi sirova incidencija raka grlića materice je 13.2/100.000, a stopa smrtonosti 5.9/100.000. Međutim za one dijagnostikovane u uznapredovaloj bolesti ili sa povratom prognoza je loša sa ukupnim preživljavanjem oko 12 meseci. Metastatska bolest će se razviti u oko 50% žena: oko 10-20% pacijentkinja sa stad. IB-IIA i oko 50-70% onih lokalno uznapredovalih dobije povrat bolesti, odnosno ponovnu pojavu aktivnog oboljenja. Standard lečenja metastatskog, rekurentnog ili perzistentnog cervikalnog karcinoma je primena sistemske hemioterapije. Cisplatin je najaktivniji pojedinačni citotoksični agens u lečenju ove bolesti, ali se kombinovana hemioterapija (režimi cispltin/ paklitaksel, cisplatin/topotekan, cisplatin/ifosfamid, karboplatin/paklitaksel) pokazala efikasnijom nego monoterapija u pogledu veće stope terapijskog odgovora (RR do 40%), dužeg preživljavanja bez progresije, uz slično ukupno preživljavanje (oko 8-11 meseci).

I pored napora iznalaženja najbolje moguće kombinacije citostatske terapije i dalje su rezultati dosta ograničeni, poslednjih godina se intenzivno sprovode klinička istraživanja koja evaluiraju ciljane agense u ovoj populaciji. Brojni dokazi podržavaju koncept da angiogeneza igra centralnu ulogu u kancerogenezi grlića materice i progresiji bolesti, pri čemu hipoksija i viralni onkogeni utiču na angiogenezu. Terapije koje ciljaju vaskularni endotelni faktor rasta (VEGF), ključni medijator tumorske angiogeneze i njegove receptore predstavljaju obećavajuću terapijsku opciju.

U GOG 240 studiji faze 3 ispitivan je bevacizumab, rekombinantno humanizovano VEGF monoklonsko antitelo u lečenju pacijentkinja sa metastatskim, rekurentnim i perzistentnim karcinomom grlića materice. Upoređivana je efikasnost dodavanja bevacizumaba kombinaciji sa dva hemioterapijska dubleta u odnosu na samo hemioterapiju. Ova studija je bila dizajnirana da odgovori na dva pitanja (2x2 faktorijal dizajn): da li paklitaksel dodat topotekanu umesto cisplatine poboljšava ukupno preživljavanje, i da li dodavanje bevacizumaba hemioterapiji može poboljšati preživljavanje. Rezultati su pokazali da je primena bevacizumaba u kombinaciji sa hemioterapijom u odnosu na samo hemioterapiju udružena sa značajno dužim ukupnim preživljavanjem (OS:17,0 vs 13,3 meseci, HR0,71,98%CI:0.54–0.94,p=0,004) i dužim vremenom bez progresije (PFS: 8,2 vs 5,9 meseci,HR 0,67, 95% CI: 0.54–0.82, p=0,0002). Ovaj povoljan efekat na preživljavanje dokumentovan je u svim predhodno definisanim prognostičkim podgrupama. Dodavanje bevacizumaba hemioterapiji omogućilo je i bolji terapijski odgovor (RR: 48% vs 36%, p=0,008), a čak i kada su target lezije bile lokalizovane u predhodno zračenim regijama pelvisa, terapija sa bevacizumabom je bila efikasna.

Tewari i sar su 2017 objavili i finalne analize GOG 240 studije gde su zaključili da benefit od uključivanja Bevacizumaba postoji i u ovoj proširenom praćenju što se evidentira u odvojenim linijama ukupnog preživljavanja .(Grafikon 1).



Grafikon 1. Ukupno preživljavanje (ref. *Krishnansu S Tewari, Michael W Sill, Richard T Penson, Helen Huang, Lois M Ramondetta, Lisa M Landrum, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240.) Lancet 2017; 390: 1654–63)*

Nakon progresije u grupi sa Bevacizumabom nije potvrđen negativni efekat, skrćeno preživljavanje nakon isključivanja Bevacizumaba u odnosu na grupu sa hemioterapijom. Autori su zaključili da ovi rezultati potvrđuju efikasnost i tolerabilnost primene antiangiogenetske terapije u uznapredovalom raku grlića materice.

Profil toksičnosti terapijske kombinacije sa bevacizumabom je u saglasnosti sa već poznatim neželjenim dejstvima bevacizumaba koja su definisana tokom lečenja drugih malignih tumora. Kombinacija hemioterapije i bevacizumaba, u odnosu na samo hemioterapiju, bila je udružena sa većom učestalošću hipertenzije gradusa ≥2 (25% vs 2%), tromboembolijskih događaja gradusa 3 (8% vs 1%) i gastrointestinalnih fistula gradusa 3 (6% vs 1%), ali sve su fistule verifikovane u grupi predhodno zračenih pacijentkinja..

Savremene globalne preporuke (NCCN) navode da je u lečenju metastatskog, rekurentnog i perzistentnog karcinoma grlića materice jedna od standardnih opcija prve terapijske linije (kategorija 1 preporuka) režim cisplatin/paklitaksel u kombinaciji sa bevacizumabom.

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ROLE OF SENTINEL LYMPH NODE DETECTION IN CERVICAL AND ENDOMETRIAL CANCER. TIME FOR A STANDARD APPROACH.

MESTO DETEKCIJE LIMFNOG ČVORA ČUVARA U KARCINOMU ENDOMETRIJUMA. VREME ZA STANDARDNI PRISTUP?

Lazar Nejkovic

Ginekološko- akušerska Klinika " Narodni front ", Beograd, Srbija

Trend porasta učestalosti obolevanja i umiranja od karcinoma endometrijuma, koji se poslednjih godina registruje širom sveta, uslovio je da ovo oboljenje postane jedan od vodećih javno-zdravstvenih problema u populaciji žena širom sveta. Preživljavanje obolelih od endometrijalnog karcinoma je skoro 90%, dok se taj procenat drastično smanjuje ukoliko su limfni čvorovi male karlice pozitivni na metastatsku bolest i iznosi oko 50%. Istraživanja su pokazala da učestalost metastaza u limfaticima iznosi oko 10% i uveliko zavisi od kliničkih, patoanatomskih i morfoloških karakteristika samog oboljenja. Međutim, limfadenektomija u tretmanu pacijentkinja obolelih od karcinoma tela materice je predmet mnogih debata na nacionalnim i međunarodnim skupovima što jasno ukazuje na činjenicu da ne postoji konzistentan stav o značaju njene uloge u terapijskom pristupu ovog oboljenja. Naime, mnogobrojna istraživanja su pokazala su da je učestalost ozbiljnih komplikacija kod pacijentkinja kod kojih je rađena sistematska limfadenektomija, značajno viša u odnosu na grupe pacijentkinja koje nisu bile podvrgnute ovoj opsežnijoj hirurškoj proceduri. Iz tog razloga, veliki broj studija je sproveden u cilju identifikacije najoptimalnijeg načina selekcije pacijentkinja kod kojih je zaista neophodno da se uradi sistematska limfadenektomija. U tom smislu, u cilju smanjenja postoperativnog morbiditeta, poslednjih godina, sve više se ispituje uloga biopsije limfnog čvora stražara - SLN (engl. *Sentinel node lymphadenectomy*) u proceni statusa limfnog sisitema male karlice u grupi žena obolelih od karcinoma endometrijuma.

Naša studija je pokazala da tehnika mapiranja limfnih čvorova stražara kod pacijentkinja sa ranim karcinomom endometrijuma predstavlja pouzdan i validan postupak koji sa visokom verovatnoćom odražava status limfnog sistema male karlice u ovoj specifičnoj grupi žena. Na ovaj način se rizik za postojanje regionalnih metastaza može individualno proceniti kod svake žene i pojedinačno odrediti potreba za kasnijom postoperativnom terapijom.

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GYNECOLOGIC ONCOLOGY

SURVIVAL OF ADVANCED STAGE HIGH-GRADE SEROUS OVARIAN CANCER PATIENTS: CHALLENGES FOR THE FUTURE

Igor Aluloski[1], Mile Tanturovski[1], Gordana Petrushevska[2], Rubens Jovanovic[2], Slavica Kostadinova Kunovska[2]

1 - Department of Gynecologic Oncology, University Clinic of Gynecology and Obstetrics Skopje, North Macedonia

2 - Institute of Pathology, Medical Faculty, University "Ss. Cyril and Methodius" Skopje, North Macedonia

Ovarian cancer is the fifth leading cause of cancer deaths and has the highest mortality rate among gynecologic cancers in women in North America and Europe. For this 2019, in 22,530 women in the United States ovarian cancer will be diagnosed and that 13,980 deaths from this disease will occur this year.

AIM: The primary objective of the study was to evaluate the overall survival of women with advanced stage (Stage IIIA-IV) high-grade serous ovarian cancer in Macedonia as well as to analyze the correlation between E-cadherin/ beta-catenin expression and clinical and pathohistological features and overall survival (OS) in advanced-stage serous ovarian carcinoma (SOC).

MATERIALS AND METHODS: The study was a cross-sectional medical record review of patients diagnosed with advanced stage HGSC in period between 2009 and 2015. We conducted immunohistochemical analysis in tumor specimens from patients to determine the expression of E-cadherin and beta-catenin. The data were analyzed. Survival was calculated using the Kaplan-Meier method.

RESULTS: A total of 81 eligible patients were identified and included in the study. The average overall survival in the studied cohort was 46.59 months. Patients that were optimally debulked and patients that had a platinum-free interval larger than 12 months had significantly longer survival in the current series. Low frequency of expression and weak expression of E-cadherin have been confirmed as independent factors for poorer overall OS of patients with advanced stage HGSC. We detected increased expression of beta-catenin in patients with FIGO Stage III or IV. The positive expression of beta-catenin was associated with shorter average survival.

CONCLUSION: Optimal surgical debulking and platinum sensitivity were associated with significantly better overall survival. Negative E-cadherin expression seems to predict unfavorable clinical outcome in these patients, equal to higher FIGO stage and residual tumor volume after primary surgery. Negative E-cadherin expression emerges as a significant independent predictor for poorer OS. Beta-catenin expression is associated with poorer prognosis in patients with serous ovarian cancer. The unraveling of the molecular mechanisms behind the pathogenesis of ovarian cancer could lead to improvement in the treatment modalities which in turn could improve survival.

ABORTED RADICAL HYSTERECTOMY - WHEN AND WHY?

ABORTIRANA RADIKALNA HISTEREKTOMIJA KOD CERVIKALNOG KARCINOMA – KADA I ZAŠTO?

Goran Dimitrov

Univerzitetska Klinika za ginekologiju i akušerstvo Skopje, Severna Makedonija

Incidenca cervikalnog karcinoma u svetu je približno 500 hiljada, od kojih su skoro 4/5 u srednje i nisko razvijenim zemljama. Većina ovih žena su dijagnosticirane u ranim kliničkim stadijumima kada je procenat izlečenja veoma visok i ovi rani stadijumi (IA2 do IIA) karcinoma cerviksa mogu biti tretirane radikalnom histeroktomijom ili primarnom radioterapijom, sa sličnim rezultatima (5-godišnje preživljavanje od 87 % do 92 %). Benefiti hirurškog tretmana uključuju simultanu limfadenektomiju za hirurški stejdžing sa mogućim terapeutskim benefitom, prezervacijom ovarijalne funkcije kod premenopauzalnih žena i bolja koitalna funkcija. Ipak određeni broj žena tretirane primarno hirurški zahtevaće adjuvantnu post operativnu hemoradijaciju, zbog nalaza koji donose veći rizik za rekurencu , a to su proširenja na limfnim čvorovima, invazija parametra i proširenje karcinoma u karlici. Mnogi hirurzi, kako bi izbegli kombinirani morbiditet ovih dva tretmana, prekinuli bi radikalnu histerektomiju i to se naziva "abandoned" ili "aborted" radikalna histerektomija. Kad je bolest proširena (pozitivni limfni čvorovi - intraoperativno), u literaturi postoji podatak da se radikalna histerektomija na globalnom nivou prekida (abortira) negde u oko 8-10 % slučajeva. Ova oblast u ginekološkoj onkologiji je sa velikom kontraverzijom, i ne postoji konsenzus u vezi najboljeg menadžmenta bolesti.

