UGOSCGRS

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20th INTERNATIONAL CONGRESS

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

MONTENEGRO HOTEL
BUDVA, MONTENEGRO
25 – 27 SEPTEMBER 2025

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

including
3rd International Symposium of the Serbian Society for Fertility Preservation and Oncofertility

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Dear Colleagues,

It is our pleasure to invite you to the 20th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska (UGOSCGRS). The Congress will be held on September 25-27th, 2025, in Budva, Montenegro.

In collaboration with national societies and numerous friends from Europe and whole world we will gather great number of gynecologists-obstetricians from our region and provide them with opportunity to listen to distinguished experts giving lectures on novelties from different areas of gynecology and obstetrics. Also, Congress attendees will be able to widen connections with colleagues from wide variety of hospitals and other health institutions. The Program of the Congress encompasses sessions on gynecology, gynecologic oncology, obstetrics, perinatology, minimally invasive surgery, assisted reproductive technologies and reproductive endocrinology.

In accordance with global trends and trying to meet requirements of contemporary clinical practice, our Association has supported the foundation of Serbian society for fertility preservation and oncofertility (SSFPO) and, during our Congress, will host the 3rd Symposium of SSFPO with the most outstanding international and regional experts as invited speakers, along with speakers from the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia. Taking into account the complexity of this pathology, one of the basic goals of Symposium will be to provide the opportunity to form wide network of collaborators from different institutions dealing with oncofertility.

Considering program and concept, meetings organized by UGOSCGRS are good forum to exchange ideas and information between different levels of medical professionals – from residents to experts in the field. Therefore, we invite colleagues to take part in the Congress by applying to Free Communication session.

We hope that this Congress will fulfill your expectations and that you will take many beautiful memories from it.

We will be delighted to welcome you in Montenegro.

With best wishes,

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

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Congress is accredited by the decision of the Montenegrin Medical Chamber No. 1187/3-8, 15.09.2025. as International Congress with 12 points for invited lecturers, 10 points for free communications, 6 points for co-authors, 3 points for poster presentations and 2 points for listeners.

Thursday, 25th of September, 2025

10.00 – 12.00	**Registration**
12.00 – 12.15	**Words of Welcome**

LECTURE HALL A

SESSION	**FERTILITY SPARING SURGERY AND ONCOFERTILITY I**
	Chairs: K. Stefanović, V. Kopitović, D. Antić, S. Spremović Rađenović, I. Takač
12.15 – 12.30	**Katarina Stefanović (Serbia)** Oncofertility today
12.30 – 12.45	**Darko Antić (Serbia)** Oncofertility in hematological malignancies
12.45 – 13.00	**Jelena Stojnić (Serbia)** Ovarian stimulation for oocyte cryopreservation in women with hematological malignancies in oncofertility
13.00 – 13.15	**Tatjana Božanović (Serbia)** The role of laparoscopy in the treatment of BOT
13.15 – 13.30	**Igor Pilić (Serbia)** Trachelectomy in Oncofertility: oncological and obstetrical outcomes
13.30 – 13.45	**Miloš Radojević (Serbia)** Cervical Cancer: Should we be less radical?
13.45 – 14.00	**Disscusion**
THE PANEL	**HUMAN PAPILLOMA VIRUS**
14.00 – 14.10	**Aleksandar Stefanović**
14.10 – 14.20	**Vesna Čolaković Popović**
14.20 – 14.30	**Vesna Ećim Zlojutro**
14.30 – 15.30	**Lunch Break**
	Commercial lecture: Ferring
15.30 – 16.00	**Vesna Ećim Zlojutro (Republic of Srpska),** **Aleksandar Stefanović (Srbija)** Tocolytic therapy aimed to improve outcomes of preterm birth
SESSION	**SPECIAL SESSION**
16.00 – 16.30	**Paja Momčilov (Serbia)** Linguistics, Logic and Obstetrical Doctrine
SESSION	**PERINATOLOGY I**
	Chairs: Ž. Miković, M. Gojnić Dugalić, S. Crnogorac, Lj. Petričević
16.30 – 16.45	**Željko Miković (Serbia)** Alloimmune thrombocytopenia – prenatal diagnosis and therapy
16.45 – 17.00	**Snežana Crnogorac (Montenegro)** Ultrasound and WES in diagnostics of monogenic disorders

17.00 – 17.15	**Miroslava Gojnić Dugalić (Serbia)** Metformin in pregnancy and Fetal Programming
17.15 – 17.30	**Olivera Kontić Vučinić (Serbia)** CMV in pregnancy: Diagnostic dilemmas
17.30 – 17.45	**Danko Natalić (Montenegro)** Post term pregnancy: protocols
17.45 – 18.00	**Disscusion**
19.00	**Opening Ceremony and Welcome Cocktail**

LECTURE HALL B

SESSION	**OBSTETRICS I**
	Chairs: G. Relić, V. Čančar, S. Janković, I. Hudić
16.30 – 16.45	**Goran Lazarević (Montenegro)** Rare complications of thromboembolic disorders after delivery
16.45 – 17.00	**Vladimir Čančar (Republic of Srpska)** Benefits and risks of antenatal administration of corticosteroids
17.00 – 17.15	**Svetlana Janković (Serbia)** Labor management in epidural analgesia: what to expect and how to avoid complications
17.15 – 17.30	**Tatjana Ilić Mostić (Serbia)** Trauma: pregnancy and delivery
17.30 – 17.45	**Gordana Vukčević Globarević (Montenegro)** Trends in deliveries in 2025
17.45 – 18.00	**Disscusion**

Friday, 26th of September, 2025

LECTURE HALL A

SESSION	**IVF AND REPRODUCTIVE ENDOCRINOLOGY**
	Chairs: S. Spremović Rađenović, T. Motrenko Simić, J. Stojnić
09.00 – 09.15	**Svetlana Spremović Rađenović (Serbia)** Iatrogenic menopause: therapeutic dilemmas
09.15 – 09.30	**Tatjana Dosev (Serbia)** Low ovarian reserve: diagnosis, etiology and IVF management
09.30 – 09.45	**Vesna Kopitović (Serbia)** Personalized approach to endometriosis: cases and solutions from practice
09.45 – 10.00	**Tatjana Motrenko Simić (Montenegro)** Updated algorithm for infertility diagnostic and treatment
10.00 – 10.15	**Dragan Stajić (Serbia)** Ultrasound diagnostics of myomas in infertility: when to operate?
10.15 – 10.30	**Milan Perović (Serbia)** Customized treatment in ovarian stimulation and triggering
10.30 – 10.45	**Disscusion**

	Commercial lecture: Merck
	Chair: Aleksandar Stefanović (Serbia)
10.45 – 11.00	**Katarina Stefanović (Serbia)** Evaluation of infertility and different IVF protocols
11.00 – 11.15	**Emir Muzurović (Montenegro)** Pre-diabetes and hypothyroidism in preconception and pregnancy
	Commercial lecture: Innventa
11.15 – 11.45	**Svetlana Spremović Rađenović (Serbia)** Dienogest Aristo in clinical practice and ESHRE guidelines for endometriosis
11.45 – 12.15	**Coffee break**
	Commercial lecture: San Pharma
12.15 – 12.30	**Saša Kadija (Serbia)** HPV infection and effective therapy of LGT lesions. Two ways of applying molecularly activated Glycyrrhizic Acid
SESSION	**ONCOLOGY**
	Chairs: A. Stefanović, V. Čolaković Popović, B. Kobal
12.30 – 12.45	**Borut Kobal (Slovenia)** Pretreatment surgical staging in locally advanced cervical cancer (LACC); is it still relevant in the PET-CT era?
12.45 – 13.00	**Iztok Takač (Slovenia)** Clinical registries in gynecological oncology – Endometrial Cancer registry
13.00 – 13.15	**Vesna Čolaković Popović (Montenegro)** Ovarian Cancer treatment: dilemmas
13.15 – 13.30	**Jelena Jeremić (Serbia)** Algorithm of reconstructions following oncological resections
13.30 – 13.45	**Aleksandra Dimitrijević (Serbia)** Hormone replacement therapy in surgical menopause following gynecological malignancies
13.45 – 14.00	**Dragan Jeremić (Serbia)** Prophylactic laparoscopic salpingo-oophorectomy in BRCA 1 and BRCA 2 Mutation Carriers
14.00 – 14.15	**Udruženje građana za borbu protiv raka jajnika i grlića materice** “Sreća, pazi, snima se” (projekcija filma)
14.15 – 14.30	**Disscusion**
	Commercial lecture: ADOC
14.30 – 15.00	**Aleksandar Stefanović (Serbia)** The importance of HPV test as a screening tool with reference to trends in Europe and globally
15.00 – 16.00	**Lunch break**
SESSION	**OBSTETRICS II**
	Chairs: P. Momčilov, T. Vejnović, V. Ećim Zlojutro, S. Janković
16.00 – 16.15	**Tihomir Vejnović (Serbia)** Uterine scar following different techniques of Cesarean Section

16.15 – 16.30	**Saša Kadija (Serbia)** Urological complications of Cesarean Section
16.30 – 16.45	**Goran Relić (Serbia)** The frequency of congenital anomalies in North of Kosovo following the war
16.45 – 17.00	**Vesna Ećim Zlojutro (Republic of Srpska)** Cerebral palsy prevention: our results
17.00 – 17.15	**Igor Hudić (Bosnia and Hercegovina)** Epidemiology of Cesarean deliveries in the Tuzla Clinic for Gynecology and Obstetrics: the range of problems
17.15 – 17.30	**Dragana Maglić (Serbia)** IUGR of unknown etiology: cases
17.30 – 17.45	**Aleksandra Vejnović (Serbia)** Results of Cesarean site histology
17.45 – 18.00	**Disscusion**

LECTURE HALL B

SESSION	**GYNECOLOGY**
	Chairs: S. Kadija, Lj. Petričević, A. Dimitrijević, Z. Vilendečić
09.00 – 09.15	**Aleksandar Stefanović (Serbia)** Medical abortion – where are we now
09.15 – 09.30	**Ljubomir Petričević (Austria)** Screening for vaginal dysbiosis
09.30 – 09.45	**Damir Hodžić (Croatia)** Functional magnetic stimulation in the treatment of women's urinary incontinence and pelvic disorders
09.45 – 10.00	**Sveto Pantović (Serbia)** The role of sling procedures and therapy of uterine incontinence
10.00 – 10.15	**Jure Knez (Slovenia)** The risk of ovarian endometriosis progression – is watch'n'wait an option?
10.15 – 10.30	**Zoran Vilendečić (Serbia)** Subtotal hysterectomy: Is it justified in contemporary gynecological practice?
10.30 – 10.45	**Disscusion**

SESSION	**PERINATOLOGY II**
	Chairs: O. Kontić Vučinić, D. Natalić, A. Jurišić, M. Petronijević, N. Karadžov Orlić
12.30 – 12.45	**Miloš Petronijević (Serbia)** Influence of E-cigarette usage on female reproductive health
12.45 – 13.00	**Aleksandar Jurišić (Serbia)** Possibilities for detection of anomalies of embryo in early pregnancy
13.00 – 13.15	**Nataša Karadžov Orlić (Serbia)** Non-placental intrauterine growth restriction: causes, diagnosis and management
13.15 – 13.30	**Svetlana Vrzić Petronijević (Serbia)** Beyond Baby Blues: Integrating maternal mental health into perinatal management
13.30 – 13.45	**Marijana Pešić (Montenegro)** Comparison of intravascular transfusion in the treatment of fetal anemia in hydropic and non-hydropic fetuses

13.45 – 14.00	**Zagorka Milovanović (Serbia)** Thyroid function evaluation in pregnancy: is the screening justified?
14.00 – 14.15	**Antonia Franović Mihaljević (Montenegro)** Subchorionic haematoma – diagnostics and treatment
14.15 – 14.30	**Disscusion**

SESSION	**MINIMALLY INVASIVE GYNECOLOGICAL SURGERY**
	Chairs: M. Dokić, S. Pantović, D. Stajić, T. Božanović, D. Hodžić
16.00 – 16.15	**Rajko Fureš (Croatia)** Perspectives and alternatives to laparoscopic hysterectomy
16.15 – 16.30	**Milan Dokić (Serbia)** Treatment of uterine myomas – conservative and operative approach
16.30 – 16.45	**Slađana Mihajlović (Serbia)** Role of laparoscopy in diagnostic and treatment of endometriosis
16.45 – 17.00	**Nebojša Zečević (Serbia)** Myoma class 3: Is hysteroscopic approach an option?
17.00 – 17.15	**Rastko Maglić (Serbia)** Isthmocele: actual problem, prevention and possible solutions
17.15 – 17.30	**Danka Mostić Stanišić (Serbia)** Hysteroscopy in daily clinical practice: our experience
17.30 – 17.45	**Disscusion**

Saturday, 27th of September, 2025

LECTURE HALL A

SESSION	**FERTILITY SPARING SURGERY AND ONCOFERTILITY II**
	Chairs: K. Stefanović, S. Spremović Rađenović, V. Kopitović, I. Pilić
09.00 – 09.15	**Ivana Likić Lađević (Serbia)** Non-epithelial Ovarian Cancer: Fertility Sparing
09.15 – 09.30	**Jelena Dotlić Babić (Serbia)** Mental burden of malignancy in young patients
09.30 – 09.45	**Branislav Milošević (Serbia)** Chemotherapy for gynecology cancer treatment in pregnancy
09.45 – 10.00	**Stefan Dugalić (Serbia)** Adnexal masses in pregnancy
10.00 – 10.15	**Aleksandra Beleslin (Serbia)** Oncofertility in breast cancer
10.15 – 10.30	**Olga Mihaljević (Serbia)** Hematological malignancies in pregnancy – our experience
10.30 – 10.45	**Luka Andrić (Serbia)** Oncofertility in testicular tumors
10.45 – 11.00	**Disscusion**
11.00 – 11.15	**Short break**

SESSION	FREE COMMUNICATIONS
	Chairs: V. Marković Mandić, Z. Vilendečić, M. Radojević, G. Vukčević Globarević, S. Mihajlović, V. Milošević
11.15 – 11.22	**Snežana Buzadžić (Serbia)** A rare case of cystic artery thrombosis in 24-week gestation
11.22 – 11.29	**Radomir Aničić (Serbia)** Progressive hyperandrogenism in menopause
11.29 – 11.36	**Zvjezdana Ritan Mičić (Republic of Srpska)** Neonatal outcome following $MgSO_4$ treatment for fetal neuroprotection
11.36 – 11.43	**Emilija Delević (Montenegro)** Abikossoff tumor of vulva: case report
11.43 – 11.50	**Anđela Aćimović (Serbia)** Foreign Body in the vagina leading to Vesicovaginal Fistula – case report
11.50 – 11.57	**Bojana Petrović (Serbia)** Genetic bases of recurrent isolated fetal anomalies
11.57 – 12.04	**Arnela Banićević (Republic of Srpska)** Optimization of antenatal corticosteroids in preterm birth
12.04 – 12.11	**Milutin Mitrović (Montenegro)** Fracture and retention of needle fragment during cerclage aplication: case report
12.11 – 12.18	**Ljiljana Zdelar (Serbia)** Clinical significance of anti-c antibody in pregnancy: case report
12.18 – 12.25	**Milena Šibalić (Serbia)** Peripartum cardiomyopathy in pregnancy case report
12.25 – 12.32	**Jelena Štulić (Serbia)** Significance of empirical antibiotic selection in postpartum infections
12.32 – 12.39	**Miloš Milinčić (Serbia)** Distribution of comorbidities in pregnancy following myomectomy: analysis of spontaneous and IVF conceptions
12.39 – 12.46	**Anja Stepanović (Serbia)** Treatment of a patient with invasive Mucinous Ovarian Carcinoma with intestinal differentiation
12.46 – 12.53	**Aleksandra Didanović** Cancer treatment during pregnancy
12.53 – 13.00	**Jelena Čotrić (Serbia)** Pregnancy with co-existing IUD: case report
13.00 – 13.07	**Katarina Ivanović (Serbia)** Breast Cancer diagnosed during pregnancy – case series of three patients and clinical management considerations
13.07 – 13.14	**Kosta Pantović (Serbia)** Surgical treatment of vaginal eversion following hysterectomy
13.14 – 13.21	**Disscusion**
13.30	**Evaluation and closing**

LECTURE HALL B

SESSION	PERINATOLOGY III
	Chairs: S. Vrzić Petronijević, D. Rakanović, G. Lazarević, J. Stamenković, V. Marković Mandić
09.00 – 09.15	**Jelena Stamenković (Serbia)** Fetal heart rhythm abnormalities: diagnosis and treatment
09.15 – 09.30	**Vesna Marković Mandić (Serbia)** Fetal ultrasonography in the diagnosis of CPAM
09.30 – 09.45	**Dragan Rakanović (Republic of Srpska)** PRES syndrome in pregnancy – series of cases
09.45 – 10.00	**Dejan Mitić (Serbia)** Esthetic approach in Cesarean Section
10.00 – 10.15	**Veroslava Milošević (Republic of Srpska)** Impact of gestational age on morbidity in term newborn
10.15 – 10.30	**Disscusion**

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FERTILITY SPARING SURGERY AND ONCOFERTILITY

STIMULACIJA OVULACIJE I KRIOPREZERVACIJA OOCITA KOD HEMATOLOŠKIH MALIGNITETA ŽENA U ONKOFERTILITETU

Prof. dr Jelena Stojnić

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Uvod

Incidenca maligniteta se povećava širom sveta, posebno poslednje decenije. 2018. godine dijagnostikovano je 8.6 miliona novih slučajeva kancera kod žena, sa 10% udela žena ispod 40 godina [1]. Prema GLOBOCAN svetskoj statistici, broj novih slučajeva kancera kod dece, adolescenata i mlađih odraslih (od 15 do 39 godina) je dostigao skoro 15 000 000 slučajeva u 2020. godini. 2020. godine dijagnostkovano je 89 500 novih slučajeva kancera kod mladih žena, uzrasta od 15 do 39 godina, sa porastom ukupne incidence tokom poslednje decenije u Sjedinjenim Američkim Državama. Posebno gledano, u reproduktivnoj grupi starijih od 20 godina, učestalost kancera kod žena je dvostruko veća nego kod muškaraca. Hematološki maligniteti su među prvih pet po učestalosti kod žena reproduktivne dobi [2]. Od 45% petogodišnjeg preživljavanja od svih tipova kancera u sedamdesetim godinama do 70% za one dijagnostikovane od 2013. do 2019. godine [3]. Napredak u anti-kancer terapijskim modalitetima je značajno poboljšao preživljavanje žena u reproduktivnoj dobi, tokom poslednje decenije i dostiže 70% [4]. U grupi pedijatrijskih pacijenata, adolescenata i mlađih odraslih je petogodišnje preživljavanje oko 85% u Sjedinjenim Američkim Državama (*American Cancer Society*, 2023). Prema EUROCARE podacima u evropskim zemljama su mnogo heterogeniji podaci o petogodišnjem preživljavanju, sa značajnom razlikom Zapadne i Istočne Evrope. Ova heterogenost je delom uslovljena različitom učestalošću pojednih vrsta tumora, ali i razlike u brzini dijagnostike i dostupnosti različitih terapijskim modaliteta. Uprkos regionalnim razlikama, petogodišnje stope preživljavanje su porasle tokom prethodnim decenija od 30% u šezdesetim godinama do 80% ove decenije, prema izveštaju SZO iz 2023. godine. Oko 45 000 novih slučajeva se registruje godišnje u Francuskoj [5], što čini incidencu od 12% svih novodijagnostikovanih slučajeva kancera. Hematološki maligniteti pogađaju obično decu i mlađe žene reproduktivne dobi. Stope petogodišnjeg preživljavanja od hematoloških maligniteta su u stalnom porastu, pre svega poboljašavanjem modaliteta terapije, inovativnim lekovima (imunoterapija, target terapija) i ranijoj dijagnostici kancera [6]. Naime, cilj terapije za izlečenje odnosno postizanje remisije je primarni, ali ne i jedini cilj terapije. Postizanje ili zadržavanje odgovarajućeg kvaliteta života je takođe jedan od najvažnijih ciljeva i očekivanje žena, u šta ubrajamo očuvanje reproduktivnog potencijala i fertiliteta.

Uticaj terapije na reproduktivni potencijal i fertilitet

Već je poznata i prihvaćena činjenica da nakon terapije hematoloških maligniteta hemioterapijom, radioterapijom, kao i transplantacijom kosne srži i pripremama za nju, dolazi do toksičnog delovanja na gonade, što vodi do sniženja ili gubitka fertilitet [7]. Pozitivni efekti terapije na malignu bolest su poželjna strana, ali nepovoljni i negativni efekti onkološkog lečenja na ovarijalnu funkciju su postali očigledni i spadaju u nepoželjne efekte terapije. Hemioterapija bazirana na alkilijarućim agensima dovodi do smanjenja pula primordijalnih folikula i uzrokuje ovarijalnu atrofiju putem apoptoze [8]. Posledično, ovi svi tretmani pogađaju ženski fertilitet na duže staze i ometaju odnosno smanjuju odgovor na ovarijalnu stimulaciju [9]. Žene i adolescentkinje sa hematološkim

malignitetima su, posle žena sa kancerom dojke, najviše zastupljena grupa, koja se upućuje na prezervaciju fertiliteta pre gonadotoskične onkološke terapije. Posebna specifičnost grupe žena sa hematološkim malignitetima je često sistemska priroda maligne bolesti sa ispoljenim nepovoljnim uticajem na gonadalnu finkciju, koji je ispoljen i vidljiv, čak i pre otpočinjanja onkološke terapije. Kod ovih pacijetkinja nalazimo povišene nivoe citokina i faktora rasta koji okidaju proinflamatorni sistemski odgovor [10]. Agresivni limfoidni tumori mogu izazvati sistemnske efekte kao što su paraneoplastički neurološki sindrom, groznicu, gubitak težine, noćno znojenje i preznojavanje, neadekvatnu funkciju udaljenih organa (gonadalna disfunkcija), čak i pre otpočinjanja bilo kakve terapije.

Kod muškaraca sa limfomima, prilikom pregleda spermograma pred krioprezervaciju, pre otpočinjanja terapije, uočavamo značajno smanjenje koncentracije i motiliteta u odnosu na nalaz prethodni ili zdrave kontrole. Poremećaji spermatogeneze se pripusuju multiplim uzrocima i obuhvataju groznicu, opšti stres efekat maligniteta, i imunološke poremećaje koji uzrokuju, između ostalog i devastirajući efekat na gonade [11].

Što se tiče mehanizma efekata hematoloških kancera na ovarijalnu funkciju, još uvek nije mnogo rašćišćeno i najjasnije, sa predloženim mnogobrojnim hipotezama i teorijama, od mutacije u germinativnim ćelijama u FA-BRCA DNK reparatornom sistemu [12], neobjašnjivih poremećaja gameta, do visokih koncentracija citokina i njihovih sistemskih uticaja. Takođe, pored ovog uticaja na ovarijume u smislu opadanje ovarijalne rezerve, postavlja se i pitanje uticaja na kvalitet i kvantitet odgovora na stimulaciju ovulacije u postupcima krioprezervacije i eventualnu potrebu modifikacije protokola stimulacije ovulacije kod hematološkim pacijetkinja.

Alkilirajući agensi (ciklofosfamid), koji su evidentno potvrđeni gonadotoksini, i čak i kod pacijetkinja bez prevremene ovarijalne insuficijencije nakon hemioterapije, izazivaju veoma usporen oporavak ovarijalne funkcije sa sniženim odgovorom na stimulaciju ovulacije, u poređenju sa zdravim kontrolama, na istim stimulacionim protokolima [13]. Takođe, dokumentovano je i da lečene adolescentkinje od hematoloških kancera, u mnogo većem procentu, kasnije za ostvarivanje reprodukcije, moraju koristiti metode ART (IVF), jer su već sa pojavom bolesti, pre tretmana ima snižene pokazatelje fertiliteta [14]. Jatrogeni uzorci koji dovode do prevremene ovarijalne insuficijencije su ovarijalna hirurgija, hemioterapija i radioterapija. Ovi agensi mnogostrukim mehanizmima kompromituju ovarijalnu rezervu i to najčešće direktnim dejstvom na folikule, smanjujući pul promordijalnih folikula, snižavanjem kvaliteta oocita i oštećivanjem intracelularne DNK. Dodatno, pogađaju i ovarijalnu stromu, dovodeći do fibroze i uzrokuju oštećenje vaskularnog endotela [15].

Radioterapija povećava rizik od prevremene ovarijalne insuficijencije (POI), ali izaziva i promene u uterusu i na taj način dodatno snižava fertilitet, već i u slučaju postizanja trudnoće, povećava rizik od pojave komplikacija, kao i nepovoljnog neonatalnog ishoda. Rizik oštećenja ovarijuma i uterusa zavisi od doze radijacije, tipa polja zračenja, načina frakcionisanja doze, kao i faze folikularnog razvoja. Najsenzitivniji na zračenje su preovulatorni folikuli [16]. Oociti su oštećeni pri dozi 1-5 Gy, a SLD (srednje letalna doza) je manja od 2 Gy [17]. Doza koja uvodi u infertilitet odmah nakon tretmana je oko 19 Gy kod dece, 15 Gy kod odraslih i smanjuje se sa godinama. Uz vaskularna stromalna ostećenja endotela, radijacija izaziva promene u miometrijumu sa smanjenjem debljine, funkcije i sa oštećenjem vaskularnog endotela u uterusu. [18]. Promene u uterusu rezultuju sniženim stopama živorođenja i višim stopama pobačaja, prevremenih porođaja i veoma niske telesne mase neonatusa na porođaju, ako se postigne trudnoća, uprkos procedurama za

očuvanje fertiliteta i prikupljanje oocita [19]. Ireverzibilna oštećenja uterusa, gde je trudnoća kontraindikovana, nastaje kod doze radijacije od 25 Gy u detinjstvu ili 45 Gy u odraslom dobu [20].

Totalna iradijacija tela (TBI), uobičajeno se koriste doze od 12 Gy, kao procedura pripremna za transplantaciju kosne srži, nosi rizik smanjenog fertiliteta i nepovoljnog perinatalnog i neonatalnog ishoda [21]. Izlaganje zračenju od 20-30 Gy ili do 15 Gy totalna iradijacija tela, može devastirati ovarijalnu funkciju. Doze od 6 Gy kod adultnih žena, 10 Gy kod adolescentkinja ili 15 Gy kod prepubertetskih devojčica, mogu devastirati funkciju ovarijuma [22].

Radioterapija CNS vodi između ostalog do hormonalnih promena koje utiču na fertilitet. Zračenje oštećuje funkciju hipofize i dovodi do hipopituitarizma. Doze od 30 do 40 Gy kod 80% tretiranih pacijetkinja proizvodi sekundarni hipogonadizam. Sledeći problem je hiperporlaktinemija kod 50% pacijetkinja nakon iradijacije mozga [23]. HSCT (hemopoestaka transplantacija stem ćelija) nosi sa sobom visok rizik, (više od 70%) gonadalne toksičnosti. Za žene faktori, koji značajno povećavaju rizik od infertiliteta, POI su alkilirajući agensi, iradijacija ovarijuma i transplantacija hemopoetskih stem ćelija, s tim što primena alkilirajućih agensa i iradijacije se ponašaju dozno zavisno. Kombinacija alkilirajućih agenasa i zračenja, dodatno povećava rizik.

Studija je pokazala da su stope trudnoća manje za 82% ako je žena bila izložena zračenju više od 10 Gy. Rizik od infertiliteta je tri puta veći kod preživelih od kancera, ako je terapija primenjena pre 20 godine [24]. *Bone merrow transplant survivor study* (BMT) navodi stope infertiliteta 36 puta veću kod recipijenata transplantata.

Za AML i ALL, rizik oštećenja gonada je nizak ako se uzme u obzir samo radioterapija, dok god se transplantacije ne primeni. Rizik je nizak i u slučaju primene inhibitora tirozin kinaza (CML).

U slučajevima HL rizik gonadalnog oštećenja zavisi od tipa lekova:

- Primena ABVD, koji se koristi za rane stadijume nosi nizak rizik
- BEACOPP, koji se koristi za odmakle stadijume i ne reaktivne tumore-nosi visok rizik od oštećenja gonada
- CHOP i CVAD su u upotrebi za NHL, ima relativno nizak rizik od oštećenja gonada
- Transplantacija je povezana sa visokom rizikom insuficijencije ovarijuma i totalna iradijacija tela smanjuje ovarijalnu funkciju u većoj meri nego hemioterapija.

CML (hronična mijeloidna leukemija) se javlja kod oko 25% ljudi ispod 50 godina starosti. Uglavnom se tretira sa inhibitorima tirozin kinaze u toku dužeg vremenskog perioda, može uticati na razvoj fetusa i vodi u infertilitet. Povećavane stope abortusa, kao i učestalosti fetalnih kardijalnih defekata. Pacijetkinje koje planiraju trudnoću, moraju uzeti u obzir prekidanje terapije inhibitorima tirozin kinaze [25].

Kako i zašto se pacijetkinje sa hematološkim kancerima razlikuju od ostalih tipova kancera po pitanje krioprezervacije?

Definitvna amenoreja se pojavljuje u manje od 20% svih pacijetkinja tretiranih hemioterapijom za AML, ALL i HL i ovde nam očuvanje fertiliteta može izgledati nepotrebno. Ali, praktično većina preživelih od hematoloških kancera ima smanjenu i neadekvatnu ovarijalnu funkciju, subfertilitet i imaju skraćenje vremena fertiliteta nakon hemioterapije [26].

Mnoge pacijetkinje sa dijagnozom akutne leukemije i limfoma, moraju urgentno odnosno odmah započeti sa citotoksičnom terapijom i ne mogu da čekaju 10 do 14 dana pripreme i postupka stimulacije ovulacije i punkcije folikula za krioprezervaciju oocita. Njihovo kliničko stanje zbog citopenije, velikog intraoperativnog rizika od krvarenja i infekcije, kardiopulmonalnih problema i

neadekvatne koagulacije, često su ozbiljan zadatak, čak i prepreka za proces stimulacije ovulacije i TVAO.

Hematološki kanceri imaju visoku stopu rekurencije. Permanentna amenoreja retko nastaje nakon prvog ciklusa hemioterapije, pacijentki je obično mogu razviti nakon terapije rekurentnog kancera dodatnim hemioterapijom ili HCT. Upotreba dodatne terapije kod rekurentne bolesti sa potencijalnim citotoksičim agensima ili totalna iradijacija čitavog tela, koje se obično primenjuju, vode u akutnu ovarijalnu insuficijenciju u većini slučajeva [27].

Kod hematoloških pacijetkinja je izuzetak, a to je sprovođenje stimulacije ovulacije i krioprezervacije i nakon i ciklusa hemioterapije, i zato je bitno da se obrate specijalistima reproduktivne medicine iako je tretman završen.

Opcije očuvanje fertiliteta kod hematoloških kancera obuhvataju:

- Krioprezervacija oocita i embriona

Najviše korišćena metoda, najuspešnija. U većini zemalja i jedina zakonska opcija kod single žena radi prezervacije fertiliteta zbog maligniteta. Obuhvata postupak stimulacije ovulacije, transvaginalne punkcije oocita i krioprezervaciju oocita vitrifikacijom. Vitrifikacija oocita i embriona nakon COS (kontrolisana ovarijalna stimulacija) je najčešće korišćen i najuspešniji metod za žene nakon puberteta, čija efikasnost zavisi od godina, ovarijalne rezerve i ovarijalnog odgovora na egzogene gonadotropine [28].

- Krioprezervacija ovarijalnog tkiva

Obično se koristi u urgentnim slučajevima kod adultnih, kada se tretman ne može odlagati, i jedina je opcija kod prepubertetskih devojčica. U mnogim zamljama je metoda eksperimentalna, dok u Francuskoj, Izraelu, Italiji, SAD se tretira kao rutinska. Ovde je potencijalna opasnost kod hematoloških maligniteta da mogu uzorci sadržati rezidualno maligno tkivo odnosno da postoji kontaminacija. Nakon transplantacije ovarijalnog tkiva, može doći do recidiva bolesti, iako navodi iz literature kod M. Hodgkin limfoma, označavaju rizik kao veoma nizak [29,30].

- IVM
- Ovarijalna transpozicija (ooforektomija)
- Ovarijalna supresija
- Poštedna ginekološka hirurgija za očuvanje fertiliteta

Samo prve tri metode su praktično očuvanje fertiliteta sa dokazanim rezultatima i različitom uspešnošću.

AMH kod hematoloških maligniteta i odgovor na stimulaciju ovulacije

Pitanje koje se nameće: da li je ovarijalna funkcija pogođena samim hematološkim malignitetom i pre samog početka terapije kancera?

Hematološki maligniteti izazivaju sistemsku inflamatornu reakciju sa povišenim nivooom VEGF, TGF-6 (*transforming growth factor*), citokinima IL-6 i CRP [31]. Studije na životinjama su demonstrirale da TGF-6 povišenje je povezano sa inhibicijom folikulogeneze i maturacijom oocita i ovulacije [32]. Kliničke i biološke karakteristike kao što su groznica, gubitak težine, noćno znojenje, medijastinalne mase, inflamatorni sindrom, anemije, elevacija LDH su potvrđeni prediktori preživljavanja kod limorma [33]. Asocijacija hematoloških maligniteta i oštećenja germinativnih ćelija je demonstrirana nakon histološke analize ćelija ovarijalnog korteksa kod žena sa Hodgkin limfomom, sa slikom značajno veće pojave vakuolizovanih folikula u odnosu na zdrave kontrole [34].

Ovo može objasniti sniženo oslobađanje AMH od strane granuloza ćelija (kvantitativna ovarijalna rezerva), ukazujući na disfunkciju folikula folikula kod žena sa hematološkim malignitetima uprkos znatno mlađem životnom dobu.

Više izveštaja ukazuje na smanjenje parametara ovarijalne rezerve, posebno AMH hormona u vreme dijagnostike hematološkog maligniteta, kako kod odraslih [35], tako i kod pedijatrijska populacije [36]. Katzir i sar. navode rezultate meta-analize koje uključuju 6 studija, koja je ispitivala parametre ovarijalne rezerve i odgovor na stimulaciju kod hematoloških maligniteta, kojin ukazuju na izuzetno sniženom AMH uprkos mlađem uzrastu, ali po pitanje ovarijalnog odgovora na stimulaciju, bez zabeležene razlike.

Čak, neki autori navode činjenice o ovarijalnom odgovoru za stimulaciju ovulacije kod žena sa hematološkim malignitetima, da je niži u odnosu na zdravu populaciju, kao i u odnosu na populaciju žena sa solidnim malignitetima (Ca dojke) [37].

Međutim, ne nalazimo ultrasonografski smanjen broj antralnih folikula. U postupcima stimulacije ovulacije, uz korekciju doza gonadotropina, adekvatan broj antralnih folikula, dobijamo sličan broj - komparabilan oocita, kao kod zdravih kontrola [38].

Specifičnosti stimulacije ovulacije kod ovih pacijetkinja:

- Reproduktivno mlađa populacija uz sniženje AMH
- Stimulacija ovulacije nakon hemioterapije (4 do 6 meseci nakon)
- Korekcija doza gonadotropina radi optimalnog odgovora
- Random stimulacija
- Dual stim radi većeg broja ćelija
- Aromataza inhibitori kao prevencijam OHSS
- Priprema pred TVAO-transfuzija, antikoagulantna terapija, simptomatska terapija
- Rekombinovani preparati, protokoli sa GnRh antagonistima

U proseku hematološki maligniteti imaju relativno mlađu grupu pacijetkinja i prosečno najveći broj krioprezerviranih zrelih (MII) oocita [39].

Goldberg i saradnici sa obuhvatanjem 285 pacijetkinja sa limfomima, leukemijom, mijelomom i mijelodisplastičnim sindromom u periodu od 2013 do 2023. godine. U procenu ovarijalne rezerve i ovarijalnog odgovora na stimulaciju ovulacije uključenom 230 pacijetkinja sa limfomima. Niska ovarijalna rezerva definisana kao AMH ≤1.2ng/ml i dobijeno ≤ 9 oocita. Često, u vreme stimulacije ovulacije u ovoj studiji se nalazi i deterioracija opšteg stanja pacijetkinje, sa verovatnim uticajem na ovarijalnu funkciju kod hematoloških maligniteta. Prema Poseidon kriterijumima [40,41] sa prosekom godina 26, vrednostima AMH 2.4 (1.3-3.9), srednjim AFC 21 (15-30), nulipare (81.4%) sa 96% dijagnozom limfoma, 56% je dobilo protokole sa visokom toksičnošću. Isključeni su oni sa prethodnom HT i transplantacijom hemopoetskih stem ćelija. Nalazi su prosečno trajanje stimulacije 11 dana (10-12 dana), početna doza rFSH 300 IU (225 do 300 IU), medijalna totalna doza 3000 IU (2025-3825 IU), srednje vredost dobijenih oocita 14 (8-22 oocita), medijana stopa maturacije oocita 81.3% (67.9-90.9). Prema Poseidon kriterijumima, grupa 3 i 4 obuhvataju 22.6% što su poor responder po klasifikaciji pre stimulacije, a nakon stimulacije je 19.5% imalo neočekivan suboptimalni odgovor (Poseidon 1 i 2). Nije pokazano da tip hematološkog oboljenja maligniteta, stadijum limfoma, prisustvo nepovoljnih kliničkih i bioloških parametara, povezano sa nezadovoljavajućim odgovorom na stimulaciju ovulacije, kao ni brojem dobijenih MII ćelija. Međutim, niski nivoi AMH pre gonadotoksičnog tretmana su povezani sa nepovoljnim prisutnim kliničkim i biološkim parametrima i odmaklim stadijumima limfoma.

Cobo i saradnici su izvestili o prosečnim 12.5 oocita sa medijanom od 32 godine starosti za prezervaciju fertiliteta kod hematoloških maligniteta. Još 2 studije Friedler i saradnici i Fraison i saradnici su prijavile prosečan broj M II oocita od 6 do 9.4 [42,43]. Kada se pacijetkinje sa hematološkim malignitetima u pogledu ovarijalne stimulacije porede sa ostalim faktorima fertiliteta npr muški faktor [44] elektivno krio oocita za donaciju oocita i drugim tipovma i kancera, nisu našle značajnu razliku u ovarijalnom odgovoru u odnosu na pacijetkinje sa limfomima [45,46]. Quintero i saradnici nalaze upotrebu većih ukupnih doza gonadotropina i duže trajanje stimulacije, kao i upotrebu viskodoznih protokola sa početnom dozom od 300 IU [47]. Međutim, neke studije ukazuju na redukovan odnosno lošiji odgovor u na ovarijalnu stimulaciju kod hematoloških maligniteta u poređenju sa ostalom infertilnom populacijom (tubarni, muški faktor) ili u odnosu na druge tipove kancera [48, 49]. Prema navodima Goldberga i sar., 2025. kod 22% pacijetkinja sa limfomima je imalo Po Poseidon kriterijumima 3 i 4 “poor response”, što je više nego u studiji Estevesa i saradnika 202.1 sa 8,4%.

Po pitanju trudnoće, nemačka studija je pokazala da proporcija žena sa HL koje su postigle trudnoću je sličan, kao u zdravoj populaciji, izuzev za uzrast od 40 do 44 godine i onih sa pelvičnom iradijacijom [50]. Kumulativne stope živorođenja između Dankinja koje su imale uspešno lečenje HL i zdravih pacijetkinja, pokazale su komparabilčne stope [51]. Pozitivni prediktivni faktori za trudnoću kod pacijetkinja se hematološkim malignitetima su manje od 35 godina, prisustvo partnera u vreme dijagnosze, i odsustvo transplantacije kosne srži (nisu izražene iradijaciji celog tela ili mijeblastnoj konzervativnoj terapiji). Utilizacija gameta 6% ja zastupljena i 18% pacijetkinja je pokušavalo da radi na trudnoći kod hematoloških maligniteta [52]. Meta-analiza Fraison i saradnike iz 2023. godine pokazala je stope živorođenja od 32% nakon korišćenja vitirifikacije oocita sa 4.6% ponovnom upotrebom gameta.

Naši rezultati na 13 pacijetkinja pokazuju sledeće rezultate u procesu krioprezervacije oocita zbog hematoloških maligniteta (Tabela 1). 46% je imalo prethodno ciklus hemioterapije, najčešći hematološki malignitet je Hodgkin limfom sa zastupljenošću od 38,46%, zatim Non Hodgkin limfomi 30,76% i akutna mijeblastna leukemija sa 23,07%. Više od 50 % (53,84) je započeto u lutealnoj fazi ciklusa, koja inače rezultuje dužim trajanjem stimulacije u odnosu na folikularnu. Prosek starosti paciijetkinja je 28 godina (19-39), broj dana stimulacije 12.76 ±3.7 sa dobijenih 9 ćelija u proseku (od 1 do 27 ćelija) i potrošeno 35±15 ampula gonadotropina, što odgovara proseku u infertilnoj populaciji mlađoj od 35 godina.

Tabela 1. Nalazi serije žena sa hematološkim malignitetima – krioprezervacija (u periodu od 2016 do 2025).

godine	dg	Faza stim	Preth HT	AMH (ng/ml)	AFC	Amp Gonado	Dani stim	Broj ćelija	Broj MII	Broj krio ćeli
20	ALL(comB)	lute	6	2,68	21	44	13	16	9	15
27	HL sc nod	fol		4,47	34	18	12	27	13	25
19	HL sc nod	fol	6	3,27	20	18	11	16	11	15
19	AML	lute	6	0,09	7	36	12	1	0	1
32	AML	lute	6	2,25	15	32	10	12	8	11
36	MDS sy m	lute	6	2,68	15	26	12	2	2	2
21	HL mesov	lute		2,79	16	45	13	5	4	5
39	HL	fol		0,40	5	62	2,1	1	1	1
34	NHL tip B	fol		2,12	10	24	8	8	6	8
39	NHL fol	lute		0,44	4	30	9	2	2	2
37	NHL T cell	fol		0,93	8	52	19	6	6	6
20	HL s nod	K fol		0,62	27	43	15	17	15	16
21	AML	fol	6	0,16	7	31	11	4	3	4

Nažalost, mnogi kliničari i pacijetkinje još uvek nisu u potpunosti svesni i obavešteni o mugućnostima prezervacije fertiliteta, i manje od 50% dobije adekvatnu informaciju i savet od strane reproduktivnog specijaliste [51]. Takođe, dodatno, pacijetkinje sa kancerom, prilikom savetovanja dobijaju savete o rezultatima pacijetkinja on ART zasnovane na uzrocima infertiliteta (tubarni, muški, ovarijalni) i o upotrebu zamrznutih gameta u opštoj infertilnoj populaciji. S obzirom da je upotreba zamrznutih gameta kod pacijetkinja sa kancerom veoma niska (manje od 10%) i rezultati su nedovoljni za zaključivanje [52].