Jedan od prvih izveštaja je Bremer-ov (1992 godine) koji kaže da menadžment tretmana kod napuštene (prekinute) ili kompletirane radikalne histerektomije - da su rezultati isti i komparabilni sa drugim izveštajima, a da su sa veoma malim morbiditetom. Leath i saradnici (2004 godine) saopštava da mali procenat ovih pacijentkinja (8%) koje su bile u ranom stadujumu cervikalnog karcinoma i imali abortiranu radikalnu histerektomiju, imaju favorizirачku prognozu sa postoperativnom radijacionom terapijomi i da abortirana radikalna histerektomija ne donosi značajno povećani procenat komplikacija.

U radu Garga i saradnika (2010 godine) pregled literature nije doneo zaključak da postoji razlika u preživljavanju koja je veća od 10 procenata izmedžu abortirane i kompletirane radikalne histerektomije. Iako su urinarne komplikacije kao disfunkcija vezike urinarije i fistule bile karakteristične za kompletiranu grupu radikalne histerektomije, a komplikacije u vezi zračenja, kako što su radijacioni cistitis, proktitis i nekroza kostiju bile primarne u grupi abortiranih radikalnih histeroktomija. Ziebarth i saradnici (2012 godine) zaključuju da kompletiranje radikalne histerektomije i limfadenektomija smanjuje zračnu ekspoziciju pacijentkinje, bez ugroženja bezbednosti ili ishoda u današnjoj modernoj eri adjuvantne hemoradijacije. Ali ipak daju svoje mišljenje da kod pacijentki sa kliničkim ranim stadijumom cervikalnog karcinoma i pozitivnim nalazom na lifnim čvorovima intraoperativno - da se odluka treba doneti "individualno". Jedna od najnovijih studija je studija Barquet-Munoz i saradnika(2012 godine) koja je hipotetički generirano došla do zaključka da je kod pacijentkinja sa cervikalnim karcinomom kod kojih je radikalna histerektomija prekinuta zbog pozitivnih limfnih čvorova, ne postoji razlika u preživljavanju ili disease free intervalu nasuprot grupe pacijentki sa sistematskom limfadenektomijom i odstranjenjem tumora a posle čega je sledio adjuvantni tretman sa konkomitantnom radio- hemoterapijom. Na Operativnom odeljenju 2, na Univerzitetsko Ginekološko-akušerskoj Klinici u Skoplju u periodu od 2008 do 2018 godine, na 181 urađenih radikalnih histerektomija bilo je 8 prekinutih (abortiranih) radikalnih histerektomija. Jedna od njih je izgubljena za follow-up, a sedam od njih su komparirane sa sedam randomiziranih pacijentkinja Stage IIIA FIGO. I kada se govori o komlikacijama za ove dve grupe - one su slične, međutim preživljavanje još uvek nije komparirano.

Zbog nemogućnosti sprovođenja prospektivne randomizirane studije koja bi odgovorila na ovo pitanje, skoro sva istraživanja daju zaključak da su ove dve opcije u mogućnosti (kompletiranje ili prekid radikalne histeroktomije) kod tretmana cervikalnog karcinoma i moraju biti objašnene i u saglasnosti sa voljom pacijentkinja tokom predoperativnog savetovanja.

THE IMPLEMENTATION OF LAST GUIDELINES FOR P16 USE IN ROUTINE PRACTICE

Snježana Frković Grazio

University Medical Center Ljubljana, Division of Gynecology, Department of Pathology, Ljubljana, Slovenia

The purpose of the surgical pathology report is to provide the diagnosis of the disease so that the clinician can make a management decision. The report should be clear, concise and unambiguous. The diagnostic interpretation of H&E stained cervical biopsies is subject to substantial variability between readers. The aim of standardization in diagnostic process is to reduce the rate of under- or overtreated patients.

The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions (LAST) was consensus process that was led by a steering committee and involved five working groups which consisted of experts in the field. The draft recommendations were available for public consultation, presented, finalized and voted in 2012 at the LAST Consensus Conference. The use of two-tiered system (LSIL / HSIL) across all LAT sites in both sexes was recommended, which may be further qualified with the appropriate –IN terminology. p16INK4a immunohistochemistry (IHC) was selected as the preferred biomarker for use in cervical lesions with precise guidelines regarding how and when to use this biomarker in diagnostic process in cervical pathology. The guidelines are against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, CIN 1 or CIN3.

According to the LAST guidelines p16INK4a immunohistochemistry should be used for:

1. differentiating HSIL from benign mimics (immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cut…)
2. if a diagnosis of CIN2 is considered - to help clarify the situation
3. in the case of professional disagreement
4. in cases of high-risk colposcopic referral situations where H&E is interpreted as LSIL or lower (cases with high risk for missed HSIL)

According to the guidelines any identified p16-positive area (strong and diffuse block-positive reaction) must meet H&E morphologic criteria for a high-grade lesion to be interpreted as such but the recommendations do not give us any technical guidelines regarding how to assure this in a small biopsy sample if IHC should not be routinely performed in adjunct to H&E staining.

In our laboratory we have developed our own standard protocol for sectioning of the cervical biopsies. All tissue fragments (up to 4) are processed together in one cassette and embedded in one paraffin block (if larger than 3 mm, bisected). Only if multiple mucoid very small fragments are present beside clearly visible tissue samples, these are processed (between layers of foam sponge in mesh bags) and embedded separately. At every 100-200µm (depending on quantity of the tissue) three sections are picked up with paint brush, float on the surface of the 37ºC water bath and each of them float on separate glass slide for IHC. Paraffin block is cut through-out – at each level three sections are picked up on three different glass slides for IHC. In this way usually one or up to three sets of three slides are prepared, each slide with up to six levels. The slides with paraffin sections are put in a 65°C oven for 20 minutes (so the wax just starts to melt) to bond the tissue to the glass and all slides are H&E stained. In this way we have three „copies“ of H&E slide with virtually exactly the same morphology. If p16 IHC staining is needed the slide is destained and IHC staining is performed.

This protocol is the only one which can give us optimal correlation between morphology and IHC result and in this way reduce the rate of under- or over diagnosed cases of clinically relevant HG-SIL lesions.

TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASES AT THE TERTIARY UNIVERSITY AFFILIATED CENTER – OUR EXPERIENCES

Saša Kadija

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia

Introduction: Gestational trophoblastic disease (GTD) encompasses a group of pregnancy-related disorders arising from placental trophoblastic tissue after normal or abnormal fertilization. The WHO classification of GTD includes hydatidiform mole – partial and complete, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and miscellaneous and unclassified trophoblastic lesions. GTD exhibit specific and sensitive serum marker – b-hCG. They have a varying potential for local invasion and metastases, according to which they are divided into the low-risk GTD and gestational trophoblastic neoplasia (GTN). In general, GTN respond well to chemotherapy. These disorders are rare, with the incidence varying among different geographic regions, which poses the need for their centralized treatment at the certified and experienced centers.

Aim: To assess the prevalence, clinical characteristics and treatment outcome of gestational trophoblastic diseases (GTD) at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia.

Patients and Methods: Medical records of women diagnosed with GTD at the Clinic for Gynecology and Obstetrics from January 2014 to June 2019 were retrospectively reviewed. Disease diagnosis, treatment and follow-up data were analyzed.

Results: There were 39 patients diagnosed with GTD at the Clinic for Gynecology and Obstetrics during this period. Twenty-two patients had hydatiform mole (21 partial and one patient complete mole); all were treated with uterine evacuation and followed-up until normalization of b-hCG levels. There were no GTN recorded in this group of patients. Eight patients were diagnosed with invasive mole; seven patients received chemotherapy (CT) – 5 single agent and 2 patients second line combination EMA-CO CT. There was one hysterectomy done at patients' request. All are being followed-up with no evidence of relapse or progression. There were six patients diagnosed with choriocarcinoma; 4 patients had undergone hysterectomy prior to admission to the Clinic; all of them received combination EMA-CO CT; 2 patients diagnosed with choriocarcinoma at the Clinic were treated with combination EMA-CO CT. All the patients achieved remission and are being followed-up with no sign of relapse. PSTT was encountered in 3 patients – the first one underwent hysterectomy and was lost to follow-up; the second patient underwent hysterectomy and received combination EMA-EP CT; she is followed-up regularly and shows no sign of relapse. The third patient was diagnosed with PSTT after hysterectomy performed for the pelvic tumor; metastases were confirmed within pelvic lymph nodes and in the lungs; she was treated with EMA-EP combination HT postoperatively. After 4 years of follow-up she was free of the disease; she died of gastrointestinal bleeding of unknown cause.

Conclusion: GTD are rare and specific disorders, sensitive to CT, with high curability rate, therefore demanding treatment by specialized team consisting of experienced gynecologic oncologist, pathologist and radiologist. The formation of the National treatment center and National registry of GTD as well as establishment and maintenance of collaboration among institutions dealing with the problem of GTD is of paramount importance.

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PARP INHIBITORS IN OVARIAN CANCER THERAPY - THE HEALING PATH

PARP INHIBITORI U TERAPIJI OVARIJALNOG KARCINOMA

Ivana Likić Lađević

Klinika za ginekologiju i akušerstvo, Kliničkog Centra Srbije

Karcinom jajnika je sedmi vodeći uzrok smrti od karcinoma kod žena, dok je vodeći uzrok smrti kod žena obolelih od ginekoloških maligniteta. Standardizovane stope incidencije raka jajnika su dvostruko više u razvijenim (9,3/100 000) nego u slabo razvijenim (4,9/100 000) regionima sveta. Srbija se u 2010. godini nalazila u grupi zemalja Evrope sa visokim stopama oboljevanja i smrtnosti od karcinoma jajnika. U 90 do 95% svih slučajeva je epitelijalni ovarijalni karcinom. Više od 70% žena se javlja u poodmaklomstadijumu dolesti koji zahvata gornji abdomen (FIGO stadijum III/IV), zbog nepostojanja ranih simptoma iefektivne skrining strategije. Primarni tretman je citoreduktivna hirurgija praćena sa hemoterapijom baziranom na platini i taksanu. Citoredukcija na manje od 1 cm rezidualne bolesti nakon hirurgije je nezavistandobar prediktor za prognozu. Oko 80% pacijentkinja ima inicijalno dobar odgovor na započetu hemoterapiju. Ipak dugoročno preživljavanje je jako retko zbog pojave rekurentne bolesti i rezistencije na primenjenu terapiju. To nameće potrebu da se istraži genetski mehanizam razvoja i rezistencije tumora kako bi se primenilaindividualizacija i optimizacija terapije.

Zbog toga nove strategije u tretmanu koje ciljaju specifičnu proliferaciju tumora i mehanizam preživljavanja tumora su neophodne da unaprede ishod terapije. Target terapija je novi tip terapije karcinoma koja koristi lekove ili neke druge supstance da identifikuje i napadne kancerske ćelije a da u isto vreme što manje ošteti normalne ćelije. Ova terapija deluje na procese koji se dešavaju unutar ćelije. Cilj terapije da se utiče na rast, deobu, sopstvenu reparaciju i sposobnost interakcije karcinomskih ćelija sa drugim ćelijama.