Zašto se mali broj žena vraća po ćelije?

- Potrebno je vreme da se kompletira anti-kancer terapija
- Često nedostatak partnera i zakonski limiti
- Želja za spontanom trudnoćom
- Strah od relapsa bolesti

Ali, pacijenti izražavaju želju da se oociti čuvaju i dalje (u Srbiji neograničeno čuvanje).Većina žena, i nakon uspešne terapije i uslova da koristi krioprezervirani materijal, se odlučuje za gestacijski surogat, ako je zakonski primenljivo.

Literatura:

1. American Cancer Society. Available online: https://www.cancer.org/cancer/types/cancer in children/key statistics. htlm (acessed on 28 october 2023).
2. Alviggi C, Andersen CY, Buehler K, Conforti A, Placido GD, Esteves SC, Fischer R, Galliano D, Polyzos NP, Shunkara SK, et al. Poseidon Group (patient oriented strategies encompassing individualized oocyte number). A new more detailed stratification of low responders to ovarian stimulation: from a poo ovarian response to a low prognosis concept. Fertil Steril 2016;105:1452-1453.
3. Assouline E, Crocchiolo R, Prebet T, Broussais F, Coso D, Gamerre M, et al. Impact of reduced-intensity conditioning allogeneic stem cell transplantation on women, fertility. Clin Lymphoma Myeloma Leuk 2013;13:704-10.
4. Barton SE, Najita JS, Ginsburg ES, Leisenring WM, Stovall M, Weathers RE, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report form the Childhood Cancer Survivor Study cohort. Lancet Oncol 2013; 14:873-81.
5. Behringer K, Thielen I, Mueller H, Goergen H, Eibl AD, Rosenbrock J, Halbsguth T, Eichenauer DA, et al. Fertility and gonadal function in female survivors after treatment of early unfovorable Hodgkin lymphoma (HL) within German Hodgkin Stugy Gropu HD 14 triqal. Ann Oncolm 2012; 23:1818-1825.
6. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol 2016; 12:2333-2344.
7. Brun T, Dion L, Jailard S, Bates D, Domin M, Lavoue V, Leveque J, Houot R, Duros S. Ovarian response to stimulation for fertility preservation in women with hematologic cancer. J Gynecol Obstet Hum Reprod 2021; 50:101925.
8. Cheson BD, Fischert RI, Barrington SF, Cavalli F, Schwarts LH, Zucca E, Lister TA. United Kingdom National cancer research Institute. Recommendations for initial evaluation, staging, and response asseeement of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32:3059-3068.
9. Chen M, Jiang H, Zhang C. Selected Genetic Factors Associated with Primaryx Ovarian Insuficiency. Int J Mol Sci 2023;24:24423.
10. Cobo A, Garcia-Velasco J, Domingo J, Pellicer A, Remohi J. Elective and Oncofertility preservation: factors related to IVF outcomes. Hum Reprod 2018;33:2222-2231.
11. Defossez G, Guyader L, Peyrou S, Uhry Z, Grosclaude P, Colonna M, dantony E et al. Estimates nationales de l"incidence et de la mortalite par cancer en France metropolaitane entre 1990 et 2018. Syntese. Saint-Maurice: Sante publique France, 2019, 20.
12. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. Lancet 2014; 384:1302-1310.
13. Dolmans MM, Hossay C, Nguyen TYT, Poirot C. Fertility Preservation: How to Preserve Ovarian Function in Children, Adolescens and Adults. J Clin Med 2021; 10:5247.
14. Domingo J, Gullen V, Ayllon Y, Martinez M, Munoz E, Pellicer A, Garcia-Velasco JA. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. Fertil Steril 2012;97:930-934.
15. Esteves SC, Yarali H, Vuong LN, Carvahlo JF, Ozbek IY, Polat M, Le HM, et al. Low prognosis by the POSEIDON criteria in women undertgoing assisted reproductive technology: a multicenter and multinational prevalence study of over 13000 patients. Front Endocrinol 2021;12:630550.
16. Fabbri R, Pasquinelli G, Magnani V, Arpiati M, Battaglia C, Paradisi R R, Venturolli S. Follicle features in adolescent and young adult women with Hodgkin s disease prior to chemotherapy: a preliminary report. Reprod Biomed Online 2011; 23:799-805.
17. Fraison E, Huberlant S, Labrune E, Cavallieri M, Montagut M, Brugnon F, Cuorbiere B. Live birth rate after female fertility preservation for cancer of haematopeoetic stem cell transplantation: a systematic review and meta-analysis of the three main techniques: embryo, oocyte and ovarian tissue transplantation. Hum Reprod 2023;38:489-502.

18. Friedler S, Koc O, Gidoni Y, Raziel A, Ron-El R. Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis. Fertil Steril 2012;97:125-133.
19. Fleischer RT, Vollenhoven BJ, Weston GC. The effects of chemotherapy on fertility in premenopusal women. Obstet Gynecol Surv, 2011; 66:248-254.
20. Humandian P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of Low prognosis patients in Assisted Reproductive Technology and its proposed marker of successful outcome.F1000Res2016;5:2911.
21. Goldberg i E, Sonigo C, Rakrouki S, Vinolas C, Eustache F, Puy V, Willekens C, Lazarovici J, et al. Hematological cancers in women: from fertility preservation to post-cancer fertility outcomes. Hum Reprod 2025; 40 (7) : 1315-1324.
22. GriffitsMJ, Winship AL, Hunt KJ. Do cancer therapies damage the uterus and compromise fertility? Hum Reprod Update 2020; 26:161-173.
23. Green DM, Kawashima T, Stovall M, Leisering W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from childhood cancer survivor study. J Clin Oncol 2009; 27:2677-85.
24. Katzir T, Shrem G, Meirow D, Berkowitz E, Elizur S, Cohen S, Burke Y, Retchkiman M, Or Y, et al. Fertility preservation parameters in patients with haematologic malignancy: a systemic review and meta-analysis. RBMO 2024; 49 (2).103978.
25. Kim JH, Alzahrani HS, Lee SR, Kim SH, Chae HD. Outcomes of fertility Preservation for Female Cancer Patients in a single Tertiary Center. Yonsei Med J 2023;64 (8):497-504.
26. Kufel-Grabowska J, Lukaszuk K, Blazek M, Jagielo-Gruszfeld A, Horbaczewska A, Inga-Jaworksa N, Jach R., et al. Fertility preservation during oncological treatment. Oncol Clin Pract 2023; epub ahead of print.
27. Lee Dong-Yun, Kim SK, Kim M, Hwang KJ, Kim SH. Ferttility preservation for patients with hematologic malignancies: The Korean Society for Fertility Preservation clinical guidelines. Clin Exp reprod Med 2017; 44(4):187-192.
28. Lubik-Lejawka D, Gabriel I, Marzec A, Olejek A. Oncofertility as an Essential part of Comprehensive cancer Treatment in Patients of reproductive Age, Adolescens and Children. Cancers 2024;16:1858.
29. Mayeur A, Puy V, Windal V, Hesters L, Gallotz W, Benoit A, Grynberg M, Sonigo C, Frydman N. Live birth rate after use of cryopreserved oocytes or embryos at the time of cancer diagnosis in female survivors: a retrospective study of ten years of experience. J Assist reprod Genet 2021;38:1767-1775.
30. McClaim M, Xiao S. Preserving oocytes in oncofertility. Biol Reprod 2022; 106:328-337.
31. Mahey R, Kandpal S, Gupta M, Vanamail P, Bhatla N, Malhotra N. Knowledge and awareness about fertičlity preservation among female patients with cancer: a cross-sectional study. Obstet Gynecol Sci 2020;63:480-9.
32. Miller KD, Noguera L, Devasia T, Mariotto Ab; Yasbroff KR, Jemal A, Kramer J, Siegel RL. Cancer treatment and survivorship statistics 2022. CA Cancer J Clin 2022; 72:409-436.
33. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescent and young adults, 2020. CA Cancer J Clin 2020; 70:7-30.
34. Ohbiki M, Ito Y, Inamoto Y, Miayamura K, Uchida N, Fukuda T, Fujiwara H, Nishida T et al. Improved lomg-term net survival after allogeneic hematopoietic cell transplantation in patients with hemat6ological malignancies over two decades. Transplanta Cell Ther 2023.https//doi.org/10.1016/j.tct2023.09.010.
35. Ovlisen AK, Jakobsen LH, Eloranta S, Kragholm KH, Hutchings M, Frederiksen H, Kamper P. Et al. Parethood rates and use of assisted reproductive techniques in younger Hodgkin lymphoma survivors: a Danish population-based study. J Clin Oncol 2021;39:3464-3472.
36. Paradisi R, Vicenti R, Macciocca M, Seracchioli R, Rossi S, fabbri R. High cytokine expression and reduced ovarian reserve in patients with Hodgkin lymphoma or non-Hodgkin lymphoma. Fertil Steril 2016; 106:1176-1182.
37. Peek R, Bastings L, Westphal JR, Massuger LF, Braat DD, Beerendonk CC. A preliminary study on a new model system to evaluate tumor-detection and tumour-purging protocols in ovarian cortex tissue intended for fertility preservation. Hum Reprod 2015;3 0:870-876.
38. Quintero RB, Helmer A, Huang JQ, Westphal LM. Ovarian stimulation for fertility preservationn in patients with cancer. Fertil Steril 2010; 93:865-868.
39. Shanbhlag S, Ambinder RF. Hodgkin lymphoma: a review and update of recent progress. Ca Cancer J Clin 2018; 12:1307-1311.
40. Siegel RI, Giaquinto AN, Jemal A. Cancer statistics 2024. CA Cancer J Clin 2024; 74:12-49
41. Shrem G, Azani L, feferkorn I, Listovsky T, Hussaini S, Farber B, Dahan MH, Salmon-Divon M. Effect of malignancy on Semen parameters. Life (Basel) 2022. https://doi.org/103390/life12060922.
42. Sklavos MM, Stratton P, Giri N, Alter BP, savage SA, Pinto LA. Reduced serum levels of anti-Mullerian hormone in females with inherited bone marrow failure syndrome. J Clin Endocrinol Metab2015; 100, E197-E203.
43. Sonigo C, Comtet M, Duros S, Sifer C, Sermondade N, Grynberg M. Antral follicle responsiveness to FSH, assessed by the folicular output rate (FORT), is aletred in Hodgkin 2 lymphoma when compared with breast cancer candidates for fertility preservation. J Assist Reprod Genet 2018;35:91-97.
44. Su HI, Lacchetti C,Letrneau J, Partridge H, Qamar R, Quinn G, Reinecke J, Smith JF, Tesch M, Wallace HM, Wang E, Loren AW. Fertility preservation in People with cancer: ASCO Guideline Update. J Clin Oncol 2025;43:1488-1515.
45. Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falj SJ, Gilson D, Hancock BW, Harris SJ, et al. England et Wales Hodgkin Lymphmoma Follow -up Group. Risk opf premature menopause after treatment of Hodgkin lymphoma. J Natl cancer Inst 2014; 106:dju207.
46. Trama A, Stark D, Bozovic-Spasojevic I, Gaspar N, Peccatori F, Toss A, Bernasconi A et al. Cancer burden in adolescens and young adults in Europe. ESMO Open 2023; 8, 10744.
47. Tuppi M, Kehrloesser S, Coutandin DW, Rossi V, Luh VM, Strubel A., et al. Oocyte DNA damage quality control requires consecutive interplay of CHKA 2 to CK1 to activate p63. Nat Struct Mol Biol 2018; 25:261-269.
48. Van Dorp W, Van Der Heuvel-Eibrink MM, De Vries ACH, Pluijm SMF, Visser JA, Peters R. Laven JSE. Decreased serum anti-Mullerian hormone levels in girls with newly diagnosed cancer. Hum Reprod 2014;29:337-342.

49. von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendedations for fertility preservation in women by FertiPROTEKT network. Part II: fertility preservation techniques. Arch Gynecol Obstet 2018;297:257-267.
50. Wu D, Chen H. fertility preservation in female patients with hematological disorders. BMC Pregnancy and Chilbirth 2022;22:61.
51. WHO report "Childhood Cancer Inequalities in the WHO Europena region". Available online:https.//www.who.int/europe/news/item/15-02-2022-new-who-report-highlights-scale-of-childhood-cancer-inequalities-in -the – europena region (accesed on 2 nd Novembre 2023).
52. Wu M, Zhu Q, Huang Y, Tang W, Dai J, Guo Y, Xiong J, Zhang J, Zhou S, Fu F, et al. Ovarian reserve in reproductive- aged patients before gonadotoxic treatment: a systematic review and meta-analysis. Hum Reprod Open 2023; 2023;hoad024.

TRAHELEKTOMIJA U ONKOFERTILITETU – ONKOLOŠKI I OPSTETRIČKI ISHODI

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Uvod: Iako je incidenca raka grlića materice poslednjih decenija u silaznom trendu zahvaljujući organizovanom skriningu i ranom lečenju, žene u razvijenim zemljama sve češće odlažu materinstvo za kasnije životno doba. To je dovelo do češće dijagnoze karcinoma grlića materice stadijuma IB kod pacijentkinja koje još nisu ostvarile svoje reproduktivne planove. Standardni tretman – radikalna histerektomija sa pelvičnom limfadenektomijom – onemogućava očuvanje plodnosti, što je podstaklo razvoj konzervativnog tretmana poštednog po plodnost (FST). Razvoj različitih opcija konzervativnog, fertilitet poštegnog tretmana (FST) pružio je mogućnost odabranim pacijentkinjama sa ranim stadijumima bolesti da očuvaju fertilitet, pod uslovom da imaju dobre prognostičke faktore.

Pregled literature: FST je indikovan kod pažljivo selektovanih pacijentkinja sa ranim stadijumima bolesti (IB1), negativnim limfnim čvorovima, odsustvom limfovaskularne invazije i neagresivnim histološkim tipom tumora. Među razvijenim procedurama nalaze se konizacija, jednostavna trahelektomija, vaginalna radikalna trahelektomija (VRT), laparoskopska minimalno invazivna trahelektomija, abdominalna radikalna trahelektomija (ART) i kombinacije sa neoadjuvantnom hemoterapijom.

Radikalna trahelektomija obuhvata resekciju grlića materice, gornjeg dela vagine i proksimalnog parametrijuma uz očuvanje tela materice, najčešće vaginalnim pristupom i uz laparoskopsku karličnu limfadenektomiju. Kod tumora ≥ 2 cm rizik od recidiva je značajno veći, bez obzira na vrstu operacije. Stope recidiva u literaturi variraju od 0 do 42,9%, dok se preživljavanje bez bolesti (DFS) i ukupno preživljavanje (OS) kod pažljivo selektovanih pacijentkinja kreću iznad 90%. Obstetrički ishodi ukazuju na stopu trudnoća od 30–70%, višu kod VRT i minimalno invazivnih pristupa nego kod ART. Najčešća komplikacija je prevremeni porođaj (39–57%), dok razlike u stopi živorođenosti između tehnika nisu značajne.

Klinički značaj: Optimizacija terapijskog pristupa u skladu sa stadijumom bolesti, histološkim tipom i reproduktivnim planovima pacijentkinje može omogućiti očuvanje fertiliteta bez kompromitovanja onkološke sigurnosti. Multidisciplinarni pristup je ključan, a kada više metoda pruža slične onkološke rezultate, obstetrički ishodi treba da budu odlučujući faktor.

Zaključak: Fertilitet poštedni tretmani, posebno radikalna trahelektomija, predstavljaju značajnu opciju lečenja za pažljivo selektovane pacijentkinje sa ranim stadijumima karcinoma grlića materice, omogućavajući očuvanje reproduktivnog potencijala uz očuvanje onkološke bezbednosti. U domaćoj praksi radikalna vaginalna trahelektomija se primenjuje duži niz godina, ali izostanak sistematskog praćenja onkoloških i obstetričkih ishoda ograničava mogućnost standardizacije indikacija i procedura. Neophodna su prospektivna, multicentrična istraživanja koja bi omogućila definisanje jasnih kriterijuma selekcije, optimizaciju hirurških tehnika i unapređenje protokola praćenja trudnoća, čime bi se postigli najbolji mogući onkološki i reproduktivni rezultati u našoj populaciji.

Ključne reči: trahelektomija, fertilitet-štedeći tretman, karcinom grlića materice, onkološki ishod, obstetrički ishod

TRACHELECTOMY IN ONCOFERTILITY – ONCOLOGICAL AND OBSTETRIC OUTCOMES

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Introduction: Although the incidence of cervical cancer has been declining in recent decades due to organized screening programs and early treatment, women in developed countries increasingly postpone childbearing to later in life. This has led to more frequent diagnoses of stage IB cervical cancer in patients who have not yet fulfilled their reproductive plans. The standard treatment – radical hysterectomy with pelvic lymphadenectomy – precludes fertility preservation, which has prompted the development of fertility-sparing treatment (FST). The emergence of various fertility-preserving surgical options has enabled selected patients with early-stage disease to retain their fertility, provided they have favorable prognostic factors.

Literature Review: FST is indicated in carefully selected patients with early-stage disease (IB1), negative lymph nodes, absence of lymphovascular space invasion, and non-aggressive histological tumor types. Developed procedures include conization, simple trachelectomy, vaginal radical trachelectomy (VRT), laparoscopic minimally invasive trachelectomy, abdominal radical trachelectomy (ART), and combinations with neoadjuvant chemotherapy.

Radical trachelectomy involves resection of the cervix, the upper part of the vagina, and the proximal parametrium while preserving the uterine body, most often performed via a vaginal approach combined with laparoscopic pelvic lymphadenectomy. For tumors ≥ 2 cm, the risk of recurrence is significantly higher regardless of the type of surgery performed. Recurrence rates reported in the literature range from 0 to 42.9%, while disease-free survival (DFS) and overall survival (OS) in carefully selected patients generally exceed 90%. Obstetric outcomes show pregnancy rates ranging from 30–70%, higher with VRT and minimally invasive approaches compared to ART. The most common complication is preterm delivery (39–57%), while differences in live birth rates between techniques are not significant.

Clinical Significance: Optimization of the therapeutic approach according to disease stage, histological type, and the patient's reproductive plans can enable fertility preservation without compromising oncologic safety. A multidisciplinary approach is essential, and when several methods offer comparable oncological outcomes, obstetric results should be the deciding factor.

Conclusion: Fertility-sparing treatments, particularly radical trachelectomy, represent a valuable treatment option for carefully selected patients with early-stage cervical cancer, enabling preservation of reproductive potential while maintaining oncologic safety. In domestic practice, radical vaginal trachelectomy has been performed for many years; however, the lack of systematic monitoring of oncological and obstetric outcomes limits the ability to standardize indications and procedures. Prospective, multicenter studies are needed to establish clear selection criteria, optimize surgical techniques, and improve pregnancy monitoring protocols, thereby achieving the best possible oncological and reproductive outcomes in our population.

Keywords: trachelectomy, fertility-sparing treatment, cervical cancer, oncological outcome, obstetric outcome

References:

1. Bahrehmand K, Vesztergom D, Budai B, Lengyel D, Lukács E, Novák Z. Evaluation of reproductive and oncological outcomes after fertility-sparing surgery in cervical cancer patients with tumor > 2 cm. Gynecol Oncol Rep. 2025;57:101688.
2. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility-sparing surgery in early-stage cervical cancer: Oncological and obstetrical outcomes. J Gynecol Oncol. 2016;27(6):e61.
3. Robova H, Halaska MJ, Pluta M, Skapa P, Matecha J, Lesko D, et al. Oncological and functional outcomes after fertility-sparing surgery in early cervical cancer patients: A multicenter study. Int J Gynecol Cancer. 2015;25(4):712–718.
4. Willows K, Bryant A, Farrell R. Radical trachelectomy for early stage cervical cancer. Cochrane Database Syst Rev. 2016;(2):CD008479.
5. Slama J, Dundr P, Dusek L, Cibula D. Local control and survival after less radical surgery for early-stage cervical carcinoma: A systematic review and meta-analysis. Gynecol Oncol. 2023;170(1):15–23.
6. Nezhat FR, Roman RA, Rambhatla A, Nezhat CH. Reproductive and oncologic outcomes after fertility-sparing surgery for early-stage cervical cancer: A systematic review. J Minim Invasive Gynecol. 2022;29(3):295–307.
7. Ferrandina G, Ercoli A, Fagotti A, Fanfani F, Gallotta V, Margariti PA, et al. Completion of radical hysterectomy in early-stage cervical cancer patients with intraoperative diagnosis of positive pelvic lymph nodes: A multi-institutional retrospective study. Ann Surg Oncol. 2017;24(5):1355–1361.
8. Mathevet P, Lécuru F, Magaud L, Bouttitie F, Guyon F, Houvenaeghel G, et al. Sentinel lymph node biopsy and ultra-staging in early cervical cancer: Results of a prospective multicenter study (SENTICOL II). J Clin Oncol. 2021;39(15_suppl):5506–5506.
9. Balaya V, Guani B, Mathevet P, Lecuru F. Sentinel lymph node mapping in early-stage cervical cancer: A comprehensive review. Cancers (Basel). 2022;14(8):1854.
10. Li J, Li Z, Wang H, Huang Y, Xu T, Li H, et al. Oncological and obstetric outcomes after fertility-sparing trachelectomy for early-stage cervical cancer: A retrospective study of 212 cases. BMC Cancer. 2020;20:579.
11. Vieira M, Rosa D, Ribeiro I, Costa A, Lemos N, Dias JL, et al. Oncological and obstetric outcomes after abdominal versus minimally invasive radical trachelectomy for early-stage cervical cancer: A multicenter study. Int J Gynecol Cancer. 2021;31(9):1204–1213. doi:10.1136/ijgc-2021-002473.
12. Kim M, Kim JH, Kim YB, No JH, Kim K, Kim JW, et al. Oncologic and obstetric outcomes after abdominal radical trachelectomy in early-stage cervical cancer. Obstet Gynecol Sci. 2022;65(1):34–43.

CERVIKALNI KARCINOM: DA LI BI TREBALO DA BUDEMO MANJE RADIKALNI?

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Univerzalno je prihvaćeno da radikalna histerektomija sa obostranom adneksektomijom i pelvična limfadenektomija predstavljaju standardno lečenje karcinoma grlića materice u stadijumima od Ib1 do IIa1 i taj stav je inkorporiran u smernice za lečenje karcinoma grlića materice svih relevantnih stručnih udruženja i organizacija [1]. Ovaj pristup lečenju osigurava najbolje onkološke ishode lečenja u navedenim stadijumima bolesti. Međutim, radikalna histerektomija je opterećena značajnim perioperativnim i postoperativnim morbiditetom i negativnim uticajem na kvalitet života pacijentkinja [2]. Ovo je posledica parametrektomije (koja predstavlja sastvani deo radikalne histerektomije i jednu od glavnih hirurških distinkcija u odnosu na klasičnu histerektomiju). U poređenju sa klasičnom histerektomijom, radikalna histerektomija je povezana sa višom učestalošću perioperativnog krvarenja, povreda mokraćne bešike, povreda uretera i formiranjem fistula. Bočna parametrija sadrže brojna nervna vlakna koja utiču na funkciju mokraćne bešike, creva i seksualnu funkciju. Prilikom disekcije i uklanjanja parametrija, ova nervna vlakna često bivaju oštećena. Uz to, izvođenje radikalne histerektomije zahteva značajno dužu i složeniju obuku u poređenju sa manje opsežnim zahvatima u ginekološkoj onkologiji.

Postoje brojni dokazi iz retrospektivnih studija da je rizik od zahvatanja parametrija ispod 1 % kod pacijentkinja koje imaju početni stadijum bolesti i povoljne histološke karakteristike - tumor manji od 20 mm, stromalne invazije do 10 mm (određeno histopatološkim pregledom konusa ili zahvatanjem manje od 50 % strome procenjeno preoperativno magnetnom rezonancijom), HPV zavisan histološki tip (skvamocelularni, adenokarcinom i adenoskvamozni kracinom), bez prisustva metastaza u limfnim čvorovima, bez obzira na gradus tumora, bez invazije limfnih i vaskularnih prostora [3]. Cervikalni karcinomi opisanih histoloških karakteristika se u literaturi nazivaju invazivnim cervikalnim karcinomima niskog rizika [4]. Sledstveno, nameće se ideja da bi karcinome grlića materice niskog rizika bilo bezbedno lečiti nekim od zahvata koji su manje opsežni od radikalne histerektomije tj. nekim od zahvata koji ne uključuju parametrektomiju. To mogu da budu klasična histerektomija sa pelvičnom limfadenektomijom, konizacija grlića materice sa pelvičnom limfadenektomijom ili ekscizija grlića materice omčicom (eng. *Large Loop Excision of Transformational Zone* - LLETZ) sa pelvičnom limfadenektomijom.

Jedna od prospektivnih studija kojima je ispitivana mogućnost lečenja invazivnog karcinoma grlića materice simpleks histerektomijom (za pacijentkinje koje nisu imale želju za očuvanjem fertiliteta, a nakon konizacije) ili konizacijom (za pacijentkinje motivisane da očuvaju fertilitet) u kombinaciji sa pelvičnom limfadenektomijom je bio ConCerv Trial sproveden u periodu 2010-2019. godine [5]. U poređenju sa navedenim karakteristikama cervikalnih kracinoma niskog rizika, u ConCerv studiju nisu uključivane pacijentkinje sa adenoskvamoznom diferencijacijomn tumora, sa tumorima gradusa 3 i sa prisutnom limfovaskularnom invazijom. Od 100 pacijentkinja uključenih u studiju, nakon srednjeg praćenja u trajanju od 36,3 meseca, ukupno tri pacijentkinje su razvile recidiv (jedna nakon konizacije, nijedna nakon histerektomije i dve nakon histerektomije iz drugih indikacija kod kojih je dijagnoza invazivnog cervikalnog karcinoma postavljena histopatološkim pregledom preperata histerektomije). Zaključak studije je da su klasična histerektomija sa

pelvičnom limfadenektomijom ili klasična konizacija sa pelvičnom limfadenektomijom prihvatljiva alternativa lečenja invazivnog cervikalnog karcinoma niskog rizika.

Druga važna randomizovana prospektivna multicentrična studija kojom su poređeni ishodi lečenja cervikalnog karcinoma klasičnom (jednostavnom) i radikalnom histerektomijom je SHAPE Trial [6]. Nakon ispunjavanja kriterijuma za uključivanje, pacijentkinje su randomizovane u grupu klasične i grupu radikalne histerektomije (kod obe grupe je rađena i pelvična limfadenektomija). Od 700 pacijentkinja ukuljučenih u studiju, nakon prosečno četiri i po godine praćenja, pelvični recidiv je registrovan kod 11 pacijenktinja u grupi klasične i 10 pacijentkinja u grupi radikalne histerektomije, dok je u prvoj grupi bilo 7 ekstrapelvičnih recidva a u drugoj 2. Nije uočena povezanost između grupe/tretmana i preživljavanja do rekurencije bolesti u karlici (eng. *Pelvic Recurrence-free Survival*), preživljavanja do rekurencije bolesti izvan karlice (eng. *Extrapelvic Recurrence-free Survival*), preživljavanje do rekurencije (eng. *Recurrence-free Survival*) ili ukupnog preživljavanja (eng. *Overall Survival*). Učestalost komplikacija u postoperativnom toku povezanih sa hirurgijom je bila značajno manja u grupi pacijentkinja lečenih klasičnom histerektomijom. U zaključku studije stoji da klasična histerektomija sa pelvičnom limfadenektomijom nije inferiorna u odnosu na radikalnu histerektomiju u lečenju cerivkalnog karcinoma niskog rizika.

Ove dve studije predstavljaju najkvalitetnije dokaze (tzv. dokaze prvog nivoa) da je manje radikalni hirurški zahvat od radikalne histerektomije bezbedna alternativa u lečenju cervikalnog karcinoma niskog rizika. Kao takvi, ovi nalazi mogu predstavljati osnovu za izmenu standardnog lečenja.

Pored pristupa koji podrazumeva deeskalaciju hirurške opsežnosti u lečenju cervikalnog karcinoma (makar za tumore niskog rizika), razmatra se i mogućnost povratka minimalno invazivnog pristupa hirurškom lečenju invazivnog karcinomu grlića materice. Naime, od uvođenja laparoskopskog pristupa radikalnoj histerektomiji pa do objavljivanja rezultata LACC trajala 2018. godine u razvijenim zemljama je konstantno rastao udeo radikalnih histerektomija urađenih minimalno invazivnim pristupom (laparoskopski ili robotski). Međutim, rezultati ove studije (skoro četiri puta niže preživljavanje do progresije u grupi pacijentkinja operisanih minimalno invazivnim pristupom) su imali snažan uticaj na stručna udruženja te su najvažnije smernice za lečenje karcinoma grlića materice u godinama nakon objavljivanja rezultata LACC trajala menjane te minimalno invazivni pristup radikalnoj histerektomiji više nije bio deo standardnog lečenja [7]. Dodatnu nadu za povratak minimalno invazivnog pristupa su doneli rezultati ConCerv i SHAPE trajala. Naime, kako je sprovođenje ConCerv studije započeto znatno pre odbjavljivanja rezultata LACC studije, u ovoj studiji 96/100 pacijentkinja je operisano minimalno invazivnim pristupom. U SHAPE studiji 281/338 pacijentkinja u grupi klasične histerektomije je operisana minimalno invazivnim pristupom, a u grupi radikalne histerektomije 243/342. Ako se posmatra učestalost pojave rekurentne bolesti, ona u grupi klasične histerektomije iznosi 3,2 % (minimalno invazivni pristup) naspram 3,5 % (otvoreni pristup), a u grupi radikalne histerektomije 2,9 % (minimalno invazivni pristup) naspram 3,0 % (otvoreni pristup). Istraživačkom analizom podataka SHAPE studije (eng. *Exploratory data analysis*) nije utvrđeno postojanje statistički značajne razlike između grupe minimalno invazvino i otvoreno operisanih pacijentkinja ni u jendom od analiziranih ishoda [8]. Poređenje podataka iz SHAPE i LACC studije koji se tiču tumora prečnika do 2 cm (prema SHAPE kriterijumima) ukazuje da su pacijentkinje iz SHAPE studije imale bolje trogodišneje preživljavanje bez bolesti (96,5 naspram 92 %).

Međutim, iako privlačni iz ugla entuzijasta za minimalno invazivni pristup hirurškom lečenju cervikalnog karcinoma, ovi rezultati se moraju uzeti s rezervom jer je u obe studije udeo pacijentkinja operisanih minimalno invazivnim prisutpom značajno veći od pacijentkinja operisanih

laparotomijom i, što je važnije, hirurški pristup nije bio stratifikacioni faktor pri randomizaciji. Ovo važi i za laparoskopsku/robotsku pelvičnu limfadenektomiju. Štaviše, naknadnom (posthoc) analizom pacijentkinja ukuljučenih u LACC studiju utvrđeno je da je stopa rekurencije u smislu peritonealne karcinomatoze značajno viša u grupi pacijentkinja operisanih minimalno invazivnim pristupom (23 %) u odnosu na grupu operisanih laparotomijom (9%) [9]. U SHAPE studiji 6 od 7 ekstrapelvičnih recidiva je registrovano u grupi minimalno invazivnog pristupa, kao i sva četriri slučajeva smrti od kancera.

Zanimljivo je da se nepovoljan efekat mininalno invazivnog pristupa radikalnoj histerektomiji gubi u podgrupi pacijentkinja koje su imale konizaciju pre radikalne histerektomije. Naime, u ovoj podgrupi pacijentkinja nema značajne razlike u preživljavanju bez bolesti između pacijentkinja operisanih mininalno invazivnim i otvorenim pristupom (dok u podgrupi pacijentkinja koje nisu imale konizaciju minimalno invazivni pristup je nosio još veći rizik od rekurencije nego u celoj grupi).

Iako postoje obećavajući rezultati da minimalno invazivni pristup ima svoje mesto u lečenju cervikalnog karcinoma niskog rizika, još uvek nedostaju podaci iz randomizovanih prospektivnih studija dizajniranih da ispitaju bezbednost minimalno invazivnog pristupa. Bez dovoljno kvalitetnih dokaza ne može se očekivati promena standardnog lečenja. U isto vreme, danas posedujemo dovoljno kvalitetnih dokaza da možemo očekivati promenu standardnog lečenja cervikalnog karcinoma niskog rizika u smislu pomeranja od radikalne histerektomije ka klasičnoj histerektomiji sa pelvičnom limfadenektomijom ili konizaciji uz pelvičnu limfadenektomiju.

Literatura:

1. Cibula D, Rosaria Raspollini M, Planchamp F, Centeno C, Chargari C, Felix A, Fischerová D, Jahnn-Kuch D, Joly F, Kohler C, Lax S, Lorusso D, Mahantshetty U, Mathevet P, Raj Naik M, Nout RA, Oaknin A, Peccatori F, Persson J, Querleu D, Rubio Bernabé S, Schmid MP, Stepanyan A, Svintsitskyi V, Tamussino K, Zapardiel I, Lindegaard J. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. Radiother Oncol. 2023 Jul;184:109682. doi: 10.1016/j.radonc.2023.109682. Epub 2023 May 1. PMID: 37336614.
2. Frumovitz M, Sun CC, Schover LR, Munsell MF, Jhingran A, Wharton JT, Eifel P, Bevers TB, Levenback CF, Gershenson DM, Bodurka DC. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol. 2005 Oct 20;23(30):7428-36. doi: 10.1200/JCO.2004.00.3996. PMID: 16234510.
3. Vranes B, Milenkovic S, Radojevic M, Soldatovic I, Kesic V. Risk of Parametrial Spread in Small Stage I Cervical Carcinoma: Pathology Review of 223 Cases With a Tumor Diameter of 20 mm or Less. Int J Gynecol Cancer. 2016 Feb;26(2):416-21. doi: 10.1097/IGC.0000000000000604. PMID: 26745697.
4. Ramirez PT, Pareja R, Rendón GJ, Millan C, Frumovitz M, Schmeler KM. Management of low-risk early-stage cervical cancer: should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? Gynecol Oncol. 2014 Jan;132(1):254-9. doi: 10.1016/j.ygyno.2013.09.004. Epub 2013 Sep 14. PMID: 24041877; PMCID: PMC4286394.
5. Schmeler KM, Pareja R, Lopez Blanco A, Humberto Fregnani J, Lopes A, Perrotta M, Tsunoda AT, Cantú-de-León DF, Ramondetta LM, Manchana T, Crotzer DR, McNally OM, Riege M, Scambia G, Carvajal JM, Di Guilmi J, Rendon GJ, Ramalingam P, Fellman BM, Coleman RL, Frumovitz M, Ramirez PT. ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer. 2021 Oct;31(10):1317-1325. doi: 10.1136/ijgc-2021-002921. Epub 2021 Sep 7. PMID: 34493587; PMCID: PMC11910188
6. Plante M, Kwon JS, Ferguson S, Samouëlian V, Ferron G, Maulard A, de Kroon C, Van Driel W, Tidy J, Williamson K, Mahner S, Kommoss S, Goffin F, Tamussino K, Eyjólfsdóttir B, Kim JW, Gleeson N, Brotto L, Tu D, Shepherd LE; CX.5 SHAPE investigators; CX.5 SHAPE Investigators. Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer. N Engl J Med. 2024 Feb 29;390(9):819-829. doi: 10.1056/NEJMoa2308900. PMID: 38416430.
7. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1895-1904. doi: 10.1056/NEJMoa1806395. Epub 2018 Oct 31. PMID: 30380365.
8. Plante M, Mahner S, Sebastianelli A, Bessette P, Lambaudie E, Guyon F, Piek J, Smolders R, Tidy J, Williamson K, Hanker L, Goffin F, Tsibulak I, Eyjolfsdottir B, Gleeson N, Lee JY, Ke Y, Kwon JS, Ferguson SE, Shepherd L, Tu D. Minimally invasive compared to open surgery in patients with low-risk cervical cancer following simple hysterectomy: An exploratory analysis from the Gynegologic Cancer Intergroup/Canadian Cancer Trials Group CX.5/SHAPE trial. Int J Gynecol Cancer. 2025 Jan;35(1):100001. doi: 10.1016/j.ijgc.2024.100001. Epub 2024 Dec 18. PMID: 39878257.
9. Ramirez PT, Robledo KP, Frumovitz M, Pareja R, Ribeiro R, Lopez A, Yan X, Isla D, Moretti R, Bernardini MQ, Gebski V, Asher R, Behan V, Coleman RL, Obermair A. LACC Trial: Final Analysis on Overall Survival Comparing Open Versus Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. J Clin Oncol. 2024 Aug 10;42(23):2741-2746. doi: 10.1200/JCO.23.02335. Epub 2024 May 29. PMID: 38810208.

NON-EPITHELIAL OVARIAN CANCER: FERTILITY SPARING

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Introduction: Non-epithelial ovarian cancers are rare, accounting 3-10% of all ovarian cancers. Wide spectrum of histopathological types includes malignant germ cell tumors, sex cord–stromal tumors, ovarian sarcomas and small-cell carcinomas of the ovary. Age distribution also varies, so germ cell tumors mostly occur in younger women, but can also be found in postmenopausal women. Sex cord-stromal tumors are usually found in peri- and postmenopausal women and ovarian sarcomas are biphasic. Risk factors include family history of ovarian cancers, obesity, smoking, a sedentary lifestyle, and endometriosis for clear-cell carcinoma. Patients are usually presented with sense of pressure or pain in the pelvis or abdomen as well as irregular menstruation. In contrast to epithelial ovarian cancers, fertility-sparing surgery is the standard treatment for non-epithelial cancers and platinum-based chemotherapy is applied as an adjuvant treatment. Overall prognosis is favourable, but histological diversity and rarity and variable age distribution make them challenging to treat and estimate the reproductive and oncological outcomes. The main issue after treatment in young women is reproduction and conception rates after fertility-sparing treatment that vary from 16% to 59%, while the pregnancy rates range from 67% to 100%. Therefore, the aim of this study was to investigate the oncological and reproductive outcomes of patients with non-epithelial ovarian tumors who underwent fertility-sparing surgery over 10 years at our tertiary referral university clinic.

Materials and methods: This was a retrospective study including all the patients diagnosed and treated with fertility-sparing surgery from 2010 to 2019. The patients' demographic and clinical characteristics, data regarding the treatment and the clinical, laboratory, and imaging findings during follow-up and disease recurrences were recorded. The inclusion criteria were: age gap from 18 to 45 years of age, adequately surgically staging, fertility-sparing surgery as the initial treatment, regular follow-ups after surgery for at least 12 months. The exclusion criterion was concurrent malignancies or comorbidities that might impact fertility, such as a myoma or polycystic ovary syndrome (PCOS). The preoperative assessment included: body mass index (BMI), a chest X-ray and imaging of the pelvis and abdomen (US with a follicular count and MRI), family, personal, medical, and gynecological history, a thorough gynecological examination with a colposcopy and Papanicolaou testing, as well as laboratory testing with biochemical analyses, complete blood count, coagulation factors, and tumor markers CA 125, human epididymis protein 4 (HE4), AFP, and carcinoembryonic antigen (CEA), and AMH to assess the ovarian reserve. Fertility sparing treatment was conducted in young patients and patients with a strong desire to preserve fertility. The decision was based on a preoperative assessment that indicated a low-stage disease with favorable oncological selection criteria for ovarian preservation according to current guidelines. Oncological outcomes ware measured as a recurrence-free survival and the overall survival rate. The reproductive outcomes were assessed as attempting and achieving pregnancy.

Results: In total, 39 patients were included with average age of 27± 7 years. Sex cord-stromal tumors were found in 22 (56.4%) patients, and 17 (43.6%) were diagnosed with germ cell tumors ($p = 0.423$). The single most frequent tumor was a granulosa cell tumor (53.8%), out of which 43.6% were adult-type and 10.3% were juvenile-type tumors. At the time of the diagnosis, 21 patients were diagnosed in IA stage, 13 in IC1 stage, 3 patients in IC2, one patient in IC3 and one patient in

IIIC. A unilateral salpingo-oophorectomy as the initial fertility-sparing treatment was the therapy of choice for 30.8% of the patients and 28.2% of patients had a second-step surgery. A laparotomy was the preferred approach for the initial surgery in 79.5% of the patients and for all (100%) cases of second-step surgeries. Adjuvant chemotherapy was indicated in 48.7% of the patients, from two to six cycles of BEP chemotherapy. The mean follow-up time was 62.92 ± 45.65 months (range: 9–120 months) and 56.4% of the patients were followed for more than five years. The recurrence rate in our population was observed in a quarter of the patients, most often in first two years after treatment. At the end of the first postoperative year the recurrence-free survival was 92.31%, and at the end of the third year 76.92%. The recurrence-free survival was similar for both GCTs and SCSTs ($p = 0.317$). Type of the tumor did not statistically affect recurrence-free survival rate ($p = 0.317$). In terms of reproductive outcome, ten (25.6%) patients tried to conceive and seven succeeded (pregnancy rate was 70%). The pregnancy was achieved after 1 to 6 years. Pregnancy was achieved in two patients with a dysgerminoma, one with an immature teratoma, and four with a granulosa cell tumor of the adult type. All pregnancies were uneventful.

Discussion: Fertility preservation has emerged in the last couple of decades becoming increasingly important treatment choice. This is especially important for adolescents and young adults since the frequent diagnosis of non-epithelial ovarian malignancies among them. Exception is granulosa cell tumor which could be diagnosed in postmenopausal women as well. Although these malignancies encompass wide histological types, they generally have a favourable prognosis which is a cornerstone for fertility preservation. Furthermore, this group is considered as relative chemosensitive with indolent growth patterns and lower rates of bilateral involvement. The aim of fertility sparing treatment is to preserve the uterus and contralateral ovary. Very important step during surgery which consists of unilateral salpingo-oophorectomy is adaequate staging. Patients with early-stage disease generally do not require adjuvant therapy and should only be closely monitored because adjuvant therapy does not seem to significantly impact the prognosis in such cases. Nowadays, many large retrospective studies have shown an excellent survival outcomes among patients with non-epithelial ovarian cancers, even in advanced stages. Luckily, most of these malignancies are diagnosed in early stage. In a study of pediatric patients, almost 70% of these tumors were in stage I, even though most tumors had diameters > 10 cm. In our sample, except one patient, everyone was stage I of the disease. The possibility to avoid radical treatment without compromising survival is very important for young women who have not finished reproduction.

Previous studies have showed that the five-year survival rates is as high as 98% and that the overall mortality decreases significantly with each calendar year. This decline is most significant in the first two years. Factors associated with lower rates of overall survival include disease recurrence, a residual tumor, incomplete surgical staging, and a more advanced stage at the time of the diagnosis. The worst prognosis was found for yolk sac tumors. Some studies also reported that the survival rate for those malignancies with distant metastasis is only 34%. Our study confirms that a less advanced stage at the time of the diagnosis is correlated with better survival. However, the most important risk factor for patient survival is disease recurrence. The reported recurrence rate is 5-25%.

Also, results concerning reproductive outcomes in these patients are promising and many patients managed to conceive, even spontaneously. The pregnancy rates vary from around 20% to more than 90%, while the live birth rates vary from 65% to 95%. In our study, pregnancy rate was 70% after conservative fertility-sparing surgery. All the pregnancies ended with favourable outcome.

Importantly, pregnancy after conservative treatment does not seem to negatively impact the recurrence or mortality rates.

Finally, there are still some challenges in oncofertility field regarding risk of recurrence and potential effect of chemotherapy on ovarian reserve. Since these malignancies are rare, further multicentric studies are recommended. For now, smaller studies like this one shows that fertility-sparing surgery is safe and effective but it is important to approach these patients individualised and multidisciplinary.

Conclusion: Based on our 10 years of experience, fertility-sparing treatment for non-epithelial ovarian cancers is a safe and successful option in terms of both oncological and reproductive outcomes. The overall survival rate in our study was 87.2%, while the recurrence rate was 25.6%, most commonly in patients with granulosa cell tumors. The pregnancy rate after conservative fertility-sparing surgery was 70%. The types of initial treatment and adjuvant chemotherapy did not seem to affect the fertility outcomes.

Keywords: non-epithelial ovarian cancers, oncological outcome, reproductive outcome

References

1. Cheung A, Shah S, Parker J, Soor P, Limbu A, Sheriff M, et al. Non-Epithelial Ovarian Cancers: How Much Do We Really Know? Int. J. Environ. Res. Public Health. 2022;19:1106. doi: 10.3390/ijerph19031106.
2. Ray-Coquard I, Morice P, Lorusso D, Prat J, Oaknin A, Pautier P, et al, ESMO Guidelines Committee Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2018;29:iv1–iv18. doi: 10.1093/annonc/mdy001.
3. Daviu C, Blaakaer J, Eriksson A.G.Z, Herrstedt J, Vandborg M.P, Rasmussen A.M.O, Fuglsang K. Nonepithelial ovarian cancer–The current clinical practice in the Nordic countries. Survey from the surgical subcommittee of the Nordic society of gynecological oncology (NSGO) Acta Oncol. 2022;61:939–945. doi: 10.1080/0284186X.2022.2088249.
4. Mendoza R.P, Tjota M.Y, Choi D.N.B, Chapel D.B, Kolin D.L, Euscher E.D, et al. Clinicopathologic and Molecular Characterization of Gynecologic Carcinosarcomas with a Mesonephric-Like Carcinomatous Component. Am. J. Surg. Pathol. 2025;10:1097. doi: 10.1097/PAS.0000000000002368.
5. Bennetsen A, Baandrup L, Aalborg G, Kjaer S. Non-epithelial ovarian cancer in Denmark – Incidence and survival over nearly 40 years. Gynecol. Oncol. 2020;157:693–699. doi: 10.1016/j.ygyno.2020.03.021.
6. Morice P, Scambia G, Abu-Rustum N.R, Acien M, Arena A, Brucker S, et al. Fertility-sparing treatment and follow-up in patients with cervical cancer, ovarian cancer, and borderline ovarian tumours: Guidelines from ESGO, ESHRE, and ESGE. Lancet Oncol. 2024;25:e602–e610. doi: 10.1016/S1470-2045(24)00262-6.
7. Piątek S, Szymusik I, Sobiczewski P, Michalski W, Kowalska M, Ołtarzewski M, et al. Obstetric Results after Fertility-Sparing Management of Non-Epithelial Ovarian Cancer. Cancers (Basel). 2023;15(16):4170.
8. Saani I, Raj N, Sood R, Ansari S, Mandviwala H.A, Sanchez E, et al. Clinical Challenges in the Management of Malignant Ovarian Germ Cell Tumours. Int. J. Environ. Res. Public. Heal. 2023;20:6089.

MENTAL BURDEN OF ONCOFERTILITY PATIENTS

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According to the Global Burden of Disease 2021 study which offered comprehensive data on cancer prevalence and mortality since 1990 across 204 countries it can be seen that, in recent years, there has been a significant increase in cancer rates among young people. Adolescent and young adult (AYA) cancer is generally defined as cancer diagnosed between ages 15 and 39 years. Among all cancers registered worldwide every year, approximately 500 000 cases are among AYA patients. AYA cancer patients usually have more severe physical and psychosocial consequences of cancer treatment which can negatively impact their treatment adherence. As the 5-year survival rates after current cancer treatment are on the rise, there is a growing recognition of the psychological and quality of life needs specific to AYA cancer patients.

It is well known and expected that newly diagnosed cancer patients can frequently be physically and emotionally overwhelmed by their cancer diagnosis and experience pronounced anxiety and depression. The diagnosis of malignancy carries numerous uncertainties and consequently causes concerns regarding disease prognosis and survival, possibilities and types of treatment, potential side effects of treatment, and the impact on overall quality of life. When it comes to younger patients who generally have not yet finished their reproduction another burden is the impact of both malignancy and its treatment to their fertility. Literature data indicate that many cancer patients and survivors of reproductive age consider parenthood as one of their most important life goals. Therefore it is understandable that the need to interrupt childbearing for several years or the complete inability to conceive as a consequence of their condition can have profound negative mental health impacts for this population.

Oncofertility is a specialized field that focuses on helping cancer patients preserve fertility before commencement of malignancy treatments like surgery, chemotherapy, or radiation which all could negatively affect their reproductive abilities. However, the emotional, psychological, and mental aspects of managing and balancing issue of malignancy treatment and fertility preservation are often overlooked.

The main components of the mental burden faced by oncofertility patients are fear of infertility, time pressure, treatment-related stress, quality of life, stigma and social isolation and long-term effects of the condition.

One of the biggest fears for oncofertility patients, particularly younger patients who have not yet had children, is whether cancer itself or its treatments will leave them infertile. The thought of being unable to have biological children can be devastating, leading to feelings of loss, grief, and depression.

Decisions regarding fertility preservation need to be made in a very short time just after the diagnosis confirmation. This is a period during which patients still have to reconcile with the fact that they have a serious life-threatening illness which can also impact their reproduction. In addition they need to think of fertility preservation often with little emotional or mental preparation. Many patients are told they need to act quickly to preserve their fertility before starting cancer treatments, which can lead to additional stress. Contrary, sometimes the process of fertility preservation (e.g., egg or sperm freezing) can delay the start of cancer treatments,

creating more pressure and causing patients to feel they are risking their cancer prognosis for the sake of future fertility.

Many oncofertility preservation procedures, such as egg retrieval or sperm collection, are invasive and potentially painful or involve specific therapy such as hormonal stimulation that can have numerous side effects (mood swings, fatigue, bloating, etc.). Such therapies add another layer of physical and emotional and stress especially for patients already coping with the physical effects of cancer and its treatments.

In addition, even if fertility preservation is successful, there is always uncertainty about whether a person will be able to successfully use preserved reproductive materials in the future. The possibility of being unable to conceive later on can add to the mental burden.

Cancer treatments often come with significant changes to patients' appearance, such as hair loss, weight changes, or surgical scars. These changes can exacerbate feelings of loss of control over one's body and may negatively affect a person's self-esteem and mental health. The combination of fertility concerns and changes in physical appearance can affect patients' sexual identity, leading to reduced sexual desire or difficulty engaging in intimate relationships which may have negative impact on reproduction.

For patients in relationships, the prospect of infertility and the pressure to promptly have children can create tension and strain. This can lead to marital stress and complicate the dynamics of intimate relationships, where the partner with the malignancy may feel guilty or fearful about not being able to provide a family for the other. The increased rate of relationship brake-ups have been noted in oncofertility patients. Contrary, some relationships are strengthened even more during the process of malignancy treatment and reproduction achievement.

For both men and women, the fear of infertility can lead to a sense of shame or embarrassment due to societal expectations of parenthood and family-building. This can make patients feel isolated or misunderstood which enhances the feeling of depression even more. Literature data show that numerous cancer patients (especially those not comfortable discussing their reproductive concerns) report inadequate emotional and social support during the oncofertility process from their family, friends, colleagues and medical professionals generally because of stigma and misconceptions.

Literature data indicate that majority of patients who preserve fertility are confident and satisfied with their decision, even if further reproduction is not successful, whereas patients who do not preserve fertility report higher rates of decisional regret. However, the process of navigating oncofertility does not end once fertility is preserved or treatments are completed. Patients may continue to experience anxiety until achievement of pregnancy and delivery of a healthy child. Moreover, patients can have post-traumatic stress for years as they deal with the emotional consequences of their experience. The threat of infertility may continue to linger, even if the immediate cancer treatment is successful.

Therefore, integrating psychological support into clinical care of oncofertility patients is critical to ensure that patients with new, persistent, or worsening psychological symptoms are captured and appropriately treated. To mitigate the mental burden of oncofertility, it is essential for patients to receive comprehensive care that includes emotional and psychological support. Previous investigations suggested that several important issues should be addressed during the psychological counseling of oncofertility patients such as pre-existing psychological distress, choice of fertility preservation strategy in the face of an uncertain relationship future, decision

making regarding use of third party donations of reproductive materials, treatment expectations regarding pregnancy and miscarriage, ethical issues related to treatment and decisional regret on case of declined fertility preservation. Strategies and resources to help oncofertility patients include counseling with mental health professionals specialized in fertility or oncology who can guide patients through the decision-making process, connecting with other patients experiencing similar challenges in support groups and supporting patients by medical professionals to openly communicate with chosen doctors, partners, family and friends in order to alleviate feelings of loneliness or misunderstanding.

References:

1. Chen M, Zhang Y, Zhang F, Jiang F, Wang X. Psychological State and Decision Perceptions of Male and Female Cancer Patients on Fertility Preservation. Support Care Cancer. 2022;30(7):5723-5728.
2. Di Mattei VE, Perego G, Rancoita PMV, Taranto P, Carnelli L, Mangili G, Sarais V, Bergamini A, Candiani M. Psychological Aspects Associated With Fertility Preservation in Oncology: An Exploratory Study. Front Psychol. 2020. doi: 10.3389/fpsyg.2020.608651.
3. Kagawa K, Yoshikawa Y, Koizumi T, Suzuki N. Psychological Aspects of and Support for Survivors Attempting to Conceive During or After Cancer Treatments: A Mixed-Methods Systematic Review. J Adolesc Young Adult Oncol. 2025;14(2):129-136.
4. Lawson AK, Klock SC, Pavone ME, Hirshfeld-Cytron J, Smith KN, Kazer RR. Psychological Counseling of Female Fertility Preservation Patients. J Psychosoc Oncol. 2015;33(4):333-353.
5. Liu BY, Sun C, Zhang QX, Lim PY, Lee K. Predictors of self-perceived burden among patients with cancer in Hebei, China. Support Care Cancer. 2025. doi: 10.1007/s00520-025-09590-8.
6. Mocanu E, Purandare NC, Hull L. Reproductive cancer cryopreservation services: Patient information, clinical advice, and support. Int J Gynaecol Obstet. 2025;169(3):867-871.
7. Murray CJL; GBD 2021 Collaborators. Findings from the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2259-2262.
8. Sbaity E, Ramadan N, Slim A, Diab T, Kazarian H, Tarhini A, Charafeddine M, Ghazeeri G, Bazarbachi A, El Cheikh J, El Saghir NS, Assi HI. Fertility preservation in female cancer patients: assessing awareness, attitudes, concerns, experiences, and the role of counseling in quality of life. J Assist Reprod Genet. 2025;42(5):1401-1414.
9. Stal J, Benedict C, Partridge AH, Pozo-Kaderman C, Mack JW. Fertility preservation and mental health among cancer patients of reproductive age. Fertil Steril. 2025. doi: 10.1016/j.fertnstert.2025.07.007.
10. Wang Y, Logan S, Stern K, Wakefield CE, Cohn RJ, Agresta F, Jayasinghe Y, Deans R, Segelov E, McLachlan RI, Gerstl B, Sullivan E, Ledger WE, Anazodo A. Supportive oncofertility care, psychological health and reproductive concerns: a qualitative study. Support Care Cancer. 2020;28(2):809-817.

CHEMOTHERAPY TREATMENT FOR CERVICAL CANCER IN PREGNANCY: A CASE REPORT OF SUCCESSFUL TWIN PREGNANCY

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Introduction

Cervical cancer is the most common gynecological malignancy diagnosed during pregnancy, with an incidence of 1.4–4.6 per 100,000 pregnancies. Currently, the management of cervical cancer in pregnancy is still a challenge and lack of study. It mainly depends on multiple factors, such as the International Federation of Gynecology and Obstetrics (FIGO) stage, histologic features, and gestational age at the time of diagnosis. The optimal therapy for pregnant women with cervical cancer remains a challenge mainly due to the lack of methods to monitor and ensure clinicians and patients that delaying delivery for fetal maturity without affecting maternal outcomes. Contemporary guidelines, such as ESGO/ESTRO/ESP (2023), outline potential diagnostic and therapeutic modalities depending primarily on the stage of the disease and gestational age, and emphasize a multidisciplinary approach and individual treatment to ensure effective oncological control while potentially preserving the pregnancy.

The latest guideline ESGO/INCIP Guidelines for the management of patients with gynecological cancers during pregnancy from just a month ago in 2025 more precisely define usage of chemotherapy for cervical cancer in pregnancy. The choice of chemotherapy regimen for cervical cancer when indicated should, like in non-pregnant patients, be based on cancer (sub)type and stage with prefer paclitaxel/carboplatin in weekly regimen or every 3 weeks. Before each cycle of chemotherapy during pregnancy, assessment by an obstetrician should be performed to assess maternal and fetal health, and the risk of premature labor. Adaptations to standard treatment can be considered with regard to expected fetotoxic effects. Chemotherapeutic agents are expected to reach the fetal compartment to some extent depending on their pharmacokinetic characteristics. Platinum-based chemotherapy, especially cisplatin, carries a risk for ototoxicity in the newborn, therefore carboplatin is preferred for gynecological malignancies except in germ cell cancers, where a cisplatin-based regimen is more effective. Chemotherapy is not recommended before the12th week of gestation. Three-weekly chemotherapy should not be given after 35 weeks of gestation (to avoid hematopoietic suppression/neonatal chemotherapy toxicity). Weekly chemotherapy should not be given after 36 weeks of gestation. Chemotherapy dosing should be identical to non-pregnant women and based on actual maternal weight. Port-a-cath placement should be preferred over peripherally inserted central catheters for chemotherapy administration because of increased risk of thrombosis. For the prevention of chemotherapy induced nausea, ondansetron and metoclopramide can be used. If preterm delivery is expected,

corticosteroids for fetal lung maturation and magnesium sulfate for neuroprotection should be considered in accordance with standard obstetric recommendations. When corticosteroids are indicated, methylprednisolone and prednisolone should be used instead of dexamethasone. If cancer is diagnosed in the third trimester and only 1 cycle of chemotherapy is possible before delivery, patients should be counseled on the fetal risks of late preterm birth versus the maternal/fetal impact of a single cycle of chemotherapy during pregnancy. During pregnancy before the onset of treatment, a fetal anatomy scan should be performed to identify fetal or placental abnormalities. Serial ultrasounds for fetal growth are recommended in patients under going cancer treatment, including surgery chemotherapy. After cervical surgery or right before each cycle of chemotherapy, assessment of cervical competence (or length) is advised, or signs of preterm labor should be investigated. Vaginal progesterone and cerclage should be used according to standard obstetric recommendations. Fetal anemia should be monitored using middle cerebral artery peak systolic velocity doppler when giving high-risk hematotoxic agents such as carboplatin et ifosfamide. In case of anemia (multiples of the median (MOM) > 1.5) delay/stop of chemotherapy, reduction of dosage, change of chemotherapy regimen or even blood transfusion should be considered. Cesarean delivery is recommended in case of invasive cervical cancer, in which case it is important to avoid a lower uterine surgical incision or laceration toward the tumor. A corporeal/classical incision is preferred, especially for large tumors. A vaginal delivery can be considered in cases of previous complete removal of cervical cancer by conization. The child exposed to cancer treatment in utero needs to be examined thoroughly by a neonatologist. Newborns exposed to chemotherapy in utero must be screened for transient neonatal myelosuppression, especially in cases of a short interval between the last course of chemotherapy and birth. If cardiotoxic treatment was administered during pregnancy, an echo cardiogram can be considered. After platinum exposure, hearing function should be screened at birth with auditory brainstem response testing. Breastfeeding should be avoided when systemic anticancer therapy is required postpartum. Systemic anticancer therapy can be (re)started within the first days after uncomplicated vaginal delivery and after 1 week following ce sarean delivery. A discussion regarding contraception is recommended at the postpartum visit for fertile patients requiring ongoing cancer treatment. Before considering a subsequent pregnancy, an oncologic assessment to exclude recurrence or treatment related toxicities are recommended.

Neoadjuvant chemotherapy (NACT) is promising therapeutic strategy for managing cervical cancer in pregnant patients. It helps control disease progression when delaying delivering. NACT may contribute to tumor size, however its full effects on fetus and the mother, especially in cases of twin pregnancies, are not yet fully understood.

Case Presentation

A 34-year-old patient at 17 weeks of twin pregnancy was referred to our clinic following a diagnosis of microinvasive squamous cell carcinoma of the cervix, confirmed by cervical biopsy. Clinical examination at our institution raised suspicion of invasive disease. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed a cervical tumor measuring 10×11×18 mm, without evidence of parametrial or vaginal invasion. The disease was staged as FIGO rIB1. Multidisciplinary tumor board recommended a simple trachelectomy/cervical conization. Conization, followed by prophylactic cerclage placement, was performed at 19 weeks of gestation. Histopathological examination of the conization specimen, four weeks after the procedure was done, confirmed a FIGO pIB1 lesion with lymphovascular space invasion and tumor involvement at the resection margin. Following histopathological confirmation, considering of 24 weeks, a repeated pelvic MRI demonstrated post-interventional changes at the cervix consistent with scarring, without

visible residual malignancy. NACT (Paclitaxel/Carboplatin) in four weekly cycles was recomended. Delivery was planned upon achieving fetal lung maturity and a minimum interval of two weeks after the final chemotherapy cycle. A cesarean section should be scheduled, immediately followed by definitive oncologic surgery—radical hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy. Chemotherapy was administered between the 26th and 29th weeks of gestation. At 28 weeks, fetal lung maturation was induced with dexamethasone. Two weeks after the final chemotherapy cycle, a follow-up pelvic MRI revealed no progression, findings consistent with the previous scan. A final board decision, in line with prior plans, was made to deliver at 35 weeks and proceed with further oncologic treatment. At 35 weeks of gestation, two vital neonates were delivered via cesarean section. At the same surgical act a radical hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy (Wertheim-Meigs procedure) was performed. Final histopathology revealed FIGO stage IIA2 disease with positive residual status (pT2A2, N0, MX, LV1, R1). The patient continued treatment with external beam radiotherapy, followed by four intracavitary brachytherapy applications. Over the past 12 months, the patient has undergone regular clinical and ultrasound follow-ups every three months, and biannual abdominal and pelvic MRIs. No evidence of disease recurrence has been observed. Both the patient and her children are currently in good health.

Conclusion

This case illustrates that cervical cancer in twin pregnancy can be effectively managed by following current guidelines and using multidisciplinary approach, ensuring favorable both perinatal and oncological outcomes. Chemotherapy with Paclitaxel and Carboplatin has shown to be relatively safe for fetuses, but with limited efficacy in controlling progression of the primary cancer.

Literature:

1. Amant F, Berveiller P, Boere IA, Cardonick E, Fruscio R, Fumagalli M, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019 Oct 1;30(10):1601-1612.
2. Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. Int J Gynecol Cancer. 2023 May 1;33(5):649-666.
3. Perrone AM, Bovicelli A, D'Andrilli G, Borghese G, Giordano A, De Iaco P. Cervical cancer in pregnancy: Analysis of the literature and innovative approaches. J Cell Physiol. 2019 Sep;234(9):e14975-14990.
4. Korenaga TK, Tewari KS. Gynecologic cancer in pregnancy. Gynecol Oncol. 2020 Jun;157(3):799-809.
5. Howe T, Lankester K, Kelly T, Watkins R, Kaushik S. Cervical cancer in pregnancy: diagnosis, staging and treatment. The Obstetrician & Gynaecologist 2022; 24: 31–39.
6. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018 Oct;143 Suppl 2:22-36. doi: 10.1002/ijgo.12611. Erratum in: Int J Gynaecol Obstet. 2024 Mar;164(3):1229-1230.
7. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021 Oct;155 Suppl 1(Suppl 1):28-44.
8. Ilancheran A. Neoadjuvant chemotherapy in cervical cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016 May;33:e102-7.
9. de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, et al; International Network on Cancer and Infertility Pregnancy (INCIP). Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337-346. doi: 10.1016/S1470-2045(18)30059-7. Epub 2018 Jan 26. Erratum in: Lancet Oncol. 2021 Sep;22(9):e389.
10. Zagouri F, Korakiti AM, Zakopoulou R, Kyriazoglou A, Zografos E, Haidopoulos D, et al Taxanes during pregnancy in cervical cancer: A systematic review and pooled analysis. Cancer Treat Rev. 2019 Sep;79:e101885.
11. Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013 Feb;121(2 Pt 1):337-343.
12. Amant, Frédéric et al. ESGO/INCIP Guidelines for the management of patients with gynecological cancers during pregnancy. Articles in Press101975, June 12, 2025.

ADNEXAL MASSES IN PREGNANCY - DIAGNOSTICS AND THERAPEUTIC CHALLENGES IN PERINATOLOGY PRACTISE

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Adnexal masses in pregnancy represent a clinically significant entity due to their potential implications for both the mother and the fetus. The incidence ranges from 0.2% to 2% of pregnancies, with most masses incidentally detected during early routine ultrasound examinations. While the majority of these lesions are benign and may regress spontaneously, a minority of cases are complicated by torsion, rupture, infection, or, rarely, malignant transformation.

The diagnostic approach relies heavily on precise ultrasound assessment utilizing validated morphological scoring systems (IOTA criteria) and Doppler studies. In selected cases, especially those with atypical or rapidly growing lesions, non-contrast MRI in the second trimester can provide valuable additional information.

Therapeutic management is based on a combination of gestational age, size and characteristics of the mass, and the presence of symptoms. Conservative monitoring is recommended for most patients; however, surgical intervention is indicated in cases suspicious for malignancy, torsion, or rupture. Recent guidelines support minimally invasive approaches, including laparoscopy during the second trimester, provided that strict patient selection and surgical expertise are ensured.

Emphasis will be placed on analyzing perinatal outcomes based on the latest cohort studies from 2023 to 2025. A multidisciplinary team approach involving obstetricians, perinatologists, oncologists, anesthesiologists, and neonatologists is crucial to optimize outcomes for both mother and child.

References:

1. Cathcart AM, Nezhat FR, Emerson J, Pejović T, Nezhat CH, Nezhat CR. Adnexal masses during pregnancy: diagnosis, treatment, and prognosis. Am J Obstet Gynecol. 2023;228(6):601–12.
2. Barcroft J, Pandrich M, Del Forno S, Cooper N, Linton-Reid K, Landolfo C, et al. Evaluating use of two-step International Ovarian Tumor Analysis strategy to classify adnexal masses identified in pregnancy: pilot study. Ultrasound Obstet Gynecol. 2024;64(6):808–17.
3. Gaughran J, Mukkudem-Petersen J, D'Arcy R, Hutchinson A, Smith J, O'Sullivan R, et al. Adnexal masses in pregnancy: a single-centre study. Cureus. 2024;16(7):e68931.
4. Dur R, Vural F, Gulec UK, Bostanci EI, Gundogan S, Erdemoglu M, et al. Adnexal masses and pregnancy: a single-center retrospective study. J Obstet Gynaecol Res. 2024;50(5):789–96.
5. Bruno M, Franchi D, Di Legge A, Mascilini F, Manganaro L, Fanfani F, et al. Ultrasound features and clinical outcome of patients with adnexal masses during pregnancy: a 2022–2023 series. Diagnostics (Basel). 2023;13(20):3247.

ONCOFERTILITY IN BREAST CANCER

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Breast cancer is the most common cancer diagnosed in women worldwide, meaning that 1 in 8 women will develop breast cancer during the lifetime. A new American Cancer Society reported the rising incidence in women by 1% a year from 2012 to 2021. Although the incidence of breast cancer rises with age, there has been a steeper increase in breast cancer in women under 50 years of age (increasing 1.4% a year). Breast cancer is also the most common cause of death in women younger than 40 years of age. Treatment of breast cancers includes surgery, hormone therapy, targeted drugs and immunotherapy, but chemotherapy is the one that poses a significant risk for fertility in women of reproductive age. Side effect of chemotherapy as gonadotoxic treatment is premature ovarian insufficiency and impaired fertility. So, young women diagnosed with breast cancer are not only facing the burden of malignancy and survival, but of future reproduction and possible inability to have children. All of this expose patients to enormous stress and fear, so the management of these patients should be multidisciplinary, considering all aspects of the cancer treatment. In terms of fertility preservation, it is important to refer a patient to fertility specialist as soon as the diagnosis is made. In general, timing is crucial for any cancer patient and their treatment. Timely referral to oncofertility centre enables doctors to have enough time to prepare a patient for fertility preservation cycle by not delaying specific cancer treatment. This is also important for the patients who fear that fertility preservation procedures will affect and postpone their treatment. Apart from time constraints, there is also a financial burden, restrictions on patient-related criteria and type of centre where fertility preservation procedures are performed, as well as limited awareness. Some previous studies show that many patients never come back after initial consultation with fertility specialist.

Nowadays, advances in diagnosis and treatment markedly improved survival. So later, after successful treatment, those patients might want children, but they are unfortunately left with infertility due to aggressive gonadotoxic nature of chemotherapy. Therefore, oncofertility centres play a major role in providing information and options before breast cancer treatment.

Standard treatment of reproductive-age women is surgery followed by chemotherapy and this gives a window opportunity of approximately 6 weeks. Sometimes, preferred treatment is neoadjuvant therapy before surgery, that also mandates promptly oncofertility specialist consultation. The highest risk of gonadotoxic systemic therapies is with alkylating cyclophosphamide given as (neo)adjuvant therapy leading to treatment-induced amenorrhoea and diminished ovarian reserve. There are also some patient-related factors that influence the risk of gonadotoxic effect of chemotherapy. In the first place is age of the patients since the ovarian reserve naturally drastically falls after the age of 35. For example, patients who are older than 40 years have >80% chances of amenorrhoea induced by chemotherapy. On the other hand, this risk is <20% in patients who are younger than 30 years of age. Some studies qualify anthropometric

and lifestyle factors as an important ones that might have an impact on the ovarian reserve after gonadotoxic treatment.

Pre-treatment ovarian function is based on AMH levels and these values help us predict post-treatment recovery of the ovaries. As mentioned, age is very important risk factor for premature ovarian insufficiency, so when estimating the risk of post-treatment ovarian insufficiency, age, dose and type of gonadotoxic treatment and AMH levels are taken into consideration. The use of GnRH agonist during chemotherapy could be offered in young patients with breast cancer to protect ovarian function. In the study of Lambertini et al, there were 142 per 1000 cases of premature ovarian insufficiency with GnRH agonist, in contrast to 309 per 1000 cases (OR 0,37). The rate of post-treatment pregnancies was also much higher in the group of patients with GnRH agonist.

As a result, oncofertility has emerged with its strategies. According to European Society of Human Reproduction (ESHRE) options for fertility preservation are oocyte cryopreservation and embryo cryopreservation in all countries where these techniques are applied. In Serbia, available options without cost to the patients are based on more specific selection criteria according to national oncofertility guideline. These criteria are: patients younger than 40, nulliparous women without previously cryopreserved oocyte or embryos and in cases of non-metastatic solid tumors and hormone receptor positive breast cancers where chemotherapy is indicated.

Fertility preservation in women with breast cancer was reported in numerous studies and ESHRE guideline is based on the study of 380 cycles using a GnRH antagonist regimen. According to ESHRE guideline for fertility preservation in breast cancer letrozole and random start protocols are acceptable. Random start protocol is an option in cases where urgent treatment is indicated. Moreover, letrozole reduces estrogen levels and meta-analysis reported its use does not impair the efficacy of controlled ovarian stimulation (COS). Less data exists on safety of ART after cancer treatment.

The systematic review and meta-analysis by Arecco et al reported fewer recurrences and death among women who underwent controlled ovarian stimulation before chemotherapy in comparison to patients not exposed, with no difference in event free survival. There was only 6 days delay in the start of chemotherapy in COS patients. Other studies showed there was no significance in terms of survival rate between patients who started neoadjuvant treatment 4 weeks, 4-8 weeks or >8 weeks after diagnosis. Reported data show that adjuvant chemotherapy is even equally effective up to 12 weeks after diagnosis, although recommended period is 60 days, especially for more aggressive malignancies.

Data on pregnancy after cancer treatment are limited. One metanalysis that included 39 studies showed 35% in reduction of the likelihood of subsequent pregnancy after diagnosis, but those patients had better disease-free survival and overall survival.

Additional concern in breast cancer patients is presence of BRCA1 or BRCA2 mutations which is present in 10% of patients younger than 40 years of age. Luckily, development of genetic testing has enabled preimplantation genetic testing that analysis DNA for cancer gene mutations.

To conclude, fertility preservation is an essential component of breast cancer care allowing patients to preserve fertility without compromising oncological outcome. As survival outcomes for breast cancer patients continues to improve, it is essential to preserve quality of life and maintain hope and possibility of future parenthood.

References

1. Arecco L, Blondeaux E, Bruzzone M, Ceppi M, Latocca MM, Marrocco C, et al. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022;37(5):954-968.
2. Lambertini M, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. J Clin Oncol. 2021;39:3293–3305.
3. Nolan K, Boland MR, Hill ADK. Pregnancy After Breast Cancer - Prognostic Safety and Pregnancy Outcomes According to Oestrogen Receptor Status: A Systematic Review. J Breast Cancer. 2022;25(6):443-453.
4. ESHRE Guideline Group on Female Fertility Preservation; Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, Demeestere I, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020;2020(4):hoaa052.
5. Hershlag A, Mullin C, Bristow SL. Is Fertility Preservation Feasible and Safe With Neoadjuvant Therapy for Breast Cancer? JCO Glob Oncol. 2020;6:356-359.
6. Marklund A, Eloranta S, Wikander I, Kitlinski ML, Lood M, Nedstrand E, et al. Efficacy and safety of controlled ovarian stimulation using GnRH antagonist protocols for emergency fertility preservation in young women with breast cancer-a prospective nationwide Swedish multicenter study. Hum Reprod. 2020;35(4):929-938.
7. Arecco L, Perachino M, Damassi A, Latocca MM, Soldato D, Vallome G, et al. Burning Questions in the Oncofertility Counseling of Young Breast Cancer Patients. Breast Cancer (Auckl). 2020;14:11782234209541 79.
8. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2018;36(19):1981-1990.

HEMATOLOGICAL MALIGNANCIES IN PREGNANCY – OUR EXPERIENCE

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Introduction

Hematological malignancies during pregnancy are extremely rare, but they represent one of the most challenging scenarios in contemporary obstetric and oncologic practice. The estimated prevalence is between 1 in 1,000 and 1 in 10,000 pregnancies, corresponding to less than 0.1% of all cancers in women of reproductive age. Nevertheless, the incidence is expected to rise as maternal age at childbirth increases and more women postpone childbearing into their thirties and forties, when the risk of cancer is higher.

The most frequently encountered hematological malignancies in pregnancy are Hodgkin lymphoma, non-Hodgkin lymphomas, and acute leukemias, while chronic leukemias and myelodysplastic syndromes are rarely reported. Their clinical presentation is often nonspecific: fatigue, pallor, anemia, lymphadenopathy, or splenomegaly. Many of these symptoms can mimic normal pregnancy-related changes, leading to diagnostic delays. In addition, physiological leukocytosis of pregnancy and iron-deficiency anemia can mask early hematologic abnormalities.

The pathophysiology of cancer progression in pregnancy is still debated. Hormonal changes, altered immunity, and increased vascularization may affect tumor behavior. Some reports suggest that pregnancy may accelerate tumor growth, particularly in high-grade malignancies, while in others the course remains unchanged. From the fetal perspective, concerns arise from both the disease itself and from diagnostic and therapeutic interventions. Imaging is restricted by the need to minimize fetal radiation exposure, while systemic chemotherapy carries gestational-age–dependent risks.

Management requires careful coordination between obstetricians, hematologists, oncologists, neonatologists, and anesthesiologists. International consensus guidelines address that therapeutic decisions should balance maternal prognosis and fetal well-being, while respecting patient autonomy. When feasible, chemotherapy can be administered safely after the first trimester, and continuation of pregnancy is generally advised if the malignancy is not rapidly progressing.

Given the rarity of the condition, reports from single tertiary centers are crucial for building knowledge and guiding clinical practice.

We present our institutional experience over a 25-year period, focusing exclusively on hematological malignancies diagnosed in pregnancy.

Methods

We retrospectively analyzed 28 pregnant women with hematological malignancies, managed at the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, from 2001- 2025year period. Clinical records were reviewed for maternal age, type of malignancy, gestational age at diagnosis, therapy administered during pregnancy, timing, and mode of delivery, as well as maternal and neonatal outcomes.

The youngest patient was 16 years old, the oldest 40, with a mean age of 30.5 years. Most malignancies were diagnosed in the second trimester. Diagnoses were: acute lymphoblastic leukemia (ALL, n=3), acute myeloid leukemia (AML, n=5), Hodgkin lymphoma (HL, n=11), non-Hodgkin lymphomas (NHL, n=4), chronic myeloid leukemia (CML, n=1), hairy-cell leukemia (n=1), myelodysplastic syndrome (n=1), and chronic lymphocytic leukemia (CLL, n=2).

Results

During pregnancy, 19 of patients (67.9%) received chemotherapy, while in seven cases (25%) treatment was postponed until after delivery.

Seven (25%) pregnancies were terminated due to maternal deterioration and disease progression. The remaining 18 (64.3%) were delivered between 33-39 gestational weeks: 2 vaginal deliveries (9.5%) and 16 (90.5%) cesarean sections, according to the recommendation of the institutional Multidisciplinary Cancer and Human Reproduction Board. Three pregnancies are ongoing at present (all in second trimester): two CLL patients are being followed without active therapy, and one HL patient is currently receiving ABVD.

Six (21.4%) mothers died following completion or termination of pregnancy due to progression of their disease. Seven (25%) neonates died in the perinatal period. Importantly, no congenital anomalies were recorded. Regarding tumor course during gestation, progression was documented in 10 cases (35.7%), remission in 3 (10.7%, 1 HL and 2 CLL), and stable disease (53.6%) in the remaining patients.

Conclusion

Our series confirms that hematological malignancies in pregnancy, while rare, are associated with considerable maternal and neonatal risks. The maternal mortality rate in our cohort was 21.4%, and neonatal mortality reached 25%, yielding an overall maternal survivor 78.6% and neonatal 66.7%. These figures are lower than those reported in some larger series, such as the 22-year experience from our institution encompassing all pregnancy-associated cancers, which documented a one-year maternal survival rate of 87.5% and neonatal survival of 76.2%. The difference can be explained by the fact that hematological malignancies, compared with solid tumors, often have a more aggressive course and require systemic treatment.

Our findings are consistent with international data. Barzilai et al. emphasized that lymphomas and acute leukemias dominate the spectrum of hematologic malignancies during pregnancy and carry a poorer prognosis when treatment is delayed. Di Ciaccio et al. stressed the importance of initiating chemotherapy as soon as maternal condition requires, even during pregnancy, as postponement may compromise survival. In our study, the majority of women received chemotherapy during pregnancy, and this approach appeared feasible without major congenital risks.

The mode of delivery was predominantly cesarean section, in line with the consensus that operative delivery allows better coordination of oncologic care and reduces maternal stress. However, vaginal delivery remains possible in selected cases without obstetric contraindications.

Fetal outcomes in our series underline the vulnerability of neonates. Seven perinatal deaths, mostly related to prematurity, highlight the need to prolong gestation whenever possible. International guidelines recommend aiming for delivery beyond 35 weeks to minimize complications of prematurity. In our cohort, most deliveries occurred preterm, reflecting the urgency of maternal treatment initiation.

Our results highlight the crucial role of multidisciplinary teams. All pregnancies were managed within a dedicated board that included oncologists, hematologists, obstetricians, and neonatologists, ensuring individualized decision-making. This model is strongly supported by international guidelines (Amant et al., 2019) and should be considered the standard of care.

In conclusion, hematological malignancies during pregnancy are rare but severe conditions that require highly specialized care. Maternal and neonatal mortality remain significant despite advances in therapy. Early diagnosis, timely initiation of appropriate treatment, and multidisciplinary management are essential to optimize outcomes.

Our experience contributes to the growing body of evidence and supports the continued effort to develop standardized protocols for these complex cases.

References

1. Milošević B, Likić Ladjević I, Dotlić J, et al. Cancer during pregnancy: Twenty-two years of experience from a tertiary referral center. Acta Obstet Gynecol Scand. 2024;103(6):716–728. doi:10.1111/aogs.14756.
2. Barzilai M, Avivi I, Amit O. Hematological malignancies during pregnancy. Mol Clin Oncol. 2019;10(1):3–9.
3. Di Ciaccio PR, Mills G, Tang C, Hamad N. Managing haematological malignancies in pregnant women. Lancet Haematol. 2021;8(9):e623–e624.
4. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019;30(10):1601–1612.
5. Houlihan OA, Buckley D, Maher GM, McCarthy FP, Khashan AS. Maternal and perinatal outcomes following a diagnosis of Hodgkin lymphoma during or prior to pregnancy: a systematic review. BJOG. 2023;130(3):336–347.

ONCOFERTILITY IN PATIENTS WITH TESTICULAR CANCER

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Introduction

Testicular cancer is the most common malignancy in young men and occurs during the most sensitive life period for reproduction. The incidence of TC has increased during recent decades, predominantly in industrialized countries, and it continues to rise. Thanks to the high cure rate, the focus of contemporary care is no longer just survival, but also the preservation of quality of life after treatment. The most important component in this context is fertility preservation, because the loss of reproductive potential is strongly associated with psychological stress and reduced quality of life.

Histology, Diagnosis, and Therapy

Testicular neoplasms are broadly classified into two major groups: germ cell tumors (GCTs), which are by far the most common, and non-germ cell tumors (sex cord–stromal and other rare types).

Within the category of GCTs, there are two principal subgroups defined by their developmental pathway and epigenetic characteristics. The majority of malignant post-pubertal GCTs arise from germ cell neoplasia in situ (GCNIS). Histologically and clinically, these tumors are divided into seminomas and non-seminomas. Non-seminomas encompass a spectrum of somatic and extra-embryonal components, including embryonal carcinoma, yolk sac tumor, choriocarcinoma, and post-pubertal teratoma (PPT).

In contrast, non-GCNIS–derived tumors consist of pre-pubertal type teratoma and yolk sac tumor, which typically present in early childhood, as well as spermatocytic tumors, which usually occur in older men.

Basic diagnostic procedures include scrotal ultrasound, serum tumour markers, and orchiectomy, followed by stage-guided therapy (chemotherapy, radiotherapy, retroperitoneal lymph node dissection). All of these procedures may have direct or indirect consequences for spermatogenesis and hormonal balance. It is therefore crucial to initiate a discussion about fertility preservation immediately after diagnosis, before starting therapy.

According to recent data, stage I survival exceeds 95–100%, and even in metastatic disease it is around 90%. However, this success in terms of cure often comes at the price of impaired fertility, whether due to malignancy itself, the host immune response (cytokines, fever, malnutrition), or as a result of treatment.

Intrinsic and Endocrine Effects of Disease

The mere presence of a tumor negatively affects spermatogenesis in both the affected and the contralateral, clinically healthy testis. These changes likely reflect a combination of the local tumour effect (reduction of functional parenchyma) and the systemic inflammatory–metabolic response. Elevated hormones (FSH, LH, β-hCG) and reduced testosterone contribute to subfertility and sexual dysfunction.

In germ cell tumours, high concentrations of β-hCG further disrupt spermatogenesis, while in some cases the development of antisperm antibodies contributes to infertility.

Impact of Therapy on Fertility

Surgical management includes radical orchiectomy, and in the case of bilateral tumours or a tumour in a solitary testis it leads to permanent sterility. Retroperitoneal lymph node dissection can cause anejaculation or retrograde ejaculation, but nerve-sparing techniques have significantly reduced this risk.

In selected cases, onco-TESE (onco-testicular sperm extraction) is performed at the time of orchiectomy, whereby spermatozoa are harvested from preserved areas of the testis and cryopreserved for future use.

Chemotherapy and radiotherapy, although highly effective at eradicating the tumour, are gonadotoxic. Platinum-based regimens typically induce temporary azoospermia; meta-analyses and cohort studies show recovery of spermatogenesis in approximately 48% of patients at 2 years and up to ~80% at 5 years after completion of chemotherapy. Alkylating agents carry the greatest risk of permanent azoospermia, and that risk is dose-dependent. In addition, modifications of chemotherapy protocols (e.g., replacing the MOPP regimen with ABVD in testicular lymphoma) can increase the chances of fertility recovery. Radiotherapy also causes dose-dependent impairment of spermatogenesis, with doses above 1.2 Gy almost invariably leading to permanent azoospermia.

The DNA fragmentation index (DFI) peaks 3–6 months after chemotherapy/radiotherapy and most often returns close to baseline by 12 months; therefore, it is recommended to postpone attempts at conception for ≥12 months after gonadotoxic therapy.

Fertility Preservation Options

The most important and most reliable method of fertility preservation remains semen cryopreservation. Samples are most often obtained by masturbation; when this is not possible, vibratory stimulation or electroejaculation is used. In azoospermic patients, testicular aspiration and extraction (TESE, micro-TESE), as well as epididymal methods, are employed.

Cryopreservation involves the use of cryoprotectants (glycerol, egg yolk), while rapid- and ultra-rapid-freeze methods provide better post-thaw motility and viability. Long-term outcomes show that pregnancy is possible even with sperm cryopreserved for more than 20–25 years, whereas fertilisation rates after ICSI range between 26% and 55%.

For adult men and couples planning parenthood, the goal is to maximise the potential for biological offspring while using available resources rationally. The ideal scenario is cryopreservation of an ejaculate before orchiectomy, or at least immediately after it but before any gonadotoxic therapy.

The timing of attempts at conception after treatment is crucial for safety and outcome. It is commonly recommended to wait at least twelve months after completing chemotherapy or radiotherapy, as this is the period in which spermatogenesis and the DNA fragmentation index recover, thereby reducing the risk of adverse reproductive outcomes. After that interval, a semen analysis should be obtained and, if needed, an assessment of genetic material integrity.