PARP inhibitori su indikovani kao monoterapija u terapiji održavanja kod odraslih pacijentkinja sa relapsirajućim, osetljivim na platinu, *BRCA* mutiranim (germinativnim i/ili somatskim) seroznim epitelijalnim karcinomom jajnika, jajovoda ili primarnim peritonealnim karcinomom visokog stepena koji su postigli odgovor (potpuni ili delimičan) na hemoterapiju baziranu na platini. *PARP* je familija nuklearnih proteina sa enzimskim osobinama koji su potrebni za efikasnu popravku prekida jednolančane *DNK*, a važan aspekt *PARP*-indukovane popravke zahteva da, nakon modifikacije hromatina, *PARP* sebe auto-modifikuje i odvoji se od *DNK* da bi olakšala pristup enzimima za popravkuputem uklanjanja baza (*BER*). Kada se *PARP* inhibitori vežu za aktivno mesto na *PARP* vezan za *DNK*, oni sprečavaju disocijaciju *PARP*, zarobljava je na *DNK*, i time blokiraju popravku. U ćelijama koje se umnožavaju (replikuju) to dovodi do prekida dvostrukog lanca *DNK* (*DSB*) kada replikaciona viljuška stigne do *PARP-DNK* adukta. U normalnim ćelijama, homologna rekombinaciona popravka (*HRR*), za koju su potrebni funkcionalni *BRCA 1* i *2* geni, efikasno popravlja ove prekide dvostrukog lanca. U odsustvu funkcionalnog *BRCA 1* ili *2*, *DNK* ne mogu biti popravljeni putem *HRR*. Umesto toga, aktiviraju se alternativni putevi kod kojih postoji veća verovatnoća za javljanje greške, kao što su put za spajanje nehomolognih krajeva (*NHEJ*), što dovodi do povećane nestabilnosti genoma. Nakon nekoliko ciklusa replikacija, nestabilnost genoma može doći do neodrživih nivoa i dovesti do smrti ćelije karcinoma, zbog toga što ćelije karcinoma imaju više oštećene *DNK* u odnosu na normalne ćelije.

Kod in vivo modela BRCA deficijencije, primena PARP inhibitora nakon terapije platinom dovela je do odlaganja progresije tumora i povećanja ukupnog preživljavanja u poređenju sa primenom terapije platinom bez PARB inhibitora.

Prvi rezultati kliničke aktivnosti PARP inhibitora zabeleženi su kod pacijenata sa *BRCA* mutacijama u fazi i istraživanja u *singl* terapiji olaparibom (prvi lek koji je odobrila *FDA - Food and Drug Agency*). Bilo je uključeno 50 pacijentkinja sa *BRCA* mutacijama. Dvadeset pacijentkinja je imalo parcijalni (*PR*) ili kompletni (*CR*) odgovor korišćenjem kriterijuma za solidne tumore *RECIST* (*Response Evaluation Criteria in solid tumors*). Tri pacijentkinje su imale stabilnu bolest (*SD*) više od 4 meseca. To sve rezultuje kliničkim benefitom od 46% (23/50). Srednje vreme trajanje odgovora je bilo 28 meseci.

SPECIFICATIONS OF CERVICAL ADENOCARCINOMA IN RELATION TO SQUAMOUS CELL CARCINOMA

OSOBENOSTI ENDOCERVIKALNOG ADENOKARCINOMA U ODNOSU NA SKVAMOZNI KARCINOM GRLIĆA MATERICE

Radomir Živadinović

Ginekološko akušerska klinika Niš

Učestalost adenokarcinoma grlića materice u odnosu na skvamozni tip je manja i iznosi oko 5 do 15% (češće kod žena Jevrejske populacije). Poslednji epidemiološki podaci govore da je incidenca ovog tipa karcinoma u porastu, naročito u populaciji žena mladjoj od 40 godina. Prema poslednjim podacima jedne veće studije radjenje u Švedskoj u odnosu na period kada je citologija uvedena u skrining cervikalnog karcinoma, incidence adenokarcinoma je sa 7% povećana na 25,7% i taj procenat u komparaciji mladjih pacijentkinja je povećan tri puta. Najveći procenat adenokarcinoma grlića materice je *HPV* pozitivan i to pre svega *HPV* 18 i 45 u oko 77%, dok je *HPV* 16 pozitivnost prisutna u oko 15%. Za razliku od adenokarcinoma, skvamozni tip je najčešće *HPV* 16, 31, 33 pozitivan. Razlog za ovakvu distribuciju treba tražiti i u različitosti u filogenetskom stablu samog virusa i vrsti odnosno poreklu epitela tj lokalnom virusnom tropizmu. U odnosu na skvamozne karcinome, procenat *HPV* pozitivnih adenokarcinoma je nešto manji. Statistički gledano nešto više od 10% endocervikalnih adenokarcinoma je HPV negativno. Jedan od razloga ovakve distribucije treba tražiti u heterogenosti podtipova adenokarcinoma, od kojih su neki podtipovi *HPV* negativni i imaju drugačiju etiopatogenezu i faktore rizika.

2014. Svetska zdravstvena organizacija *WHO*, je dala novu klasifikaciju endocervikalnih adenokarcinoma koja je i dalje aktuelna (Tabela 1). Najčešći podtip adenokarcinoma je uobičajni, *usual type* adenocarcinoma koji je najčešće *HPV* pozitivan, manje agresivan sa boljom prognozom u odnsou na ostale podtipove. Drugi podtip su mucinozni adenokarcinomi koji obuhvataju (*gastric, intestinal, signet-ring cell*) tip , koji se redje *HPV* pozitivni, agresivniji su i imaju lošiju prognozu. Medju njima se posebno izdvaja Gastrični tip koji je najagresivniji i *HPV* negativan. Za razliku od *HPV + usual* adenokarcinoma, gde je *disease-free survival (DFS)* 74%, kod gastričnog tipa je duplo manji i iznosi 38% . Gastrični tip se u odnosu na *usual* brže širi ekstracervikalno tako da je u momentu dijagnoze 60% stadijum bolesti veći od II, za razliku od *usual* tipa gde se bolest detektuje u I stadijumu u preko 80%. Sem gastričnog u grupu *HPV* negativnih izdvajaju se *clear cell* i mesonephroidni tip.

Od drugih podtiva adenokarcinoma treba spomenuti *villoglandular carcinoma, endometrioid carcinoma, clear cell carcinoma*, serozni, mezoephroidni i ostale redje podtipove kao što je mešoviti neuroendokrini. Viloglandularni tip ima najbolju prognozu, HPV je pozitivan kao i najveći procenat mucinoznih karcinoma i češći je kod mladjih pacijentkinja. Serozni i *clear cell* tip pokazuju *HPV* pozitivnost u oko 30% dok je endometrijalni tip *HPV* pozitivan u samo 13%.

Tabela 1. 2014 *World Health Organization (WHO) classification of glandular tumors of the uterine cervix*

Glandular tumors and precursors
Endocervical adenocarcinoma, usual type
Mucinous carcinoma, NOS
Gastric type
Intestinal type
Signet-ring cell type
Villoglandular carcinoma

Glandular tumors and precursors
Endometrioid carcinoma
Clear cell carcinoma
Serous carcinoma
Mesonephric carcinoma
Adenocarcinoma admixed with neuroendocrine carcinoma

Zahvaljujući poznavanju ovih karaktreistika u odnosu na infekciju humanim papiloma virusa, *HPV* test može poslužiti kao dobar parametar u diferencijalnoj dijagnozi različitih podtipova adenokarcinoma grlića materice. Imunohistohemijski marker i to pre svega *p16 INK* i *CEA*, kao i čitav panel ostalih markera pre svega *Ki 67*, može takodje pomoći u njihovoj boljoj diferencijaciji. *HPV* pozitivni tipovi adenokarcinoma, kao što je *usual* tip, su tako *p16 INK* pozitivni a marker diferencijacije *CEA* negativni za razliku od *HPV* negativnih, u koji spada gastrični tip, koji su *p16 INK* negativni a *CEA* izrazito pozitivni. Za razliku od gastričnog tipa, *clear cell* karcinom je *CEA* negativan, što može takodje biti od pomoći u diferencijalnoj dijagnozi. Imunohistohemijski marker *p53* takodje može biti koristan u diferencijalnoj dijagnozi jer su vrednosti ovog markera najčešće povećani kod *HPV* negativnih adenokarcinoma kao što je gastrični i intestinalni za razliku od *usual HPV* pozitivnog tipa gde je ovaj marker pozitivan u samo 3% slucajeva.

Dijagnoza adenokarcinoma grlića materice je teška, tako da standardne dijagnostičke procedure, citologija i kolposkopija, upravo najveći procenat lažno negativnih nalaza imaju kod ovog histološkog tipa karcinoma grlića materice. Prekancerozne promene na gladularnom epitelu se definišu kao adenokarcinom in situ, *AIS,* ili glandularne intraepitelne neoplazije *GIN*. S obzirom da se tadi o jednorednom epitelu, diferencijancija njihovog stadijuma i težine je teška kako citologu tako i patologu. Citolog ne može da se u klasifikovanju nalaza osloni na princip diferencijacije i zahvaćenosti debljine epitela već svoju citološku impresiju bazira na principu težine ćelijske atipije i trodimenzionalnom ćeliskom aranžmanu u specifične forme pseudoglandula , acinusa, nuklearne protruzije, perjanice, vatrometa itd. Ovakvi dijagnostički parametri povećavaju subjektinost u ekspresiji citologa što znatno smanjuje validnosti uspešnost u detekciji adenopromena. Sa druge strane problem u citološkoj dijagnostici predstavlja i kolekcioniranje i uzorkovanje ćelija s obzirom na njihovu fraginost i lak gubitak citoplazme. Poseban problem je nedovoljno uzorkovanje kao posledica uzimanja uzorka štapicem sa vatom. Svi ovi problemi su doveli do epidemioloških podataka koji pokazuju da uvodjenje citologije nije dovelo značajno do smanjenja incidence adenokarcinoma grlića materice. Senzitivnost citologije u detekciji *AIS* i invazivnog adenokarcinoma koji se navodi u literaturi se kreće od 44 do 63%.

U tom smislu sve veći broj radova ističe neophodnost uvodjenja *HPV* tipizacije u skrining cervikalnog karcinoma. Za razliku od citologije *HPV* test statistički značajno povećava senzitivnost detekcije adenokarcinoma. Najnovije studije pokazuju da primarno *HPV* skrining povećava detekciju adenokarcinoma u odnosu na citologiju za više od dva puta. *HPV* test može imati ne samo dijagnostičku već i prediktivnu, prognostičku vrednost. Tako pozitivan test na *HPV* 18 i 45, kada citološki nalaz ne pokazuje nikakve promene, može biti prvi indikator da će se u narednih 10 godina kod ovih pacijentkinja razviti adenokarcinom.

Na sreću adeno promene su u najvećem procentu udružene sa skvamoznim, u oko 70%, pa se otkriju kao uzgredni nalaz skvamoznih intraepitelnih lezija. Citološki nalaz kod adeno promena tako samo u 25% ukaže na sumnju da se radi o adenokarcinomu dok je u 64% patološki citološki nalaz adenokarcinoma od strane citologa opisan kao skvamozna lezija.

Kolposkopska dijagnostika je kod adenokarcinoma takodje veliki dijagnostički problem. Standardne kolposkopske slike AW epitela, mozika, punktacije, ne moraju biti prisutne kod adeno promena. Kolposkopska slika može pokazati samo uvećanje volumena grlića, atipiju krvnih sudova , konfluenciju i promenu koloriteta papila u smislu malih ostrvaca u cilindričnom epitelu. Ako je proces prisutan u endocervikalnim kriptama sam otvor kripte moze biti edematozan u vidu manžetne oko otvora žlezda ili može

biti u vidu *skip* lezija bez ikakvih kolpoksopskih manifestacija. Blizina prelazne zone u smislu kliničke težine promene kod adeno promena nije važna jer lezija može biti fokalna mala daleko od prelazne zone a da bude uznapredovali oblik adenokarcinoma. Svaki otvor endocervikalne kripte u suštini ovde može predstavljati posebnu zonu transformacije. Poseban problem su transformacione zone tip 3 sa nevidljivom prelaznom zonom.

Uzorkovanje i histološka dijagnotika adeno promena takodje može biti problematična i neadekvatna. Endocervikalna kiretaža adeno promena pokazuje nisku senzitivnost i može dati lažno negativne rezultate. Problem je u tome što kireta ne može da uzorkuje endocervikalne kripte koje su stromi. Upravo iz tih razloga je ekscizija u smislu *LOOP*-a ili klasične konizacije jedini dijagnostičko terapijski put kod citološke i kolposkopske sumnje na adeno promene grlića materice.

Sem etiopatogeneze i dijagnostike, adenokarcinomi se razlikuju od skvamoznih lezija i po faktorima rizika i social-epidemiološkim parametrima. Broj seksualnih partnera i pušenje su signifikantno povezani sa skvamoznim ali ne i adenokarcinomima. Faktori rizika adenokarcinoma su više slični faktorima rizika endometrijalnog karcinoma, kao što su: upotreba hormonske terpije, gojaznost, genetski faktori. Pušenje nije faktor rizika za adenokarcinome a upotreba barijerne kontracepcije nije faktor zaštite. Što se tiče *HPV* pozitivnosti, kao što smo već pomenuli, adenokarcinomi su u odnosu na skvamozne češće *HPV* negativni (20 do 30% *HPV* negativnih adenokarcinoma grlića materice).