For prepubertal patients, standard methods are not applicable; the only option is experimental cryopreservation of testicular tissue containing spermatogonial stem cells. Although still without clinically proven success in humans, animal models support the promise of these techniques.

Barriers in Practice

In practice, fertility preservation is frequently hampered by organisational and financial obstacles. High costs and limited or uneven geographic availability of fertility centres reduce access to services, while time pressure during oncology consultations and short windows before therapy leave little room for informed choice. Insufficient awareness among patients—as well as healthcare providers—further contributes to missed semen banking. Psychosocial and ethical-legal aspects also shape decisions: fear of transmitting a genetic predisposition or of disease recurrence, dilemmas around posthumous use of cryopreserved semen, and the specific circumstances of minors (assent/parental consent). All of this underscores the need for systematic counselling, clearly defined protocols, and financial/logistical facilitation to narrow the gap between recommendations and real-world practice.

The Role of the Gynecologist in Oncofertility for Testicular Tumors

The gynecologist's role in caring for men with testicular cancer and their partners is twofold: clinical-organisational and advisory. The gynecologist initiates a discussion about reproductive plans at the time of diagnosis and enables urgent triage to andrology and a sperm bank before treatment starts, coordinating onco-TESE when this is the only realistic option. In parallel, the gynecologist provides care for the partner, including an assessment of ovarian reserve, provides preconception counselling and, if needed, expedites oocyte/embryo vitrification. In collaboration with the oncologist and urologist, the gynecologist harmonises the timing of oncologic and reproductive procedures, advises effective contraception during therapy and throughout the recommended recovery period, and helps select the ART strategy (IUI versus IVF/ICSI) depending on the quality/source of sperm and the number of available straws. Special attention is paid to sexual function and psychological support for the couple, as well as to ethical-legal questions (consent, posthumous use, minors). Finally, the gynecologist leads preconception and prenatal care when pregnancy is planned after completion of oncologic treatment, with standard obstetric surveillance and coordination with the oncology team.

Conclusion

Fertility preservation is a key component of the management of testicular cancer, equally important as oncologic outcome. Sperm cryopreservation remains the only routinely available and proven-effective method, while surgical, gonadoprotective, and experimental techniques are valuable adjuncts, particularly in complex cases. An active role of clinicians in education and timely referral is crucial to preserving reproductive potential and improving quality of life in these patients.

Future Directions

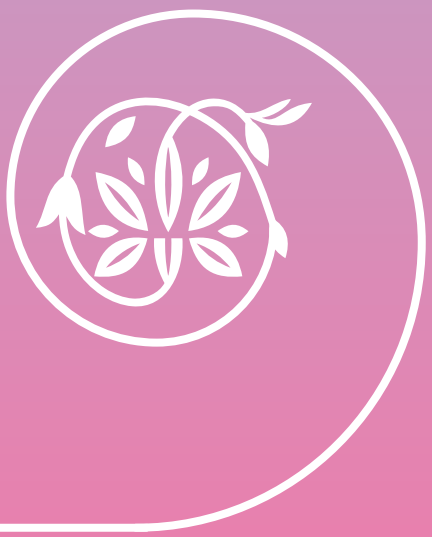
Future research directions include improving tissue-preservation techniques, developing methods for in vitro maturation of spermatogonia, and the use of genetic testing to reduce the risk of transmitting hereditary mutations.

References

1. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine (Baltimore). 2018;97(37):e12390.
2. Looijenga LHJ, Van der Kwast TH, Grignon D, et al. Report from the International Society of Urological Pathology (ISUP) consultation conference on molecular pathology of urogenital cancers: IV: Current and future utilization of molecular-genetic tests for testicular germ cell tumors. Am J Surg Pathol. 2020;44(7):e66–79.
3. Su HI, Lacchetti C, Letourneau J, et al. Fertility preservation in people with cancer: ASCO guideline update. J Clin Oncol. 2025;43(12):1488–1515.

4. Parekh NV, Lundy SD, Vij SC. Fertility considerations in men with testicular cancer. Transl Androl Urol. 2020;9(Suppl 1):S14–23.
5. Meistrich ML. Effects of chemotherapy and radiotherapy on spermatogenesis in humans. Fertil Steril. 2013;100(5):1180–1186.
6. Hamano I, Hatakeyama S, Ohyama C. Fertility preservation of patients with testicular cancer. Reprod Med Biol. 2017;16(3):240–251.
7. Sonnenburg DW, Brames MJ, Case-Eads S, et al. Utilization of sperm banking and barriers to its use in testicular cancer patients. Support Care Cancer. 2015;23(9):2763–2768.
8. Fode M, Ohl DA, Sonksen J. A step-wise approach to sperm retrieval in men with neurogenic anejaculation. Nat Rev Urol. 2015;12(11):607–616.
9. Albamonte MI, Vitullo AD. Preservation of fertility in female and male prepubertal patients diagnosed with cancer. J Assist Reprod Genet. 2023;40(12):2755–2767.
10. Nangia AK, Krieg SA, Kim SS. Clinical guidelines for sperm cryopreservation in cancer patients. Fertil Steril. 2013;100(5):1203–1209.
11. Meistrich ML. Risks of genetic damage in offspring conceived using spermatozoa produced during chemotherapy or radiotherapy. Andrology. 2020;8(3):545–558.
12. Tverye A, Nangia A, Fantus RJ. Testicular cancer survivorship and fertility preservation. Urol Clin North Am. 2024;51(3):429–438.
13. Sineath RC, Mehta A. Preservation of fertility in testis cancer management. Urol Clin North Am. 2019;46(3):341–351.
14. Benedict C, Thom B, Kelvin JF. Fertility preservation and cancer: challenges for adolescent and young adult patients. Curr Opin Support Palliat Care. 2016;10(1):87–94.
15. Oldenburg J. Hypogonadism and fertility issues following primary treatment for testicular cancer. Urol Oncol. 2015;33(9):407–412.
16. Ferrari S, Paffoni A, Filippi F, et al. Sperm cryopreservation and reproductive outcome in male cancer patients: a systematic review. Reprod Biomed Online. 2016;33(1):29–38.
17. Pape J, Fernando J, Megaritis D, et al. Oncological treatments have limited effects on the fertility prognosis in testicular cancer: a systematic review and meta-analysis. Andrology. 2025;13(4):731–746.

PERINATOLOGY



METFORMIN IN PREGNANCY AND FETAL PROGRAMMING

Prof. Dr. Miroslava Gojnić Dugalić

Introduction

Metformin is a biguanide with a long history of clinical use in type 2 diabetes mellitus (T2DM). Over the past two decades, it has also been increasingly prescribed during pregnancy, most commonly for gestational diabetes mellitus (GDM), as an adjunct to insulin in pregestational T2DM, and in specific cases for women with polycystic ovary syndrome (PCOS). Clinical guidelines vary: in the United States (ADA/ACOG), insulin remains the first-line therapy, while metformin is regarded as an acceptable alternative with informed consent. In contrast, the United Kingdom's NICE guidelines recommend metformin as the first pharmacological option when lifestyle interventions fail to achieve glycemic targets within 1–2 weeks.

Historical Background

Biguanides are derived from the plant Galega officinalis. Metformin was first synthesized in the early 20th century and introduced into clinical practice in France in 1957 by Jean Sterne under the name Glucophage. In the United States, its approval was delayed until 1995 due to concerns following the withdrawal of related biguanides (fenformin, buformin) associated with lactic acidosis.

Mechanism of Action

Primary effects:

1. Inhibition of hepatic gluconeogenesis (partly through AMPK activation and inhibition of mitochondrial complex I)
2. Enhancement of peripheral glucose utilization
3. Modest reduction in intestinal glucose absorption

Secondary effects:

1. Modulation of bile acid metabolism and gut microbiota
2. Systemic insulin sensitisation in muscle, adipose tissue, and endothelium

Pharmacokinetics in Pregnancy and Placental Transfer

Metformin is not metabolised and is excreted unchanged via the kidneys. Its clearance increases during pregnancy. The drug crosses the placenta through organic cation transporters, with cord blood concentrations reaching 50–100% of maternal levels at delivery. Ex vivo perfusion studies confirm its rapid transfer. While clinical trials have not demonstrated an increased risk of congenital malformations, concerns remain regarding potential long-term metabolic effects in offspring.

Fetal Programming and the Relevance of Metformin

The DOHaD (Developmental Origins of Health and Disease) concept proposes that the intrauterine environment "programs" future metabolic and cardiometabolic health via lasting changes in placental function, epigenetic regulation, and energy metabolism. Because metformin crosses the placenta and influences key energy-sensing pathways (AMPK/mTOR), it may alter nutrient transfer and signalling, underscoring the importance of evaluating its long-term effects on offspring growth and metabolism.

Summary of Evidence: Growth, Adiposity, and Metabolism in GDM

Randomised controlled trials and follow-up studies (e.g., MiG/TOFU cohorts) have demonstrated that children of mothers treated with either metformin or insulin generally show similar fat distribution and metabolic outcomes at ages 7–9 years. However, some evidence suggests that metformin-exposed children may be slightly larger in body size by age 9.

A 2019 PLOS Medicine meta-analysis found that metformin use was associated with lower birth weight, followed by accelerated catch-up growth and higher BMI in mid-childhood compared with insulin exposure. This growth pattern—characterised by reduced birth weight and rapid postnatal weight gain—is recognized within the DOHaD framework as a potential risk factor for later cardiometabolic disease, although its clinical significance remains uncertain.

Placental Transport and Fetal Exposure

Metformin, a hydrophilic cation, utilizes organic cation transporters (primarily OCT3/SLC22A3) in the trophoblast for transplacental passage. Both in vivo and ex vivo studies confirm efficient transfer, with cord blood concentrations approximating maternal levels. The placenta itself is a pharmacological target: metformin reduces mitochondrial respiration and ATP production in trophoblasts, potentially altering nutrient transfer and endocrine function. Through AMPK activation and mTOR inhibition, metformin may modify amino acid and glucose transport, with downstream effects on foetal growth. Epigenetic modifications (DNA methylation, histone modifications, and non-coding RNAs) may provide long-term molecular “memory” of exposure.

Clinical Guidelines (2025)

Gestational Diabetes Mellitus (GDM):

- ADA/ACOG: Insulin is preferred first-line. Metformin may be considered when insulin is refused or contraindicated, with counselling regarding placental transfer and the ~40–50% likelihood of requiring additional insulin.
- NICE: If glycaemic goals are not achieved after 1–2 weeks of lifestyle modification, initiate metformin; add insulin if necessary. Severe hyperglycaemia warrants insulin upfront.

Pregestational T2DM: Metformin may be continued, often in combination with insulin.

PCOS: Metformin may be continued during pregnancy, though the long-term implications for offspring remain under investigation.

Dosing and Titration in Pregnancy

- Initiation: 500 mg once daily with food, increasing to 500 mg twice daily
- Titration: up to 850–1000 mg twice daily (maximum 2000–2500 mg/day), depending on tolerance and glycaemic control
- Formulations: Extended release may improve gastrointestinal tolerance
- Contraindications: eGFR <30 mL/min/1.73 m^2; caution advised with eGFR 30–45 mL/min/1.73 m^2; discontinue around iodinated contrast exposure

Maternal and Neonatal Outcomes

Maternal effects: Comparable glycaemic control to insulin, with reduced gestational weight gain and possibly lower risk of hypertensive disorders.

Neonatal effects: Reduced risk of macrosomia and neonatal hypoglycaemia, slightly lower birth weight, and no increase in small-for-gestational-age infants. Composite perinatal outcomes are

broadly similar between metformin and insulin. Long-term follow-up suggests increased adiposity in childhood, though its clinical impact is uncertain.

Long-Term Considerations: Fetal Programming

Meta-analyses consistently demonstrate lower birth weight, followed by accelerated postnatal growth and increased BMI in childhood after in utero metformin exposure. Cohort studies (MiG TOFU, PedMet) have reported greater central adiposity and obesity at ages 5–10 years. Emerging evidence suggests possible alterations in steroidogenesis (particularly in males) and immunomodulatory effects.

Safety and Monitoring

- Common adverse effects: Gastrointestinal intolerance (nausea, diarrhoea), mitigated by gradual titration or use of extended-release formulations
- Rare risks: Lactic acidosis (extremely rare; associated with renal failure or severe hypoxia)
- Long-term considerations: Possible vitamin B12 deficiency with prolonged use—periodic monitoring advised
- Breastfeeding: Minimal transfer into breast milk; no adverse neonatal outcomes reported; generally considered safe

Neurodevelopmental Outcomes

Current evidence indicates no adverse effects on neurodevelopment up to adolescence. An AJOG 2024 meta-analysis (7 studies, >14,000 children) found no increased risk of developmental delays up to age 14. A Finnish cohort study similarly reported no differences in cognitive or neuropsychological outcomes between metformin- and insulin-exposed children at age 9.

Animal Data and Translational Implications

Animal studies present mixed findings: some suggest protective effects (e.g., reduced inflammation, protection against neural tube defects), while others demonstrate long-term adverse metabolic outcomes. Primate models have reported fetal growth restriction and renal alterations, though extrapolation to humans remains limited.

Key Take-Home Messages

- Neurodevelopment: No evidence of increased risk up to age 14
- Growth and adiposity: Lower birth weight, accelerated postnatal catch-up growth, and modestly higher adiposity in mid-childhood
- Mechanisms: Likely mediated by AMPK–mTOR signalling, altered placental energetics, and epigenetic regulation
- Contextual factors: Maternal phenotype (obesity, PCOS, glycaemic status) likely modulates outcomes. In obese women without diabetes, metformin does not appear to confer long-term benefits for offspring.

Literature

1. Dutta D, Feig DS, Lowe WL Jr, et al. Metformin versus insulin in pregnancy: 11-year safety follow-up of offspring and mothers in seven cohorts. Endocrine Society Annual Meeting (ENDO); 2024 Jun 1–4; Boston, MA, USA. Washington (DC): Endocrine Society; 2024. Available from: https://medicalxpress.com/news/2024-06-metformin-safe-insulin-pregnancy-year.html
2. Balsells M, Garcia-Patterson A, Corcoy R. Long-term impact of metformin on mothers with gestational diabetes and their children: systematic review and meta-analysis. Endocr Pract. 2024;30(6):511–20. doi:10.1016/j.eprac.2024.05.001.
3. Hanem LGE, Rönö K, Säävälä J, et al. In utero exposure to metformin and long-term outcomes in children: a register-based cohort study from Finland. BMJ Open Diabetes Res Care. 2022;10(1):e002736. doi:10.1136/bmjdrc-2021-002736.

4. Gordon M, Aroda V, Rizzo A, et al. Prenatal exposure to metformin and neurodevelopmental outcomes in childhood: systematic review and meta-analysis. Am J Obstet Gynecol. 2024;231(2):123–34. doi:10.1016/j.ajog.2024.03.021.
5. Wouldes TA, Battin M, Coat S, et al. School-age growth and development of children following randomization to metformin or insulin for gestational diabetes: follow-up of the MiG trial. Diabetes Care. 2019;42(5):701–8. doi:10.2337/dc18-2201.
6. Rosario FJ, Jansson T, Powell TL. Metformin bioaccumulates in the human fetus and impacts growth and organ development: evidence from animal and human studies. Am J Obstet Gynecol. 2023;229(5):391–403. doi:10.1016/j.ajog.2023.06.045.
7. El-Khayat W, El-Zanaty A, Mahmoud H, et al. Metformin in obese non-diabetic pregnant women: a randomized controlled trial. Egyptian Board of Women's Health J. 2023;10(3):178–85. doi:10.21608/ebwhj.2023.329463.

POSTTERM PREGNANCY – GUIDELINES

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Abstract: Postterm pregnancy - a pregnancy that has reached or extended beyond 42 0/7 weeks of gestation from the last menstrual period (LMP). The overall incidence of postterm pregnancy in reviewed literature was 4-7%. Accurate determination of gestational age is essential to accurate diagnosis and appropriate management of postterm pregnancies. In these cases, antepartum fetal surveillance and induction of labor have been evaluated as strategies to decrease the risks of perinatal morbidity and mortality. This review analyzes the current understanding of late-term and postterm pregnancies and checked guidelines and expert opinions for management.

Keywords: postterm pregnancy; labour induction; Cook cervical ripening balloon, late pregnancy; perinatal complications; ultrasound dating

Advanced maternal age has been defined as women who are 35 years or older at estimated date of delivery. A few large studies demonstrated a significant association between chromosomal abnormalities and possible congenital malformations in children born to women aged 35 years or older However, the the other risks increase with increasing age at the time of the pregnancy. (chronic medical conditions such as diabetes, hypertension, and obesity). [1,2] Recent studies have commonly divided the age of individuals pregnant at age 35 years and older into 5-year intervals: 35–39 years, 40–44 years, 45–49 years, and 50 years and older, which better stratifies the possible pregnancy risks associated with advancing age. [3]

Timing of delivery is a shared decision-making process, with consideration of maternal and fetal factors. The rate of stillbirth at 39 weeks of gestation in women aged 40 years and older is very similar as the rate of stillbirth for women aged 25–29 years who are beyond 41 weeks of gestation. [4]

In our facility one year ago, searching for safe and effective solutions for postterm pregnancies, we introduced mechanical mode of induction: Cook Cervical Ripening Balloon, alone or combined with pharmacological means. The mean time of balloon application was around 12 hours. The incidence of cesarean section is comparable to other methods, but some advantages are evident: safety, non-invasive, continuous monitoring is not needed. Results showed that efficacy was near 100% in multiparas, regarding successful vaginal birth. [5-7]

References:

1. ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. Number 55, September 2004 (replaces practice pattern number 6, October 1997). Management of Postterm Pregnancy. Obstet Gynecol. 2004 Sep;104(3):639-46. doi: 10.1097/00006250-200409000-00052. PMID: 15339790.
2. 2. Schimmel MS, Bromiker R, Hammerman C, Chertman L, Ioscovich A, Granovsky-Grisaru S, et al. The effects of maternal age and parity on maternal and neonatal outcome. Arch Gynecol Obstet 2015;291:793–8. doi: 10.1007/s00404-014-3469-0
3. 3. Smithson SD, Greene NH, Esakoff TF. Pregnancy outcomes in very advanced maternal age women. Am J Obstet Gynecol MFM 2022;4:100491. doi: 10.1016/j.ajogmf.2021.100491
4. 4. Bahtiyar MO, Funai EF, Rosenberg V, Norwitz E, Lipkind H, Buhimschi C, et al. Stillbirth at term in women of advanced maternal age in the United States: when could the antenatal testing be initiated? Am J Perinatol 2008;25:301–4. doi: 10.1055/s-2008-1076605
5. Wen C, Wang J. Application of intrauterine balloons in cervical ripening. Expert Rev Med Devices. 2023 Jul-Dec;20(10):843-849. doi: 10.1080/17434440.2023.2249809. Epub 2023 Aug 22. PMID: 37602436.
6. Diguisto C, Le Gouge A, Arthuis C, Winer N, Parant O, Poncelet C, Chauleur C, Hannigsberg J, Ducarme G, Gallot D, Gabriel R, Desbriere R, Beucher G, Faraguet C, Isly H, Rozenberg P, Giraudeau B, Perrotin F; Groupe de Recherche en

Obstétrique et Gynécologie (GROG). Cervical ripening in prolonged pregnancies by silicone double balloon catheter versus vaginal dinoprostone slow release system: The MAGPOP randomised controlled trial. PLoS Med. 2021 Feb 11;18(2):e1003448. doi: 10.1371/journal.pmed.1003448. PMID: 33571294; PMCID: PMC7877637.

7. Gao J, Zhang C, Xin H. Developing a nomogram for estimating the risk of needing to perform a caesarean section after induction of labour in pregnancies using a COOK® Cervical Ripening Balloon. Technol Health Care. 2024;32(3):1745-1755. doi: 10.3233/THC-230761. PMID: 37980578.

INFLUENCE OF E-CIGARETTE USE ON FEMALE REPRODUCTIVE HEALTH

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Unlike men, who have continuous spermatogenesis throughout most of their lifetime, women are born with a fixed supply of follicles, and this number progressively declines with age until the menopause. Beside age, the speed of follicle depletion can be regulated by genetic, hormonal and environmental influences. Every day, women are exposed to multiple chemicals and radiation sources that can increase the chance of developing permanent infertility and premature ovarian failure (POF). Iatrogenic (chemotherapy, radiotherapy) and xenobiotic agents (e.g., chemicals, pharmaceuticals) are potent ovotoxicants capable of accelerating ovarian reserve depletion. Smoking cigarettes negatively impacts ovarian reserve and fertility. Vaping also reduce ovarian reserve and negatively impacts ART outcomes. Electronic cigarettes (e-cigarettes) are often considered a “safe substitute” for conventional cigarette. The composition of the fluid is not always clearly defined a more than 80 compounds were detected in liquids and aerosols. E-cigarettes contain nicotine, and the addition of flavorings increases the toxicity of e-cigarette vapor in a significant manner. The heat generated by the e-cigarette leads to the oxidation and decomposition of its components, eventually forming harmful constituents in the inhaled vapor. The effects of these toxicants on male and female reproduction are well established in conventional cigarette smokers. Nicotine has limited impact on the ovary, while flavoring, because ovarian damage including morphological damage, disruption of oxidative balance and promotion of apoptosis, with VG having the most significant effect. Moreover, LN e-liquids may lead to more severe ovarian damage than HN e-liquids at an equal intake of total nicotine. At a consistent level of total nicotine intake, e-liquids with low nicotine concentrations cause more damage to the ovaries than those with high nicotine concentrations.

The prevalence of e-cigarette usage is alarming, and warnings should be made about the impact of vaping on reproductive health.

Keywords: apoptosis; e-cigarette; ovary; reproductive health; infertility;

BEYOND BABY BLUES: INTEGRATING MATERNAL MENTAL HEALTH INTO PERINATAL MANAGEMENT

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Perinatal depression is a common and clinically significant mood disorder, affecting approximately one in seven individuals during pregnancy or the first year postpartum. The incidence varies based on contributing factors, including the country's cultural environment and economic conditions. Perinatal depression is characterized by persistent sadness, loss of interest, low self-esteem, sleep and appetite disturbances, anxiety, irritability, self-blame, and difficulties in bonding with the infant. Feelings of hopelessness, humiliation, or worthlessness may also be present [1]. In contrast, postpartum blues (baby blues), with an incidence of 39% represents a transient state with similar but milder symptoms—tearfulness, mood swings, irritability, insomnia, and fatigue—typically resolving within the first weeks after delivery without causing functional impairment or meeting criteria for a mental disorder [2]. Perinatal depression, however, is more severe, often lasting for months if untreated, and leading to significant impairment in maternal functioning [3].

Untreated perinatal depression can negatively affect both mother and child, contributing to impaired caregiving, long-term developmental and behavioural problems in the child, strained family relationships, and increased suicide risk. Routine screening using validated tools such as the Edinburgh Postnatal Depression Scale (EPDS) is therefore essential. Despite its prevalence, up to half of perinatal depression cases remain undiagnosed, largely due to stigma and reluctance to disclose symptoms, often out of fear of abandonment or inadequate support [4]. Raising awareness, reducing stigma, and ensuring access to effective interventions are key to improving maternal mental health and fostering healthy family dynamics. Effective management includes psychotherapy, partner and social support, neuromodulation, hormonal therapy, and pharmacological interventions that are generally considered safe in pregnancy and lactation [5].

To further explore the prevalence and determinants of perinatal depression, a prospective study was conducted at the Clinic for Gynaecology and Obstetrics, University Clinical Center of Serbia, from October 2023 to January 2024. A total of 205 healthy women were assessed before childbirth (≥37 gestational weeks), and again at two weeks and two months postpartum, using sociodemographic, psychological, and obstetric questionnaires, relationship quality measures (DAS-32), and mental health scales (EPDS, DASS-21). Depression prevalence was 26.3% before delivery, 20% at two weeks, and 21.9% at two months postpartum. DASS-21 results showed a significant correlation before delivery and at two weeks postpartum ($p = 0.02$). Globally, Li et al. reported a postpartum depression prevalence of 17.3% at two months postpartum [6], which is less than our finding. Poorandokht et al. reported a higher prevalence of 38.8% between two weeks and six months postpartum [7], while Shi et al. reported 14.6% at six weeks postpartum [8].

Key risk factors included miscarriages before childbirth ($p < 0.01$), difficult birth experience ($p < 0.01$), caesarean instead of planned vaginal delivery ($p = 0.03$), and epidural anaesthesia ($p = 0.04$) at two weeks postpartum. The significant association between depressive symptoms in the early postpartum weeks and unplanned caesarean sections indicates an interrelation between

depressive symptoms and delivery method. Zareba et al. also noted the correlation between depressive symptoms and complications during childbirth, such as blood loss over 1000 mL and prolonged second and third stages of labour [9]. Previous studies have shown different results regarding the impact of epidural anaesthesia. Edipoglu et al. found no significant association in the prevalence of depressive symptoms between groups who received and did not receive epidural anaesthesia during childbirth [10], whereas Tan et al. found this association significant, which is consistent with our findings [11]. Another risk factor was financial dissatisfaction at two months ($p = 0.035$). Satisfaction with financial status is a psychological factor significantly associated with postpartum depressive symptoms in previous research in Serbia [12] and other populations [13,14], as confirmed in this study. Relationship quality was strongly associated with depressive symptoms across all three time points ($p < 0.01$). Partner relationships, measured by the DAS-32 test, showed a significant correlation with DASS-21 test results, which measure levels of depressive symptoms, anxiety, and stress. As DAS-32 scores, indicating better partner relationships, increase, DASS-21 scores decrease, indicating lower levels of depressive symptoms, anxiety, and stress. This highlights the critical influence of partner relationships on the development of perinatal depressive symptoms. Earlier research showed a connection between partner support levels and the development of depressive symptoms [6].

These findings emphasize the need for preventive and therapeutic interventions targeting modifiable risk factors during pregnancy and labour. Psychotherapy, partner involvement, and tailored obstetric care represent key strategies to reduce the burden of perinatal depression and improve outcomes for both mothers and infants.

References:

1. Liu X, Wang S, Wang G. Prevalence and Risk Factors of Postpartum Depression in Women: A Systematic Review and Meta-analysis. J Clin Nurs. 2022 Oct;31(19-20):2665-2677.
2. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. Lancet. 2014 Nov 15;384(9956):1775-88.
3. Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 4. Obstet Gynecol. 2023 Jun 01;141(6):1232-1261.
4. Zauderer C. Postpartum depression: how childbirth educators can help break the silence. J Perinat Educ. 2009 Spring;18(2):23-31.
5. Frieder A., Fersh M., Hainline R., Deligiannidis K.M. Pharmacotherapy of Postpartum Depression: Current Approaches and Novel Drug Development. CNS Drugs. 2019;33:265–282.
6. Li Q., Yang S., Xie M., Wu X., Huang L., Ruan W., Liu Y. Impact of some social and clinical factors on the development of postpartum depression in Chinese women. BMC Pregnancy Childbirth. 2020;20:226.
7. Poorandokht A., Mitra T., Parvin A., Shiva Y. Prevalence and related factors of postpartum depression among reproductive aged women in Ahvaz, Iran. Health Care Women Int. 2020;41:255–265.
8. Shi X., Ying Y., Yu Z., Xing M., Zhu J., Feng W., Xu D., Zhang W., Zhou M., Wang J., et al. Risk factors for postpartum depression in Chinese women: A cross-sectional studyat6weeks postpartum. J. Psychosom. Res. 2021;140:110295.
9. Zaręba K., Banasiewicz J., Rozenek H., Wójtowicz S., Jakiel G. Peripartum Predictors of the Risk of Postpartum Depressive Disorder: Results of a Case-Control Study. Int. J. Environ. Res. Public Health. 2020;17:8726.
10. Edipoglu I.S., Aslan D.D. Association of postpartum depression and epidural analgesia in women during labor: An observational study. Braz. J. Anesthesiol. 2021;71:208–213.
11. Tan H.S., Tan C.W., Sultana R., Chen H.Y., Chua T., Rahman N., Gandhi M., Sia A.T.H., Sng B.L. The association between epidural labour analgesia and postpartum depression: A randomised controlled trial. Anaesthesia. 2024;79:357–367.
12. Dmitrovic B.K., Dugalic M.G., Balkoski G.N., Dmitrovic A., Soldatovic I. Frequency of perinatal depression in Serbia and associated risk factors. Int. J. Soc. Psychiatry. 2014;60:528–532.
13. Qi W., Zhao F., Liu Y., Li Q., Hu J. Psychosocial risk factors for postpartum depression in Chinese women: A meta-analysis. BMC Pregnancy Childbirth. 2021;21:174.
14. Robertson E., Grace S., Wallington T., Stewart D.E. Antenatal risk factors for postpartum depression: A synthesis of recent literature. Gen. Hosp. Psychiatry. 2004;26:289–295.

UPOREDNA ANALIZA PRIMJENE FETALNE INTRAVASKULARNE TRANSFUZIJE U LIJEČENJU FETALNE ANEMIJE KOD HIDROPIČNIH I NEHIDROPIČNIH FETUSA

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Uvod

Fetalna anemija je relativno rijetko, ali ozbiljno stanje. Prema etiopatogenezi, fetalne anemije se dijele na imunološke i neimunološke. Imunološke fetalne anemije su posljedica imunološkog odgovora majke do kog dolazi zbog eritrocitne aloimunizacije. Najčešći uzročnik imunološke fetalne anemije je RhD antigen, te tako nastaje RhD aloimunizacija, dok su imunizacije na ostale eritrocitne antigene znatno rjeđe zastupljene. Uzroci neimunoloških fetalnih anemija su infekcija parvovirusom B19 (PB19) i druge kongenitalne infekcije, alfa talasemija, placentalni i fetalni tumori, akutno i subakutno fetomaternalno krvarenje, kao i sindrom međublizanačke transfuzije (twin to twin transfusion syndrome-TTTS) i blizanačka anemija-policitemija sekvenca (twin anemia-polycythemia sequence-TAPS).

Rh aloimunizacija može imati različite posljedice na fetus, od beznačajnih do najtežih kao što je fetalna smrt. Iz tog razloga je neophodno sprovesti adekvatnu antenatalnu dijagnostiku.

Nivo fetalnog hemoglobina postepeno raste u toku trudnoće, stoga se anemija fetusa može klasifikovati na osnovu stepena devijacije vrijednosti hemoglobina od srednje vrijednosti za gestaciono doba [1] ili na osnovu MoM (*multiples of the median*) [2, 3]. Fetalna anemija se definiše i putem hematokrita manjeg od 30%, što je podjednako pouzdano kao i nivo hemoglobina. Hematokrit kao kriterijum se često koristi u kliničkoj praksi. Klinički, teška fetalna anemija se prezentuje hidropsom, polihidramnionom, hidropsom placente, kao i smanjenom ili odsutnom biofizičkom aktivnošću fetusa [4].

Nekoliko ultrasonografskih i Dopler metoda se upotrebljava u dijagnostici fetalne anemije. Prva manifestacija hidropsa koji se javlja kao posljedica fetalne anemije je ascites, praćen zadebljavanjem placente i hepatomegalijom. Rijetko se javljaju i pleuralne i perikardne efuzije [5]. Dijametar fetalne jetre iznad 90. percentile [6], prečnik slezine na više od 2SD [7], Dopler merenja srednje brzine krvi u fetalnoj aorti [1] i PSV splenične arterije [8] u većini slučajeva koreliraju sa fetalnom anemijom. Fetalna anemija je često povezana sa hiperdinamskom cirkulacijom zbog fetalne kompenzacije usljed hemodinamskih adaptacionih mehanizama [9]. Stoga je ultrazvučna metoda koja je pokazala najbolje rezultate MCA-PSV. Vrijednost MCA-PSV iznad 1,5 MoM (*multiples of the median*) za gestaciono doba često korelira sa umjerenom do teškom fetalnom anemijom koja zahtijeva intrauterinu transfuziju sa skoro 100% senzitivnošću i relativno niskom pojavom lažno pozitivnih rezultata od 12%. Na taj način se primjena invazivnih procedura može izbjeći kod gotovo 80% trudnoća [3, 10].

Nekada je uzimanje uzoraka fetalne krvi amniocentezom ili kordocentezom bila metoda izbora za dijagnostiku fetalne anemije. Pronalaskom MCA-PSV, kordocenteza se koristi samo ukoliko je na MCA-PSV izmjerena vrijednost veća od 1,5 MoM. Izvodi se u okviru predterapijske procjene, to jest pred primjenu same intrauterine transfuzije [4].

Liječenje fetalne anemije intrauterinom transfuzijom

Postoje dva tipa intrauterine transfuzije:

- intrauterina intraperitonealna transfuzija (IPT)
- intrauterina intravaskularna transfuzija.

U kliničkom žargonu, naziv intrauterina transfuzija (IUT) podrazumijeva isključivo intravaskularnu transfuziju. Intravaskularna transfuzija se koristi za liječenje teških FA najranije od 18. nedelje gestacije, a najčešće od 20. do 35. nedelje gestacije. Prije 20. nedelje, a pogotovo 18. Nedelje, zahvat je tehnički teško izvesti zbog malog kalibra i gracilnosti krvnih sudova, te zbog otežane vizualizacije [11]. Dodatno, rizik za fetalnu smrt je utoliko veći ukoliko je gestacijska dob niža, a navodi se da je taj rizik 10 puta veći ukoliko se intravaskularna transfuzija primenjuje pre 22. nedelje. Nakon 35. nedelje najbolja opcija lečenja je porođaj [12].

U bilo kojoj fetalnoj bolesti sa teškom anemijom, može se razmotriti intrauterina transfuzija. Međutim, kao i kod svake invazivne procedure, posebno kada je u pitanju fetus, poznavanje indikacija i poznavanje bolesti koja je uzrokovala samu anemiju su jako bitni za dobar ishod ove procedure. Glavna indikacija za intrauterinu transfuziju je i dalje fetalna anemija kao posljedica aloimunizacije na antigene fetalnih eritrocita. Kada je u pitanju neimuna etiologija anemije, transfuzije su se pokazale uspješnim u liječenju anemija uzrokovanih parvovirusom B19, fetomaternalnom hemoragijom, TAPS i placentalnim i fetalnim tumorima.

Cilj i metod istraživanja

Uporediti hematološke i doplerske parametre, komplikacije i ishode intrauterine transfuzije prilikom liječenja fetalne anemije kod hidropičnih i nehidropičnih fetusa.

Sprovedena je retrospektivna studija u kojoj je analizirano 32 trudnice, tj. fetusa kod kojih je primjenjivana IUT u periodu od 2015. do 2021. godine na Odjeljenju visokorizičnih trudnoća na GAK "Narodni front", koje su podijeljene u dvije grupe, jedna sa fetusima koji imaju razvijen hidrops uz anemiju, a druga grupa fetusa koji imaju anemiju, ali bez hidropsa. Podaci o IUT za ovaj period su uzeti iz protokola Odjeljenja visokorizičnih trudnoća ustanove "Narodni Front", a podaci o ishodima trudnoća su prikupljeni iz zdravstvenog informacionog sistema i iz istorija bolesti.

Rezultati i diskusija

U istraživanje je uključeno 32 trudnice, tj. fetusa kod kojih je primenjivana IUT u periodu od 2015. do 2021. godine na Odjeljenju visokorizičnih trudnoća na GAK "Narodni front". Prosječna životna dob trudnica je bila 31.9 ± 4.9 godina. Najmlađa trudnica je imala 19 godina, a najstarija 43 godine. Prosječna starost trudnoće u kojoj je rađena prva IUT je 28.5 ± 4.1 nedelja gestacije. Najranije je IUT rađena u 20. nedelji gestacije, a nakasnije u 34. nedelji gestacije.

Najčešće je bila prisutna RhD inkompatibilija kod polovine majki-fetusa, zatim RhD, RhC kod 15% i Parvo B19 kod 13%. Najčešće registrovana su bila anti-D antitijela kod dvije trećine, zatim kombinovana anti-D i anti-C1 antitela, kao i IgM i IgG Parvo B19. U grupi bez hidropsa najčešća inkompatibilija je bila RhD, a zatim RhD RhC. *Sánchez-Durán et al.* su retrospektivno, sagledavanjem prethodnih 15 godina u tercijernoj univerzitetskoj bolnici, ispitivali pacijente sa aloimunizacijom i njihove ishode. Anti-D antitijela su bila najfrekventnija sa 53,3%, zatim anti-K sa 18,9%, pa anti-E sa 10% [13].

Najčešći uzrok fetalne anemije je bila eritrocitna aloimunizacija (84.37%), zatim kongenitalna infekcija parvovirusom B19 (12.5%), a kod jednog slučaja (3.12%), uzrok fetalne anemije je ostao nepoznat.

Transfuziju na rođenju je primila polovina novorođenčadi. Dvije trećine trudnica se porodilo carskim rezom. *Al-Dughaishi et al.* su u svojoj studiji, koja je ispitivala aloimunizaciju na fetalne eritrocitne antigene kod trudnica iz Omana, imali 14 carskih rezova na 29 porođaja (48,2%) [14].

16% novorođenčadi je transporotovano u Institut za neonatologiju. Hidrops je bio prisutan kod 11 novorođenčadi (34.40%), dok je 21 bilo bez hidropsa (65.60%). Kod 5 fetusa (45.5%) se hidrops povukao nakon primjene IUT, kod 1 fetusa (20%) nakon primene 1 IUT, kod 2 fetusa (40%) nakon primene 2 IUT, kod 2 fetusa (40%) nakon primene 3 IUT, kod 1 fetusa (20%) nakon primene 4 IUT. Smrtni ishod je bio prisutan kod dvoje novorođančadi, a FMU kod troje. Tri trudnoće u grupi sa fetalnim hidropsom su imale smrtni ishod u toku trudnoće, a dva novorođenčeta smrtni ishod nakon porođaja. U grupi bez fetalnog hidropsa nije bilo intrauterinih smrti, kao ni smrti nakon porođaja. Poređenjem ove dve grupe utvrđeno je da je statistički značajno učestaliji smrtni ishod u grupi sa fetalnim hidropsom. Prosječna nedelja gestacije u kojoj je bio porođaj je 34. nedelja. Prosječan Apgar skor u prvom minutu je bio 6.9, a u petom minutu 7.7. Novorođenčad su prosječno bila teška 2674.5 g, prosječne dužine 47.6 cm, sa prosječnim obim glave 34 cm. Broj porođaja je bio slične učestalosti između grupa, bez značajne razlike. Broj pobačaja je bio veći u grupi trudnica koje su imale hidropični fetus, razlika je statistički značajna u odnosu na grupu nehidropičnih fetusa. Broj fetus mortus-a u prethodnoj trudnoći je bio prisutan kod trećine trudnica u grupi sa fetalnim hidropsom, a u petini trudnica u grupi bez hidropsa, bez statistički značajne razlike. Van Kamp et al. su takođe uvidjeli veći broj pobačaja u grupi trudnica sa hidropičnim fetusom sa 13 pobačaja od 80 hidropičnih fetusa, naspram 6 pobačaja u 130 nehidropičnih fetusa [15].

Najčešći tip inkompatibilije u grupi sa hidropsom je bio RhD kod skoro polovine trudnica, a zatim Parvo B19 kod približno trećine trudnica. U grupi bez hidropsa najčešća inkompatibilija je bila RhD, a zatim RhD + RhC. Shodno tome, najčešće su RhD antitijela registrovana u obe grupe, zatim Parvo B19 u grupi hidropsa i RhD, RhC u grupi bez hidropsa. Poređen je i perinatalni ishod kod grupe sa i bez fetalnog hidropsa. Učestalost carskog reza se nije statistički značajno razlikovala između grupa. Trećina novorođenčadi sa hidropsom je transportovana u Institut za neonatologiju, u poređenju sa 10% novorođenčadi bez hidropsa, ali bez statistički značajne razlike. Tri trudnoće u grupi sa fetalnim hidropsom su imale fetalnu smrt, a dva novorođenčeta neonatalnu smrt. U grupi bez fetalnog hidropsa nije bilo intrauterine smrti, kao ni smrti nakon porođaja. Poređenjem ove dve grupe utvrđen je statistički značajno učestaliji smrtni ishod u grupi sa fetalnim hidropsom. Karakteristike novorođenčadi koja su u toku trudnoće primala IUT prema fetalnom hidropsu: novorođenčad sa hidropsom su rođena u statistički značajno ranijoj nedelji gestacije. Prosječan Apgar skor u prvom i petom minutu su bili statistički značajno niži kod novorođančadi sa fetalnim hidropsom. Prosječan Apgar skor u prvom minutu je bio 6,9 a u petom minutu 7,7. U studiji sprovedenoj u Omanu, prosječni Apgar skor u prvom minutu je bio 8, dok je u petom minutu bio 9 [14]. Prosječan Apgar skor u prvom i petom minutu su bili statistički značajno niži kod novorođančadi sa fetalnim hidropsom. Tjelesna težina i dužina su bili statistički značajno niže u grupi sa fetalnim hidropsom. Novorođenčad u našoj studiji su prosječno bila teška 2674.5 g, prosječne dužine 47,6 cm, sa prosječnim obimom glave 34 cm. U studiji Urutherakumar et al. koja je ispitivala kratkoročne ishode posle IUT radi fetalne anemije, prosječna težina na porođaju bila je 2358 g [16]. Tjelesna težina i dužina su bili statistički značajno niži u grupi sa fetalnim hidropsom. Prosječna tjelesna težina na rođenju kod pacijenata sa blagom anemijom i bez hidropsa u studiji Weisz et al. je bila 2343 g, a kod pacijenata sa teškom anemijom od kojih je 18% imalo hidrops 2390

g [17]. Najmanje jednu transfuziju je primilo ukupno 32 fetusa. Poređene su karakteristike fetusa na početku i na kraju IUT. Gestacijska starost trudnoće pri prvoj IUT kod fetalnog hidropsa je bila prosječno 26 nedelja, a bez hidropsa 30 nedelja, razlika je statistički značajna. Manja gestacijska starost trudnoće je bila udružena sa fetalnim hidropsom. Vrijednost hematokrita i hemoglobina prije IUT su bile statistički značajno niže kod fetalnog hidropsa. Takođe, vrijednost hematokrita i hemoglobina nakon IUT su bile statistički značajno niže u grupi fetalnog hidropsa. Kod Van Kamp et al. su vrednosti hemoglobina u vrijeme prve IUT bile statistički značajno bolje kod nehidropičnih fetusa, nego kod onih sa hidropsom, a vrijednosti hematokrita su bile blizu nivoa statističke značajnosti tj. nešto veće kod fetusa bez, nego kod onih sa hidropsom. Hemoglobin i hematokrit su bili viših vrijednosti kod fetusa bez hidropsa i na rođenju [18].

Prosječno je i u grupi sa i u grupi bez hidropsa prvom intravaskularnom transfuzijom dato 57 ml krvi, hematokrita 0.7 L/L. U studiji Deolindo Santiago et al. koja se bavila procjenom odgovarajuće količine krvi koju je potrebno dati u transfuziji, da bi se izvršila korekcija fetalne anemije, fetusima sa hidropsom je u prosjeku dato 45 ml krvi, a fetusima bez je dato 39,1 ml krvi. Da bi se koncentracija hemoglobina podigla za 1 g/L, bilo je potrebno u prosjeku 11,2 ml transfundovanih eritrocita [19]. Početni i završni MCA-PSV se nisu razlikovali između grupe fetusa sa hidropsom i grupe bez. Friszer et al. su ispitivali kako optimalno tempirati intrauterinu transfuziju kod aloimunizacije na eritrocitne antigene fetusa. Na osnovu 111 fetusa koji su primili intrauterinu transfuziju u ovoj studiji, MCA-PSV je sa svakom intrauterinom transfuzijom imao sve manju pozitivnu prediktivnu vrijednost, gdje je za prvu IUT pozitivna prediktivna vrijednost bila 75,3%, dok su za drugu i treću bile 46,7% i 48,8%. Negativna prediktivna vrednost za MCA-PSV sa pragom od 1,5 MoM je ostajala visoka i za drugu i treću IUT sa 88,9% i 91,7% [20]. Drugu transfuziju je primilo ukupno 23 fetusa (71.8%), 8 (72.7%) iz grupe sa fetalnim hidrosom i 15 (71.4%) iz grupe bez fetalnog hidropsa. U Holandskoj studiji iz 2001. godine, fetusi sa blagim hidropsom su imali više potrebe za ponovnim intrauterinim transfuzijama nego fetusi bez hidropsa i fetusi sa teškim hidropsom [21].

Poređene su karakteristike fetusa na početku i na kraju druge intravaskularne transfuzije. Gestacijska starost trudnoće kod fetalnog hidropsa je bila prosječno 27 nedelja, a bez hidropsa 31 nedelja, razlika je statistički značajna. Manja gestacijska starost trudnoće je bila udružena sa fetalnim hidropsom. Vrijednost hematokrita i hemoglobina prije druge intravaskularne transfuzije su bile statistički značajno niže kod fetalnog hidropsa. Takođe, vrijednost hematokrita i hemoglobina nakon intravaskularne transfuzije su bile statistički značajno niže u grupi fetalnog hidropsa. Najteže je predvidjeti stopu pada hematokrita između prve i druge transfuzije, jer su u ovoj fazi supresija eritropoeze i procenat fetalnih eritrocita u fetalnoj cirkulaciji varijabilni [22]. Karakteristike krvi date drugom intravaskularnom transfuzijom: prosječno je u grupi sa hidropsom dato 63 ml, a u grupi bez hidropsa 70 ml krvi, bez statistički značajne razlike u količini krvi primljenoj drugom intravaskularnom transfuzijom. Prosječni HCT date krvi je bio 0.7 L/L u obije grupe, bez značajne razlike. Početne i završne vrijednosti MCA-PSV se nisu razlikovale između grupa. MCA-PSV se pokazao statistički boljim prediktorom razmaka između prve i druge transfuzije, međutim procjenom pada vrijednosti hemoglobina poslije druge transfuzije se može bolje procijeniti kada planirati treću transfuziju [23].

Treću transfuziju je primilo ukupno 13 fetusa (41%), 5 (45.45%) iz grupe sa fetalnim hidropsom i 8 (38%) iz grupe bez fetalnog hidropsa. Poređene su karakteristike fetusa na početku i na kraju treće intravaskularne transfuzije. Gestacijska starost trudnoće kod fetalnog hidropsa je bila prosječno 27 nedelja, a bez hidropsa 31 nedelja, razlika je statistički značajna. Manja gestacijska starost trudnoće je bila udružena sa fetalnim hidropsom. Vrijednost hematokrita i hemoglobina prije treće intravaskularne transfuzije se nisu statistički značajno razlikovale između grupa. Takođe,

vrijednosti hematokrita i hemoglobina se nisu značajno razlikovale poslije treće intravaskularne transfuzije.

Četvrtu intravaskularnu transfuziju je primilo 5 fetusa (15.6%), 3 sa hidropsom (27%) i 2 bez (9.5%). Prosječno je starost trudnoće sa 4 IUT bila 30 nedelja, sa početnim HCT 0.3 L/L i HGB od 90 g/L. Završni HCT je bio 0.4 L/L, a HGB 135 g/L.

Petu IUT je primilo 4 fetusa (12.5%), 3 sa hidropsom (27.2%) i jedan bez (4.7%). Prosječno je starost trudnoće sa 5 IUT bila 31 nedelja, sa početnim HCT 0.2 L/L i HGB od 85 g/L. Završni HCT je bio 0.4 L/L, a HGB 138 g/L.

Šestu IUT je primilo 3 fetusa (9.4%), 2 sa hidropsom (18.2%) i jedan bez (4.8%). Prosječno je starost trudnoće sa 6 IUT bila 33 nedelje, sa početnim HCT 0.2 L/L i HGB od 87 g/L. Završni HCT je bio 0.4 L/L, a HGB 127 g/L. Svi fetusi koji su primili četvrtu, petu i šestu IUT su živi.

Karakteristike date krvi u toku četvrte, pete i šeste IUT: prosječan hematokrit je bio 0.8 L/L u sve tri IUT. MCA-PSV na početku četvrte IUT je bio 69, a na kraju 50. MCA-PSV na početku pete IUT je bio 74, a na kraju 55. MCA-PSV na početku šeste IUT je bio 69, a na kraju 60.

Planiranje ponovljenih IUT je bitno, jer svaka IUT nosi 1,5-3% rizika za fetalnim morbiditetom i mortalitetom [24, 25]. Rizik za neželjenim događajima je posebno veliki kod slučajeva fetalne anemije koja se javila rano u toku gestacije, te je za njenu korekciju bilo potrebno 5 do 6 transfuzija tokom trudnoće [26]. Pretpostavlja se da MCA-PSV gubi na prediktivnoj vrijednosti sa svakom subsekventnom transfuzijom, jer je viskoznost transfundovane adultne krvi veća od fetalne krvi i jer su eritrociti odraslih manje skloni deformacijama [27, 28].

Reference:

1. Nicolaides KH, Bilardo CM, Campbell S. Prediction of fetal anemia by measurement of the mean blood velocity in the fetal aorta. Am J Obstet Gynecol 1990; 162: 209–212.
2. Abbasi N, Johnson JA, Ryan G. Fetal anemia. Ultrasound Obstet Gynecol 2017; 50: 145–153.
3. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000; 342: 9–14.
4. Prefumo F, Fichera A, Fratelli N, Sartori E. Fetal anemia: Diagnosis and management. Best Practice and Research: Clinical Obstetrics and Gynaecology 2019; 58: 2–14.
5. Saltzman DH, Frigoletto FD, Harlow BL, Barss VA, Benacerraf BR. Sonographic evaluation of hydrops fetalis. Obstetrics and Gynecology 1989; 74: 106–111.
6. Roberts AB, Mitchell JM, Pattison NS. Fetal liver length in normal and isoimmunized pregnancies. Am J Obstet Gynecol 1989; 161: 42–46.
7. Oepkes D, Meerman RH, Vandenbussche FPHA, van Kamp IL, Kok FG, Kanhai HHH. Ultrasonographic fetal spleen measurements in red blood cell-alloimmunized pregnancies. Am J Obstet Gynecol 1993; 169: 121–128.
8. Bahado-Singh R, Oz U, Deren O, Kovanchi E, Hsu CD, Copel J et al. Splenic artery Doppler peak systolic velocity predicts severe fetal anemia in rhesus disease. Am J Obstet Gynecol 2000; 182: 1222–1226.
9. Abdelshafi S, Okasha A, Elsirgany S, Khalil A, El-Dessouky S, AbdelHakim N et al. Peak systolic velocity of fetal middle cerebral artery to predict anemia in Red Cell Alloimmunization in un-transfused and transfused fetuses. European Journal of Obstetrics and Gynecology and Reproductive Biology 2021; 258: 437–442.
10. Moise KJ. The usefulness of middle cerebral artery Doppler assessment in the treatment of the fetus at risk for anemia. Am J Obstet Gynecol 2008; 198: 161.e1-161.e4.
11. Canlorbe G, MacÉ G, Cortey A, Cynober E, Castaigne V, Larsen M et al. Management of very early fetal anemia resulting from red-cell alloimmunization before 20 weeks of gestation. Obstet Gynecol 2011; 118: 1323–1329.
12. Klumper FJ, van Kamp IL, Vandenbussche FPHA, Meerman RH, Oepkes D, Scherjon SA et al. Benefits and risks of fetal red-cell transfusion after 32 weeks gestation. Eur J Obstet Gynecol Reprod Biol 2000; 92: 91–96.
13. Sánchez-Durán MÁ, Higueras MT, Halajdian-Madrid C, Avilés García M, Bernabeu-García A, Maiz N et al. Management and outcome of pregnancies in women with red cell isoimmunization: A 15-year observational study from a tertiary care university hospital. BMC Pregnancy and Childbirth 2019; 19: 1–8.
14. Al-Dughaishi T, Al-Rubkhi IS, Al-Duhli M, Al-Harrasi Y, Gowri V. Alloimmunization due to red cell antibodies in Rhesus positive Omani Pregnant Women: Maternal and Perinatal outcome. Asian Journal of Transfusion Science 2015; 9: 150.
15. van Kamp IL, Klumper FJCM, Meerman RH, Oepkes D, Scherjon SA, Kanhai HHH. Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in the Netherlands, 1988-1999. Acta Obstet Gynecol Scand 2004; 83: 731–737.

16. Urutherakumar V, Welsh A, Henry A. Short-term outcomes following intrauterine transfusions for fetal anaemia: A retrospective cohort study. Australian and New Zealand Journal of Obstetrics and Gynaecology 2020; 60: 738–745.
17. Weisz B, Rosenbaum O, Chayen B, Peltz R, Feldman B, Lipitz S. Outcome of severely anaemic fetuses treated by intrauterine transfusions. Archives of Disease in Childhood: Fetal and Neonatal Edition 2009; 94. doi:10.1136/ADC.2008.143560.
18. van Kamp IL, Klumper FJCM, Meerman RH, Oepkes D, Scherjon SA, Kanhai HHH. Treatment of fetal anemia due to red-cell alloimmunization with intrauterine transfusions in thein the Netherlands, 1988-1999. Acta Obstet Gynecol Scand. 2004 Aug;83(8):731-7.
19. Santiago MD, Rezende CADL, Cabral ACV, Leite HV, Osanan GC, Reis ZSN. Determining the volume of blood required for the correction of foetal anaemia by intrauterine transfusion during pregnancies of Rh isoimmunised women. Blood Transfusion 2010; 8: 271.
20. Friszer S, Maisonneuve E, Macé G, Macé M, Castaigne V, Cortey A et al. Determination of optimal timing of serial in-utero transfusions in red-cell alloimmunization. Ultrasound Obstet Gynecol 2015; 46: 600–605.
21. van Kamp IL, Klumper FJCM, Bakkum RSLA, Oepkes D, Meerman RH, Scherjon SA et al. The severity of immune fetal hydrops is predictive of fetal outcome after intrauterine treatment. American Journal of Obstetrics and Gynecology 2001; 185: 668–673.
22. Oepkes D, van Scheltema PA. Intrauterine fetal transfusions in the management of fetal anemia and fetal thrombocytopenia. Seminars in Fetal and Neonatal Medicine 2007; 12: 432–438.
23. Ghesquière L, Houfflin-Debarge V, Behal H, Coulon C, Subtil D, Vaast P et al. Should optimal timing between two intrauterine transfusions be based on estimated daily decrease of hemoglobin or on measurement of fetal middle cerebral artery peak systolic velocity? Transfusion (Paris) 2017; 57: 899–904.
24. van Kamp IL, Klumper FJCM, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FPHA et al. Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. Am J Obstet Gynecol 2005; 192: 171–177.
25. Carbonne B, Castaigne-Meary V, Cynober E, Gougeul-Tesnière V, Cortey A, Soulié JC et al. [Use of peak systolic velocity of the middle cerebral artery in the management of fetal anemia due to fetomaternal erythrocyte alloimmunization]. Journal de gynecologie, obstetrique et biologie de la reproduction 2008; 37: 163–169.
26. Canlorbe G, MacÉ G, Cortey A, Cynober E, Castaigne V, Larsen M et al. Management of very early fetal anemia resulting from red-cell alloimmunization before 20 weeks of gestation. Obstet Gynecol 2011; 118: 1323–1329.
27. Welch R, Rampling MW, Anwar A, Talbert DG, Rodeck CH. Changes in hemorheology with fetal intravascular transfusion. Am J Obstet Gynecol 1994; 170: 726–732.
28. Egberts J, Hardeman MR, Luykx LM. Decreased deformability of donor red blood cells after intrauterine transfusion in the human fetus: possible reason for their reduced life span? Transfusion (Paris) 2004; 44: 1231–1237.

SIGNIFICANCE OF FETAL ULTRASONOGRAPHY IN THE DIAGNOSIS OF CPAM

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Congenital Cystic Adenomatoid Malformation (CCAM) / Congenital Pulmonary Airway Malformation (CPAM) present rare congenital lung tumor with unknown incidence. Macroscopically it is intrapulmonary mass containing cysts diameter of <1mm to >10cm. Microscopically "adenomatoid" increase in terminal respiratory structures are seen. Tissue within malformation doesn`t function in normal gas exchange. CPAM is slightly more localized in the left lung. Rarely may it be bilateral which is fatal.

Classification

Based on histological appearance [1] there are three types of CPAM:

- Type I- Macrocystic– single or multiple large, thick-walled cysts >2 cm
- Type II– Mixed with areas that are solid intermixed with moderate sized cysts 0.5-2 cm
- Type III– Solid or microcystic - firm homogenous mass - microscopic cysts (<5 mm). It is the only truly "adenomatoid" malformation.

Other histological classification recognizes two types [2]:

- Macrocystic CCAM– single or multiple cysts ≥5 mm; with sonographic cystic appearance.
- Microcystic CCAM– cysts <5 mm; more solid; sonographic echogenic appearance.

Based on anatomical appearance there are four types [3]:

- Type 0– Tracheobronchial– rarest; small cysts; lethal
- Type 1 - Bronchial/bronchiolar- the most common form (50% - 70%), from distal bronchus or proximal bronchiole. It consists of small number of large echo lucent cysts, 3-10 cm. Single dominant cyst may also be seen. This type may be large and cause hydrops due to mass effect.
- Type 2- Bronchiolar- arise from terminal bronchioles (15% to 30%). It consists of smaller cysts 0.5 - 2 cm with solid areas which are difficult to distinguish from surrounding tissue. It has the highest incidence of associated anomalies (60%) and prognosis depends on these findings.
- Type 3- Bronchiolar/alveolar- from acinar-like tissue (5% - 10%). It`s cysts are small the mass appears to be solid and highly echogenic. They may be large and distort the thoracic contents. Prognosis depends on the extent.
- Type 4- Distal acinar– alveolar (5% - 15%). Cysts are large up to 10 cm. It is associated with malignancy, specifically pleuropulmonary blastoma.

Many centers use fetal ultrasound and MRI to classify CPAM prenatally.

Natural history – Prenatally

Mass effect leads to both ipsilateral and contralateral pulmonary hyperplasia. Prognosis depends on size and secondary physiologic derangements caused by tumor. Small CPAM, which is the most common, doesn`t affect fetal heart or lungs and doesn`t cause respiratory problems after birth. Close monitoring before birth is necessary. Large CPAM is connected with restriction of normal lung growth causing mediastinal deviation or "shift" and subsequent polyhydramnios as

a consequence of esophageal compression and decreased swallowing. Occurrence of hydrops is predictor of fetal death. CPAM is usually isolated and sporadic. Associated anomalies (most commonly cardiac and renal) occur in 15% -20%.

Natural history – At birth

About 24% of CPAM are asymptomatic. 60-70% are complicated by RDS occurs due to air trapping, mediastinal compression, and pulmonary hypoplasia.

Natural history – During life

During life CPAM may be complicated by recurrent infections, rhabdomyosarcoma, adenocarcinoma. Resection is mandated in symptomatic patients. In asymptomatic patients need for resection is a subject of debate.

Prenatal diagnosis

Prenatal diagnosis is made by US with presented echogenic lung mass which gradually disappears over gestation. Rapid growth is connected with higher incidence of developing venous outflow obstruction, cardiac failure and hydrops. In cases with hydrops there is high risk of stillbirth. In the cases when hydrops is not present there is 95% chance of survival. The greatest period of growth is during the end of II trimester, between 20 and 26 weeks. After diagnosis US is performed weekly until 28 weeks. After 28 wg if CVR less than1.0 and CPAM didn't demonstrate rapid growth, US is performed monthly.

Determining severity of CPAM before delivery may be done by calculating CCAM Volume using formula *CAM volume = Length x Height x Width x 0.52*. In order to include differences in gestational age, CPAM volume ratio (CVR) is calculated size: $CVR=\frac{LxHxWx0.52}{HC}$.

CVR allows direct comparison in fetuses of different gestational age. Also, serial measurements of the CPAM in the same fetus enable estimation of progression, or regression. CVR ≥ 1.6 is connected with higher risk for developing heart failure, and risk of hydrops - 80%, while CVR <1.6 - risk of hydrops is 2%. Continued monitoring is important to make sure the volume of the lesion doesn't increase and require treatment before birth.

In differential diagnosis bronchopulmonary sequestration (BPS), bronchogenic cyst, congenital diaphragmatic hernia (CHD) and mediastinal masses should be considered.

BPS is easier to distinguish from types 1 and 2 as they have more macrocystic appearance. BPS and type 3 have similar US appearances and they are distinguished by location (ie, BPS is intra-abdominal) and vascular supply. CPAM is supplied and drained through the pulmonary circulation, while BPS has arterial flow directly from the aorta.

In CDH intestine in the thorax may appear cystic and mimic CCAM and/or BPS. The difference may be made by the presence of peristalsis suggesting CDH, visualization of the stomach.

Management of CCAM/CPAM during pregnancy

Management of CPAM includes multidisciplinary team approach. After visualizing lung lesion and observing fetal anatomy, weekly US is performed between diagnosis and 28 weeks. After 28 weeks if CVR <1.0 / not demonstrated rapid growth, US is performed monthly. Fetal echocardiogram is always indicated evaluating heart function and structure. MRI may be done to provide additional anatomic detail about the lung lesion. Karyotype/CMA are not absolutely indicated, but is useful especially in treatment decisions.

Termination of pregnancy (TOP) may be considered in the presence of associated anomalies, abnormal karyotype, or early-onset circulatory compromise.

Delivery should be planned by the severity of CPAM. In small lesions delivery is planned in facility with expert neonatal services/pediatric surgery options. In large lesions, with evidence of fetal compromise respiratory support/ECMO should be considered.

Fetal intervention for CPAM

In large CPAM goal is to decrease the size of CPAM in order to reduce the chance of fetal heart failure. Treatment options depend on type of CPAM (microcystic or macrocystic) and gestational age. Treatment options are steroids to prevent growth of lesion, draining fluid from the cyst, sclerotherapy, open fetal surgery to remove CPAM, EXIT procedure and C-section to resection.

References:

1. Hellmund A, et al. Prenatal Diagnosis and Evaluation of Sonographic Predictors for Intervention and Adverse Outcome in Congenital Pulmonary Airway Malformation. PLoS One. 2016 ;11(3):e0150474.
2. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. Hum Pathol, 1998. 8: 155–17.
3. Adzick NS, Harrison MR. Management of the fetus with a cystic adenomatoid malformation. World J Surg,1993. 17: 342–349.
4. Adzick NS, Harrison MR, Crombleholme TM, Flake AW, Howell LJ. Fetal lung lesions: management and outcome. Am J Obstet Gynecol, 1998. 179: 884–889.
6. Crombleholme TM, Coleman B, Hedrick H, Liechty K, Howell L, Flake AW. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. J Pediatr Surg, 2002.37: 331–338.
6. Muntean A, Marsland L, Sikdar O, Harris C, Ade-Ajayi N, Patel SB, Cook J, Sellars M, Greenough A, Nicolaides K, Davenport M. Neonatal Surgery for Congenital Lung Malformations: Indications, Outcomes and Association With Malignancy. J Pediatr Surg. 2025;60(5):162253.

ESTETSKI PRISTUP KOD CARSKOG REZA

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Carski rez je najčešća operacija u ginekologiji i akušerstvu. Frekvenca carskog reza se povećava iz godine u godinu zbog brojnih razloga. Dok je 1990. godine stopa carskog reza u svetu iznosila 7%, danas je ona dostigla 21% sa predikcijom da u 2030. godini ona bude 28%. U nekoliko zemalja broj carskih rezova je veći od broja vaginalnih porođaja pri čemu vodi Turska sa procentom od 57,2 [3,4]. Svetska zdravstvena organizacija je juna 2010. godine zvanično povukla svoju preporuku o stopi carskog reza od 15%. Njihovo zvanično saopštenje je glasilo: Potrebno je učiniti svaki napor da se obezbedi carski rez ženi kojoj je to potrebno a ne da se teži određenom procentu.

Kod miliona žena danas porođaj se završava carskim rezom što rezultuje ožiljkom koji može u daljem periodu da dovede do uticaja na kvalitet života. Bez obzira što estetski ishod nije prioritet kod carskog reza ipak odgovarajuća hirurška tehnika sa boljim kozmetičkim rezultatima je nešto o čemu bi moglo da se razgovara sa pacijentkinjama kad god je to moguće [1,2].

Zadnjih decenija žene sve više ulažu u sebe i svoj izgled kroz brojne hirurške i kozmetičke procedure što je stvorilo potrebu za što boljim, estetski prihvatljivijim a u isto vreme i sigurnim rezom na koži kod carskog reza. Istorijski gledano, rez na koži je pretrpeo evolucijske promene, od niskog uzdužnog, preko Maylarda i Joel-Cohena do Pfannenstiela, međutim, ostaje i dalje pitanje da li može bolje i lepše [5-7].

Veći ožiljak, njegov položaj i izgled utiče na život pacijentkinja, njihovo emocionalno stanje i može da izazove prihosocijalne poremećaje. Mišljenje pacijentkinja i krajnje zadovoljstvo nakon hirurške procedure koja završava ožiljkom često je zanemareno. Istraživanja su pokazala da psihosocijalni distres, uključujući anksioznost i društvenu izolaciju, više zavisi od doživljaja pacijentkinja svojim stanjem nego od kliničke objektivne procene ožiljka nakon operacije. Zbog ovoga je i predloženo da i pacijent bude uključen u procenjivanje stanja ožiljka i da da kritičku perspektivu koja bez sumnje utiče na kvalitet života [1,8].

Položaj reza na koži kod carskog reza značajno utiče na intraoperativni pristup, postoperativni tok i estetski ishod. Dok Pfannenstielov rez na koži, postavljen 2-3 cm iznad pubične simfize predstavlja standard za carski rez, nema podataka u literaturi o nižim rezovima na koži tokom carskog reza.

U ovom predavanju predstavićemo novi rez na koži, suprasimfizni poprečni rez (SSTI), definisan kao rez na koži tačno iznad gornje ivice pubične simfize (0 cm). Cilj je da se postigne optimalno prikrivanje ožiljka a da se ujedno postigne zadovoljavajuća sigurnost pri operaciji, kako za pacijenta tako i za hirurga.

Na Klinici za ginekologiju i akušerstvo Univerzitetskog Kliničkog Centra u Nišu, u periodu od 2014. do 2024. godine, urađen je carski rez kod 500 pacijentkinja izvođenjem suprasimfiznog reza na koži, uključujući elektivne i urgentne carske rezove.

Tehnika rada SSTI se ogleda u inciziji na koži na 0 cm od gornje ivice simfize, u dužini od 12-15 cm (slika 1). Nakon toga asistent povlači kožu iznad reza kranijalno, omogućavajući koso presecanje potkožnog masnog tkiva do fascije u nivou Pfannenstielovog reza. Fascija se preseca transverzalno 1,5 cm obostrano od srednje linije a zatim se disekcija fascije dovršava manuelno. Posle oštrog odvajanja fascije od mišića u srednjoj liniji u dužini od 5 cm, rektusi se odvajaju u longitudalnom pravcu a peritoneum se otvara digitalno u gornjem intermuskularnom prostoru i proširuje

manuelnim povlačenjem u lateralnom smeru. Na ovaj način ulaz u trbušnu duplju je nekoliko santimetara iznad reza na koži čime se postiže siguran, odgovarajući intraoperativni pristup (slika 2,3).

Sam carski rez se izvodi modifikovanom Misgav-Ladach tehnikom.

Od 500 pacijentkinja, 382 (76,4%) su imale prvi carski rez sa SSTI, 115 (23%) je imalo drugi carski rez sa istom incizijom dok su 3 (0,6%) imale SSTI po treći put. Pacijenkinje su bile od 20 do 42 godine života. Suprasimfizalna incizija je uspešno urađena kod svih, bez potrebe da se uradi konverzija u drugi rez na koži. Prosečno trajanje carskog reza je bilo 15 min (od 10-18 min), dok je prosečan gubitak krvi iznosio 380 ml (od 200-500 ml). Nije bilo produžavanja operativnog vremena ili povećanja stopa komplikacija kod pacijentkinja kod kojih je rađen ponovni carski rez. Proces zarastanja rana je bio zadovoljavajući, komplikacije rane su bile prisutne kod 44 pacijentkinje i to: serom (2,6%), površna infekcija (1,4%) i hematom (0,4%). Nije bilo povrede bešike niti povreda creva. Nije bilo statistički značajnih razlika u komplikacijama između prvog, drugog i trećeg carskog reza.

Estetski ishod, zadovoljstvo ožiljkom, naročito visinom reza na koži bio je subjektivno ocenjen izuzetno visokom ocenom, 9,6 od 10 (sprovedeno ocenjivanje od strane pacijentkinja 3 meseca nakon operacije).

Probleme sa ožiljkom i to samo hipertrofične promene prijavilo je 35 pacijentkinja (7%) a svih 500 pacijentkinja je dalo preporuku za suprasimfizni tip incizije na koži.

Carski rez, najčešća hirurška procedura u akušerstvu, povezana sa potencijalnim brojnim komplikacijama, takođe je i metoda koja može da dovede do fizičkih i emocionalnih promena kod žena [9]. Pored optimizacije hirurške procedure, prevencije i rešavanja postoperativnih komplikacija, povećana pažnja je data zadovoljstvu pacijentkinja u kozmetičkom smislu. Razlog tome je bolje shvatanje dugoročnih posledica ožiljka na svakodnevni život i uticaj na osećaj blagostanja, sreće sa svim ostalim socioekonomskim implikacijama [2,9-12].

Ova studija pokazuje da je SSTI sigurna i estetski povoljna alternativa tradicionalnom rezu po Pfannenstielu. Bez obzira što donja granica visine reza na koži tokom carskog reza nije istraživana do sada u literaturi, naši rezultati pokazuju odličnu izloženost donjeg uterusnog segmenta, malu stopu komplikacija i vrlo visok stepan zadovoljstva pacijentkinja visinom reza na koži.

Vrlo je važno da se primeti da je SSTI uspešno izveden i kod svakog sledećeg carskog reza koji je bio praćen prvim suprasimfiznim rezom, bez komplikacija prilikom rađanja bebe ili komplikacija rane. Kod pacijentkinja sa drugim i trećim carskim rezom nije bilo značajnog povećanja operativnog vremena kao ni povećanja stopa komplikacija, te možemo da kažemo da ova incizija može da bude sigurna za ponavljane procedure (Slika 4).

Najvažniji deo ovog istraživanja bila je anketa sprovedena 3 meseca nakon carskog reza. Ocena od 9,6/10 je iskazala veoma visok stepen zadovoljstva pacijentkinja koje su bile i voljne da preporuče SSTI. Nizak rez na stomaku omogućava nesmetano nošenje bilo kakve odeće. Kako sadašnji tretman ožiljaka ima brojna ograničenja, vrlo često pacijentkinje sa vidljivim ožiljkom imaju veliki problem da ga sakriju ili da na drugi način kompenzuju njegovo postojanje [8,13,14].

Ograničenje ove studije je u tome da je samo u jednom centru izvođeno istraživanje, međutim, dug vremenski period i veliki broj pacijentkinja daju sigurno značajnu vrednost rezultatima.

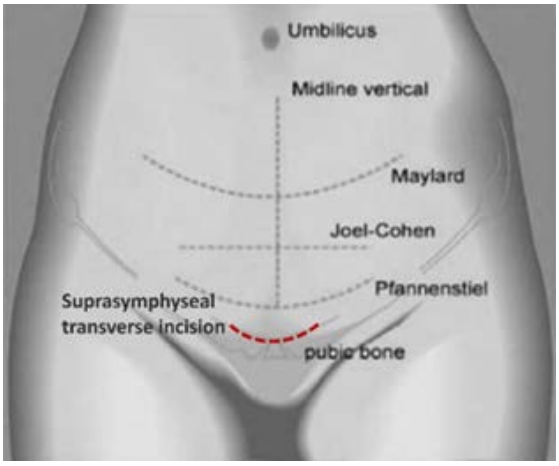
U zaključku možemo da kažemo da je suprasimfizni rez na koži kod carskog reza, izveden na 0 cm od gornje ivice simfize, siguran, izvodljiv i estetski superioran čak i kod ponovljenih carskih rezova.

Dalja istraživanja su neophodna da bi se uočila ograničenja i mogući nedostaci a kako bi se nova tehnika u carskom rezu prihvatila i standardizovala.

Literatura

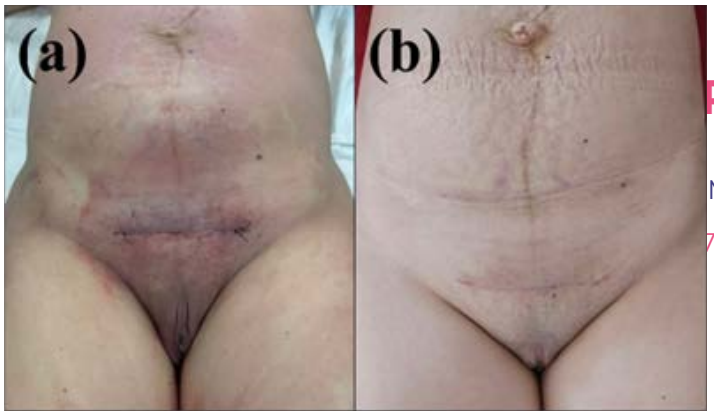
1. Brown BC, Moss TP, McGrouther DA, et al. Skin scar preconceptions must be challenged: importance of self-perception in skin scarring. J Plast Reconstr Aesthet Surg. 2010; 63 (6): 1022-1029.
2. Ozbasli E, Takmaz O, Albayrak N, et al. Cosmetic Outcome of Robotic Surgery Compared to Laparoscopic Surgery for Benign Gynecologic Disease. JSLS. 2022; 26 (2): e2021.00081.
3. World Health Organization (WHO). Caesarean section rates continue to rise, amid growing inequalities in access. Published 16 June 2021 (access 08 May 2025) Available from: https://www.who.int/news/item/16-06-2021-caesarean-section-rates-continue-to-rise-amid-growing-inequalities-in-access
4. Charoenboon C, Srisupundit K, Tongsong T. Rise in cesarean section rate over a 20-year period in a public sector hospital in northern Thailand. Arch Gynecol Obstet. 2013; 287 (1): 47–52.
5. Angolile CM, Max BL, Mushemba J, et al. Global increased cesarean section rates and public health implications: A call to action. Health Sci Rep. 2023; 6 (5): e1274.
6. Abuelghar WM, El-Bishry G, Emam LH. Caesarean deliveries by Pfannenstiel versus Joel-Cohen incision: A randomised controlled trial. J Turk Ger Gynecol Assoc. 2013; 14 (4): 194-200.
7. Mathai M, Hofmeyr GJ, Mathai NE. Abdominal surgical incisions for caesarean section. Cochrane Database Syst Rev. 2013; 2013 (5): CD004453.
8. Brown BC, McKenna SP, Siddhi K, et al. The hidden cost of skin scars: quality of life after skin scarring. J Plast Reconstr Aesthet Surg. 2008; 61 (9): 1049-1058.
9. Zuarez-Easton S, Zafran N, Garmi G, et al. Postcesarean wound infection: prevalence, impact, prevention, and management challenges. Int J Womens Health. 2017; 9: 81-88.
10. Wolder DP, Swiercz GM, Michalska A, et al. Optimization of the cosmetic appearance of skin scar after caesarean section - part I: obstetric practice. Ginekol Pol. 2023; 94 (9): 754-758.
11. Dahlke JD, Mendez-Figueroa H, Maggio L, et al. The Case for Standardizing Cesarean Delivery Technique: Seeing the Forest for the Trees. Obstet Gynecol. 2020; 136 (5): 972-980.
12. Cooper SM, Blanchard CT, Szychowski JM, et al. Does Time of Wound Complication after Cesarean Delivery Differ by Type of Skin Closure? Am J Perinatol. 2019; 36 (9): 981-984.
13. Gizzo S, Andrisani A, Noventa M, et al. Caesarean Section: Could Different Transverse Abdominal Incision Techniques Influence Postpartum Pain and Subsequent Quality of Life? A Systematic Review. PLoS ONE. 2015; 10 (2): e0114190.
14. Block L, Gosain A, King TW. Emerging Therapies for Scar Prevention. Adv Wound Care (New Rochelle). 2015; 4 (10): 607-614.

Slike

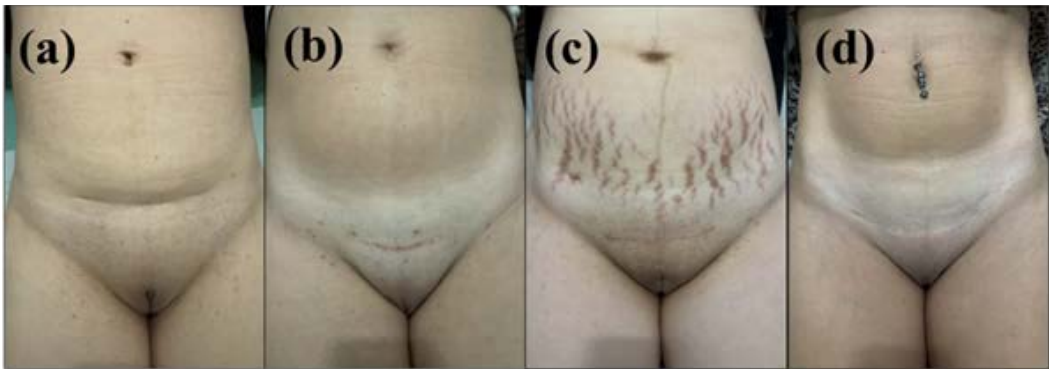


Slika 1. Naslov: Tipovi reza na koži kod carskog reza, uključujući suprasimfizni transverzalni rez (SSTI)

Slika 2. Faze suprasimfiznog transverzalnog reza (SSTI). Legenda: (a) Abdomen pre reza. (b) Suprasimfizni rez na koži. (c) Trakcija kože prema gore. (d) Rez na fasciji. (e) Digitalna separacija rectusa.



Slika 3. Suprasimfizni transverzalni rez (SSTI) odmah nakon zahvata i posle tri meseca
Legenda: (a) Suprasimfizni transverzalni rez (SSTI) odmah nakon zahvata. (b) SSTI tri meseca postoperativno.



Slika 4. Upoređenje između Pfannenstiela, prvog SSTI, and ponovljenih SSTI
Legenda: (a) Rez po Pfannenstiel-u. (b) Suprasimfizni transverzalni rez (SSTI) posle prvog carskog reza. (c) SSTI posle dva carska reza. (d) SSTI posle tri carska reza.

OBSTETRICS

BENEFITI I RIZICI ANTENATALNE PRIMJENE KORTIKOSTEROIDNE TERAPIJE

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Antenatalna primjena kortikosteroida predstavlja standardnu intervenciju u savremenoj perinatologiji, sa ciljem ubrzavanja fetalne plućne maturacije i smanjenja rizika od neonatalnih kompolikacija u slučajevima prijetećeg prijevremenog porođaja.

Šezdesetih godina prošlog vijeka Graham (Mont) Liggins, akušer koji je radio u Nacionalnoj ženskoj bolnici u Aucklandu, proučavao je početak porođaja kod ovaca.Njegova hipoteza, nova u to vrijeme, bila je da je fetus, a ne majka, ključni okidač za početak porođaja, te da su fetalni glukokortikoidi taj okidač. Pokazao je da inhibicija proizvodnje fetalnih glukokortikoida fetalnom hipofizektomijom ili adrenalektomijom spriječava početak porođaja, dok primjena glukokortikoida fetusu, rezultira porođajem, neovisno o dužini gestacije [1].

U zaključku njegovog rada, objavljenog 1969. godine, navodi se da je „djelimična aeracija pluća uočena kod jagnjadi rođenih vaginalno nakon primanja deksametazona, što može biti rezultat ubrzane pojave aktivnosti surfaktanta“.

Prvi izvještaj o ovom ispitivanju, s ishodima 282 žene, objavljen je u časopisu Pediatrics 1972. godine, Rezultati su bili fascinantni. Rana neonatalna smrtnost smanjena je s 15 % na 3%, a incidence respiratornog distress sindroma (RDS) sa 26 % na 9 % [2].

Arenatalni kortikosteroidi (AKS) se široko koriste prije prijevremenog porođaja (prije 37 sedmica gestacije) kako bi se smanjila neonatalna smrtnost, sindrom respiratornog distresa i intraventrikularno krvarenje [3]. Međutim, potencijalna prekomjerna upotreba AKS-a je zabrinjavajuća, jer se do polovine svih beba izloženih AKS-u naknadno rodi u terminu (≥ 37 sedmica gestacije), kada su neonatalne koristi minimalne [4, 5]. Prekomjerna izloženost fetusa glukokortikoidima može doprinijeti programiranju bolesti kasnije u životu [6].

U sistematskom pregledu i meta-analizi, dvije studije pokazale su da je izloženost AKS-u povezana sa smanjenom vjerovatnoćom neurološkog razvoja kod djece u dobi od 18-22 mjeseca koja su rođena ekstremno prijevremeno (definirano kao 22-27 sedmica gestacije i/ili porođajna težina od 401-1000 g) [7,8]. Nasuprot tome, kod djece rođene kasno prije termina (34–36 sedmica gestacije), jedna studija je otkrila da je izloženost AKS-u povezana s većim rizikom od neželjenih neuroloških ishoda [9]. Praćenje iz studije Antenatal Late Preterm Steroids Trial izvijestilo je o sličnim neurološkim ishodima kod djece u dobi od 7 godina koja su bila izložena AKS-u ili placebu u 34–36 sedmica gestacije [10, 11].

Trenutno standardne doze antenatalnih kortikosteroida (betamatezon ili deksametazon) su jasno definisane na osnovu brojnih studija koje su pokazale njihovu efikasnost i sigurnost u tim količinama:

- Betametazon: 2x12 mg intramuskularno u razmaku od 24 sata
- Deksametazon: 4x6 mg intramuskularno na svakih 12 sati

Međutim postavlja se pitanje: Da li bi manje doze mogle biti jednako efikasne, a možda i sigurnije za dugoročni razvoj fetusa?

Neka istraživanja i kliničke studije sugerišu da manje doze (npr. polovina standardne), mogu imati sličan efekat na plućnu maturaciju, ali je broj tih studija još ograničen [12].

U toku su klinička ispitivanja (npr. "LOWCOST" studija) koja pokušavaju utvrditi da li manje doze smanjuju rizik od potencijalno štetnih efekata na razvoj mozga, ponašanje i metabolizam djeteta kasnije u životu.

Trenutne međunarodne smjernice (WHO, ACOG, RCOG) ne preporučuju rutinsko smanjenje doze.

Antenatalni kortikosteroidi se često koriste u medicini, kako bi se spriječili problemi kod prevremenih porođaja i poboljšala fetalna zrelost. Međutim, postoje i istraživanja koja se bave potencijalnim štetnim dejstvima ovih lijekova učinkom na ravoj, štetnim metaboličkim efektima, slabim imunološkim odgovorom fetusa i poptencijalnih psiholoških problema nakon njihove primjene.

Učinak na fetalni razvoj: Neki radovi ukazuju na mogućnost da upotreba kortikosteroida može uticati na fetalni razvoj, uključujući rizik od poremećaja rasta ili neuroloških problema [13].

Metabolički efekti: Postoje indikacije da mogu izazvati metaboličke promjene kod novorođenčadi, kao što su problemi sa težinom ili glukoregulatornim funkcijama [14].

Imunološki odgovor: Kortikosteroidi mogu uticati na imunološki sistem fetusa, potencijalno povećavajući rizik od infekcija kod novorođenčadi [15].

Psihološki efekti: Neka istraživanja sugerišu da može postojati povezanost između upotrebe antenatalnih kortikosteroida i kasnijih psiholoških problema kod djece [16].

Primjena antenatalnih kortikosteroida mora biti vođena jasno definisanim kliničkim indikacijama i vremenski optimalno tempirana. U rizčnim trudnoćama, kada postoji vjerovatnoća prevremenog porođaja, primjena antenatalnih kortikosteroida ostaje opravdana, efikasna i klinički preporučena intervencija.