Na osnovu svega možemo reći da adenokarcinomi endocerviksa predstavljaju heterogenu grupu promena koji se razlikuje od skvamoznih po etiopatogenezi, faktorima rizika i kliničkoj simptomatologiji. Ove promene predstavljaju i dalje sa razvojem nauke i tehnologije, enigmu koja zahteva individualizaciju u pristupu, kliničko iskustvo i dalje ispitivanje novih dijagnostičkih procedura, imunohistohemijskih i genetskih markera.

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NEONATOLOGY

NEWBORN FROM PREGNANCY COMPLICATED BY MATERNAL HYPERTENSION DISEASE

NOVOROĐENČE IZ TRUDNOĆE KOMPLIKOVANE HIPERTENZIVNOM BOLEŠĆU MAJKE

Tatjana Nikolić

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije

Trudnoća komplikovana hipertenzivnom bolešću majke rizična je kako za trudnicu, tako i za fetus u razvoju i buduće novorođenče. Akutna ili hronična uteroplacentarna insuficijencija nastala u sklopu hipertenzije, osnov je perinatalnog i neonatalnog morbiditeta, kao i mogućeg letalnog ishoda.

Povećan morbiditet, potreba za intenzivnom neonatalnom negom i lečenjem, kao i povećan mortalitet ove dece, uglavnom se smatraju posledicom nezrelosti i uteroplacentarne insuficijencije koja je rezultirala intrauterusnim zastojem rasta. Međutim, hipertenzivna bolest majke može i direktno uticati na fetus. Postoji čitav spektar različitih patoloških stanja novorođenčeta koja se direktno ili indirektno mogu dovesti u vezu za hipertenzijom tokom graviditeta. Među njima se najčišće navode porođajna asfiksija, respiratorni distres uzrokovan hiposurfaktozom, tranzitornom tahipnejom ili sindromom mekonijalne aspiracije, bronhopulmonalna displazija, nekrotični enterokolitis, sepsa i hematološki poremećaji.

U kojoj meri ova komplikacija trudnoće utiče na njihov dugoročni morbiditet i neurorazvojni ishod teško je reći, s obzirom na to da su hipertenzivna oboljenja u trudnoći heterogeni poremećaji. Pozivajući se na hipotezu "fetalnog porekla" brojnih različitih bolesti adultne dobi, više studija je povezalo hiperteziju majke u trudnoći sa povećanim rizikom njihove dece ka razvoju endokrinih, nutricionih, metaboličkih i kardiovaskularnih bolesti u adolescenciji. Rezultati studija koje su pratile neurorazvojni ishod ove dece značajno se razlikuju, od onih koje ukazuju na protektivni efekat hipertenzije po razvoj intraventrikularne hemoragije ekstremno nezrele novorođenčadi, do nalaza povećane učestalosti mentalne retardacije, cerebralne paralize i lošijeg neurorazvojnoj ishoda.

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PERINATOLOGY

CAN WE RECOGNIZE THE SIGNS OF FETAL HEART FAILURE ON TIME?

KAKO MOŽEMO PREPOZNATI SRČANU INSUFICIJENCIJU PLODA

Jelena Dukanac Stamenković

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije, Beograd, Srbija

Razvojem fetalne medicine, i pre svega ultrazvučne dijagnostike, fetus je postao pacijent. Dugo se smatralo da se srčana insuficijencija može proceniti samo kliničkim pregledom kod dece i odraslih. Za fetusa se smatralo da ima srčanu insuficijenciju samo onda kada je evidentan bio fetalni hidrops. Danas se međutim zna da srčana insuficijencija može postojati i pre pojave hidropsa, odnosno da je hidrops samo završni, najteži oblik SI.

Hidrops može biti kardiogeni, inflamatorni (infekcija) ili metabolički.

U odnosu na ponašanje srčanog mišića nakon porođaja ili kod odraslih nezrelost miokarda fetusa i «skučenost « komora od strane okolnih struktura

imaju za posledicu oslabljena relaksacija i povećana rigidnost komora kao i ograničen Frank-Starlingov mehanizam.

Brojne studije su pokazale da fetalno srce može da podigne ukupni *cardiac output* za svega 30-40% za razliku od adultnog koji može da poveća minutni volumen za 300-400% onda kada je to potrebno.

Kriterijumi srčane insuficijencije su: kardiomegalija, patološki venski protok, oslabljena srčana funkcija, redistribucija arterijskog protoka i hidrops.

Najčešći uzroci srčane insuficijencije su: teški poremećaji ritma (tahikardije, AV blok), anemija, srčane mane sa teškom valvularnom regurgitacijom, ne-srčane anomalije (dijafragmalna hernija, cistični higrom), twin-to-twin transfuzija (fetus recipient), cirkulatorne promene (npr. IUGR, prevremeno zatvaranje ductusa arteriosusa).

Pravovremeno prepoznavanje znakova srčane insuficijencije omogućava nam da primenom terapije ili planiranjem porođaja smanjimo stepen oštećenja i popravimo perinatalni ishod.

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NEW LOOKS IN HYPOXIA PREVENTION THROUGH FETAL PROGRAMMING

Miroslava Gojnić Dugalić

Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Belgrade, Serbia

Understanding fetus condition, time for preventing when fetus pervades the limits of its possibilities. During the development and growth of all organs, including fetal brain, oxidative stress and negative effect of free radicals present a drastic negative effect in the fetal brain development and later problems in the growth, development, neurological, psychological and intellectual advancement of children. Brain of both fetus and neonate has higher oxygen demand than in adults.

Methodology & theoretical orientation: Asphyxia is hypoxia with acid-base imbalance. Compensatory mechanisms of fetal adaptation and adjustment to effects of oxidative stress are crucial for fetal programming, and should be in mind all the time. Analyzing women cases from 2013 to 2018, with all kinds of diabetes, fetus as IUGR or macrosomia, we noticed that adaptation of fetus has limitation from genetic aspect and surroundings with which we can interfere. There is a close relation between: clinical pictures, Doppler flow, gaining body weight of fetus during last trimester, histopathological and biochemical response, inflammation and oxidative stress. We have analyzed neonatal intensive care, as well as the children that are 5 years old now.

Findings: There were no complications in newborns, with normal oxygen and acid-base status, considering neurological development. In clinical conclusion & significance: Fetal programming, as a part of modern humanity trend for decreased morbidity and mortality of the population, presents an area of special interest for perinatologists. Clinical observation of maternal conditions, placental analysis, uteroplacental circulation analysis, as well as their secondary manifestations to the growth and development of the fetus, are the foundation for timely reaction and prevention of complications in both mother and fetus as well as neonate later. That is the goal of every perinatologist, as well as the future of newborns.

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IMMUNOMODULATORY EFFECT OF PROGESTERONE-INDUCED BLOCKING FACTOR (PIBF) IN PREGNANCY

IMUNOMODULATORNI EFEKAT PROGESTERENOM INDUCIRANOG BLOKIRAJUĆEG FAKTORA (PIBF) U TRUDNOĆI

Igor Hudić

Department of Obstetrics and Gynecology, University Clinical Medical Center, Tuzla, Bosnia and Herzegovina

Preterm birth is the leading cause of perinatal morbidity and mortality and the vast majority of mortality and morbidity relates to early delivery before 34 weeks.

In the presence of progesterone, lymphocytes of pregnant women release a protein, progesterone induced blocking factor (PIBF), which mediates the immunomodulatory and anti-abortive effects of progesterone.

The aim was to analyze the maternal serum PIBF concentration with regard to the prediction of preterm birth and compare serum concentrations of progesterone, estradiol, anti-inflammatory and pro-inflammatory cytokines and serum PIBF concentration in women with threatened preterm delivery who were on dydrogesterone supplementation with those of women with threatened preterm delivery who were not on dydrogesterone supplementation.

The study population consisted of 284 pregnant women in 24-28 gestation weeks aged from 18–35 years recruited in the period 9th November 2008 - 31st July 2013.

After dydrogesterone treatment serum PIBF and progesterone concentrations significantly increased. Treated women had significantly higher serum levels of IL-10 and lower concentrations of IFNγ than controls. In samples that were taken within 5 days of labor, PIBF concentrations were significantly lower than in those obtained more than 5 days before labor. Among women that delivered preterm, median concentrations of urine and serum PIBF were significantly lower than in women who delivered at term.

Dydrogesterone treatment of women at risk of preterm delivery results in increased PIBF production. Preterm birth is predictable in the case of lower than normal pregnancy PIBF values within 5 days before labor and may be useful in the diagnosis and management of pregnancies at risk of preterm birth.

IMMUNE FACTORS OF PLACENTAL DYSFUNCTION - DIAGNOSTIC AND THERAPEUTIC DILEMMAS

IMUNOLOŠKI FAKTORI POREMEĆAJA PLACENTACIJE – DIJAGNOSTIČKE I TERAPIJSKE DILEME

Vesna Mandić Marković

Ginekološko-akušerska klinika "Narodni front", Beograd

Razvoj decidue nakon implantiranja blastociste u zidu uterusa podrazumeva značajno remodelovanje tkiva koje uključuje fizičke i humoralne promene imunih ćelija i esencijalno je za uspostavljanje uspešne trudnoće. Prilikom formiranja decidue ključna je i modulacija imunog odgovora majke koji postaje otporan na paternalne antigene. Neadekvatna formacija decidue u ranoj trudnoći može da uzrokuje infertilitet, neuspeh implantacije ili komplikacije trudnoće, kao što su ponavljani pobačaji, preeklampsija i preterminski porođaj.

Polovina slučajeva sa problemom implantacije/placentacije – ponovljenih neuspelih embriotransfera i ponavljanih pobačaja je posledica neadekvatnog imunološkog odgovora majke.

U dijagnozi imunoloških faktora koriste se različite metode, a ključno je određivanje *NK* ćelija - perifernih iz krvi (*pNK*) i iz endometrijuma (*uNK*). Primena *pNK* kao markera endometrijalne imune disfunkcije kontroverzna zbog odsustva veze između nivoa u krvi i endometrijumu. Dokazano je da je kod žena sa ponavljanim spontanim pobačajima povećan broj uNK ćelija; snižen procenat endometrijalnih CD8+T limfocita, uz povećanje B limfocita. U slučajevima neuspeha implantacije prisutna je neadekvatna aktivacija endometrijalnog imunog sistema.

Adekvatna i efektivna terapija u slučajevima ponovljenih problema implantacije i placentacije ne postoji, a primenjuju se krotikosteroidi, intravenski imuniglobulin (*IVIG*) i intralipid. *IVIG* deluje kao imunomodulator vršeći protekciju embriona od imunog sistema majke putem različitih mehanizama: smanjenje aktivnosti *NK* ćelija, povećanje aktivnosti supesorskih T ćelija, blokiranje funkcije anti-*HLA* antitela, prevencija aktivacije komplementa, *down* -regulacija stimulišućih receptora i *up*-regulacija inhibitornih receptora na površini različitih imunih ćelija. Intralipid, značajno jeftinija, sigurnija alternativa *IVIG*-u, je efektivan u smanjenju aktivacije *NK* ćelija i produkciji proinflamatornih citokina. Studije poređenja *IVIG* i intralipida nisu našle razliku u ishodu između njih. Različite studije nisu dokazale veći procenat uspeha trundoća uz primenu terapije, naročito u slučajevima kada je terapija primenjivana empirijski, te je primena kontroverzna.