Literatura:

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972:50;515-25.
2. Prenatal Corticosteroids for reducing morbidity and mortality after preterm birth. Wellcome Witnesses to Twentieth Century Medicine Volume 25. Reynolds LA, Tansey EM (Eds). The Wellcome Trust Centre for the History of Medicine at UCL, 2005. Available from www.histmodbiomed.org/witsem/vol25.html.
3. E. McGoldrick, F. Stewart, R. Parker, and S. R. Dalziel, "Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at Risk of Preterm Birth," Cochrane Database of Systematic Reviews 12 (2020): CD004454, https://doi.org/10.1002/14651858.CD004454.pub4.
4. E. M. Frier, C. Lin, R. M. Reynolds, et al., "Consortium for the Study of Pregnancy Treatments (Co-OPT): An International Birth Cohort to Study the Effects of Antenatal Corticosteroids," PLoS One 18, no. 3 (2023): e0282477, https://doi.org/10.1371/journal.pone.0282477.
5. A. H. Jobe, "Antenatal Corticosteroids-A Concern for Lifelong Outcomes," Journal of Pediatrics 217 (2020): 184–188, https://doi.org/10.1016/j.jpeds.2019.09.015.
6. R. M. Reynolds, "Glucocorticoid Excess and the Developmental Origins of Disease: Two Decades of Testing the Hypothesis – 2012 Curt Richter Award Winner," Psychoneuroendocrinology 38, no. 1 (2013): 1–11, https://doi.org/10.1016/j.psyneuen.2012.08.012.
7. K. Ninan, S. K. Liyanage, K. E. Murphy, E. V. Asztalos, and S. D. McDonald, "Evaluation of Long-Term Outcomes Associated With Preterm Exposure to Antenatal Corticosteroids," JAMA Pediatrics 176, no. 6 (2022): e220483, https://doi.org/10.1001/jamapediatrics.2022.0483
8. S. Chawla, G. Natarajan, S. Shankaran, et al., "Association of Neurodevelopmental Outcomes and Neonatal Morbidities of Extremely Premature Infants With Differential Exposure to Antenatal Steroids," JAMA Pediatrics 170, no. 12 (2016): 1164–1172, https://doi.org/10.1001/jamapediatrics.2016.1936.
9. A. Aviram, K. E. Murphy, S. D. McDonald, et al., "Antenatal Corticosteroids and Neurodevelopmental Outcomes in Late Preterm Births," Archives of Disease in Childhood 107 (2021): 250–255.
10. C. Gyamfi-Bannerman, E. A. Thom, S. C. Blackwell, et al., "Antenatal Betamethasone for Women at Risk for Late Preterm Delivery," New England Journal of Medicine 374, no. 14 (2016): 1311–1320, https://doi.org/10.1056/NEJMoa1516783.
11. C. Gyamfi-Bannerman, R. G. Clifton, A. T. N. Tita, et al., "Neurodevelopmental Outcomes After Late Preterm Antenatal Corticosteroids," JAMA 331, no. 19 (2024): 1629–1637, https://doi.org/10.1001/jama.2024.4303.

12. Schmitz T, Doret-Dion M, Sentilhes L, et all ; Neonatal outcomes for women at risk of preterm delivery given half dose versus full dose of antenatal betamethasone: a randomised, multicentre, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2022 Aug 20;400(10352):592-604.
13. Van De Meent, M.; Kleuskens, D.G.; Derks, J.B.; Groenendaal, F.; Onland, W.; Ganzevoort, W.; Lely, A.T.; Hooijmans, C.R.; Kooiman, J. Effects of Antenatal Corticosteroid Therapy in Animal Models of Fetal Growth Restriction: A Systematic Review and Meta-Analysis. BMC Pregnancy Childbirth 2025, 25, 281. [Google Scholar] [CrossRef]
14. Heidemann LA, Procianoy RS, Silveira RC. Prevalence of metabolic syndrome-like in the follow-up of very low birth weight preterm infants and associated factors. J Pediatr (Rio J). 2019;95(3):291–7.
15. Räikkönen K, Gissler M, Kajantie E, Tapiainen T. Antenatal corticosteroid treatment and infectious diseases in children: a nationwide observational study. Lancet Reg Health Eur. 2023 Oct 12;35:100750. doi: 10.1016/j.lanepe.2023.100750. PMID: 37860637; PMCID: PMC10583166.
16. Räikkönen K, Gissler M, Tapiainen T, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Psychological Developmental and Neurosensory Disorders in Children. JAMA Netw Open. 2022 Aug 1;5(8):e2228518. doi: 10.1001/jamanetworkopen.2022.28518. PMID: 36001315; PMCID: PMC9403777.

TRAUMA - TRUDNOĆA I PORODAJ

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UVOD

Trauma u trudnoći predstavlja jedinstven izazov jer treba da zbrinemo dva pacijenta: majku i plod. Trauma u trudnoći je značajan uzročnik morbiditeta i mortaliteta, kako majke tako i fetusa. Vodeći uzrok smrti traumatizovane trudnice su saobraćajne nezgode, a nakon toga nasilje i napadi. Moguće komplikacije su: gubitak trudnoće, prevremeni porođaj, abrupcija posteljice i ruptura materice [1].

EPIDEMIOLOGIJA

Trauma je vodeći neakušerski uzrok smrti trudnice, a oko 20% žena zahteva hitnu operaciju. Sama trudnoća ne pogoršava preživljavanje majke, ali će preživljavanje majke posle traume da zavisi od ukupne težine povrede [2]. Učestalost traume povećava se sa svakim tromesečjem trudnoće. Oko 8% povreda javlja se tokom prvog trimestra, 40% povreda tokom drugog trimestra i 52% tokom trećeg trimestral [3]. Trauma čini 0,3% do 0,4% hospitalizacija trudnica [4].

POVREDE MAJKE

Saobraćajne nezgode su najčešći uzroci povrede trudnice - 55%, zatim padovi - 22%, napadi - 22% i opekotine -1% [5]. Mlađe trudnice imaju veći rizik za traumu od starijih [5]. Povrede glave i hemoragijski šok su glavni uzroci smrti majke nakon traume.

POVREDE FETUSA

Vodeći uzrok smrti fetusa koja je vezana za traumu majke su saobraćajne nezgode (82%), povrede vatrenim oružjem (6%) i padovi (3%). Smrt majke je uzrok smrti fetusa u 11% slučajeva [6]. Smrt fetusa u prvom trimestru se obično javlja zbog hipotenzije majke i hipoperfuzije materice. Optimalni tretman majke je najbolja strategija za preživljavanje fetusa. U ranoj trudnoći, jedini način da se spasi fetus jeste da majka preživi.

PREHOSPITALNO ZBRINJAVANJE

O trudnoći treba misliti kod svake traumatizovane žene u reproduktivnom dobu. Kada je moguće uzeti kratku akušersku anamnezu kao deo inicijalne obrade. Ako je anamnestički dobijen podatak da je trudnoća starija od 18-20 nedelja, materica mora biti izmeštena ulevo u ležećem položaju. Ako ne postoji mogućnost da se uzme akušerska anamneza, ali postoje očigledni znaci trudnoće, pacijentkinja se tretira kao trudna. Ako je traumatizovana pacijentkinja trudna smernice napredne životne podrške (Advanced Trauma Life Support - ATLS) i prehospitalno zbrinjavanje su slični kao kod pacijentkinja koje nisu trudne. Stabilizacija majke ima prioritet.

SEKUNDARNO ZBRINJAVANJE

Sekundarno zbrinjavanje podrazumeva inspekciju od glave do pete, palpaciju i auskultaciju sa fokusom na mehanizam povrede, koje oružje je korišćeno, upotreba alkohola i droga i korišćenje sigurnosnog pojasa u automobilu. Potrebno je uzeti detaljnu ličnu, hirušku i akušersku anamnezu sa posebnim osvrtom na određivanje gestacijske starosti ploda. Inicijalne laboratorijske analize obuhvataju kompletnu krvnu sliku (KKS), koagulacioni status (PT, PTT, INR, fibrinogen), elektrolite

i analizu urina. Nakon značajne traume treba uraditi arterijske gasne analize, uključujući vrednosti serumskih bikarbonata i serumskih laktata. Ako je potrebno uraditi i toksikološke analize. Odrediti krvnu grupu, Rh faktor i uraditi interreakciju. Rh faktor i status antitela su veoma važni. Kleihauer-Betke (KB) test meri količinu fetalnog hemoglobina koji je dospeo u cirkulaciju majke (fetomaternalno krvarenje) i treba da se uradi kod svake traumatizovane trudnice. Pozitivan KB test može da pokaže veći rizik za prevremeni porođaj nezavisno od Rh statusa i može da ukaže na potrebu za dužim fetalnim monitoringom.

DIJAGNOSTIKA I TRUDNOĆA

Indikacije za korišćenje imidžing studija kod traume su slične kod trudnica i žena koje nisu trudne. Zabrinutost o mogućim neželjenim efektima visokih doza jonizujućeg zračenja ne treba da spreči izvođenje dijagnostičkih rendgenskih procedura, ako postoje medicinske indikacije. Fiziološke i anatomske promene tokom trudnoće imaju uticaj na rezultate pa treba voditi računa prilikom interpretacije snimaka.

Fetus je najosetljiviji na jonizujuće zračenje tokom perioda organogeneze (2-7 nedelje nakon začeća) i tokom fetalnog perioda (8-15 nedelje nakon začeća) [9]. Nekancerski zdravstveni efekti nisu otkriveni ni u jednoj fazi trudnoće, ako je izlaganje manje od 5 rad-a. Do spontanog abortusa, zastoja u rastu i mentalne retardacije može doći ako su u pitanju veće doze zračenja. Ultrazvuk nije pokazao značajne zdravstvene rizike ni na majku ni na fetus. Ultrasonografija bi trebalo da bude prvi imidžing test koji se koristi za procenu suspektnih intraabdominalnih poremećaja kod majke, jer ne izlaže majku i fetus jonizujućem zračenju [8].

PROMENE U TRUDNOĆI KOJE SU ZNAČAJNE ZA TRAUMU

Kod traumatizovanih trudnica anatomske i fiziološke promene u trudnoći imaju uticaj na procenu i tretman. Da bi se izbegla aortokavalna kompresija tokom procene i tretmana povređena trudnica mora biti postavljena na tablu koja je nagnuta na levu stranu pod uglom od 30° vodeći računa o imobilizaciji vratne kičme. Ako to nije izvodljivo ručno izmestiti matericu ulevo sa jednom ili obe ruke ili izdignuti desni bok.

REANIMACIJA

Ciljevi reanimacije su kontrola krvarenja i nadoknada volumena kako bi se uspostavila adekvatna perfuzija i isporuka kiseonika ka vitalnim organima i uterusu. Takođe treba prevenirati i/ili lečiti koagulopatiju. Svim traumatizovanim trudnicama treba da se plasiraju dve široke venske linije u najkraćem mogućem roku. Imajući u vidu rizik od autokavalne kompresije zbog gravidne materice i samim tim smanjen venski priliv iz donjih ekstremiteta, gornji ekstremiteti su obično najbolja lokacija za intravenski pristup. Međutim, povrede grudnog koša, naročito penetrantne povrede, mogu da izazovu prekid dotoka krvi iz ruku ka srcu i tada se preporučuje postavljanje intravenskih linija ispod dijafragme. MAST može da se koristi za kompresiju donjih ekstremiteta, ali je naduvavanje abdominalnog dela pantalona kontraindikovano kod trudnica zbog opasnosti od ekstremne kompresije materice i remećenja protok krvi [7]. Korišćenje unapred zagrejanih tečnosti, grejača tečnosti i zagrevanje pacijenta su od ključnog značaja za sprečavanje hipotermije.

Upotreba vazopresora je ista kao kod povređenih pacijentkinja koje nisu trudne. Međutim, kao strategija za odražavanje krvnog pritiska i poboljšanje minutnog volumena kod trudnica popunjenost vaskularnog korita je poželjnija nego vazokonstrikcija. Adrenalin i noradrenalin će obično biti efikasni u popravljanju krvnog pritiska majke, ali oba ova leka kompromituju protok krvi kroz matericu i treba ih izbegavati ako je to moguće. Efedrin i dopamin (5 mcg/kg/min) mogu da poboljšaju hemodinamski status majke, a da se pri tom održava protok krvi kroz matericu.

TRETMAN SRČANOG ZASTOJA MAJKE

Reanimacija majke je najefikasniji način reanimacije fetusa. Ako se srčani zastoj trudnice dešava u hospitalnim uslovima brz odgovor od strane reanimacionog tima smanjuje interval između srčanog zastoja i ekstrakcije i omogućava bolji ishod kako za majku tako i za fetus, čak i kod traume. Ukoliko trudnica doživi srčani zastoj prve mere reanimacije uključuju kompresiju grudnog koša, poziv u pomoć, uspostavljanje oksigenacije, ventilacije i vaskularni pristup u cilju optimizacije cirkulacije. Važan faktor u razmatranju hitnog carskog reza je gestacijska starost ploda.

Principi kardiopulmonalne reanimacije (CPR) kod odmakle trudnoće se baziraju na preporukama za ACLS – naprednu životnu podršku Američke kardiološke asocijacije (AHA). Tokom reanimacije u trudnoći tim treba da prati revidirane AHA smernice iz 2010. godine sa modifikacijama prema anatomskim i fiziološkim promenama u trudnoći. Glavne modifikacije uključuju: brzu kontrolu disajnih puteva, izmeštanje materice ulevo i izbegavanje aortokavalne kompresije, optimalnu kompresiju grudnog koša u bočnom položaju, oprez kod korišćenja natrijum-bikarbonata, traženje reverzibilnih uzroka kao što je predoziranje magnezijumom i rano razmatranje potrebe za perimortem carskim rezom kako bi se reanimacija učinila uspešnijom i postigao bolji ishod kako za majku tako i za dete [13]. Perimortem carski rez je carski rez koji je iniciran nakon što je pokrenuta reanimacija i predstavlja veliki izazov u toku reanimacije majke. Pražnjenjem uterusa rešava se aortokavalna kompresija, povećava se minutni volumen za 60%–80%, povećava se stopa preživljavanja majke i omogućava se i pristup detetu. AHA preporučuje “pravilo 5 minuta”, tj. da se ekstrakcija nakon srčanog zastoja izvrši u roku od 5 minuta. Ako je gestacijska starost <20 nedelja hitan carski rez ne treba razmatrati jer uterus ne kompromituje venski priliv i CO. Ako je gestacijska starost 20-23. nedelje hitan carski rez će značiti uspešniju reanimaciju majke, ali plod verovatno neće preživeti, a ako je gestacijska starost ≥24-25. nedelja, hitan carski rez se radi u interesu i majke i ploda. Za vreme i nakon carskog reza se sprovode sve potrebne mere reanimacije [14].

Reference

1. Brown H. Trauma in pregnancy. Obstet Gynecol 2009;114(1):147-160.
2. Shah A, Kilcline BA. Trauma in pregnancy. Emerg Ailed Clin North 4-1m 2003; 21:615-629.
3. Howell P In: Chestnut DH, ed. Chestnut’s Obstetric Anestbesia Principles and Practice. 4th ed. Philadelphia, PA: Mosby Inc; 2009:1149-1163.
4. Fisgus JR, Tyagaraj K, Nlahboobi SK. In: Smith CE, ed. Trauma Anesthesia. 1st ed. New York, NY: Cambridge University Press; 2008:402-416.
5. Weiss HB, Songer TJ, Fabio A. Fetal deaths related to maternal injury. JAMA 2001; 286(15):1863-1868.
6. Mattox KL, Goetzl L. Trauma in pregnancy. Crit Care Med 2005;33: S385-S389.
7. Muench MV Baschat AA, Reddy UM, et al. Kleihauer-Betke testing is important in all cases of maternal trauma. Trauma 2004;57(5):1094-1098.
8. Goodwin H, Holmes JF Wisner DH. Abdominal ultrasound examination in pregnant blunt trauma patients. J Trauma 2001;50(4):689-693
9. Baysinger CL. Imaging during pregnancy. Anesth Analg 2010;110(3):863-867.
10. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol 2009;114(6):1326-1331;
11. Bouttonnet M, Faitot V, Keita H. Airway management in obstretic. Ann Fr Anesth Reanim. 2011;30(9):651-64
12. Hull SB, Bennett S. The pregnant trauma patient: assessment and anesthetic management.Int Anesthesiol Clin 2007;45(3):1-18.
13. Ruffolo DC. Trauma care and managing the injured pregnant patient. J Obstet Gynecol Neonatal Nurs 2009;38(6):704-714.
14. Petrone P, Asensio JA. Trauma in pregnancy: assessment and treatment. Scand Surg 2006;95:4-10.

PLACENTA ACCRETA SPECTRUM AFTER DIFFERENT CESAREAN SECTION TECHNIQUES

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3 Egon and Ann Diczfalusy Foundation

Introduction: Cesarean section (CS) is the most common operation in women of reproductive age. Because of its frequency, any impact of CS on women's health has great clinical, economic and social significance. Chronic complications of CS become a significant part of patient morbidity after CS. The basis for their occurence is a niche in the CS scar.

Objectives: To compare the frequency of chronic complications of CS (uterine rupture - RM, scar dehiscence - SD and hysterectomy due to placenta accreta spectrum - PAS) and the characteristics of the uterine scar between uterine closure techniques applied at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Vojvodina (UKCV).

Material and Methods: A series of cases of RM, SD and PAS were analyzed in a retrospective segment and the frequency was examined in relation to the uterine closure technique for the period 2008-2022. The prospective segment analyzed the thickness of the scar, as well as the histological structure of 147 samples of the uterine scar, which were divided into three groups in relation to the uterine closure technique on the previous cesarean section: group A – uterine closure by Vejnović modification; group B – single-layer, continuous locking uterine suturing; group C – double-layer uterine closure. Measurements and sample collection were performed intraoperatively, in patients who had one previous cesarean section. The histological analysis included the representation of fibrosis, muscle tissue and proliferation and the findings were compared in relation to the uterine closure technique.

Results: RM was recorded in 30/243 cases (3.56/10,000 births, 1.15/1000 CS). SD was recorded in 208/243 (2.47/1000 births, 7.99/1000 CS). There were 51 cases of PAS (5.22/10,000 births, 1.64/1,000 CS). The representation in complications of group A was lower compared to groups B and C (SD: group A 11.1%, group B 83.3% group C 33.3%; PAS group A 15.4%, group B 61.3% group C 53.8%). In patients who had peripartum hysterectomy due to PAS, no cases were found in which all previous CSs were performed using the technique of group A. The thickness of the scar was significantly greater in group A compared to group B and group C (5.45±2.19 mm vs. 3.65 ±1.69mm vs. 3.73±1.45mm; $p<0.001$). There was no statistically significant difference in the representation of fibrosis, muscle tissue and proliferation between the examined groups.

Conclusions: There are differences in scar thickness and frequency of RM and PAS among different uterine closure techniques. After Vejnović modified technique, a thicker scar occurs, and the frequency of complications is lower. The difference in the healing of the uterus among the techniques is manifested by the thickness of the scar, rather than the difference in the histological structure.

UČESTALOST ANOMALIJA DECE NA SEVERNOM KOSOVU PRE I POSLE RATNIH DEJSTAVA

Goran Relic

Milijana Relic, Aleksandar Vasic, Zoran Jaksic, Sasa Zakic

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Uvod

Od velikog broja etioloških faktora koji uzrokuju kongenitalne anomalije izdvajaju se faktori spoljne sredine, posebno iradijacione nokse (1-3).

Osiromašeni uranijum (OU), (U236) (dobija se kao otpadni produkt pri obradi urana U235 za rad atomskih postrojenja, koristi se i u ratne svrhe zbog visoke probojnosti u odnosu na ostale materijale (Irak 1991, Bosna 1996. i kod nas na Kosovu i Metohiji 1999.g (4).

Podaci iz literature pokazuju povećanje kongenitalnih anomalija na teritorijama tretiranih osiromašenim uranijumom (U236). U Mostaru (2000. god) od 1463 novorođenčadi -2,26% imalo je velike malformacije (1451 je bilo živorođeno i 12 mrtvorođeno).

Cilj rada

Utvrditi učestalost kongenitalnih anomalija dece i pre i posle ratnih dejstava, i prikaz pojedinih veoma retkih anomalija registrovanih u našem porodilištu.

Materijal i metode rada

Statistička obrada analiziranih podataka uključuje deskriptivnu statističku analizu, odnosno analizu srednjih vrednosti, varijanse, standardne devijacije, standardne greške i koeficijenta varijacije, da bi se ocenila homogenost ispitivanih podgrupa u okviru ispitivane i kontrolne grupe. Dobivene vrednosti su tabelarno i grafički prikazane.

Kliničko ispitivanje i utvrđivanje anomalija novorođenčadi

Minor anomalije: Dysplasio coxae, Pes varus, Pes equinovarus, Pes calcaneus, Microtio et atresio meati acustici externi

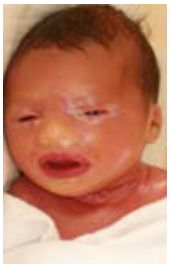
Major anomalije: Atresio ani, Haernia ventralis, Neuroblastoma congenitalis, VSD et atresio a. Pulmonalis, Craniosynostosis, Polydactilia, Stenosis pilory, Ductus arteriosus persistens, Cystis ovari, Labium leporinum, Frenulum brevi

Rezultati

U periodu nakon ratnih dejstava, 2000-2009. godine na ginekološko-akušerskom odeljenju Zdravstvenog centra Kosovska Mitrovica, od ukupno 3129 porođaja registrovano je 26 dece (0,8%) sa major anomalijama.

Tabela 1. Učestalost dece rođene sa major anomalijama nakon ratnih dejstava (2000-2009. god.) u odnosu na broj porođaja na ginekološko-akušerskom odeljenju Zdravstvenog centra Kosovska Mitrovica

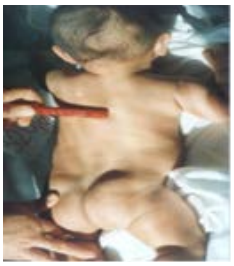
GODINA	DECA ROĐENA SA ANOMALIJAMA		POROĐAJI
	Br	%	n
2002	0	0	243
2003	0	0	352
2004	0	0	399
2005	0	0	410
2006	2	0,4	434
2007	8	1,9	415
2008	9	2,0	448
2009	7	1,6	428
UKUPNO	26	0,8	3129



Slika 1. Ihtioza

Slika 2. Mikrocija i atrezija srednjeg uva

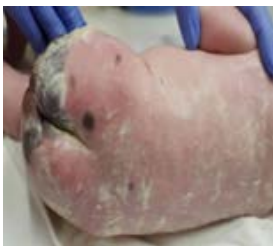
Slika 3. Retinoblastom



Slika 4. Neuroblastom

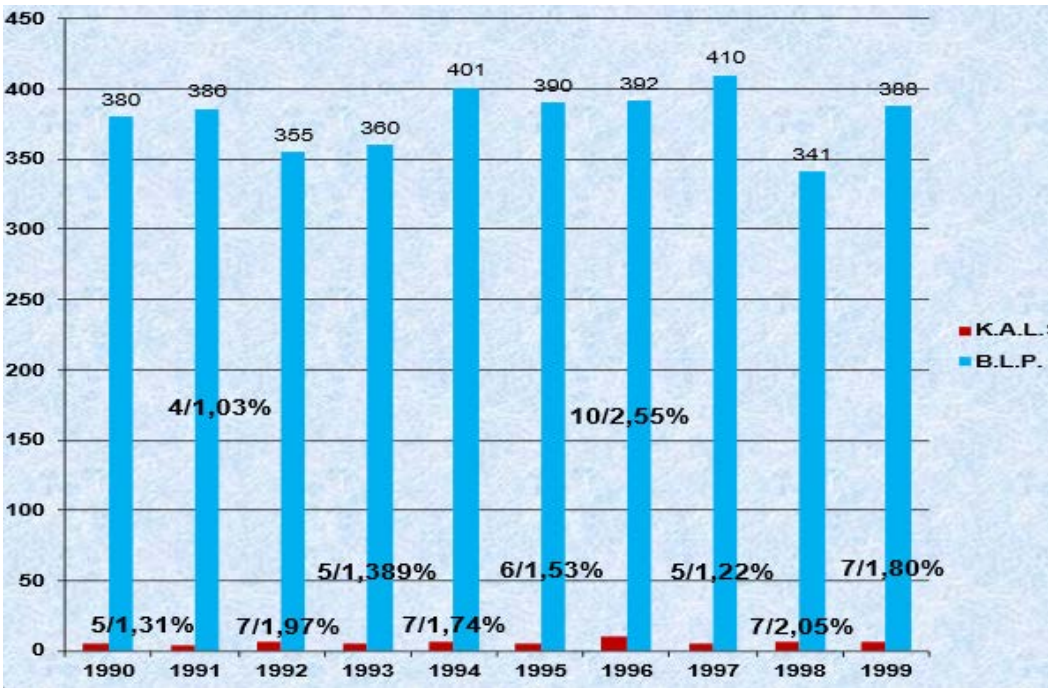
Slika 5. Teratom

Slika 6. Hipospadija



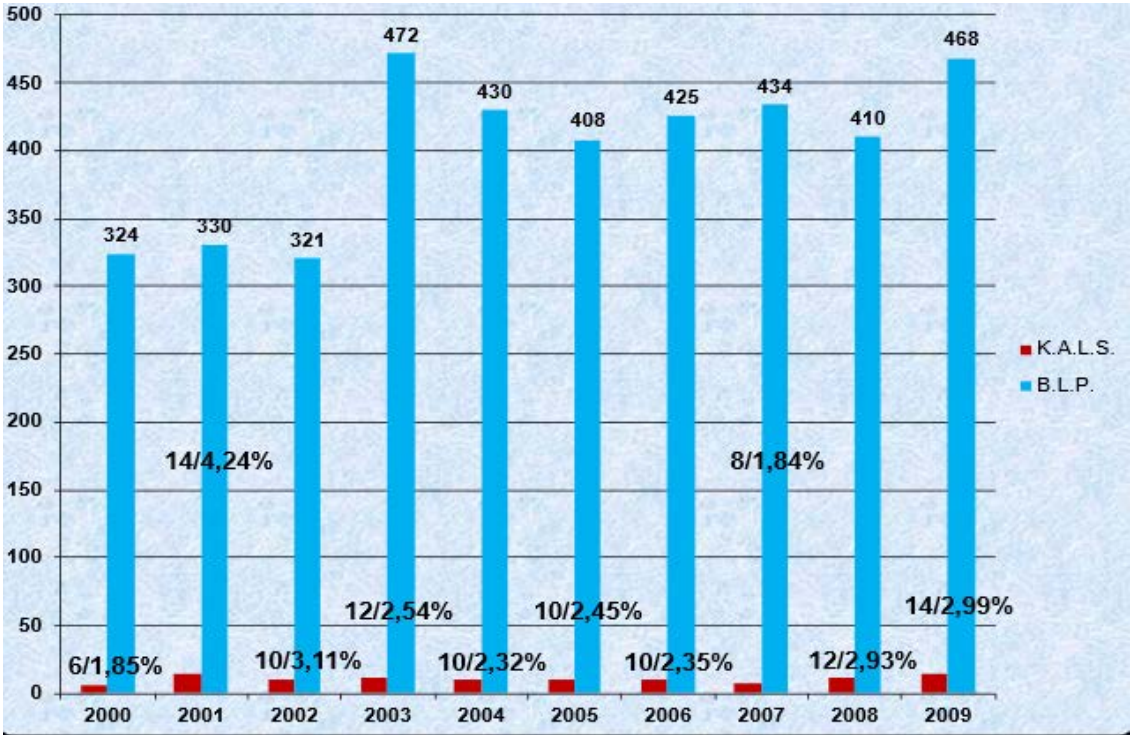
Slika 7. Dzinovski kongenitalni melanocitni nevus

Broj kongenitalnih anomalija periodu 1990-1999.g u skladu je sa literarnim podacima.



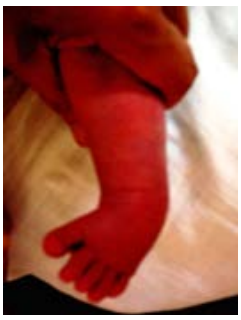
Grafikon 1. Kongenitalne anomalije lokomotornog sistema lečene na odeljenju ortopedije ZC Kosovska Mitrovica u periodu 1990-1999.g.

Kongenitalne anomalije- uocava se povećan broj kongenitalnih anomalija lokomotornog sistema dece lečene na odeljenju ortopedije u posleratnom periodu u odnosu na predratni.

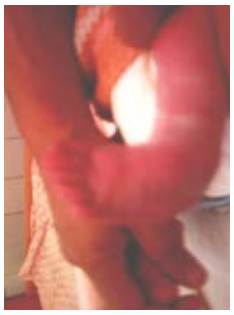


Grafikon 2. Kongenitalne anomalije lokomotornog sistema lečene na odelenju ortopedije ZC Kosovska Mitrovica u periodu 2000-2009. g.

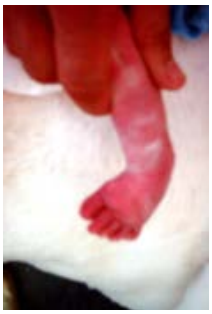
Slika 8. Pes eqinovarus



Slika 9. Talus vertikalis

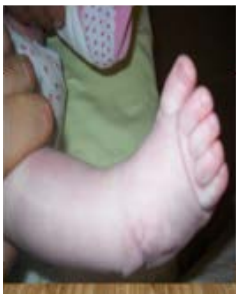


Slika 10. Pes metatarsus adductus

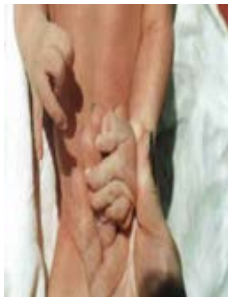


Slika 11. Vertical talus

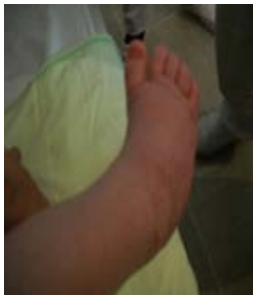
Slika 12. Talus vertikalis



Slika 13. Pes metatarsus varus



Slika 14. Polidaktilija i sindaktilija



Slika 15. Pes valgus

Diskusija i zaključak

Najteži poremećaji koji nastaju kao posledica dejstva OU su: mutageni, teratogeni i kancerogeni. Istraživanja sprovedena u " in vivo" i " in vitro" eksperimentima ukazuju da ekspozicija OU povećava: mutagenu aktivnost ćelija i transformiše humane osteoblastne ćelije u tumorske (5,6,7,8,9,10).

Podaci naše studije pokazuju povećanu učestalost koštanih anomalija dece nakon ratnih dejstava u odnosu na predratni preiod. Takođe, registrovali smo u našem porodilištu veoma retke anomalije novorođenčadi kao sto su: ihtioza (učestalost, prema podacima iz literature je, 1 :300 000 porođaja), dzinovski kongenitalni melanocitni nevus (1:500000 porođaja), mikrocija i atrezija srednjeg uva (1:20000 porođaja), retinoblastom (1:19000 porođaja), neuroblastom (1:10000 porođaja), veći broj cheilognatopalatoschisis (1:1000 porođaja), različitih teratoma, hipospadija. Učestalost koštanih anomalija (pes eqinovarus, pes metatarsus adductus, talus vertikalis itd.) velika je u odnosu na relativno mali broj porođaja u našem porodilištu.

Imajući u vidu da je etiologija ovih patoloških stanja multifaktorijalna, u cilju što objektivnijeg ispitivanja, potrebno je dalje praćenje i utvrđivanje stvarnog značaja osiromašenog uranijuma na njihovo nastajanje (odredjivanje osiromaseng uranijuma u krvi ploda i majke, plodovoj vodi, zemljistu, odredjivanje ucestalosti hromosomskih aberacija u pobacenim fetusima itd. Posebno

treba organizovati prospektivna istraživanja u cilju što objektivnijeg izučavanja ovog problema radi preduzimanje adekvatnih metoda zdravstvene zaštite.

Literatura

1. Relic Goran."Učestalost spontanih pobačaja, prevremenih porođajaporemećaja u razvoju trudnoće kod žena na kosovu i metohiji nakon nato bombardovanja" Projekat odobren od strane Ministarstva za nauku i tehnologiju republike Srbije, br .145110.2006.
2. Friedman A, Janulewicz Lloyd PA, Carlson J, Quinn E, Keating D, Toomey R, Heeren T, Coughlin SS, Markenson G, Krengel M, Sullivan K. Preliminary Findings from the Gulf War Women's Cohort: Reproductive and Children's Health Outcomes among Women Veterans Int J Environ Res Public Healt 2022 Jul 11;19(14):8483. doi: 10.3390/ijerph19148483
3. Yang Chen , Joel N Meyer , Helene Z Hill , Gudrun Lange , Michael R Condon , Jacquelyn C Klein , Duncan Ndirangu , Michael J Falvo. Role of mitochondrial DNA damage and dysfunction in veterans with Gulf War Illness. PLoS One. Journal List v.15(9) September 7, PMC 2025
4. Berisha Kida E, Jahiu G, Karaj T. Prevalence of post-traumatic stress disorder and traumatic exposure among teachers in post-war communities Discov Ment Health. 2025 May 6;5(1):69. doi: 10.1007/s44192-025-00194-6.PMID: 40327261
5. Sofia Marcolini 1, Philine Rojczyk , Johanna Seitz-Holland , Inga K Koerte , Michael L Alosco , Sylvain Bouix 2; Post-traumatic Stress and Traumatic Brain Injury: Cognition, Behavior, and Neuroimaging Markers in Vietnam Veterans. JAlzheimers Dis 2023;95(4):1427-1448. doi: 10.3233/JAD-221304
6. Lei Chang L, Gong YM, Wang SW, Shi PL, Li MZ, Wen X, Wang DX, Zheng YB, Associations of posttraumatic stress disorder symptoms with amyloid burden in cognitively normal older adults. Front Aging Neurosc 2024 Dec 3:16:1422862. doi: 10.3389/fnagi.2024.1422862. eCollection 2024
7. Sun X, Deng Y, Fang L, Ni M, Wang X, Zhang T, Chen Y, Cai G, Pan F. Association of Exposure to Heavy Metal Mixtures with Systemic Immune-Inflammation Index Among US Adults in NHANES 2011-2016 Biol Trace Elem Res,2024 Jul;202(7):3005-3017. doi: 10.1007/s12011-023-03901-y. Epub 2023 Oct 10
8. Miller AC, Brooks K, Stewart M, Anderson B, Shi L, McClain D, Page N. Genomic instability in human osteoblast cells after exposure to depleted uranium: delayed lethality and micronuclei formation. J Environ Radioact 2023;64(2-3):247-59. doi: 10.1016/s0265-931x(02)00053-x.
9. Miller AC, Mog S, McKinney L, Luo L, Allen J, Xu J, Page N. Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects Carcinogenesis 2021 Jan;22(1):115-25. doi: 10.1093/carcin/22.1.115
10. Predrag Kuzmanović , \Sofija Forkapić ,Dušan Mrđa , Jan Hansman , Jovana Knežević Radić. The impact of depleted uranium on the environment in Serbia Sci Total Environ 2025 Jul 1:984:179734. doi: 10.1016/j.scitotenv.2025.179734. Epub 2025 May 26

PREVENCIJA CEREBRALNE PARALIZE U PORODAJU – NAŠA ISKUSTVA

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Cerebralna paraliza nije bolest u tradicionalnom smislu, već klinički opis djece koja dijele karakteristike neprogresivne povrede mozga ili lezije stečene tokom antenatalnog, perinatalnog ili ranog postnatalnog perioda. Kliničke manifestacije cerebralne paralize uveliko variraju u vrsti poremećaja kretanja, stepenu funkcionalne sposobnosti i ograničenja te zahvaćenim dijelovima tijela. Cerebralna paraliza je najčešći uzrok doživotnog fizičkog invaliditeta koji se javlja u djetinjstvu u većini zemalja, a pogađa oko 1 od 500 novorođenčadi s procijenjenom prevalencijom od 17 miliona ljudi širom svijeta

Cerebralna paraliza se obično javlja kao posljedica događaja prije, tokom ili nakon rođenja koji rezultuju povredom djetetovog mozga u razvoju. Mnogobrojni su uzroci nastanka cerebralne paralize. Najveći faktor rizika je rođenje prije 37. nedelje trudnoće (prijevremeni porođaj). Ostali faktori rizika za majku uključuju određena medicinska stanja, abnormalnosti posteljice, preeklampsiju i određene bakterijske i virusne infekcije. Kod fetusa, faktori rizika uključuju kongenitalne i genetske abnormalnosti, nisku porođajnu težinu ili ograničen rast fetusa, višestruku trudnoću, određene infekcije i produženi nedostatak kiseonika tokom porođaja. Iako poremećaj pogađa pojedince tokom cijelog života, većina istraživačkih napora i strategija upravljanja cerebralnom paralizom trenutno se fokusira na potrebe djece. Kliničko liječenje djece s cerebralnom paralizom usmjereno je na maksimiziranje funkcije i sudjelovanja u aktivnostima te minimiziranje učinaka faktora koji mogu pogoršati stanje, poput epilepsije, problema s hranjenjem, dislokacije kuka i skolioze.

Naši rezultati: Analizirani su podaci iz Porodilišta i Odjeljenja Intezivne njege na Klinici za dječije bolesti u toku 2023. godine. Analizirana je gestacijska starost, ordiniranje MgSO4 (bolus ili puna doza), način porođaja i ishod novorođenčadi u prvih 7 dana.

U toku 2023.godine bilo je 322 prevremenih porođaja od ukupno 3132 porođaja što predstavlja 10,2%. MgSO4 je ordiniran kod 58 pacijentkinja do 33. nedelje gestacije. Bilo je 11 blizanaca. Ukupno je porođeno 69 novorođenčadi od kojih je najmanje imalo 480 gr, a najteže je bilo 2200 gr. Carski rez je urađen u 70% slučajeva. Kompletna doza MgSO4 doza je data u 39 slučajeva ili 68%. Najveći broj novorođenčadi je bio tjelesne mase od 1500 do 1999 gr, sa Apgar skorom 5-7 i to 49% i preko 8 kod 46%.U prvih sedam dana je egzitiralo 11 novorođenčadi ili 15,9 %.

Zaključak: Dijagnoza cerebralne paralize se ne može postaviti neposredno nakon porođaja. Simptomi se javljaju obično prije druge godine. Mnogi autori navode da primjena magnezijum sulfata tokom prijevremenog porođaja i hlađenje visokorizične dojenčadi može smanjiti stopu i težinu cerebralne paralize.

Literatura:

1. Emily S Shepherd et al.Magnesium suphate for women at risk of preterm birth for neuroprotection of the fetus.Cochrane Database Syst.Rev 2024
2. Emly S Sepherd.Magnesium Sulfate Before Preterm Birth for Neuroprotection Obstet. Gynecol.2024
3. Bachnas MA et al. The role of magnesium sulfate (MgSo4) in fetal neuroprotection.JMatern Fetal Neonatal Med 2021
4. Magee LA .Magnesium Sulfate for fetal Neuroprotection .J Obstet Gynecol Can.2019,Apr
5. HT Wolf et al.Magnesium sulphate for teal neuroprotection at imminenst risk for preterm delivery:a systematic review with meta-analysis and trial sequential analysis.BJOG 2020.Sep

INTRAUTERUSNI ZASTOJ RASTA PLODA NEPOZNATE ETIOLOGIJE – RETROSPEKTIVNA ANALIZA I PRIKAZ SLUČAJEVA

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Jelena Štulić, Rastko Maglić, Milica Mandić

GAK Narodni Front

Uvod: Intrauterusni zastoj rasta ploda (engl. Intrauterne growth restriction – IUGR) je stanje u kojem fetus ne dostiže svoj genetski predviđeni rastni potencijal, a povezano je sa povećanim perinatalnim morbiditetom i mortalitetom. Uzroci mogu biti maternalni, fetalni ili kombinovani, dok se u značajnom broju slučajeva etiologija ne može utvrditi (IUGR nepoznate etiologije).

Cilj: Prikazati moguće etiološke faktore i dijagnostički pristup kod pacijentkinja sa IUGR-om, sa posebnim osvrtom na slučajeve nepoznate etiologije.

Materijal i metode: Retrospektivnom analizom medicinske dokumentacije obuhvaćene su pacijentkinje porođene na Klinici GAK „Narodni front“ sa dijagnozom IUGR-a (telesna masa ploda <10. percentila za gestacijsku dob). Analizirani su rezultati amniocenteze, TORCH serologije, eventualnog testiranja na Parvo B19, molekularnog kariotipa, nalaza detaljnog ultrazvučnog pregleda, doplerskih merenja (umbilikalna i uterine arterije, cerebro-placentalni indeks), prisustvo hipertenzije kod majke, način završavanja porođaja i Apgar skor. Posebno su prikazana tri slučaja IUGR-a nepoznate etiologije.

Rezultati: Preliminarni nalazi ukazuju na značaj kombinovanog dijagnostičkog pristupa, uključujući genetska i infektivna ispitivanja, doplersku evaluaciju uteroplacentne cirkulacije i detaljnu anatomsku procenu ploda, u identifikaciji uzroka IUGR-a. Kod tri analizirana slučaja nepoznate etiologije, uprkos kompletnom dijagnostičkom protokolu, etiološki faktor nije identifikovan, a odluka o završavanju trudnoće doneta je na osnovu ultrazvučnih i kardiotokografskih parametara.

Zaključak: IUGR nepoznate etiologije predstavlja dijagnostički izazov koji zahteva multidisciplinarni pristup i pažljivo praćenje fetalnog stanja. Dopuna standardnog algoritma dijagnostičkim procedurama, uz individualizovan plan praćenja, može doprineti pravovremenom donošenju odluka i smanjenju perinatalnog rizika.

IVF AND REPRODUCTIVE ENDOCRINOLOGY

IATROGENIC MENOPAUSE- THERAPEUTIC DILEMMAS

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The term “premature ovarian insufficiency (POI) “is used in last few years instead of formerly used “premature ovarian failure”. The term POI describes better continuum of slow and imperceptible declining of ovarian function in a young woman, which lasts for several years and results in an earlier menopause. POI is substantially less emotive term than term “premature ovarian failure” which signaled a single and definite event in time.

The average age for cessation of menstrual cycles is 50-52 years. There has been no change in the average age of menopause in last 3 to 4 decades.

But iatrogenic causes of POI are becoming more common as access increases to surgical management options as well as chemotherapy and radiotherapy. One in 49 women will be diagnosed with cancer before the age of 40 years. Eighty percent of those affected by childhood cancer will survive long-term. The risk of nonsurgical POI is 13 fold higher in cancer survivors compared with their no cancer affected siblings [1].

Research is increasingly providing information about the pathogenesis and treatments to enable better preservation of ovarian function during cancer treatment, to improve health consequences of hormone insufficiency and to improve fertility options.

The aim of this narrative review is to discuss the best practice options in management of iatrogenic POI using the current literature and own experiences.

Frequency of causes of premature ovarian insufficiency: Idiopathic – 25%, Iatrogenic – 37%. Autoimmune – 19%, Genetic – 19%.

From the analysis of the frequency of the causes of POI, it is evident that the most frequent causes are iatrogenic. Before the age of 20 years, fifty percent of the women diagnosed with POI were shown to have a genetic cause.

Risk factors for chemotherapy-induce ovarian failure: patient age (>40 years), familial ovarian history, ovarian follicle reserve, history of previous ovarian and pelvic surgery, previous chemotherapy, previous pelvic and abdominal radiotherapy, persistent high level of follicle stimulating hormone (FSH), class of the chemotherapeutic agent (alkylating vs. no alkylating), dosing and length of chemotherapy, concomitant diseases.

Definite	Probable	Unlikely	Unknown
N-mustard	Doxorubicin	Methotrexate	VM-26
L-phenylalanine mustard	Vinblastine	Fluorouracil	Daunorubicin
Chlorambucil	Cytosine arabinoside	6-mercaptopurine	Bleomycin
Busulfan	Cis-platinum	Vincristine	Melphalan
Cyclophosphamide	Carmustine		Dacarbazine
Procarbazine	Lomustine		Vindesine
	VP-16 (etoposide)		

POI: Premature ovarian insufficiency

Picture 1. Risk of POI with chemotherapeutic medications (Fenton A 2015).

The use of alkylating agents will lead to POI in approximately 40% of women. A combination of chemotherapy and total body or abdominopelvic radiotherapy is particularly deleterious. Ovarian function may recover, but generally menopause will still occur early [2]. The somewhat routine practice of removing healthy ovaries or ovary ("one is enough") at the time of hysterectomy is, fortunately, diminishing with time and we hope will disappear. A New Zealand prospective cohort of 257 women under the age of 46 years demonstrated that hysterectomy without oophorectomy brought forward the age of menopause by 3.7 years [3]. A rapid decline in anti-Mullerian hormone (AMH) is seen after hysterectomy [4]. Research has now also linked ovarian drilling for polycystic ovary syndrome and removal of endometriotic cysts to an earlier age at menopause [5, 6].

Data at St. Marianna University School of Medicine and the Rose Ladies Clinic of 827 POI patients showed that 131 (15.8%) had possible iatrogenic causes. Of the iatrogenic POI cases, 64% occurred following ovarian surgeries (i.e., except for bilateral oophorectomy). An analysis of 75 patients who underwent surgery for benign ovarian cysts prior to the onset of ovarian insufficiency is reported. Of these 75 patients, 66 (88.0%) underwent cystectomy. For the majority of the 75 patients, the surgical indication was the presence of endometriotic cysts (57 patients; 76.0%). Twelve patients (16.0%) underwent multiple surgeries (all bilateral cystectomies). The mean age of the patients at the time of surgery was 27.8 ± 5.5 years, and the mean period of onset of ovarian insufficiency was 5.8 ± 3.8 years. In patients with cystectomy, their age at the time of surgery and period of onset of ovarian insufficiency were well correlated Cystectomy of endometriotic cysts is a potential risk factor for ovarian insufficiency after surgery, with, at times, the onset of ovarian insufficiency long after cystectomy. Some patients may be unaware that their menstrual disturbance is causally related to the ovarian surgery. Therefore, it is important to monitor ovarian reserve for an extended period of time after ovarian surgery. It is particularly important to monitor ovarian reserve over the long-term in patients who wish to conceive in the future and to suggest a variety of infertility treatments appropriate for their ovarian reserve [7].

Treatment of patients suffering from iatrogenic POI

HRT must be performed when the diagnosis of POI is made, except where contraindicated.

Estrogen deficiency in POI patients is known to cause the early aging of blood vessels, bones, and other tissue and shorten patients' life expectancy.

Patients who suffered from cancer in childhood, who survive in 80% cases, and consequently develop POI, are whole life candidates for hormone therapy, to the average time of menopause in the population, to about 50 years of life. Therapy for this group of patients is challenging from the beginning- induction of puberty and growth, development of secondary sexual characteristics and normal dimensions of internal and external genitals. Combined HRT (i.e. estrogen and progesterone) restored endothelial dysfunction in women with POI, decreased the risk of ischemic heart disease, and prevented the increase in cardiovascular disease mortality associated with bilateral oophorectomy. Thus, HRT is indicated for the treatment of vasomotor and urogenital symptoms in women with POI. It is also recommended to maintain bone health and prevent osteoporosis. The bone density has to be controlled periodically, for checkup is the hormone therapy alone sufficient to maintain bone density. Estrogen replacement mitigated the decline in cognition associated with early oophorectomy. Continuous estrogen replacement is desirable to avoid symptoms of estrogen deficiency. Some women using oral contraceptives will be symptomatic during the pill-free period, and the conventional 3 + 1 regimen results in no hormone replacement for 25% of the time. Cyclical rather than continuous, combined regimens stimulating active functioning of the endometrium are necessary for women desiring pregnancy by oocyte donation. This may lead to a slightly higher risk of hyperplasia/carcinoma of the endometrium. Cycle length can be individualized, but probably should not exceed 12 weeks to protect the endometrium. For that reasons, women with POI should be informed that HRT before the age of normal menopause is mandatory if not contraindicated. It has not been found to increase the risk of breast cancer. POI patients with lifestyle risk factors for VTE should be advised to reduce them.

Genital tumors and hormone sensitive genital tumors are not contraindication for estrogen – progesterone therapy. In the interesting retrospective survey study conducted by van der Hoef and all, the assessment of the uptake of hormone replacement therapy (HRT) in cervical cancer patients with iatrogenic menopause was done. In total, 293 women under the age of 51 and treated with radiotherapy for cervical cancer between 2010 and 2020 were identified. Survival in relation to HRT use was assessed via a retrospective chart study, and the severity of menopausal symptoms, motivations and barriers to starting HRT were examined via questionnaires: Overall HRT uptake was 78.1 %, Overall survival was higher for HRT users ($\chi 2$ (1) = 4.3, p = 0.038). Questionnaires were sent to 193 patients and 100 completed it (response rate 51.8 %). Main reasons for HRT use were relief of hot flushes and improvement in QoL. For women below age 51, QoL was indeed higher for current HRT users than for non-HRT users (EQ-index 0.8 vs. 0.7, p = 0.008). According to the results, authors concluded that HRT prescription rate was inversely correlated with age. Survival was not negatively affected by HRT use. It is interesting that the main medication used by most women in the study was tibolon, and authors discussed that in the following way: „ In our cohort the most commonly prescribed type of HRT was tibolone, followed by estrogen only and a fixed-dose combination. Tibolone, a synthetic steroid with estrogenic, progestogen and androgenic properties, has long been the preferred HRT in our clinic and is favored over other standard HRT preparations due to its ease of administration, low risk of vaginal bleeding and lower likelihood of breast tenderness. Studies also indicate beneficial effects of tibolone on both libido and mood. However, the suppression of menopausal symptoms by tibolone appears slightly weaker than estrogen-containing regimes, so this may explain why one in three women switched from tibolone to estrogen-containing regimes “[8].

The surgical menopause in adult patients cause the sudden cessation of ovarian function with rapid drop of hormones and therefore very pronounced symptoms, and the main reason for starting therapy in this group of patients is vasomotor disturbances i.e. hot flushes.

Patients cured because of hormone dependent breast cancer may not use estrogen progesterone therapy for POI. Nolvadex , often use as the adjuvant therapy have estrogenic effects on vascular endotel, bones and genitourinary system, but have no effects on CNS receptors and do not resolve hot flushes. Aromatase inhibitors deprives all tissues from estrogens and the risk of cardiovascular diseases doubled in aromatase inhibitor users compared to Nolvadex therapy.

ESE recently approved local estrogen use for urogenital symptoms in breast cancers survivors suffering from POI [9].

References:

1. Hudson MM. Reproductive outcomes for survivors of childhood cancer. Obstet Gynecol. 2010; 116:1171–83. doi: 10.1097/AOG.0b013e3181f87c4b.
2. Fenton A. Premature ovarian insufficiency: Pathogenesis and management. J Midlife Health 2015; (6): 142-153 doi: 10.4103/0976-7800.172292
3. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: A prospective cohort study. BJOG. 2005; 112:956–62. doi: 10.1111/j.1471-0528.2005. 00696.x
4. Atabekoglu C, Taskin S, Kahraman K, Gemici A, Taskin EA, Ozmen B, et al. The effect of total abdominal hysterectomy on serum anti-Müllerian hormone levels: A pilot study. Climacteric. 2012; 15:393–7. doi: 10.3109/13697137.2011.642426.
5. Fenton A, Panay N. Does routine gynecological surgery contribute to an early menopause? Climacteric. 2012; 15:1–2. doi: 0.3109/13697137.2012.647623.
6. Api M. Is ovarian reserve diminished after laparoscopic ovarian drilling? Gynecol Endocrinol. 2009; 25:159–65. doi: 10.1080/09513590802585605.
7. Ishizuka B. Current understanding of etiology, simptomatology and treatment options in premature ovarian insuffitiency (POI): Front Endocrinol 2021: (12) : 1-14
8. Van der Hoef C. Dsane LB, Schuur N, Lorwers Y, Mens JW, Hivary Bhal N, Van Doorn HC. Hormone replacement therapy in women with iatrogenic premature ovarian insufitiency after radiotherapy for cwevical cancer: A retrospective cohort and survey study. Maturitas 2024 (185) 108004
9. Lambrinoudaki I. ESE MHT guidelines [Internet]. Presented at: 15th European Congress on Menopause and Andropause: Empowering Science and Healthcare; 2025 May; Valencia, Spain.

ONCOLOGY

PRETREATMENT SURGICAL STAGING IN LOCALLY ADVANCED CERVICAL CANCER (LACC); IS IT STILL RELEVANT IN PET-CT (18F-FDG PET/CT) ERA?

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Metastases in para-aortic lymph nodes in cervical cancer occur with a frequency that increases with the stage of the disease, with retrospective and prospective studies confirming the importance of surgical evaluation of lymph nodes. Recent guidelines recommend PET/CT over CT in initial staging of LACC to detect extra pelvic disease making PET-CT the most reliable imaging method, but it does not detect microscopic metastases in 9–22% of cases, which can affect the scope of treatment. New development of PET/CT technology (Time of flight-TOF) might improve this shortcoming but until now the surgical evaluation of para-aortic lymph nodes (PALND) is recommended for selected patients, as it can affect survival. Retrospective analyses show that surgical assessment improves 4-year progression-free survival (49% vs. 36%) and overall survival (54% vs. 40%). Research such as Uterus-11 and a Spanish retrospective study confirm the safety of PALND and its impact on treatment adaptation. Further research, including the PAROLA and DEBULK studies, will provide clearer answers about the role of PALND in optimizing treatment for locally advanced cervical cancer.

Keywords: PET/CT, pelvic and para-aortic laparoscopic lymphadenectomy, locally advanced cervical cancer, surgical treatment options.

Introduction

In cervical cancer, the frequency of para-aortic lymph node metastases increases with advancing disease stage with retrospective and prospective studies confirming the importance of surgical evaluation of lymph nodes. Data from the Gynaecologic Oncology Group (GOG) show that PALN involvement confirmed by biopsy occurs in 5% of patients with FIGO stage IB, 17% with stage IIB, and 25% with stage IIIB. Due to the high rate of undetected pathological lymph nodes, an accurate assessment of the lymph nodes is crucial for making appropriate therapeutic decisions.

Diagnostic methods and treatment planning

Recent guidelines recommend PET/CT over CT in initial staging of LACC to detect extra pelvic disease making PET-CT the most reliable imaging method, but it does not detect microscopic metastases in 9–22% of cases, which can affect the scope of treatment. New development of PET/CT technology (Time of flight-TOF) might improve this shortcoming but according to results of Gouy et al. false negative results can still be detected even when new technology is used, that allows the resolution between 4 and 6 mm.

The surgical evaluation of para-aortic lymph nodes (PALND) is thus recommended for selected patients, especially for those with pelvic uptake and negative PALND at PET/CT.

The European Society of Gynaecological Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology (ESGO/ESTRO/ESP) still potentially recommend PALND at least to the level of the inferior mesenteric artery in cases where imaging studies do not show PALND involvement. These recommendations (level C) apply to patients with locally advanced cervical cancer (LACC) (stages T1b2, T2a2, T2b, T3a/b, and T4a) and to patients with pT1a2 LVSI-positive tumors and pT1b1 or pT2a1 tumors with clear surgical margins.

The 2025 NCCN guidelines recommend extended field radiotherapy (EFRT) for patients with pathological PALN 8after surgery or imaging Patients with negative PALN (by imaging or after surgical removal) or with disease limited to the pelvis are treated with external beam radiation therapy (EBRT) and concurrent chemotherapy and immunotherapy for stages III-IVA.

Morbidity and safety of laparoscopic PALND surgical removal was evaluated in many studies. The overall conclusions, although the reports are not uniform, could be summarized that the procedure has low morbidity and no important delay in start of radiotherapy.

A retrospective analysis of 685 patients from three Gynecologic Oncology Group (GOG) studies compared survival between surgical and radiological PALN staging in LACC. The results showed that patients who had a surgical PALN assessment had significantly better 4-year progression-free survival (PFS) (49% vs. 36%) and overall survival (OS) (54% vs. 40%) compared to patients who had only a radiological PALN assessment. It is important to note that PET-CT was not used in the radiological assessment of PALN.

Guoy et al. have investigated the role of surgical assessment of PALN in LACC in a retrospective analysis. They found that patients with PALN micrometastases (≤5 mm) had similar survival outcomes as those without metastases, suggesting a potential therapeutic benefit of lymphadenectomy. However, the analysis included only 13 patients with micrometastases, making the sample size too small to draw definitive conclusions.

An OncoGF study reported that sensitivity, specificity, positive and negative predictive value of PET/CT were 23.5, 93.3, 47.1 and 82.8% respectively since out of 151 negative PET/CT imaging results 26 had positive histological PALN metastases.

The Uterus-11 prospective study included 240 patients with LACC who were divided into a group with radiological (CT/MRI) or surgical lymph node assessment. The surgical evaluation did not significantly delay the start of chemoradiation (only 5 days), and in 33% of patients, the stage was higher than the previous imaging evaluation. There were no differences in PFS and OS in the entire group, but a post hoc analysis indicated improved cancer-specific survival (CSS) and PFS in patients with RMV FIGO IIB. A significant limitation was the incorrect calculation of the sample size, as the study predicted a 5-year DFS in 36% of patients in the control group, but with modern chemoradiotherapy techniques, we achieve a 5-year DFS in 60% of patients.

A Spanish retrospective study involving 634 patients over 16 years showed that surgical assessment with PALND to the left renal vein is safe, with serious complications occurring in less than 2% of patients. The study did not show differences in OS, PFS, and CSS between the groups with surgical or radiological assessment, but the PALN radiological assessment group received EBRT in 58% of cases (compared to 34% in the surgical assessment group). The actual beginning of EBRT was only 18 days. An important finding was the 9.6% incidence of isolated (skip) metastases in the infrarenal area, which highlights the importance of extending LND to the left renal vein. The study also mentions the limitations of PET-CT, particularly the rate of false positive results in the pelvis, due to inflammation.

We are currently waiting for the results of two studies. PAROLA is an international phase III study that compares surgical and radiological assessment of PALN with PET-CT in patients with FIGO stage IIIC1 RMV. The goal is to improve DFS in the PALN-surgical group, as PET-CT does not detect pathological PALN in 25% of cases. Results are expected in 2030. DEBULK is a phase III study (KGOG 1047) that examines whether surgical removal of large or multiple lymph nodes prior to concurrent chemoradiation improves 3-year PFS in patients with RMV FIGO stage IIIC.

Data from University Medical Centre Ljubljana

Surgical staging in patients with LACC started in 2010 and lymphadenectomy was mainly focused on pelvic nodes. The reason for surgical staging in that period was mainly because of low sensitivity of CT and MRI and relatively high rate of false negative results in the pelvis. PET/CT was introduced one year earlier, but the waiting list was not acceptable for these patients. Beside staging we also debulked enlarged or suspect lymph nodes from the pelvis.

From 2019 we perform sentinel node from pelvis and PALN resection up to inferior mesenteric artery. Since 2023 we are trying to select patients with LACC for surgical staging based on negative PET/CT findings in para-aortic area and positive pelvic nodes on imaging, but the problem of obtaining a test date early enough after diagnosis still remains.

Therefore only 4 patients out of 23, who had surgical staging performed in 2023 followed this concept.

Conclusion

Imaging or surgical staging contributes to LACC treatment by individualization of external beam radiotherapy. PET/CT remains the most reliable imaging method for assessing the progression of the disease, but in case of microscopic metastases the results may be false negative. Therefore when PET/CT is positive in the para-aortic region or in the case of positive lymph nodes in the pelvis and negative in the para-aortic region, surgical staging at least to the inferior mesenteric artery should be considered.

Literature

1. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. Cancer. 2008 May 1;112(9):1954-63.
2. Leblanc E, Katdare N, Narducci F, Bresson L, Gouy S, Morice P, Ferron G, Querleu D, Martinez A. Should Systematic Infrarenal Para-aortic Dissection Be the Rule in the Pretherapeutic Staging of Primary or Recurrent Locally Advanced Cervix Cancer Patients With a Negative Preoperative Para-aortic PET Imaging? Int J Gynecol Cancer. 2016 Jan;26(1):169-75.
3. Marnitz S, Tsunoda AT, Martus P, Vieira M, Affonso Junior RJ, Nunes J, Budach V, Hertel H, Mustea A, Sehouli J, Scharf JP, Ulrich U, Ebert A, Piwonski I, Kohler C. Surgical versus clinical staging prior to primary chemoradiation in patients with cervical cancer FIGO stages IIB-IVA: oncologic results of a prospective randomized international multicenter (Uterus-11) intergroup study. Int J Gynecol Cancer. 2020 Dec;30(12):1855-1861.
4. Díaz-Feijoo B, Franco S, Torné A, Benito V, Hernández A, Lago V, Rovira R, Acosta Ú, Agustí N, Gil-Moreno A; SEGO Spain-GOG Group. Implications of extraperitoneal paraaortic lymphadenectomy to the left renal vein in locally advanced cervical cancer. A Spanish multicenter study. Gynecol Oncol. 2020 Aug;158(2):287-293.
5. Leblanc E, Katdare N, Narducci F, Bresson L, Gouy S, Morice P, Ferron G, Querleu D, Martinez A. Should Systematic Infrarenal Para-aortic Dissection Be the Rule in the Pretherapeutic Staging of Primary or Recurrent Locally Advanced Cervix Cancer Patients With a Negative Preoperative Para-aortic PET Imaging? Int J Gynecol Cancer. 2016 Jan;26(1):169-75.
6. Pomel C, Martinez A, Bourgin C, Beguinot M, Benoit C, Naik R, Dauplat J, Lebouedec G, Ferron G. Survival effect of laparoscopic para-aortic staging in locally advanced cervical cancer: a retrospective cohort analysis. BJOG. 2017 Jun;124(7):1089-1094. doi: 10.1111/1471-0528.14492. Epub 2017 Jan 27. PMID: 28128517.
7. De Cuypere M, Lovinfosse P, Goffin F, Gennigens C, Rovira R, Duch J, Fastrez M, Gebhart G, Squifflet JL, Luyckx M, Charaf G, Crener K, Buxant F, Bucella D, Jouret M, Hustinx R, Kridelka F. Added value of para-aortic surgical staging compared to 18F-FDG PET/CT on the external beam radiation field for patients with locally advanced cervical cancer: An ONCO-GF study. Eur J Surg Oncol. 2020 May;46(5):883-887. doi: 10.1016/j.ejso.2019.11.496. Epub 2019 Nov 11. PMID: 31784203.

CLINICAL REGISTRIES IN GYNECOLOGICAL ONCOLOGY – ENDOMETRIAL CANCER REGISTRY

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Clinical registries are designed to collect quality data about the care for cancer patients in order to improve it. They gather data that are generated during diagnosis and cancer treatment and also post-treatment follow-up. Hospital-based registries maintain data on all patients diagnosed and/or treated for cancer at a particular healthcare facility. The focus of the hospital-based cancer registry is on improving patient care at that hospital. These registries also focus on administrative processes, clinical research, and professional education. Analysis of collected data allows an improvement in the quality of patient care and a comparison with other health care providers. The aim of the present article is to describe the current version and practice of hospital-based endometrial cancer registry at the University Medical Centre Maribor.

At the Department of Gynecologic and Breast Oncology of the Maribor General Hospital we introduced seven different hospital-based clinical registries for gynecological (vulvar, vaginal, cervical, endometrial, ovarian, fallopian tube cancer) and breast cancer in 1994. Computer programs have been designed for all of them and articles on the use of this software to follow-up patients with ovarian malignancies were published in 1996 and 1999 and for breast cancer patients in 2019. Moreover, data stored in these databases articles were published in 2008 on cervical cancer, in 2016 on endometrial cancer, in 2019 on vaginal cancer and in 2021 on vulvar cancer.

Since then, the principles for treating gynecological cancers have been revised on several occasions. Therefore, based on our experience and new approaches to treatment, we have frequently amended the questionnaires content. In recent years, molecular genetic methods have been gaining ground in the field of diagnostics, and we need to include them in the register. At the same time, new treatments are becoming available, and we need to take all this into account and keep the clinical register up to date. We particularly emphasize the importance of including fertility-sparing treatments for younger patients with endometrial cancer. Consequently, these options should be integrated into the overall treatment plan and reflected in the patient registry. It was redesigned into a form that is currently in use.

Over the last 30 years, we have collected data on gynecological cancers patients treated at our institution. Hospital-based registries are important tools for policy formulations and region-specific data creation. The computer programs that were developed for this purpose enable a rapid and reliable collection, processing and analysis of different data of patients with gynecological cancers, including general data, history, diagnostic procedures, histopathological examination results, treatment methods, and post-treatment follow-ups.

The gynecological cancers registries enable the collection of data to enhance diagnosis and the treatment of gynecological cancer patients, the organization of day-to-day service, as well as the comparison of our treatment results with national and international standards. Incomplete or incorrect data entry, however, might pose a limitation of the clinical registry, which depends on

several healthcare professionals involved in the diagnostic procedures, treatment, and follow-up of gynecological cancer patients.

Key words: hospital-based clinical registry, computer program, gynecological cancers, endometrial cancer

Introduction

Cancer registries are established with the goal of systematic collection, storage, analysis, interpretation and reporting of data on subjects with cancer. There are two main types of cancer registries: hospital-based and population-based cancer registry. The former deals with recording information on cancer patients treated in hospital, while the latter collects data on all new cancer patients in a well-defined population with the intention of describing the extent and nature of the cancer burden in this particular community and assist in the establishment of public health priorities. Their data provides a source for etiological studies and may help in assessing the effectiveness of cancer control activities [1].

One of the oldest population-based cancer registries in Europe was established in Slovenia. It is called the Cancer Registry of the Republic of Slovenia and was founded at the Institute of Oncology Ljubljana in 1950. This registry is monitoring the population burden for all malignant and pre-malignant oncological diseases in Slovenia [2]. The fourth extensive report on the survival of Slovenian cancer patients diagnosed between 1997 and 2016 was presented recently showing increasing survival of cancer patients over the last 20 years [3]. In order to improve the survival rate, earlier stages of the disease should be detected and modern treatments widely available. The challenge in the future is to establish monitoring of quality of care by establishing clinical registries for the five most common cancers [4].

It is true that additional data can provide more guidance to improve the quality of care. Acquiring this kind of data requires establishing a clinical registry where a significantly more extensive set of clinical data are collected. This would be easier to do if the Slovenian health care system was based on a single information platform [3]. The first special clinical registry in Slovenia was the Clinical Registry of Skin Melanoma founded in 2017 [5].

Following the aims of the National Cancer Control Plan 2017 – 2021, the Institute of Oncology Ljubljana is establishing a system for collecting and reporting the extended information for patients diagnosed with the most common cancers: breast, prostate, colon and rectum, lung and skin melanoma [2].

Department of Gynecologic and Breast Oncology of University Medical Centre Maribor has a long tradition of collecting clinical data on gynecological cancers. In 1994 we introduced seven different hospital-based clinical registries for gynecological (vulvar, vaginal, cervical, endometrial, ovarian, fallopian tube cancer) and breast cancer. A computer program has been designed for all of them and articles on the use of this software to follow-up patients with ovarian malignancies were published in 1996 and 1999 and for breast cancer patients in 2019 [6-8].

In 1994 comprehensive forms for monitoring patients with endometrial cancer (EC) were introduced at the Department of Gynecological and Breast Oncology, Maribor General Hospital. Following the clinical development in treatment approaches EC, this form has been revised several times. The amendments were based on our experience and new approaches to treatment. The form of Endometrial-Online computer program that we use nowadays was designed in 2014. The Endometrial-Online computer program enables collection, processing, and analysis of 139 different data, that include patient's general data, history, diagnostic procedures, histopathological

examination results, treatment methods, and post-treatment follow-ups in a rapid and reliable way. The purpose is the collection of data on cancer patients with the intention of improving diagnosis and treatment. It enables improved day-to-day healthcare service, and comparison of our treatment outcomes with national and international standards. Limitations of such clinical registries can be in incomplete or incorrect data entry because of several healthcare professionals taking part in diagnostic work up, treatment and post-treatment follow-up of endometrial cancer patients.

In this article the endometrial cancer registry will be presented.

Endometrial cancer registry

Registry for endometrial cancer records data known to be associated with high risk for endometrial cancer as age, menstrual history, infertility, polycystic ovary syndrome, postmenopausal hormone therapy, obesity, alcohol consumption, metabolic syndrome, diabetes and history of cancer [9].

Endometrial cancer is the fifteenth most common cancer among women worldwide and it is the sixth most common cancer in women. According to GLOBOCAN there were 420, 368 new cases and 97,723 cancer deaths worldwide in 2022 [10].

The crude incidence of endometrial cancer in Slovenia in the period 2017 - 2021 was 16,4/100.000 and the age standardized incidence was 16,4/100.000 with approximately 350 new cases yearly [11].

The five-year survival rate for all histological types in all age groups is 80%. There are currently around 5 000 women diagnosed with cervical cancer in Slovenia. Gynecologists at primary, secondary and tertiary level, radiotherapeutic oncologists, oncologic internists and many other health professionals are involved in the management of patients with endometrial cancer and accompany them along the path of diagnosis, treatment and rehabilitation. In Slovenia, almost 90% of all patients undergo primary surgery, of which 75% are operated on in tertiary institutions (Oncology Institute Ljubljana, University Clinical Centre Ljubljana, University Clinical Centre Maribor) and 25% in secondary institutions. Treatment can have a significant impact on the quality of life of patients [12].

Material and methods

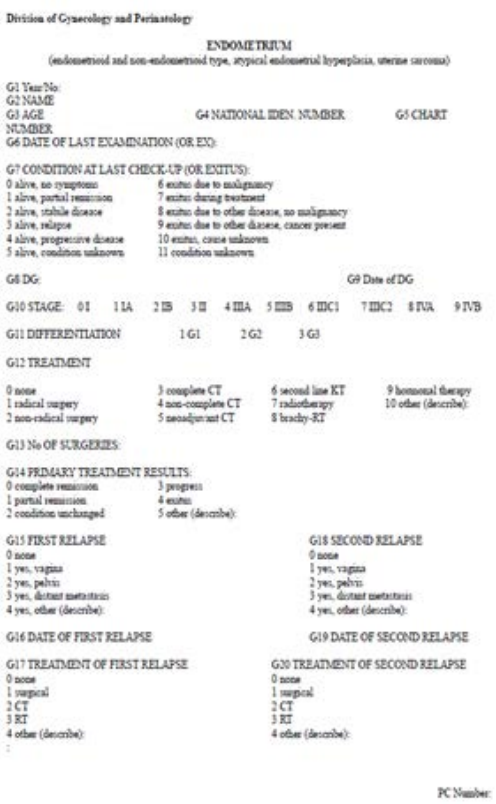
Over the past decades, the treatment of endometrial cancer has changed dramatically in terms of surgery and systemic treatment. Regarding our previous experience with collecting cancer patient data including all relevant data, the context of the inquiry for endometrial cancer has been modified and redesigned for current use. The updated inquiry protocol served as a model for developing an adequate computer program with the purpose of recording data during diagnostics, treatment and follow-up of patients.

After the patients complete their primary treatment, data are recorded using the computer program. Paper forms are used first, during a patient's interview with the attending physician, and the data are later transferred to the computer program. The form is available and filled with new information upon any following visit. The front page of the program contains basic information regarding the stage of the disease, initial treatment and its results, relapses and their treatment. It is followed by a patient's history with signs and symptoms, clinical and ultrasound examination together with different examinations and tests used to determine the stage of the disease. In the following three figures details about surgery, chemotherapy and radiotherapy are included, together with detailed pathological and histologic reports.

Results

The inquiry for endometrial cancer covers 174 different items divided into following sections: general data, medical history, clinical examination, ultrasound examination, tests and examinations, surgical treatment, histopathology, systemic treatment and radiotherapy, and follow-up.

General data are partly collected with the establishment of endometrial cancer diagnosis consisting of identification and treatment data at the end of primary treatment (Figure 1).



Division of Gynecology and Perinatology

ENDOMETRIUM

(endometrioid and non-endometrioid type, atypical endometrial hyperplasia, uterine sarcoma)

G1 Year No:
G2 NAME
G3 AGE
G4 NATIONAL IDEN. NUMBER
G5 CHART NUMBER
G6 DATE OF LAST EXAMINATION (OR EX):

G7 CONDITION AT LAST CHECK-UP (OR EXITUS):
0 alive, no symptoms
1 alive, partial remission
2 alive, stable disease
3 alive, relapse
4 alive, progressive disease
5 alive, condition unknown
6 exitus due to malignancy
7 exitus during treatment
8 exitus due to other disease, no malignancy
9 exitus due to other disease, cancer present
10 exitus, cause unknown
11 condition unknown

G8 DG:
G9 Date of DG

G10 STAGE: 0 I 1 IA 2 IB 3 II 4 IIIA 5 IIIB 6 IIIC1 7 IIIC2 8 IVA 9 IVB

G11 DIFFERENTIATION 1 G1 2 G2 3 G3

G12 TREATMENT

0 none
1 radical surgery
2 non-radical surgery
3 complete CT
4 non-complete CT
5 neoadjuvant CT
6 second line KT
7 radiotherapy
8 brachy-RT
9 hormonal therapy
10 other (describe):

G13 No OF SURGERIES:

G14 PRIMARY TREATMENT RESULTS:
0 complete remission
1 partial remission
2 condition unchanged
3 progress
4 exitus
5 other (describe):

G15 FIRST RELAPSE
0 none
1 yes, vagina
2 yes, pelvis
3 yes, distant metastasis
4 yes, other (describe):

G16 DATE OF FIRST RELAPSE

G17 TREATMENT OF FIRST RELAPSE
0 none
1 surgical
2 CT
3 RT
4 other (describe):

G18 SECOND RELAPSE
0 none
1 yes, vagina
2 yes, pelvis
3 yes, distant metastasis
4 yes, other (describe):

G19 DATE OF SECOND RELAPSE

G20 TREATMENT OF SECOND RELAPSE
0 none
1 surgical
2 CT
3 RT
4 other (describe):

PC Number:

Figure 1: General data

ENDOMETRIUM

HISTORY

NAME

A1 MENARCHE (age):

A2 MENSTRUAL CYCLE REGULARITY
0 regular
1 irregular

A3 LENGTH OF MENSTRUAL CYCLE (days)

A4 MENSES PHASE (days)

A5 MENSTRUAL FLOW
0 normal
1 low
2 heavy

A6 MENSTRUAL PAIN
0 no
1 yes

A7 IRREGULAR MENSTRUAL CYCLES
0 no
1 amenorrhea
2 oligomenorrhea (> 35 days)
3 polymenorrhea (< 21 days)
4 hypomenorrhea
5 hypermenorrhea
6 menorrhagia (> 7 days)
7 intermittent bleeding (spotting)
8 contact bleeding (postcoital bleeding)
9 continued bleeding (prolonged period)
10 pre-pubertal bleeding

A8 TIME SINCE LAST PERIOD (days)

A9 No. OF PREGNANCIES

A10 No. OF DELIVERIES

A11 No. OF MTOP

A12 No. OF MISCARRIAGES

A13 INFERTILITY
0 no (go to A16)
1 yes

A14 DURATION of INFERTILITY (years)

A15 STEIN-LEVENTHAL SYNDROME
0 no
1 yes

A16 HORMONAL CONTRACEPTIVES
0 never (go to A18)
1 previously
2 now

A17 No of YEARS OF CHC (combined hormonal contraception)

A18 SMOKING
0 no
1 1-5 cigarettes/day, number of years:
2 6-10 cigarettes/day, number of years:
3 > 10 cigarettes/day, number of years:

A 19 MENOPAUSE
0 not yet (go to 42)
1 natural
2 induced

A20 AGE AT MENOPAUSE

A21 HORMONE REPLACEMENT THERAPY (ESTROGENS)
0 never (go to 45)
1 prior (specify):
2 currently (specify):

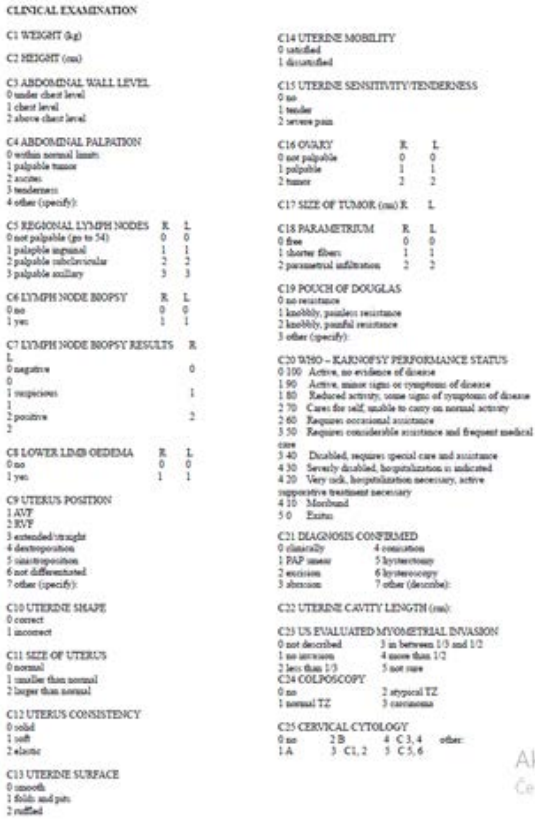
A22 No. OF YEARS OF HRT

A23 PREVIOUS OF PRESENT DISEASES
0 no
1 high blood pressure, without therapy
2 high blood pressure, with therapy
3 diabetes, without therapy
4 diabetes, with therapy
5 obesity
6 endometrial hyperplasia, without atypia
7 endometrial hyperplasia, with atypia
8 complex hyperplasia, without atypia
9 complex hyperplasia, with atypia
10 breast cancer
11 ovarian cancer
12 cervical cancer
13 gastrointestinal cancer
14 other (describe):

Figure 2: Medical history

Sixteen anamnestic data sets focus on known risk factors for endometrial cancer, current symptoms, and signs. Among the risk factors, detailed data on menstrual history, sexual and reproductive data, infertility, birth control and hormone replacement therapy are recorded. Detailed data are listed in Figure 2. The anamnestic data include signs and symptoms, the duration of symptoms is recorded, as well as the presence of other chronic diseases and the time since last gynecological examination.

Next section covers clinical examination with 34 parameters, including clinical status during abdominal and vaginal examination as well as the clinical appearance of uterus, cervix, vagina and adnexa. Eventually, the WHO Karnofsky status is determined (Figure 3).


CLINICAL EXAMINATION

C1 WEIGHT (kg)

C2 HEIGHT (cm)

C3 ABDOMINAL WALL LEVEL
0 under chest level
1 chest level
2 above chest level

C4 ABDOMINAL PALPATION
0 within normal limits
1 palpable tumor
2 ascites
3 tenderness
4 other (specify):

C5 REGIONAL LYMPH NODES R L
0 not palpable (go to 54) 0 0
1 palapble inguinal 1 1
2 palpable subclavicular 2 2
3 palpable axillary 3 3

C6 LYMPH NODE BIOPSY R L
0 no 0 0
1 yes 1 1

C7 LYMPH NODE BIOPSY RESULTS R L
0 negative 0 0
1 suspicious 1 1
2 positive 2 2

C8 LOWER LIMB OEDEMA R L
0 no 0 0
1 yes 1 1

C9 UTERUS POSITION
1 AVF
2 RVF
3 extended/straight
4 dextroposition
5 sinistroposition
6 not differentiated
7 other (specify):

C10 UTERINE SHAPE
0 correct
1 incorrect

C11 SIZE OF UTERUS
0 normal
1 smaller than normal
2 larger than normal

C12 UTERUS CONSISTENCY
0 solid
1 soft
2 elastic

C13 UTERINE SURFACE
0 smooth
1 folds and pits
2 ruffled

C14 UTERINE MOBILITY
0 satisfied
1 dissatisfied

C15 UTERINE SENSITIVITY/TENDERNESS
0 no
1 tender
2 severe pain

C16 OVARY R L
0 not palpable 0 0
1 palpable 1 1
2 tumor 2 2

C17 SIZE OF TUMOR (mm) R L

C18 PARAMETRIUM R L
0 free 0 0
1 shorter fiber: 1 1
2 parametrial infiltration 2 2

C19 POUCH OF DOUGLAS
0 no resistance
1 knobbly, painless resistance
2 knobbly, painful resistance
3 other (specify):

C20 WHO – KARNOFSY PERFORMANCE STATUS
0 100 Active, no evidence of disease
1 90 Active, minor signs or symptoms of disease
1 80 Reduced activity, some signs of symptoms of disease
2 70 Cares for self, unable to carry on normal activity
2 60 Requires occasional assistance
3 50 Requires considerable assistance and frequent medical care
3 40 Disabled, requires special care and assistance
4 30 Severely disabled, hospitalization is indicated
4 20 Very sick, hospitalization necessary, active supportive treatment necessary
4 10 Moribund
5 0 Exitus

C21 DIAGNOSIS CONFIRMED
0 clinically 4 conization
1 PAP smear 5 hysterectomy
2 excision 6 hysteroscopy
3 abrasion 7 other (describe):

C22 UTERINE CAVITY LENGTH (cm):

C23 US EVALUATED MYOMETRIAL INVASION
0 not described 3 in between 1/3 and 1/2
1 no invasion 4 more than 1/2
2 less than 1/3 5 not sure

C24 COLPOSCOPY
0 no 2 atypical TZ
1 normal TZ 3 carcinoma

C25 CERVICAL CYTOLOGY
0 no 2 B 4 C 3, 4 other:
1 A 3 C1, 2 5 C 5, 6


C26 CERVICAL ABRASION SPECIMEN
0 no 1 normal 2 carcinoma

C27 PULMONARY X-RAY
0 no 1 normal 2 metastasis 3 other:

C28 LIVER ULTRASOUND
0 no 1 normal 2 steatosis 3 stones

4 metastasis 5 other:

C29 EGS
0 no 1 normal 2 inflammation 3 stomach ulcer

4 carcinoma 5 other:

C30 MAMMOGRAPHY
0 no 1 normal 2 tumor R L 3 microcalcifications:

4 carcinoma

C31 UROGRAPHY
0 no 1 normal 2 dilatation R L 3 dysfunction

4 other:

C32 CYSTOSCOPY
0 no 1 normal 2 inflammation 3 carcinoma

C33 RECTOSCOPY
0 no 1 normal 2 hemorrhoids 3 carcinoma

C34 HISTEROSCOPY
0 no 1 yes, once 2 yes, twice

C35 ESR C36 L C37 Hb C38 T C39 CEA C40 CA 125

OP1 OPERATION
0 no (go to RT 1)
1 yes

OP2 DATE OF OPERATION

OP3 ASCITES

OP6 PERITONEAL WASHING
1 diaphragm surface NEG SUSP POS
2 paracolic right NEG SUSP POS
3 paracolic left NEG SUSP POS
4 pelvic peritoneum NEG SUSP POS

OP7 PROCEDURE
1 laparoscopy
2 exploratory laparotomy
3 cyst enucleation R L R+L
4 ovariectomy / oophorectomy R L R+L
5 salpingectomy R L R+L
6 adnexectomy R L R+L
7 hysterectomy
8 appendectomy
9 omentectomy
10 pelvic lymphadenectomy
11 paraaortic lymphadenectomy
12 bladder resection
13 intestine resection
14 colostomy
15 ileostomy
16 metastases removal
17 adhesiolysis
18 other:

OP8 RESIDUAL TUMOR
0 none 1 0–2 cm² 2 >2 cm²

OP9 INTRAOPERATIVE COMPLICATIONS
0 none 1 yes (describe):

OP10 BLOOD LOSS DURING SURGERY (ml)

OP 11 BLOOD TRANSFUSION DURING/AFTER SURGERY
0 none 1 yes

OP12 PERIOPERATIVE ANTIBIOTICS
0 none 1 yes

OP13 POSTOPERATIVE ANTIBIOTICS
0 none 1 yes

OP14 POSTOPERATIVE COMPLICATIONS
0 none
1 bleeding
2 urinary tract infection
3 febrile condition
4 intra-abdominal abscess
5 atonic bladder
6 atonic colon
7 ileus
8 urinary fistula
9 colonic fistula
10 deep vein thrombosis
11 pulmonary embolism
12 exitus
13 other (describe):

OP 15 PATIENT DISCHARGED AFTER SURGERY ON DAY:

Figure 3: Clinical examination

Figure 4: Tests, investigations and surgery

For the diagnosis, it is important to indicate how the diagnosis was made (hysteroscopy or abrasion, cervical canal abrasion), the ultrasound features (depth of invasion into the myometrium, invasion in cervix, parametrium, adnexa, peritoneum), spread to other pelvic organs, the presence of pathological pelvic lymph nodes, and whether additional imaging was performed.

RT1 RADIATION THERAPY
0 not performed (go to ChT1)
1 preoperative
2 postoperative
3 palliative

RT2 TYPE OF RADIATION THERAPY
0 radiotherapy
1 intracavitary RT
2 interstitial radiotherapy

RT3 SOURCE OF RADIATION

RT4 TOTAL RADIATION DOSE (Gy)

RT5 COMPLICATIONS
DURING/AFTER RADIATION THERAPY
0 none
1 rectal bleeding
2 rectal stenosis
3 vaginal stenosis
4 incontinence
5 lymphedema
6 fistula
7 pyometra
8 other (describe):

CT1 CHEMOTHERAPY
0 not present (go to HT1)
1 primary
2 secondary
3 neoadjuvant CT
4 palliative
Duration of ChT:

CT2 PRIMARY CHEMOTHERAPY DRUG
1 cisplatin
2 carboplatin
3 cyclophosphamide
4 methotrexate
5 adriamycin
6 treosulfan
7 etoposide
8 bleomysin
9 paclitaxel
10 other (specify):

CT3 PRIMARY CT CYCLE FREQUENCY (DAYS)

CT4 NO. OF PRIMARY CT CYCLES
CT5 G-CSF: 0 none 1 yes (specify):

CT6 DOSE REDUCTION
0 none
1 yes

CT7 COMPLICATIONS DURING/AFTER PRIMARY CT
0 none
1 anemia
2 leukopenia
3 thrombocytopenia
4 nausea
5 vomiting
6 kidney damage
7 nerve damage
8 liver damage
9 alopecia
10 enanthem
11 exitus
12 other (specify):

C18 PRIMARY CT RESULTS
0 not rated
1 not known
2 clinically complete
3 clinically partial response
4 clinically stable
5 progres
6 exitus

HT1 HORMONAL THERAPY
0 no (go to HYST1) 1 yes

HT2 HORMONAL THERAPY DRUG

HT3 HORMONAL THERAPY DOSE

HT4 DURATION OF HT
From..... To.....