IMPACT OF EPIDURAL ANALGESIA ON BIRTH DYNAMICS, COMPLICATIONS AND NEONATAL OUTCOME

UTICAJ EPIDURALNE ANESTEZIJE NA DINAMIKU POROĐAJA, POJAVU KOMPLIKACIJA I NEONATALNI ISHOD

Dragan Rakanović

Urgentni centar, UKC Republike Srpske

Uvod: Neuroaksijalne tehnike anestezije su najoptimalniji i najefikasniji vid analgezije u akušerstvu. Razvojem i modifikacijom tehnika epiduralne analgezije unazad 20 godina, kao i prilagođavanjem doza primijenjenih lijekova, optimalizovana je analgezija, uz istovremeno smanjenje instrumentalnog završavanja poroda ili carskog reza, uticaja na dinamiku porođaja, pojavu maternalnih komplikacija i neonatalni ishod. Moderna analgezija u akušerstvu se zasniva na promjeni niskih doza lokalnih anestetika i rastvora opioidnih analgetika sa ciljem minimiziranja rizika sistemske toksičnosti lokalnih anestetika, visoke ili totalne spinalne anestezije, kao i smanjenja hemodinamskih efekata i transfera lijekova kroz placentu. Razblaženi rastvori lokalnih anestetika smanjuju učestalost motornog bloka koji se može povezati sa instrumentalnim završavanjem porođaja ili sa pojavom oštećenja nerava nakon porođaja.

Epiduralna analgezija se povezivala sa većom učestalošću instrumentalnog završavanja porođaja. Kao razlog za smanjenje učestalosti instrumentalnog završavanja porođaja navode se niže koncentracija lijekova korištenih za epiduralnu anesteziju i modifikacija anesteziooloških tehnika, odnosno izvođenje takozvane kombinovane spinalno-epiduralne anestezije ili epiduralne anestezije sa punkcijom dure. Istovremeno se pominje i pojava motorne blokade kod upotrebe visokih doza anestetika, što se takođe povezuje sa većom učestalošću instrumentalnog završavanja porođaja.

Analizom 38 randomizovanih studija nije nađena veza između epiduralne analgezije i rizika za završetak porođaja carskim rezom, iako debate još uvijek postoje. Takođe, započinjanje epiduralne analgezije u ranoj fazi porođaja (ispod 4 cm dilatacije cervikalnog kanala) povezivalo se sa većom učestalošću završetka carskim rezom. Ali, randomizovane studije u poslednjoj dekadi nisu potvrdile nevedenu povezanost. Nasuprot tome, izražen bol u ranoj fazi porođaja, koji se povezuje sa makrozomijom, malrotacijom i disfunkcionalnim porođajem, vjerovatniji je razlog za povećanu učestalost završetka ovakvih porođaja carskim rezom.

Epiduralna analgezija i dinamika porođaja: Dok pojedine studije napominju da može doći do produžavanja prvog porođajnog doba, druge navode da se prvo porođajno doba skraćuje. Studije u poslednjih desetak godina pokazuju da je epiduralna analgezija započeta u ranoj fazi porođaja povezana sa skraćenjem prvog porođajnog doba. Ali, različiti rezultati mogu biti povezani sa metodološkim pristupom i analizom podataka. Metodološko određivanje vremena početka porođaja, pregled porodilje i kasnije utvrđivanje cervikalne dilatacije kada je već postignuta potpuna dilatacija (zbog efektivne analgezije i odsustva simptoma pritiska na rektum kao znak da je dilatacija potpuna), smanjenje ili povećanje kontraktilnosti uterusa pod dejstvom epiduralne analgezije predstavljaju faktore koji mogu dovesti do različitih podataka o dužini trajanja prvog porođajnog doba. Mada, generalno se smatra da epiduralna analgezija skraćuje prvo porođajno doba. Drugo porođajno doba biva produženo pod dejstvom epiduralne analgezije i to prosječno za 15 minuta, što nema značajnijeg kliničkog efekta. Ipak, produžavanje perioda aktivne ekspulzije ploda nosi sa sobom rizike kako za plod (mehanička ventilacija, sepsa, povrede plexus brachialis-a, encefalopatija, čak i smrtni ishod), tako i za majku (horioamnionitis, atonija, krvarenja, groznica) iako je taj rizik relativno mali. Svakako da su dodatne, kvalitetne randomizovane studije neophodne da se utvrdi stvarni uticaj na dinamiku poroda. Fetalna bradikardija se povremeno javlja nakon započinjanja epiduralne analgezije i povezana je sa smanjenom koncentracijom kateholamina (adrenalin) u cirkulaciji porodilje (koji djeluju kao tokolitici) zbog brzog obezboljavanja porodilje. Ovaj uticaj na neonatalni ishod ipak je još uvijek nejasan, ali konzervativne terapijske mjere najčešće su uspješne i rijetko dolazi do završetka porođaja carskim rezom.

Uticaj epiduralne analgezija na dojenje je takođe kontraverzan. U zavisnosti od studije, pominje se pozitivan ili negativan uticaj na dojenje ili da nema uticaja na dojenje. Značajniji faktori od epiduralne analgezije su veza majke i bebe, kontakt između majke i bebe i podrška dojenju. Kontrola bola, naročito nakon carskog reza, ima direktan pozitivan uticaj na uspješno dojenje i napredovanje u tjelesnoj težini djeteta.

Epiduralna analgezija u porođaju može da dovede do pojave povišene temperature koja sa svoje strane dovodi do lošijeg nenatalnog ishoda – nizak Apgar skor, hipotonija, epi napadi, asistirana ventilacija. Razlozi za povišenu temperaturu su neinfektivne prirode i zapaljenskih su karakteristika, zavise od koncentracije citokina u cirkulaciji i temperatura se javlja češće kod porodilja koja već imaju povišene koncentracije proinflamatornih citokina. Međutim, razlozi za pojavu temperature su ipak češći (i treba ih analizirati) zbog akušerskih razloga, a ne zbog epiduralne analgezije.

Podaci o efektima epiduralne analgezije na neonatuse i razvoj autizma i drugih neurokognitivnih poremećaja takođe su različiti. Pojedine opservacione studije napominju na mogućnost veze između ovih poremećaja i izlaganja porodilja anesteticima (računajući i carski rez), ali u ovom trenutku nema dokaza da se treba razmatrati promjena kliničke prakse tokom porođaja i carskog reza.

Studije sugerišu na pozitivan uticaj epiduralne analgezije na pojavu postpartalne depresije. Utvrđeni odnos bola i pojave depresije opštoj populaciji svakako se može primijeniti i u slučaju porodilja. Ipak, na pojavu depresije utiču i drugi faktori – ranija anksioznost ili depresija, gojaznost i trauma urogenitalnog trakta tokom porođaja.

Zaključak: Napredak i razvoj akušerske anestezije doveo je do značajnog smanjenja komplikacija tokom porođaja. Ipak, i dalje je neophodno poboljšavanje određenih segmenata, koja uključuju adekvatnu terapiju bola nakon porođaja i sprječavanje nastanka hroničnog bola, uticaj bola na razvoj perinatalne depresije, povišena temperatura izazvana epiduralnom analgezijom, uticaj epiduralne analgezije na trajanje drugog porođajnog doba i instrumentalno završavanje porođaja. Svakako da se individualizovanim pristupom porodilji, odnosno terapiji i intervencijama tokom porođaja svi navedeni problemi svode na minimum.

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VOLUME ULTRASOUND OF FETAL ANOMALIES

VOLUMNI ULTRAZVUK FETALNIH ANOMALIJA

Mesud Šehić

Kantonalna bolnica Goražde

Prema statistikama Svjetske zdravstvene organizacije 5-7% novorođenčadi se rađa sa nekom anomalijom. U antenatalnoj dijagnostici najšire primjenjivana neinvazivna metoda je ultrazvuk.Anomalije mozga i kraniofacijalne anomalije su među najčešćim anomalijama ploda. Kombinacija transvaginalnog pristupa i *3D* ultrazvučne tehnologije obezbjeđuje nam više informacija o razvoju fetalnog mozga i kongenitalnim anomalijama. Detaljni neurosonogram obezbjeđuje dragocjene podatke o morfologiji fetalnog mozga. Sistematski pristup sondom visoke rezolucije sa korištenjem multidimenzionalne tehnike prikaza može signifikantno povećati ukupnu stopu detekcije defekata centralnog nervnog sistema. Sonografska evaluacija fetalnog CNS je integralni dio prenatalnog skrininga fetalnih anomalija. Transvaginalni *3D* ultrazvuk uveden u 2000. godini je značajno pridonio razvoju fetalne neurosonografije. Prenatalna dijagnoza hipogenezije ili agenezije *corpus callosuma* može biti priličan izazov ,kada sonografski markeri nisu specifični ili prisutni za vrijeme rutinske egzaminacije u drugom trimestru. Odsutan *CSP*, kolpocefalična ventrikulomegalija i paralelan prikaz prednjeg roga mogu ukazivati na *ACC*. Gore nabrojani znaci nisu prisutni u većini slučajeva kod trudnoća manjih od 24 nedelje. Ventrikulomegalija je prisutna u 74,3%, a kolpocefalija u 68,6% slučajeva u kasnom drugom trimestru. S druge strane veoma lako se prikazuje *ACC* u sagitalnom i koronalnom presjeku. Grupa najfrekventnijih lezija obično nazvana „*Dandy Walker continuum* ili *spectrum*“ može imati sličan ultrazvučni izgled i prenatalna diferencijacija može biti izazov za ultrasoničare. Brojne studije izvještavaju da se neurosonografijom tačna dijagnoza može postići u preko 90% slučajeva kada je izvedena od strane eksperta. Rascjep usana i nepca je najčešća kraniofacijalna malformacija. Multiplanarni prikaz je najbolji za evaluaciju proširenosti rascjepa u prednji alveolarni greben. *3D* ultrazvuk nam omogućuje lakši prikaz retronazalnog trougla, izuzetno značajnog za dijagnozu rascjepa nepca u prvom trimestru. Evaluacija mandibule je veoma značajna jer su njene anomalije komponente više od 100 genetskih sindroma. Prisustvo ili odsustvo mandibularnog gapa prilično tačno može odrediti da li se radi o mikrognatiji.

U radu su detaljno obrađeni načini akvizicije, modovi renderiranja i alati koji se koriste u prikazu fetalnog mozga i lica. Prikazana je normalna anatomija i anomalije gdje je volumni ultrazvuk izrazito superioran u dijagnostici fetalnih anomalija, sa posebnim osvrtom na mediosagitalnu ravan mozga i anomalije koje se u istoj prikazuju, poput agenezije *corpus callosuma, Dandy Walker* sindroma, kao i diferencijalna dijagnoza promjena u posteriornoj *fossi*. Prikazani su normalno lice i nepce, kao i anomalije usana i nepca u prvom i drugom trimestru trudnoće.

Volumni ultrazvuk predstavlja veoma moćno „oružje“ u tačnoj dijagnostici kompeksnih fetalnih anomalija, ako je u rukama iskusnog eksperta.

„IN UTERO" FETAL THERAPY AS AN OVERVIEW AND ROMANIAN SINGLE CENTER EXPERIENCE

I.D.SUCIU[1], L.POP[2], O. D.TOADER[2,3], N. SUCIU[2,3]

[1] Department of General Surgery, Bucharest Clinical Emergency Hospital, Romania

[2] Department of Obstetrics and Gynecology, Polizu Hospital, National Institute for Mother and Child Health „Alessandrescu - Rusescu", Bucharest, Romania

[3] Department of Obstetrics and Gynecology, „Carola Davila" University of Medicine and Pharmacy, Bucharest, Romania

With an incidence of 1/2000, Spina Bifida is associated with a large spectrum of disabilities, being the most common congenital, non–lethal condition of the central nervous system. Although it can be diagnosed early in pregnancy, it can progress during fetal life due to the damage that occurs to local nerves and due to ventriculomegaly.

Prenatal open fetal surgery has been in practice for a number of years. There is evidence that prenatal surgery reduces the need for shunt placement and improves the outcome compared with postnatal classical surgery. The side effects of prenatal surgery are related to preterm birth and the pathologies associated with womb scar, which is a legacy for the rest of her life, including higher risk for all her future pregnancies. Minimally invasive prenatal surgery for spina bifida has occurred as an improved way of decreasing the rate of these complications.

Currently there are two techniques, one which requires laparotomy, but is minimally invasive to the womb, and a second one in which the surgery is being done percutaneously. This technique not only that so far have an improved outcome, but also allows vaginal delivery at term with no scar dehiscence reported so far.

In conclusion, although the results are promising, this technique does require continued refinement.

ADVANTAGES AND LIMITATIONS OF PRENATAL DIAGNOSTICS OF CONGENITAL HEART DEFECTS

Svetlana Vrzić- Petronijević

Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, University of Belgrade

Introduction. The advancement of technology allowed us to get an insight into fetal development and pathology, thus introducing the whole new specialty – fetal medicine. Specificity of fetal physiology and cardiovascular system require the multidisciplinary approach. On basis of pediatric cardiology, fetal cardiology has grown and nowadays it makes essential part of the fetal-maternal medicine. Congenital heart malformations are known to be among the most frequent birth defects occurring in about 3% of pregnancies, but are also responsible for at least 20% of infant deaths.. Modern prenatal care presumes regular ultrasound check-ups in order to eventually diagnose structural heart defects.

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. In case of congenital heart defects, there is two-step protocol for timely prenatal diagnosis: 1. evaluation of fetal heart anatomy during the second trimester anatomy scan and 2. fetal echocardiography performed by specially educated gynecologist – perinatologist and eventually specially educated pediatric cardiologist in case of established diagnosis, for evaluation of postnatal outcome, method of treatment, operational risks, prognosis and the remote effect of such treatment.

In case of complex cardiac anomaly with an unfavorable postnatal prognosis termination of pregnancy is an option defined by *Law on prevention and diagnostics of genetic diseases: Genetically caused anomalies and rare diseases* with no upper limit of gestational age.

Objectives were to evaluate the possibilities for prenatal fetal heart defects diagnostics in Serbia and how legislation, social issues and treatment availability influence the course of pregnancy after prenatal diagnosis.

Methods. We reviewed the medical records and fetal echocardiography findings of 9055 fetuses in Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia in period 1991 – 2014.

Results. Among 638 fetuses with congenital heart defects, 295 (46.2%) survived neonatal period. During early neonatal period died 68 (10.6%). Pregnancy was terminated in 258 (40.4%) cases.

Conclusions. Pregnancy termination is the most frequent choice in presence of legally defined medical indications.

FREE COMMUNICATIONS

MANAGEMENT OF INHERITED THROMBOPHILIA IN PREGNANT WOMEN, WITH OR WITHOUT THERAPY WITH LOW MOLECULAR WEIGHT HEPARIN - PROSPECTIVE ANALYTICAL STUDY

Stefan Dugalić[1,2], MD, Miloš Petronijević [1,2], MD, PhD , Aleksandar Stefanović[1,2], MD, PhD, Katarina Stefanović[1,2], MD, PhD, Svetlana Vrzić Petronijević[1,2], MD, PhD, Dejana Stanisavljević[2,3], MD, PhD, Zoran Vilendečić[1,2], MD, PhD, Milena Mitrović[1,2], MD, PhD, Jelena Dotlić[1,2] MD, PhD, Milena Perišić Mitrović[1], Miloš Radojević[1], MD, Danka Mostić Stanišić[1], MD, PhD, Branislav Milošević[1], MD, Dragana Božić[1], MD, Ivana Jovanović[1], MD

1 - Clinical Centre Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia

2 - Faculty of Medicine, University of Belgrade, Belgrade, Serbia

3 - Department for Medical Statistics and Informatics, Belgrade, Serbia

Background. Prophylactic use of low-molecular-weight heparin (LMWH) during pregnancy in women with hereditary thrombophilia is frequent concerning earlier recognized adverse pregnancy outcomes (APO) in those cases. Previous studies regarding LMWH prophylaxis for APO in women with inherited thrombophilia were performed in high risk patients with previous adverse health outcomes in medical, family and/or obstetric history. Literature data from meta-analysis studies have shown that LMWH may prevent recurrent placenta-mediated pregnancy complications. According to data of relevant studies in recent five years, we have seen that we cannot conclude that therapeutic effect of LMWH in pregnancies with hereditary thrombophilia are absolutely universal.

Our primary aim was to investigate the effects of LMWH prophylaxis on pregnancy outcomes in Serbian women with inherited thrombophilia.

Methods. In prospective analytical cohort study we included all referred women with inherited thrombophilia between 11 and 15 weeks of gestation and followed-up to delivery. Patients were allocated in group with LWMH prophylaxis (study group) and control group without LWMH prophylaxis. The groups were compared for laboratory parameters; Doppler flows of umbilical artery at 32^{nd}-34^{th} and 36^{th}-38^{th} gestational weeks, and for obstetric and perinatal outcomes.

Results. Mean resistance index of the umbilical artery Ri in 32-34 and 36-38 weeks of gestation were significantly higher in the control group compared to study group (0.71±0.02 vs. 0.64±0.02; and 0.67±0.05 vs. 0.54±0.08, respectively). Missed abortions, intrauterine fetal death, were statistically significantly more frequent in control group compared to the patients in study ($p<0.001$). The frequencies of fetal growth restriction and adverse pregnancy outcomes were significantly higher in the control group compared to the study group ($p= 0.008$ and $p<0.001$, respectively).

Conclusions. In our research we have concluded that the prophylaxis with LMWH has enabled better perinatal outcomes in pregnant women compared to those cases in which we did not use that kind of therapy.

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APPENDECTOMY AND ANAESTHESIA DURING PREGNANCY

APENDEKTOMIJA I ANESTEZIJA U TRUDNOĆI

Ilić-Mostić T,[1,2] Gunjić J,[2] Mostić Stanišić D,[2] Milenković D[2], Dugalić S

School of Medicine, University of Belgrade [1], Clinic for Obstetrics and Ginecology, Clinical Center of Serbia, Belgrade [2]

Sažetak:

Učestalost procedura apendektomije tokom trudnoće je 0,2-1.5%. Zbog toga je, u cilju bezbednosti majke i ploda, neophodno dobro poznavanje fizioloških promena u trudnoći, kao i i uticaja anestezije i operacije na fetus u razvoju. Kritični period tokom embrionalnog razvoja je period organogeneze, koji traje od 15. do 60. dana gestacije.

Poznato je samo pet lekova sa teratogenim dejstvom na ljudsku populaciju, a pri tome nijedan od njih nije anestetički agens.Većina anestetičkih lekova, uključujući intravenske indukcione agense, lokalne anestetike, opioide i mišićne relaksante mogu se bezbedno koristiti kod trudnica. Jedino je korišćenje benzodijazepina u prvom trimestru trudnoće još uvek diskutabilno, jer su istraživanja potvrdila dokaze o teratogenom riziku. Pored lekova, i drugi štetni faktori tokom anestezije, kao što su hiperkapnija, hipoksemija i hipotermija mogu biti teratogeni. Zbog toga je ključni cilj tokom anestezije u trudnoći održavanje normalnog parcijalnog pritiska kiseonika i ugljen dioksida u arterijskoj krvi trudnice, kao i adekvatan protok krvi kroz placentu.

Spontani pobačaji i prevremeni porođaj su najčešće komplikacije nakon operacije majke.

Zaključak: Svaku hiruršku intervenciju, pa tako i apendektomiju u anesteziji treba izbeći tokom prvog trimestra trudnoće, ili ukoliko je moguće - odložiti. Regionalna anestezija može biti bolji izbor od opšte zbog izbegavanja rizika od otežane intubacije i aspiracije, kao i manje izloženosti fetusa medikamentima. Tokom perioperativnog perioda nastaviti sa održavanjem intrauterine fiziološke sredine uz izbegavanje hipotenzije, hipoksemije, hipokapnije, hipotremije i acidoze.

Ključne reči: apendektomija i anestezija u trudnoći, asfiksija fetusa

Summary:

The incidence of appendectomy during pregnancy is 0.2-1.5%. The crucial period in the growth of the fetus is organogenesis, which happens between the 15th and 60th day of gestation.

To date, only 5 drugs are proven human teratogens and none of them is an anaesthetic agent. The majority of anaesthetics, including intravenous induction agents, local anaesthetics, opioids and muscle relaxants, may be used without any risk to the pregnant woman. Exceptionally, the use of benzodiazepine in the first trimester of pregnancy is still debatable as many studies confirm the presence of risks to humans. In addition to the teratogenic effect of drugs, attention should be paid to other teratogenic factors during anaesthesia, such as hypercapnia, hypoxemia and hypothermia. The aim of anesthesia in pregnant women is to maintain normal partial pressure of oxygen and carbon dioxide in arterial blood, as well as sufficient flow of blood to the placenta.

Conclusion: Anaesthesia and surgery should be avoided during the first trimester of pregnancy, or postponed, if possible. Regional anaesthesia might be preferable to general anaesthesia. It eliminates the risk of aspiration and difficult intubation, and also provides lower exposure of the fetus to medications. In perioerative period care should be taken to keep the intrauterine environment in physiological range, and to avoid hypotension, hypoxaemia, hypocapnia, hypothermia and acidosis.

Key words: appendectomy and anaesthesia during pregnancy, asphyxia of the fetus

PERIOPERATIVE AND EARLY POSTOPERATIVE COMPLICATION ANALYSIS IN PATIENTS WITH UTERINE MYOMAS: LAPAROTOMY VS. LAPAROSCOPIC APPROACH

ANALIZA PERIOPERATIVNIH I RANIH POSTOPERATIVNIH KOMPLIKACIJA U PACIJENTKINJA SA MIOMIMA UTERUSA OPERISANIH LAPARASKOPSKIM I KLSAIČNIM, ABDOMINALINIM PRISTUPOM

Ilić M.[1], Lacković M.[1], Stojanović M.[1], Veselinović A.[1], Mitić N.[1], Mihajlović S.[1,2]

[1] KBC „Dragiša Misović Dedinje “, Bolnica za Ginekologiju i akušerstvo, Beograd, Srbija
[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

Uvod: Miomi uterusa su najčećši benigni tumori ženskog reproduktivnog trakta. Po tipu, miomi su mogu podeliti na subserozne, intramuralne i submukozne. Prema lokalizaciji mioma, možemo ih podelit na miome fundusa, prednjeg zida, zadnjeg zida, istmikocervikalni miome i miome roga uterusa. U savremenoj kliničkoj praksi postoji više kliničkih pristupa rešavanju ove delikatne problematike, kako hirurških, tako i farmakoloških. Među hirurškim pristupima u poslednjim godinama najveći primat se daje minimalno invazivnoj hirurgiji. Miomektomija predstavlja standardu hirurišku proceduru u cilju prezervacije reproduktivne moći žene, a minimalno invazivni pristup nam daje mogućnost laparaskopskog i histeroskopskog pristupa, u zavisnosti od samih karakteristika mioma, kao i iskustva i veštine operatora.

Cilj rada: Procena intraoperativnik komplikacija, kao i ranih postoperativnih komplikacija kod pacijentkinja podvrgnutiv minimalno invazivnom i klasičnom, abdominalnom pristupu zbrinjavanja mioma uterusa.

Materijal i metode: Retrospektivnom studijom su obuhvaćene pacijentkinje sa miomima uterusa operisane u Bolnici za Ginekologiju i akušerstvo KBC “Dragiša Mišović” u toku 2018. i 2019. godine. U istraživanje je uključeno 63 pacijentkinja, podeljenih u dve grupe: grupu I od 39 pacijentkinje kojima je urađena abdominalna miomektomija i grupu II od 24 pacijentkinje kojima je učinjena momektomija laparaskopskim putem. Obrađeni su sledeći parametri: godine starosti, broj abortusa i porođaja, postojanje hipertenzije i dijabetesa, postojanje prethodne miomektomije, karakteristike mioma (tip, lokalizacija i dimenzije), lapraskopija i laparatomija po redu i vrsta laparatomije, iskustvo operatora, trajanje operacije, perioperativno krvarenje i transfuzije, parametri hemograma pre i posle operacije, trajanje postoperativne hospitalizacije, nalaz histopatološkog pregleda odstranjenog mioma i postoperativne komplikacije. Analiza perioperativnih komplikacija obuhvatila je ispitivanje pojave intraoperativnih i postoperativnih komplikacija, i to: lakših komplikacija poput postoperativne anemije, febrilnog stanje, pozitivne mikrobiološke kulture, i težih komplikacija poput proširenja obima operativnog zahvata, perioperativnog krvarenja, postoperativna ileusa, pojave hematoma na uterusu i u prednjem trbušnom zidu, dehiscencije operativne rane, bakteriemije posle operacije, relaparotomije, neplanirane histerektomije, produžene postoperativne hospitalizacije.

Rezultati: Od ukupno 63 pacijentkinje, kod ukupno 24 primenjen je minimalno invazivni pristup, kod 37 abdominalni, a kod 2 pacijentkinje učinjena je konverzija operativnog pristupa i one su zbrinute abdominalno. U pogledu ispitivanih perioperativnih komplikacija, između ispitivanih grupa nije bilo statistički značajnih razlika, kako u pogledu učestalosti pojedinačnih komplikacija, tako ni u pogledu ukupnih učestalosti pojave težih i lakših komplikacija. Od posmatranih komplikacija, kod ispitanica u prikazanom istraživanju su registrovane sledeće teže komplikacije: krvarenje, transfuzije i produžena hospitalizacija. Učestalost i količina perioperativnih transfuzija se nisu razlikovali između ispitivanih grupa. U obe grupe registrovane su sledeće lakše komplikacije: postoperativna febrilnost, anemija i cervikovaginalna infekcija, čija učestalost nije bila statistički značajno veća ni u jednoj ispitivanoj grupi.

Zaključak: pristup minimalno invazivnom i abdominalnom hirurškom zahvatu kod pacijentkinja sa miomima uterusa i učestalost njegovih komplikacija u ispitivanoj studiji zavisio je od adekvatnosti pristupa hirurškom zahvatu, u odnosu na kritičnost prema samim karakteristikama mioma, procenjenim komorbiditetima pacijentkinje i iskustvu operatura.

DEXAMETHASONE EFFECT ON DOPPLER BLOOD FLOW IN WOMEN AT RISK OF THE PRETERM DELIVERY

Svetlana Janković

Department of Obstetrics and Gynecology "Narodni front", Belgrade, Serbia; Belgrade University Medical School, Belgrade, Serbia

INTRODUCTION: Antenatal intramuscular administration of corticosteroids in women with the risk of preterm delivery is important to improve the production of the fetal lung surfactant.

AIM: The aim of this study was to compare the effects of antenatal administration of dexamethasone on fetal and uteroplacental circulation in pregnancies with the risk of preterm delivery.

MATERIAL AND METHODS: We evaluated thirty-two healthy pregnant women with singleton pregnancies considered at risk for preterm delivery, from 30 to 32 gestational weeks, with normal fetoplacental vascular resistance. We evaluated the effects of four doses of 6 mg dexamethasone applied intramuscular to the mother. The Doppler studies were performed on maternal uterine arteries, umbilical artery, fetal middle cerebral artery (MCA) just before dexamethasone administration and repeated 24 hours after completion of the therapy. The data were analyzed using analytical and descriptive statistical tests.

RESULTS: No significant change was observed in umbilical artery PI following dexamethasone therapy. Uterine artery PI was significantly different, while there were no significant differences in uterine artery RI. In the fetal middle cerebral artery(MCA) flow there was a significant decrease in PI 24 hours after the administration (p=0.0001).

CONCLUSIONS: Our results indicate significant decrease in fetal middle cerebral artery impedance a 24 hours after maternal administration of the dexamethasone. Further research and clinical studies including larger sample sizes or pregnancies are needed.

CERVICAL CARCINOMA WITH BILATERAL OVARIAN METASTASES AND RECCURENT VAGINAL BLEEDING INDUCED BY ORAL ANTICOAGULANT USE

PRIKAZ SLUČAJA: KARCINOM CERVIKSA UDRUŽEN SA POSTOJANJEM OBOSTRANIH OVARIJALNIH METASTAZA I REKURENTNIM VAGINALNIM KRVARENJEM INDUKOVANIM UPOTREBOM ORALNIH ANTIKOAGULANTNIH LEKOVA

Lacković M.[1], Stojanović M.[1], Ilić M.[1], Veselinović A.[1], Mitić N.[1], Mihajlović S.[1,2]

[1] KBC „Dragiša Misović Dedinje “, Bolnica za Ginekologiju i akušerstvo, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

Uvod: Karcinom cerviksa je najčešći ginekološki karcinom u svetskim razmerama. Dijagnoza ovog oboljenja se postavlja nakon histološke evaluacije bioptata uzetog prilikom kolposkopskog pregleda. Ukoliko se dijagnoza postavi u ranom stadijumu bolesti, najoptimalniji vid lečenja je hirurški. Kod uznapredovalih karcinoma cerviksa primenjuje se kombinovana hemo-radioterapija. Prognostički faktori uslovljeni su stadijumom oboljenja u kome se postavi dijagnoza.

Cilj rada: Procena stadijuma oboljenja karcinoma cerviksa, koji predstavlja najznačajniji indikator dugogodišnjeg preživljavanja i izbor adekvatne terapije kod pacijentkinje sa uznapredovalim karcinomom cerviksa.

Prikaz slučaja: Osamdesetogodišnja pacijentkinja tretirana oralnim antikoagulantim lekovima (OAL) usled kompleksnog kardiovaskularnih oboljenja (atrijalna fibrilacija, multipla valvularna insuficijencija, prisustvo koronarnog arterijskog stenta, hipertenzija) pregledana je od strane svog izabranog ginekologa zbog ponovljenog vaginalnog krvarenja u nekoliko navrata. Izabrani ginekolog uputio je pacijentkinju kardiologu u cilju remodelovanja terapije OAL. Pacijentkinja je primljena u našu bolnicu sa vredonsti INR 4. Ginekološkim pregledom je konstaovano postojanje erozija na površini grlića materice, a ultrazvučnim pregledom male karlice utvrđeno je postojanje obostrane adneksalne tumorske promene promera 5x5 cm, sa povišenim vaskularnim protocima i redukovanim indeksima otpora. Pacijentkinja je pre dvanaest godina podvrgnuta obostranoj mastektomiji i radioterapiji zbog karcinoma dojke. Obzirom na vaginalno krvarenje, PAPA i kolposkopija nisu inicijalno urađeni. Biohemijski tumorski marker za jajnik (CA125) bio je povišen (232 U/ml). Nakon korekcije antikoagulantne terapije, krvarenje se nastavilo. Biopsijom cervikalne mukoze patohistološki je utvrđeno postojanje slabo diferentovanog (G3) infiltrativnog adenokarcinoma. Snimci magnetne resonance su pokazali da ne postoji zahvaćenost drugih organa male karlice, kao ni udaljenih metastaza i potvrdili su postojanje prethodno ultrazvučno opisanih promena jajnika. Obzirom na sve prethodno prikulpljene rezultate analiza, pacijentkinji je dijagnostikovano postojanje karcinoma cervika stadijuma IIB u skladu sa FIGO klasifikacijom. Uzimajući u obzir stadijum oboljenja, prisustvo kardiovaskularnog oboljenja i starost pacijentkinje, multidisciplinarni onkološki konzilujum predložio je kombinovanu hemo-radioterapiju kao najbolji vid lečenja. Pacijetkinja je trenutno podvrgnuta prethodno pomenutom vidu lečenja, dobrog je opšteh stanja i redovno dolazi na zakazane kontrole. Preliminarni rezultati ukazuju da nema dalje ekspanzije malignog procesa.

Zaključak: Terapijske strategije za karcinom cerviksa ne bi trebalo da uključuju kombinovani pristup radikalne hirurgije i postoperativne radioterapije obzirom na značajan porast morbiditeta zabeleženog u literaturi i nepostojanje očiglednog uticaja na preživljavanje pacijenata. Neoadjuvantna radioterapija praćena radikalnom hirurgijom predstavljala bi kontraverznu alternativu prethodno navedenom. Kombinovana hemo-radioterapija predstavlja efektivan terapijski modalitet u lečenju adekvatno dijagnostikovanih pacijentkinja.

URETHRAL BULKING AGENTS IN TREATMENT OF URINARY STRESS INCONTINENCE

URETHRAL BULKING AGENTS U LIJEČENJU STRES INKONTINENCIJE

A. Mojsović

Odjel urologije, Opća bolnica Šibenik, Hrvatska

UVOD
Mid uretral sling (MIS) je zlatni standard preporučen od IUGA (Internatonal UroGynocological association) i EAU (Europian association of Urology) za liječenje stres urinarne inkontinencije (SUI), međutim brojni medijski i politički potencirani skandali povezani s *mesh* metodama dovode u fokus druge načine liječenja SUI. Napominjemo međutim da aktualni pravosudni epilozi nisu direktno povezani sa *sling* metodama liječenja SUI.

CILJ
Izvršiti analizu operacija liječenja SUI s *urethral bulking agents* (UBA) i pokazati njihovu učinkovitost.

METODOLOGIJA
Od 2.mjeseca 2017. uveli smo tehnike liječenja SUI s više UAB*:* „URODEX" , „UROLASTIC" i „UROLON". Analizirali smo protokole svih izvršenih operativnih zahvata od 2.mjeseca 2017. do 7.mjeseca 2019., kao i nalaze kontrolnih pregleda. Osnovni parametri su nam bili uspostava potpune kontinencije, trajanje kontinencije i incidencija nuspojava. Dobivene rezultate usporedili smo s dostupnim objavljenim studijama. Prvih osam (8) pacijentica operirane su u općoj anesteziji a sve poslije u lokalnoj anesteziji periuretralnim blokom 2 %-tnim lidokainom uz preoperativnu primjenu diazepama i ketoprofena. Kao antibiotska profilaksa korišten je gentamicin. Koristili smo tri različita materijala za *bulking*, jedan neresorptivni i dva resorptivna, kao i dva načina periuretralnog *bulking*- a, sa i bez lezije uretralne sluznice.

REZULTATI
Od 02.2017. do 07.2019. u OB Šibenik trideseti tri (33) pacijentice podvrgnute su operativnim zahvatima liječenja inkontinencije s UBA prema dvije metode, periuretralnog i intrauretralnog *bulking*-a. Kod svih pacijentica postignuta je potpuna kontinencija ili značajni napredak u kontroli inkontinencije.

ZAKLJUČAK
Liječenje SUI s UBA pokazalo se kao učinkovita i sigurna metoda za naše pacijentice, čak i nakon prethodno obavljenih drugih kirurških metoda liječenja SUI. *Mid uretral sling* je zlatni standard preporučen od IUGA i EAU za liječenje stres inkontinencije, ali obje organizacije u svojim G*uidelines* dopuštaju upotrebu UBA i preporučuju ih kao metodu odabira za određene skupine pacijentica. To su pacijentice s željom proširenja obitelji, pacijentice koje ne žele *sling* metode, pacijentice koje žele zahvat s nižom stopom rizika od komplikacija, pacijentice koje su ranije imale *sling* operacije i one pacijentice koje žele ili moraju izbjeći zahvat u općoj anesteziji. Kao nedostatak napominjemo u kraće postoperativno trajanje kontinentnosti i potrebu za ponavljanjem zahvata. Nedvojbene prednosti UBA metoda su izbjegavanje opće anestezije, kraće trajanje zahvata, skraćenje hospitalizacije i manji broj komplikacija, osobito za resorptivne UAB. Naši rezultati usporedivi su, a djelomično i bolji u komparaciji s rezultatima objavljenim u recentnim studijama.

PREVALENCE AND ANTIBIOTIC SUSCEPTIBILITY OF GENITAL MYCOPLASMA HOMINIS AND UREAPLASMA UREALITICUM IN A UNIVERSITY HOSPITAL IN MACEDONIA

E. Gjorgievska Nikolovska, A. Atanasova Boshku

University clinic for Gynecology and obstetric, University St. "Cyril & Methodist" – Skopje, R. Macedonia

BACKGROUND-AIM

The aim of this study was to obtain the colonization prevalence and antibiotic susceptibility of Mycoplasma hominis (M.H) and Ureaplasma urealyticum (U.U) in a university hospital in Macedonia. This was a retrospective study evaluating data of a total of 636, sexually active women with abnormal vaginal discharge who came in an outpatient office from 2010 to 2013 year.

METHODS

Samples who were obtained with cotton swabs were microbiologically analyzed for U. urealyticum and M. hominis, together with antimicrobial susceptibility to doxycycline, ciprofloxacin, ofloxacin, erythromycin, josamycin, pristinamycin, tetracycline, clarithromycin, azithromycin

RESULTS

Ureaplasma urealiticum was identified in 241 (37.8%) Mycoplasma hominis in 9 (1, 4%), and both Ureaplasma urealiticum and Mycoplasma hominis in 23(3, 6%) patients. The U.U rate was much higher than that of M.H and mixed infection. The high colony counting (> 10^4CFU/spec) in Ureaplasma urealiticim infection patients accounted for 40.9%, while Mycoplasma hominis infection represented only 7.3%. The results of drug tolerance test showed higher sensitivity to doxycycline, tetracycline, josamicyne, clarithromycin, and azithromycin (75%, 73.4%, 88.8%, 76%, 69% respectively), and lower sensitivity to ciprofloxacin, erythromycin and ofloxacin (33%, 57%, 25% respectively).

CONCLUSION

Due to the fact that there are high percentage of resistant forms of M.H and U.U it is necessary to perform drug susceptibility test for the selection of appropriate antibiotics

BENIGN MULTICYSTIC PERITONEAL MESOTHELIOMA – CASE REPORT

MULTIČISTICNI BENIGNI PERITONEALNI MEZOTELIOM – PRIKAZ SLUČAJA

A. Stamatović, S. Crnogorac, F. Vukmirović, Z.Filipović

Dom Zdravlja 'Dimitrije-Dika Marenić' Danilovgrad

Prikazan je slučaj veoma rijetkih slobodno plutajućih mezotelnih cisti u maloj karlici koji je uspješno riješen laparoskopskom operacijom. Pacijentkinja je upućena radi eksplorativne laparoskopije zbog ultrazvučno dijagnostikovanih promjena koje su potvrđene na CT i NMR.

Proste peritonealne mezotelne ciste predstavljaju rijetke mezenterijumske ciste mezotelnog porijekla. Kod odraslih obično prolaze asimptomatski i otkrivaju se kao slučajan nalaz prilikom laparoskopije i laparotomije dok se kod djece prezentuju kliničkom slikom akutnog abdomena.

Proste mezotelne ciste imaju dobru prognozu nakon potpunog hirurškog odtranjivanja. Izuzetno su rijetke, ali se na njih mora misliti u diferencijalnoj dijagnozi prema drugim cističnim promjenama u maloj karlici i abdomenu.

RATIONAL ANTIBIOTIC USE IN SMALL GYNECOLOGICAL INTERVENTIONS

RACIONALNA PRIMENA ANTIBIOTIKA KOD MALIH GINEKOLOŠKIH INTERVENCIJA

Milan Stojanović, Aleksandra Veselinović, Miloš Ilić, Milan Lacković, Nikola Mitić, Slađana Mihajlović

KBC „Dr Dragiša Mišović“- Dedinje, Bolnica za ginekologiju i akušerstvo

Razmatrana je upotreba antibiotika kod malih ginekoloških intervencija izvedenih u Bolnici za ginekologiju i akušerstvo KBC „Dr Dragiša Mišović“- Dedinje u periodu od 01.01.2018. do 01.01.2019. godine. Tokom ovog perioda urađene su 604 male ginekološke intervencije, a upotreba antibiotika zavisila je isključivo od operatora-ginekologa, njegovog iskustva, procene kliničke slike i rizika. Upoređene su dve grupe pacijenata: pacijentkinje kojima je administriran antibiotik u profilaktičke ili terapisje svrhe, a bez indikacija i pacijentkinje koje nisu primale antibiotik. Primena antibiotika se kretala u rasponu 0-100%.Nijedna pacijentkinja iz obe grupe nije imala komplikaciju koja bi zahtevala dodatnu primenu antibiotika u terapijske svrhe.

Zvanična preporuka je da se kod malih ginekoloških intervencija (eksplorativna kiretaža, biopsija grlića, stavljanje i uklanjanje intrauterusnih kontraceptivnih uložaka, histeroskopija i histerosalpingografija) ne koristi antibiotik u profilaktičke svrhe, ukoliko ne postoji jasan rizik za nastanak pelvične inflamatorne bolesti. Nepravilna upotreba antibiotika u profilaktičke svrhe, bez konkretnih indikacija (infekcija male karlice), povezana je sa nepotrebnom izloženošću pacijenta lekovima, mogućem nastanku rezistentnih mikroorganizama i povećanju troškova lečenja. Postoji potreba za dodatnom edukacijom ginekologa o upotrebi, odnosno zloupotrebi antibiotika prilikom izvođenja ginekoloških intervencija i manjih operacija.

INCIDENCE OF EARLY NEONATAL SEPSIS CAUSED BY β-HEMOLYTIC STREPTOCOCCUS

INCIDENCA JAVLJANJA RANE NEONATALNE SEPSE UZROKOVANE BETA HEMOLITIČKIM STREPTOKOKOM

Aleksandra Veselinović, Miloš Ilić, Milan Stojanović, Milan Lacković, Nikola Mitić, Slađana Mihajlović

KBC „Dr Dragiša Mišović"- Dedinje, Bolnica za ginekologiju i akušerstvo

Apstrakt:

Neonatalna sepsa uzrokovana beta-hemolitičkim streptokokom (GBS) i dalje predstavlja vodeći uzrok smrti kod neonatusa. Incidenca je 1-2%. Za glavni faktor rizika smatra se kolonizacija gastrointestinalnog i genitourinarnog trakta majke ovim uzročnikom.
U Bolnici za ginekologiju i akušerstvo KBC „Dr Dragiša Mišović"- Dedinje praćena je incidenca javljanja rane neonatalne sepse uzrokovane GBS-om u periodu od 01.01.2018. do 31.12.2018. godine.
Metodom skrininga smatra se vagino-rektalni bris kod trudnica od 35 do 38 n.g., a pod profilaksom intrapartalno ordiniranje ciljanog antibiotika kod rizičnih grupa. Antibiotik izbora je kristalni penicilin.
Rezultati istraživanja pokazali su da je GBS infekcija identifikovana u 33% slučajeva, a incidenca rane neonatalne sespe uzrokovane beta-hemolitičkim streptokokom iznosila je 0.31%.
Može se doneti zaključak da prvovremenim skriningom i adekvatnom antibiotskom profilaksom, koji su određeni svetskim protokolima, značajno smanjujemo morbiditet i mortalitet neonatusa izazvanih ovim uzročnikom.

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Vaginal symptoms are among the most common reasons for gynecologic consultation in primary care.[2] These symptoms are often incorrectly diagnosed as contact dermatitis or skin irritation caused by the use of feminine care products. Persistent vulval itch or soreness are usually the result of irritation or contact sensitization caused by vulval medication or preservatives and perfumes in cleansing products rather than any components of feminine care products.

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Furthermore, Always® pads and liners that are dermatologically tested' have passed an additional confirmatory skin patch test for irritation potential that follows internationally acknowledged clinical testing guidelines.

Tests that have detected chemicals such as pesticide or dioxin residues in feminine hygiene products have shown them to be present in trace levels which are comparable to traces found everywhere in the environment and pose no danger to health. This has also been confirmed by several reputable health institutions in Europe.[3,4,5,6].

Each component and sub-component of every Always® product on the global market is thoroughly analyzed, and dedicated human safety experts at P&G review the safety of each product at every step of its development. 'Natural' materials (cotton, rayon) are better for the skin than synthetic materials 'Natural' and 'organic' products are becoming increasingly popular in the feminine care industry.

However, there is no scientific evidence to suggest that feminine care products made with 'natural' or 'organic' materials are better for the skin than modern synthetic materials. It is purely a matter of consumer choice; many women prefer the idea of natural fibers such as cotton for feminine hygiene products.

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Suggestions have been made that panty liners may trap heat and moisture, and in turn, promote infections such as vulvovaginal candidiasis (VVC) and bacterial vaginosis, or promote colonization by microbes that cause urinary tract infections (UTIs). Although research has shown that panty liners can increase skin temperature and skin surface moisture, the extent of these effects does not create a meaningful change in the risk of genital infections.[7,8].

In conclusion, scientific evidence shows that panty liners are safe and their use is not associated with an increased risk of vaginal or urinary tract infections, or any adverse effect on vaginal flora.[7]

There is no scientific evidence that vulval or vaginal skin health is affected by the use of feminine care products. A wide variety of perfumed and non-perfumed feminine care products by Always® are available to meet all women's needs and preference.

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- U prevenciji pobačaja i smanjivanju rizika od prevremenog porođaja
- U održavanju posle primarne tokolize
- Kod invazivnih procedura u prenatalnoj dijagnostici

SIGURNO ZA NJU ✓

SIGURNO ZA BEBU ✓

BEZ NEŽELJENIH EFEKATA ✓

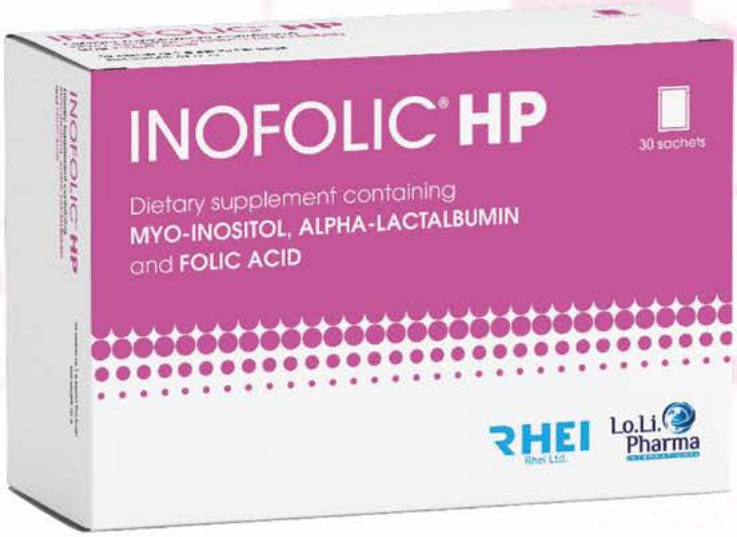
- *Smanjuje kontraktilnost miometrijuma*
- *Ojačava membrane*
- *Usporava cervikalno sazrevanje*

SASTAV		NRV%
Alfa-lipoinska kiselina	300 mg	-
Magnezijum	225 mg	60
Vitamin B6	1,3 mg	92,85

2 tablete dnevno do 36./37. nedelje trudnoće

INOFOLIC® HP

Dodatak ishrani na bazi MIOINOZITOLA, ALFA LAKTALBUMINA i FOLNE KISELINE



- Jedinstvena i optimizovana formula
- Povećava kliničku efikasnost proizvoda kod pacijentkinja sa PCOS-om
- Povećava intestinalnu apsorpciju mio-inozitola
- Povećava produkciju melatonina
- 25% više efikasnosti u poređenju sa starom verzijom
- Patententirana formula
- Prvi u klasi sa Alfa-laktoalbuminom

NOVO!

SIGURNOST I EFIKASNOST INOVATIVNE TEHNOLOGIJE ✓

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97 proizvoda

proizašlih iz osnovnih istraživanja u INEP-u,
u oblastima imunologije, imunohemije, endokrinologije glikobiologije

45 **registrovanih** kod ALIMS-a

Laboratorija INEP akreditovana prema standardu ISO 17025

Proizvodnja **sertifikovana** prema standardu kvaliteta SRPS EN ISO 13485

poliklonska antitela
antigeni
antitela obeležena sa HRPO i FITC
testovi za trudnoću
RIA testovi
IRMA testovi
FITC kompleti
RID ploče

Po smernicama **dobre prakse** u distribuciji medicinskih sredstava

Razvojni planovi:
IMUNOSENZORI
BIOČIPOVI

INEP

NUDI SARADNJU
INSTITUTIMA, **KLINIKAMA** I PROIZVOĐAČIMA IVD
U **RAZVOJU NOVIH TESTOVA**
I U NJIHOVOM **USAGLAŠAVANJU** SA ZAKONSKOM
REGULATIVOM I STANDARDIMA KVALITETA

UGOSCGRS:

Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republika Srpska
Tel: +381 11 3615592
Fax: +381 11 3615603
Mail: secretariat.ugoscgrs@gmail.com
www.ugoscgrs.rs