HT5 RESULTS OF HORMONAL THERAPY
0 not rated 4 clinically stabile
1 not known 5 progress
2 clinically complete 6 exitus
3 clinically partial

HIST1 ABRASION HYSTOLOGY/CERVIX HYSTOLOGY
0 not performed
1 normal epithelium
2 carcinoma
3 other (describe):

HIST2 ABRASION HYSTOLOGY/CORPUS BIOPSY
0 not performed
1 normal epithelium
2 inflammation
3 hyperplasia without atypia
4 hyperplasia with atypia

Figure 5: Treatment

The section containing data about surgical procedure, adjuvant therapy and postoperative results includes 32 parameters (Figure 5). For easier and faster completion of the inquiry, types of surgical procedures are listed as well as the most common complications during surgery, blood loss and postoperative complications.

In the next section, data about histopathologic examination of tumor, lymph nodes and other tissues removed during surgery are collected (Figure 6). At the end of this section, a FIGO stage after definitive histology is determined. Full data on histopathology are usually available after the patient was discharged; consequently, this part of the inquiry is completed later.

HIST3 FREE FLUID CYTOLOGY

0 not performed
1 negative
3 suspicious
4 positive

HIST4 UTERINE SIZE
1 length
2 width
3 thickness

HIST5 ENDOMETRIAL HISTOLOGY
0 not performed
1 normal epithelium
2 inflammation
3 complex hyperplasia with atypia
4 endometrioid carcinoma
5 serous carcinoma
6 papillary serous carcinoma
7 mucinous adenocarcinoma
8 adenocarcinoma of ciliary cells
9 secretory adenocarcinoma
10 mixed adenocarcinoma
11 squamous cell carcinoma
12 adenosquamous carcinoma
13 undifferentiated carcinoma
14 leiomyosarcoma
15 stromal sarcoma
16 carcinosarcoma
17 other (describe):

HIST6 TUMOR DIFFERENTIATION
0 not performed
1 G1
2 G2
3 G3

HIST7 INVASION DEPTH
0 no invasion
1 less than ½ myometrial width
2 more than ½ myometrial width
3 not specified

HIST8 CERVICAL HISTOLOGY
0 not performed
1 regular epithelium
2 carcinoma
3 other (describe):

HIST9 HISTOLOGY OF THE VAGINAL CUFF
0 not performed
1 regular epithelium
2 carcinoma
3 other (describe):

HIST10 LYMPHOVASCULAR INVASION

0 not perfomed
1 absent
2 present

HIST11 HISTOLOGY OF THE OVARIES	R	L
0 normal tissue	0	0
1 retention cysts	1	1
2 benign tumor	2	2
3 malignant tumor	3	3
4 other (describe):		

HIST12 HISTOLOGY OF THE TUBES	R	L
0 normal tissue	0	0
1 inflammation	1	1
3 malignant tumor	2	2
4 other (describe):		

HIST13 SECONDARY SPREAD
0 no
1 adnexa
2 bladder
3 intestines
4 distant (describe):

HIST14 NUMBER OF PELVIC LYMPH NODES:

HIST15 NUMBER OF POSITIVE PELVIC LYMPH NODES

HIST16 NUMBER OF PARAAORTIC LYMPH NODES

HIST17 NUMBER OF POSITIVE PARAAORTIV LYMPH NODES

HIST18 LYMPH NODES STATUS

0 negative
1 left pelvic positive
2 right pelvic positive
3 paraaortic positive
4 not known

HIST19 STAGE AFTER HISTOLOGY REVIEW (FIGO 2023)

Figure 6: Histopathology

The last section of the inquiry is designed for the follow-up (Figure 7). All 12 boxes are to be completed at every follow-up visit. Data collected at follow-ups are limited to the wellbeing of the patient, pain, vomiting, micturition, defecation and bowel movement, body weight, clinical examination, laboratory tests and the condition assessment of the patient.

Figure 7: Follow-up form.

All data collected with the paper inquiry is recorded with the computer program used for processing data and statistical analysis.

Discussion

Endometrial cancer is the most common gynecological malignancy. In recent years, the understanding of disease has changed considerably. Many new studies have contributed to progress and new understanding, especially in the field of pathology and molecular characteristics of endometrial cancer. In 2023, the new FIGO classification was introduced. The new classification system considers the subclassification of the histological type of cancer in combination with the previously known system of determining the extent of disease in the uterus and spreading to other organs. In addition to the new FIGO classification, there are several new developments in the field of molecular classification of endometrial cancer and adjuvant treatment options.

Only disease specific registries allow for comparisons of different treatments or therapeutic strategies. For that reason, there is the need for extended information on the quality of the primary treatment, adjuvant treatment, complications and time frame of work-up that influence outcome of patients with endometrial cancer. This is the kind of information that is usually not gathered in population–based registries. The need for clinical registries is evident.

The endometrial cancer inquiry we present collects extended information; a total of 174 questions about endometrial cancer patient medical history, clinical status, histopathological results, treatment and its outcome. It provides a base for improvements in monitoring the quality of care of endometrial cancer patients, and research in the field of endometrial cancer diagnosis and treatment. Some of the elements collected are essential for clinical management and others are not regularly used in patient management.

The first page of the inquiry enables a quick overview over the course of the disease and treatment in case of disease progress. Each further control, change laboratory and clinical findings are described in the summary table.

The risk of endometrial cancer is higher in women with early menarche, late menopause, those who have not given birth and those with polycystic ovaries. Obesity, diabetes and hypertension also increase the risk. Women using hormonal drugs with unopposed estrogens and tamoxifen have a higher risk of endometrial cancer. Age is a key risk factor for type II endometrial cancer. The risk factors for uterine sarcomas are not so clear due to the rarity of the disease. The risk increases with age; on average, the disease is detected around the age of 60, although women in their 20s or younger can also be affected. The use of tamoxifen and previous radiotherapy in the pelvic area also increases the risk. There is also an increase in the incidence of endometrial cancer in younger patients who are still in their childbearing years. They are often overweight and consequently have anovulatory cycles due to excess estrogen and progesterone deficiency. This results in hyperstimulation of the endometrium, leading to the formation of pre-cancerous changes in the lining of the uterus, known as complex atypical hyperplasia, which gives rise to early endometrial cancer. The risk of endometrial cancer is lower in female users of oral hormonal contraceptives and in multiparous women. Women with Lynch syndrome who have a germline mutation in the MLH1 and MSH2 genes have a 40-60% increased risk of endometrial cancer, with a median age of onset of 48 years, which is lower than in the general population [14].

A special part of the inquiry is dedicated to the signs and symptoms that are present at the presentation. Endometrial cancers confined to the uterus may present minimal symptoms of abnormal uterine bleeding (AUB) to advanced disease with pelvic-abdominal discomfort and pain, widespread lymphatic and peritoneal dissemination, ascites, and rarely even extra-abdominal metastases. AUB is the most frequent symptom of endometrial cancer [15]. Irregular uterine bleeding associated with EIN and cancer can affect women of all ages, becoming more prevalent during the fifth decade of life, especially in women older than 45 years. About 10% of postmenopausal bleeding is related to endometrial cancer [16]. Therefore, all women who are postmenopausal or women 45 and older with AUB should undergo diagnostic endometrial evaluation [17].

Next part of the inquiry focuses on thorough external abdominal, genital and vaginal examination, which should be performed during gynecologic examination to define the extent of the disease and search for concomitant lesions. Therefore, abdominal wall, abdomen, vagina, uterus and parametria are inspected and palpated. Patients' WHO Karnofsky performance status (KPS) is important for decisions regarding the intensity of the forthcoming treatment [20].

Endometrial carcinoma should be confirmed by histological examination before treatment is started. To make a diagnosis, we need sufficient (representative) material to define the histological type and other characteristics of the tumour. In the latest (fifth) edition of Female Genital Tumours, the World Health Organisation divides endometrial carcinomas into different

histological types and introduces the importance of molecular classification.

A standardized histological finding is crucial for staging, optimal treatment and prognosis. It also allows systematic data collection for epidemiological purposes and research.

Histological classification of endometrial carcinomas

In the latest (fifth) edition of the book Female Genital Tumors, the World Health Organisation divides endometrial carcinomas into the following histological types:

- Endometrioid carcinoma,
- Serous carcinoma,
- Clear cell carcinoma,
- Undifferentiated and dedifferentiated carcinoma,
- Mixed carcinoma,
- Other endometrial carcinomas (mesonephric adenocarcinoma, mesonephric carcinoma-like carcinoma, gastric type of endometrial adenocarcinoma and primary endometrial squamous cell carcinoma),
- Carcinosarcoma,
- Neuroendocrine neoplasms [18]

There are various ways to get endometrial tissue histology: Pipelle endometrial sampling, dilation and curettage (D&C), endometrial biopsy under hysteroscopy and others. The Pipelle, first described in 1984 by Cornier, can obtain endometrial tissue through negative pressure and the accuracy can exceed 95%. The Pipelle endometrial sampler is low in cost, causes minimum discomfort and carries few side effects. The major disadvantage is a higher sampling failure rate than D&C caused by an inability to access the uterine cavity or insufficient amount of tissue collected. What's more, various subsequent studies point out that Pipelle has a limited ability to identify focal lesions and is only suitable for homogeneous endometrium. D&C is one of the standard methods for the evaluation of suspected endometrial lesions. It is equally effective but more costly than Pipelle endometrial sampling. The anesthetics side effects, infection and perforation caused by the D&C procedure also limit its use. In recent years, hysteroscopy, a less invasive and accurate endoscopic technique providing a satisfactory assessment of the uterine cavity, has merged as a powerful tool in endometrial biopsy. It allows for direct visual localization of suspicious lesions for biopsy or excision, which is highly accurate in the diagnosis of EC and can reduce the false negative rate. Despite many advantages, complications associated with the procedures are inevitable. Cervical stenosis and pain are the main reasons for incomplete and failed hysteroscopy. Vasovagal reaction, local anesthetic toxicity, uterine perforation, fluid overload and uterine hemorrhage may occur, but these remain incredibly rare events [19].

In addition to the primary purpose of determining the type of endometrial carcinoma, the pathologist's task, also defined in modern ICCR (International Collaboration on Cancer Reporting) guidelines, is to determine the gradus of the tumor (only endometrioid carcinomas are graded according to the proportion of the solid component of the tumor; in the latest WHO classification, the three-step grading method has replaced the two-step grading method, as the classification into low-grade and high-grade tumors has been found to be more reproducible and simpler to apply clinically), the possible invasion of the tumor into the myometrium and the depth/proportion of the myometrium overgrown by the tumor, the possible presence and extent of lymphovascular invasion (according to the ICCR/ISGyP guidelines, focal lymphovascular invasion, as opposed to significant/extensive, is defined as the presence of tumor in less than 3 vascular spaces, according to WHO 2020 in less than 5), possible ingrowth into the cervical stroma, free serosal surface or parametrium, possible infiltration of adnexa, omentum, peritoneum, and the presence/absence and size of metastases in sentinel lymph nodes.

In recent years, however, the importance of additional methods in treatment decisions has also become increasingly clear, in particular immunohistochemical and molecular genetic tests. In fact, the comprehensive molecular genetic analysis of endometrial carcinomas within the framework of TCGA (angl. The Cancer Genome Atlas) has identified four prognostically important molecular groups of endometrial carcinomas - POLE ultramutated, microsatellite instability/MMR-

deficient tumors, tumors with a high proportion of “somatic copy-number alteration” and TP53 gene mutation present, and tumors with a low proportion of “somatic copy-number alteration” (NSMP). As the inclusion of molecular groups in the classification of endometrial carcinomas can predict the outcome of the disease or define the optimal treatment much better than “classical” histopathological indicators alone, molecular classification was included in the ESGO/ESTRO/ESP guidelines in 2020. Endometrial carcinomas are classified into prognostic groups according to “classical” factors, which are complemented by molecular characteristics. The classification into prognostic groups also defines the treatment modality. In general, the presence of mutations in the POLE gene implies a favorable prognosis and the abandonment of certain more aggressive treatments, while the presence of mutations in the TP53 gene suggests the opposite, while the presence of microsatellite instability suggests the possibility of Lynch syndrome and the likely benefit of treatment with immunomodulators. In the current FIGO classification, however, molecular factors are included in the staging itself [20].

In 2023, FIGO published an updated classification for defining the stage of the disease. Key changes in staging include the inclusion of histological tumor type (low-grade endometroid carcinoma or aggressive cancer), the inclusion of lymphovascular invasion, molecular markers (p53, POLE), and the differentiation of endometroid carcinoma of the ovary and endometrium from the spread of endometroid carcinoma from the endometrium to the ovary. The non-aggressive histological type of cancer is low-grade endometroid carcinoma (grades 1 and 2). The aggressive histological types are all others: high-grade endometroid carcinoma, serous, clear cell, undifferentiated, mixed, mesonephric-like, carcinosarcoma. In addition, the new classification distinguishes more precisely the anatomical/histological spread of the disease (subserosa, uterine serosa, adnexa; peritonei of the small pelvis or peritonei outside the small pelvis) [21].

All patients diagnosed with endometrial cancer should undergo imaging examinations for local delineation, which includes determining invasion of the myometrium, cervix, parametrium, adnexa, peritoneum and small pelvic organs and the presence of pathological pelvic lymph nodes. Appropriate methods are pelvic MRI with CS and expert transvaginal ultrasound, which should be performed by a gynecologist with additional expertise in this field. In at-risk patients (non-endometrioid type, high-grade endometrioid type, presence of aberrant p53 expression)

a remote delineation including assessment of the retroperitoneum, peritoneum and abdominal solid organs is performed, and in selected patients a chest evaluation is also performed. CT of the abdomen with contrast or abdominal ultrasound in patients with good ultrasonographic clarity are appropriate methods [22].

The division according to the risk of recurrence is based on clinicopathological and surgical prognostic factors. The most important prognostic factor is the involvement of regional lymph nodes. Additional factors are depth of invasion, differentiation, invasion of the lymphovascular space and of the cervical stroma. The risk of invasion of regional lymph nodes is six times higher with poor differentiation and five times higher with deep invasion of the myometrium. Thus, the preoperative risk assessment is based on biopsy results, tumor size and suspicion of regional lymph node involvement. Thus, the low-risk group consists of patients with less than half myometrial invasion, good and moderate differentiation and no suspicion of regional lymph node involvement. Differentiation is defined by the ratio of glandular structures to solid growth and nuclear gradus. Tumors with less than 5% of solid areas are well differentiated (G1), those with solid areas between 6% and 50% are moderately differentiated (G2) and those with more than 50% are poorly differentiated (G3) (23).

In early-stage endometrial cancer, the aim of surgery is to remove macroscopic tumor, examine for microscopic metastases and stage the tumor to assess the need for adjuvant therapy. Laparotomy has been the traditional surgical approach for the treatment of EC. Large, randomized trials and a meta-analysis have demonstrated that minimally invasive techniques have operative outcomes similar to laparotomy with respect to prognosis. Even though most patients included in these trials were low risk (e.g. G1 or G2), with only 17% of patients at higher risk (e.g. defined by G3), the laparoscopic approach can be extended to G3 tumors, since detrimental effects were not demonstrated. A robotic approach is a potential enhancement to standard laparoscopic surgery and may be especially beneficial in obese women. Standard surgery is hysterectomy with bilateral salpingo-oophorectomy. Preservation of ovaries can be considered in premenopausal patients with FIGO stage IA G1 EEC. Ovarian preservation is not recommended for patients at genetic risk for ovarian cancer (e.g. germline BRCA mutation, Lynch syndrome). Staging omentectomy should be considered in carcinosarcoma and serous type endometrial cancer [24].

The risk of lymph node metastases ranges between <5% and 40% depending on grade, myometrial invasion and histology. Because the detection of lymph node metastases has an impact on adjuvant therapy, evaluation of lymph node status is recommended in patients with non-endometrioid histology, FIGO IB or G3 disease. Lymph node evaluation could be omitted in endometrioid FIGO IA G1-G2 disease since the risk of nodal metastasis is very low (<5%) [25].

Sentinel node biopsy or sentinel lymphadenectomy has emerged as alternative to lymph node dissection for lymph node staging. Based on data provided by prospective and retrospective studies, sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It may also represent an alternative to systematic lymphadenectomy in high-intermediate-risk/high-risk disease stage I-II [24]. There is no indication for adjuvant treatment of low-risk EC as the risk of recurrence is low. Multiple studies have shown no survival benefit from adjuvant treatment and the occasional patient with a local recurrence can effectively be treated with radiotherapy (RT) at the time of recurrence. Current data from the PORTEC-1/2 studies and additional series have demonstrated the presence of POLEmut as an indicator of a favorable EC prognosis, independent of other clinicopathological variables. Hence, patients with stage I-II tumors and a POLEmut are now also considered to be low risk and unlikely to benefit from adjuvant treatment [24].

Systemic therapy is one of the specific oncological treatments for uterine cancer and has been the main form of systemic treatment in recent decades. It is indicated as complementary treatment for patients with unfavorable clinical and pathohistological factors that increase the risk of recurrence. Patients are treated with chemotherapy as part of chemoradiotherapy or with chemotherapy alone. In a small proportion of patients, uterine cancer is already metastatic at baseline or metastasizes after primary treatment. Chemotherapy with carboplatin and paclitaxel has become the standard first-line treatment. Patients whose disease progresses after first-line treatment have a poor prognosis. Although there are numerous chemotherapy options available in second-line and subsequent lines of treatment, their effectiveness is limited. Chemotherapy also has numerous side effects. Many of these can be well managed with supportive care, while some remain a limiting factor in treatment selection and can significantly affect both treatment efficacy and quality of life.

A new molecular classification of endometrial cancer has enabled new, targeted treatment for patients with uterine cancer. The main innovation is immunotherapy with immune checkpoint inhibitors (PD-1 inhibitors) in patients with metastatic endometrial cancer in the second line of

treatment, after prior treatment with chemotherapy. The European Medicines Agency (EMA) has approved the use of two PD-1 receptor inhibitors, dostarlimab and pembrolizumab, as monotherapy in cases of MMR protein deficiency in the tumor (dMMR/MSI-H carcinoma). The combination of pembrolizumab and lenvatinib (a tyrosine kinase inhibitor) has also been approved for second-line treatment of metastatic disease after prior chemotherapy, regardless of MMR protein status, i.e. even in cases where there is no MMR protein deficiency in the tumour (pMMR/MSS carcinoma). Results have recently been published showing the efficacy of pembrolizumab and dostarlimab in combination with chemotherapy in the first line of treatment for advanced or metastatic disease. There are currently no data on the efficacy of immunotherapy in adjuvant treatment – clinical trials are ongoing [26].

An important aspect of treating endometrial cancer is preserving reproductive capacity in young women with endometrial cancer. Fertility-sparing treatment in endometrial carcinoma is an option for a subgroup of women who are selected based on thorough evaluation of reproductive potential. Fertility-sparing treatments should be exclusively applied in women with early-stage, non-metastatic disease. Implicit patient evaluation should take into consideration the reproductive potential and also risk factors that affect the potential for the patient to carry a pregnancy successfully, including the status of the uterus. Fertility-sparing treatment is considered for endometrioid patients with endometrial carcinoma with Grade 1, Stage IA without myometrial invasion and without risk factors. Evidence for Grade 2 endometrioid endometrial carcinoma is limited. Therefore, fertility-sparing treatment should be discussed on a case-by-case basis. A combined approach consisting of hysteroscopic tumour resection, followed by oral progestins and/or levonorgestrel-intra-uterine device, is the most effective fertility-sparing treatment both for complete response rate and live birth rate compared with other treatment options. Gonadotropin-releasing hormone analogues should not be considered as a first-line treatment [27].

Conclusion

Endoemtrial cancer is curable if it is detected early and managed effectively. The clinical endometrial cancer registry plays a vital role in evaluating clinical practice in order to improve clinical work organization and the treatment of the disease. It allows us to continuously compare treatment results with national and international standards. The data can also be used for research projects and studies on cancer survival.

The Endometrial-Online computer program allows for rapid and reliable processing and analysis of 174 different data obtained from endometrial cancer patients, i.e. general information, medical history, diagnostics, treatment, and follow-up.

We believe that such a comprehensive hospital-based clinical registries could play a vital role in monitoring and improving the quality of care of gynecological cancer patients as well as research in the field of gynecological cancer diagnosis and treatment.

References

1. Dos Santos Silva I. Cancer Epidemiology: principles and methods. World Health Organization. International Agency for research on cancer. Lyon France, 1999: 385–403.
2. https://www.onko-i.si/eng/rrs/cr (Assessed November 25th 2021).
3. Zadnik V, Žagar T, Lokar K Tomšič, Duratović Konjević A, Bric N, Zakotnik B. Preživetje bolnikov z rakom v Sloveniji. Survival of cancer patients in Slovenia. Onkologija 2021:42–7.
4. Zakotnik B. Tomšič S. Državni program obvladovanja raka – dosežki in izzivi. National Cancer Control Plan – achievments and challenges. Onkologija 2021: 1:60–6.
5. Hočevar M. Klinični registri v onkologiji. Onkologija 2011; 1: 14–7.

6. Takač I, Ferletič M, Arko D, Gorišek B. Follow-up computer program for patients with ovarian malignancy = Računalniški program za spremljanje bolnic z rakom jajčnikov. In: Bigec M, Lavrenčič D, Kokol P (eds.). Zbornik referatov II del = Proceedings part II. IMS 1996; 3: 43–6.
7. Takač I, Gorišek B. User friendly inquiry and computer program for following patients with ovarian malignancy. Arch Gynecol Obstet 1999; 263: 60–7. DOI: 10.1007/s004040050264
8. Arko D, Takač I. Inquiry and computer program Onko-Online: 25 years of clinical registry for breast cancer at the University Medical Centre Maribor. Radiol Oncol 2019; 53(3): 348–56. DOI: 10.2478/raon-2019-0043
9. Salehiniya H, Allahqoli L, Momenimovahed Z. Risk Factors for Endometrial Cancer in the World: a Narrative Review of the Recent Literature. Clin. Exp. Obstet. Gynecol. 2024: 51: 169. https://doi.org/10.31083/j.ceog5107169
10. Bray F, Laversanne M, Sung H, Ferlay J, Siegel, Soerjomataram I. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024; 74: 229–63.
11. Zadnik V, Žagar T. SLORA: Slovenija in rak. Epidemiologija in register raka. Onkološki inštitut Ljubljana. www.slora.si (Assessed July 13th 2025).
12. Vivod G. Obravnava bolnic s sumom na raka telesa maternice. V: Sedma šola o ginekološkem raku- rak telesa maternice. Elektronski zbornik znanstvenih prispevkov. Onkološki inštitut Ljubljana. 2023; 7–10.
13. Takač I. Epidemiologija in etiologija raka telesa maternice. V: Sedma šola o ginekološkem raku- rak telesa maternice. Elektronski zbornik znanstvenih prispevkov. Onkološki inštitut Ljubljana. 2023; 11–15.
14. Salehiniya H, Allahqoli L, Momenimovahed A. Risk Factors for Endometrial Cancer in the World: A Narrative Review of the Recent Literature. Clin. Exp. Obstet. Gynecol. 2024; 51(7): 169.
15. Pessoa JN, Freitas AC, Guimaraes RA, Lima J, Dos Reis HL, Filho AC. Endometrial Assessment: When is it Necessary? J Clin Med Res. 2014; 6(1): 21–5.
16. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. Mayo Clin Proc. 2008 Jan;83 :9–112.
17. Wouk N, Helton M. Abnormal Uterine Bleeding in Premenopausal Women. Am Fam Physician. 2019; 99: 435–43.
18. Car M. Patološka klasifikacija karcinomov endometrija. V: Sedma šola o ginekološkem raku- rak telesa maternice. Elektronski zbornik znanstvenih prispevkov. Onkološki inštitut Ljubljana. 2023; 20–4.
19. Shen Y, Yang W, Liu J, Zhang Y. Minimally invasive approaches for the early detection of endometrial cancer. Mol Cancer. 2023; 22: 53.
20. Lebič Belcijan N, Frković Graziio S. Sodobni principi patohistološke diagnostike endometrijskih karcinomov v luči FIGO 2023 - obseg in način poročanja morfoloških, imunohistokemičnih in molekularno genetskih značilnosti tumorjev. V: Rak endometrija. Znanstveni simpozij – zbornik prispevkov. Ljubljana. 2024; 9–12.
21. Janša V, Cvjetićanin B. Predstavitev nove FIGO klasifikacije. V: Rak endometrija. Znanstveni simpozij – zbornik prispevkov. Ljubljana. 2024; 6–8.
22. Pirš B, Meglič L. Algoritev obravnave raka endometrija. V: Rak endometrija. Znanstveni simpozij – zbornik prispevkov. Ljubljana. 2024; 17–18.
23. Meglič L. Kirurško zdravljenje nizkorizičnega raka endometrija. V: Sedma šola o ginekološkem raku- rak telesa maternice. Elektronski zbornik znanstvenih prispevkov. Onkološki inštitut Ljubljana. 2023; 45–8.
24. Oaknin, A. et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2022; 33; 860–77.
25. Katsoulakis E, Mattes, M.D, Rineer, J.M. et al. Contemporary analysis of pelvic and para-aortic metastasis in endometrial cancer using the SEER registry. Int J Gynaecol Obstet. 2014; 127: 293–6.
26. Škof E. Imunoterapija pri raku telesa maternice. V: Sedma šola o ginekološkem raku- rak telesa maternice. Elektronski zbornik znanstvenih prispevkov. Onkološki inštitut Ljubljana. 2023; 69–72.
27. Rodolakis A, Scambia G, Planchamp F, Acien M, Di Spiezio Sardo A, Farrugia M et al. ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma. Hum Reprod Open. 2023; doi: 10.1093/hropen/hoac057.

ALGORITAM REKONSTRUKCIJE VULVE NAKON ONKOLOŠKIH RESEKCIJA

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Genitoperinealna regija kod žena je delikatna zona za rekonstrukciju defekata tkiva raznih etiologija (traume, porođaja, infekcija i onkoloških resekcija). Vulvo-vaginalna regija predstavlja delikatnu i kompleksnu zonu po pitanju reproduktivne, seksualne, urinarne funkcije, kao i sveopšteg psiho-fizičkog kvaliteta života žene [1, 2]. Hirurgija predstavlja zlatan standard u lečenju malignih tumora vulve, koji su zastupljeni u 3-5% svih ginekoloških maligniteta, a hirurške tehnike se konstantno vremenom i novim iskustvima unapređuju [3, 4]. U oko 90% slučaja u pitanju su planocelularni karcinomi [5, 6]. Prema statističkim podacima iz literature karcinom vulve je dijagnostikovan u 39% slučaja u stadijumu III ili IV bolesti [7]. Prema Centru za kontrolu bolesti (CDC), oko 6500 žena je dijagnostikovano sa karcinomom u 2020. godini godini. U najvećem broju slučajeva, primarni karcinom vagine je redak, a češće se javlja kao rezultat lokalne invazije malignih tumora okolne regije, oko 1 na 100000 žena su dijagnostikovane sa in situ lezijama ili invazivnim karcinomima godišnje, sa prosečnom starosnom dobi od 60 do 70 godina starosti. Faktori rizika su brojni: konzumiranje cigareta, predhodna anamneza vulvarnih lezija i cervikalnih intraepitelijalnih neoplazija, lichen sclerosus, imunodeficijencije, prisustvo humanog papiloma virusa (HPV), povećan broj seksualnih partnera, kao i rano stupanje u intimne odnose. Tip tumora, stadijum bolesti, hirurški pristup onkologa, i očekivanja u pogledu očuvanja funkcionalnosti ove regije, utiču i doprinose pravljenju algoritma za rekonstrukciju vulvo-perinealne regije. Kod većih tumora, lokalni recidivi su učestaliji od udaljenih metastaza i mogu se uspešno lečiti hirurgijom i zračnom terapijom. Nakon radikalnih ekcizija zapuštenih tumora zaostaju ekstenzivni mekotkivni defekti, čija rekonstrukcija doprinosi boljem kvalitetu života pacijentkinja. Lokalni recidivi su češći od pojave metastaza kod pacijentkinja sa većim tumorima [4]. Brojne hirurgije recidiva, zračne terapije i široke ekcizije tumora dovode do nastanka ekstenzivnih mekotkivnih defekata, koji odlažu zarastanje rana i povećavaju postoperativni morbiditet, što sve negativno utiče na kvalitet života pacijentkinja. Rekonstrukcije postresekcionih defekata mekih tkiva vulvo-perinealne regije doprinose smanjenju morbiditeta i poboljšanju kvaliteta života [8]. Anatomska povezanost vulve i vagine sa karličnim misićima, mokraćnom bešikom i rektumom je od izuzetnog značaja, kako bi se shvatila dinamika i povezanost donjeg genitalnog reproduktivnog i urinarnog trakta.

Karcinomi vulve se najčešće tretiraju en block vulvektomijom, zbog visokog procenta recidiva. Defekti mekih tkiva vulvo-perinealne regije se mogu rekonstruisati širokom paletom rekonstruktivnih opcije, od direktne suture, slobodnih kožnih transplanata, preko lokalnih i regionalnih faciokutanih i miokutanih režnjeva, kao i udaljenim režnjevima [4, 9]. Poslednjih godina, učestala je primena mišićnih i mišićno-kožnih režnjeva kod pacijentktkinja sa ginekološkim malignitetima [10, 11]. Primena mišićnih i slobodnih režnjeva produžava vreme operacije, i povećava mogućnost nastanka komplikacija poput parcijalne ili totalne nekroze režnja [4, 8, 12]. Izbor rekonstruktivne tehnike i primene odgovarajućeg režnja zavisi od osobina defekta koji se nadoknađuje (veličine, lokalizacije i kompozicije, tj. složenosti), predhodnih eventualnih zračnih terapija i hirurških zahvata. Vestibulum vulve je anatomski podeljen na tri subjedinice, sa sopstvenom jedinstvenom anatomijom. Gornju trećinu čine mons pubis i gornja usna, srednju trećinu labia proper i donju trećinu vaginalni orificium i perineum. Vaskularizacija vulve je dobra,

slična vaskularizaciji lica, što pruža brojne rekonstruktivne mogućnosti ove regije. Prvi put je opisana 1889. godine od strane Car Manchota. Gornji deo vulve potiče od a. pudendae externae superfitialis, dok je zadnji deo vaskularizovan a. pudendom externom profundom. A. pudenda interna takođe vaskularizuje ovu zonu, i daje više kutanih perforatora na bazi kojih su planirani brojni režnjevi. Takođe značajne su i anastomoze ovih arterija, kao i anastomoze sa kontralateralnim arterijama,

Manji i srednji plitki defekti mogu se rekonstruisati rotacionim režnjevima, poput lotus režnja, koji se bazira na perforatorima a. pudenda interne i pivot tačkom u srednjoj liniji perineuma, sa maksimalnim dimenzijama defekta 18x6 cm i upotrebom za uni ili bilateralne defekte.

Superiorni defekti vulve, režnjevi poput suprapubičnog, vaskularizovani su a. pudendom externom superfitialis i a. epigastricom inferior i njihovim komitantnim venama. Režnjevi su maksimalnih dimenzija 10x4 cm za pokrivanje defekata gornje i prednje vulve, prednje komisure i labiae majore i minore.

Moguće i česte postoperativne komplikacije kod direktne aproksimacije nategnutih ivica defekta su pre primene režnjeva bile dehiscencije i usporeno zarastanje rane [4]. Postoperativne dehiscencije, limfociste i limfedema su zastupljeni u 64-85% slučajeva. Primenom režnjeva, tj. rekonstrukcijom defekta tkivom koje se mobiliše iz oblžnje regije, gde ga ima u višku, omogućilo je primarno zatvaranje defekta u istom hirurškom aktu kada i uklanjanje tumora, bez bojazni od dehiscencije. Pored kozmetskog izgleda, koji je primenom režnjeva poboljšan, očuvana je i funkcija mikcije i defekacije.

U ovom radu su prikazani klinički slučajevi pacijentkinja kod kojih su nakon radikalnih ekscizija ekstenzivnih planocelularnih karcinoma i dermatofibrosarkoma vulvo-perinealne regije uz bilateralnu ingvinalnu disekciju, defekti pokriveni V-Y lokalnim klizajućim režnjevima, lokalnim fasciokutanim režnjevima i vertikalnim miokutanim režnjem m. rectus abdominus-a.

VY klizajući režanj je lokalni fasciokutani režanj kojim se mobiliše fascija i koža oko defekta kako bi se rekonstruisao primarni defekt nastao nakon radikalne ekcizije tumora. Početni rez na koži je u obliku slova V, a nakon rekonstrukcije dobija oblik slova Y uz direktno zatvaranje sekundarnog defekta. Ovaj režanj se može upotrebiti kada postoji dovoljno mobilne kože u obližnjoj glutealnoj regiji [4, 9, 13, 14]. Rekonstrukcija defekata se izvodi u primarnom aktu, kada i uklanjanje tumora. U predstojećem postoperativnom periodu režanj će nedeljama biti edematozan i eritematozan, što se vremenom gubi, kako se uspostavlja limfna drenaža i ožiljak sazreva. Prednosti V-Y klizajućeg režnja su jednostavnost izvođenja, sigurni su u smislu vaskularizacije i preživljavanja i dobre su teksture kože. Režanj se ishranjuje putem perforatora a. pudende interne i muskulokutanim perforatorima mišića koji leže ispod režnja. Senzitivna inervacija potiče od pudendalnog i zadnjeg kožnog nerva butine [15].

Prikazan je slučaj pedesetogodišnje pacijentkinje sa dijagnozom invazivnog planocelularnog karcinoma vulvarne regije stadijuma Ib, koja je primljna na Kliniku za ginekologiju i akušerstvo, Univerzitetskog Kliničkog Centra Srbije. Nakon radikalne vulvekomije sa disekcijom ingvinalnih limfnih čvorova, bilateralni defekt mekih tkiva je rekonstruisan V-Y klizajućim režnjem. Postoperativni tok je protekao uredno, režnjevi su vitalni, bez znakova dehiscencije i nekroze.

Vertikalni režanj m. rectus abdominisa je pored miokutanog režnja m. gracilisa, najprimenljiviji režanj u pokrivanju ekstenzivnih defekta genitoperinealne regije. To je aksijalni peteljkast režanj čija se vaskularizacija bazira na a. epigastrici inferior i komitantnim venama. Režanj je kompozitan, jer se sastoji od m. rectus femorisa i kože iznad njega. Rotacijom oko vaskularne peteljke za 180

stepeni može pokriti trodimenzionalne defekte vulvo-perinealne regije. Davajuća regija na trbuhu se direktno ušiva, tako da je morbiditet davajuće regije minimalan.

Prikazan je i slučaj četrdesetjednogodišnje pacijentkinje koja je primljena na Kliniku za ginekologiju i akušerstvo, Univerzitetskog Kliničkog Centra Srbije, zbog zapuštene, bezbolne, karfiolaste i nekrotične tumorske mase, koja je zahvatala čitavu vulvo-perineo-glutealnu regiju. Na prijemu je pacijentkinja lošeg opšteg stanja, anemična (hemoglobin 25, MCV 61,4, leukociti 25,9, trombociti 505). Prema anamnastičkim podacima tumor je narastao poslednjih 6 meseci. Patohistološki nalaz je ukazao na planocelularni karcinim stadijum FIGO II, klinički IVa, zbog maligne infiltracije distalnog dela vagine i glutealne regije. Pacijentkinja je operisana, učinjena je radikalna vulvektomija i bilateralna ingvinofemoralna disekcija sa parcijalnom vaginektomijom. Mekotkivni defekt dimenzija 25x12 cm je rekonstruisan sa distalno baziranim režnjem m. rectus abdominisa VRAM. Davajuća regija trbuha je direktno zatvorena. Postoperativni period je protekao uredno, bez komplikacija. Režanj je vitalan, bez znakova nekroze. Nakon tri nedelje u drugom aktu je rekonstruisana rektoanalna veza, kreiran novi ulaz za vaginu. Pacijentkinja je dalje prosleđena na zračnu terapiju.

Dermatofibrosarkom protuberans vulve je redak, sporoprogredirajući fibrozni tumor kože, niskog do srednjeg stepena maligniteta. Karakteriše ga lokalna kožna i potkožna invazija, ali i destruktivan rast i infiltracija okolnog tkiva poput mišića, fascija i kostiju. Standardna terapija je kompletna hirurška ekcizija.

Prikazana je pedesetpetogodišnje pacijentkinja sa ekstenzivnim tumorom dimenzija 18x10x8 cm u prepubičnoj regiji, koji je progredirao unazad 19 godina. Biopsija je potvrdila dijagnozu dermatofibrosarcoma protuberans, a MSCT je ukazao da nema invazije kostiju. Pacijentkinja je operisana, učinjena je radikalna ekcizija 3 cm u zdravo tkivo. Ekstenzivni mekotkivni defekt je pokriven sa dva fasciokutana režnja transponirana iz susedne regije. Postoperativni tok je protekao uredno, režnjevi su vitalni.

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

Pokrivanje ekstenzivnih defekata vulvo-perinealne regije, nakon radikalnih ekscizija tumora, primenom lokalnih, regionalnih i miokutanih režnjeva, doprinosi smanjenju postoperativnih komplikacija i poboljšanju funkcionalnog i kozmetskog izgleda, čime se značajno poboljšava kvalitet života pacijenta. Kod pacijentkinja u odmaklim stadijumima FIGO III i IVa i koje zahtevaju radikalnu vulvektomiju sa bilateralnom ingvinalnom disekcijom, pokrivanje resekcionih defekta predstavlja hirurški izazov.

Reference

1. Siegel R. L, Miller K. D, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
2. Bish S. P, Nelson G. Outcomes of enhanced recovery after surgery in gynecological oncology: A review. Curr Oncol. 2022;29(2):631-40.
3. Judson P. L, Habermann E. B, Baxter N. N, Durham S. B, Virnig B. A. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet. Gynecol. 2006;107(5):1018–1022.
4. Carramaschi F, Ramos M. L. C, Nisida A. C. T, Ferreira M. C, Pinotti J. A. V-Y flap for perineal reconstruction following modified approach to vulvectomy in vulvar cancer. Int. J. Gynecol. Obstet. 1999;65(2):157–163.
5. Del Pino M, Rodriguez-Carunchio L, Ordi J. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology. 2013;62:161–175.
6. Lazzaro L, Guarneri G. F, Rampino Cordaro E, Bassini D, Revesz S, Borgna G. Vulvar reconstruction using a “v-Y” fascio-cutaneous gluteal flap: a valid reconstructive alternative in post-oncological loss of substance. Arch. Gynecol. Obstet. 2010;282(5):521–527.

7. Di Donato V, Bracchi C, Cigna E, Domenici L, Musella A, Giannini A. Vulvo-vaginal reconstruction after radical excision for treatment of vulvar cancer: Evaluation of feasibility and morbidity of different surgical techniques. Surg. Oncol. 2017;26:511–521.
8. Chen S, Hentz R, Wei C. Short gracilis myocutaneous flaps for vulvoperineal and inguinal reconstruction. Plast. Reconstr. Surg. 1995;95(2):372–377.
9. Lee JH, Shin JW, Kim SW, Oh DY, Park JS, et al. Modified gluteal fold V-Y advancement flap for vulvovaginal reconstruction. Ann Plast Surg. 2013;71(5):571-574.
10. Confalonieri P. L, Gilardi R, Rovati L. C, Ceccherelli A, Lee J. H, Magni S. Comparison of V-Y Advancement Flap Versus Lotus Petal Flap for Plastic Reconstruction after Surgery in Case of Vulvar Malignancies: A Retrospective Single Center experience. Ann. Plast. Surg. 2017;79(2):186–191.
11. Conri V, Casoli V, Coret M, Houssin C, Trouette R, Brun J. L. Modified gluteal fold V-Y advancement flap for reconstruction after radical vulvectomy. Int. J. Gynecol. Cancer. 2016;26(7):1300–1306.
12. McCraw J. B, Massey F. M, Shanklin K. D, Horton C. E. Vaginal reconstruction with gracilis myocutaneous flaps. Plast. Reconstr. Surg. 1976;58(2):176–183.
13. Tateo A, Tateo S, Bernasconi C, Zara C. Use of V-Y flap for vulvar reconstruction. Gynecol. Oncol. 1996;62(2):203–207.
14. Benedetti Panici P, Di Donato V, Bracchi C, Marchetti C, Tomao F, Palaia I. Modified gluteal fold advancement V-Y flap for vulvar reconstruction after surgery for vulvar malignancies. Gynecol. Oncol. 2014;132(1):125–129.
15. Saber A. Y, Hohman M. H, Dreyer M. A, StatPearls. StatPearls publishing; Treasure Island (FL): Mar 20, 2024. Basic flap design.

PROFILAKTIČKA LAPAROSKOPSKA OBOSTRANA ADNEKSEKTOMIJA KOD NOSILACA BRCA1 I BRCA2 MUTACIJA

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Uvod

Nasledne mutacije u genima BRCA1 i BRCA2 značajno povećavaju rizik za razvoj karcinoma dojke i jajnika. Nosilac mutacije BRCA1 ima rizik od 39–46% za razvoj karcinoma jajnika do 70. godine, dok je taj rizik za BRCA2 mutacije procenjen na 12–20% [1]. S obzirom na to da ne postoje pouzdani skrining testovi za rano otkrivanje epitelnog karcinoma jajnika, profilaktička hirurška intervencija predstavlja ključnu preventivnu strategiju.

Profilaktička laparoskopska obostrana adneksektomija (salpingo-ooforektomija) značajno redukuje rizik od razvoja karcinoma jajnika i jajovoda, ali i smanjuje rizik od karcinoma dojke ukoliko se primeni pre menopauze [2]. Cilj ovog predavanja je da predstavi aktuelne preporuke, tehničke aspekte operativnog zahvata, kao i posledice i dileme u vezi sa ovom intervencijom kod BRCA1 i BRCA2 nosilaca.

Indikacije za profilaktičku adneksektomiju

Glavna indikacija za sprovođenje profilaktičke salpingo-ooforektomije je potvrđena germinativna mutacija BRCA1 ili BRCA2 gena.

Optimalno vreme intervencije:

- BRCA1 mutacija: preporuka je da se operacija izvodi između 35. i 40. godine života, nakon završetka reproduktivnih planova [3].
- BRCA2 mutacija: zbog kasnijeg početka karcinoma jajnika u ovoj grupi, operacija se može odložiti do 40–45. godine [4].

U oba slučaja, odlaganje intervencije može biti rizično, ali prerana operacija ima ozbiljne posledice u vidu prevremene menopauze.

Efekti profilaktičke adneksektomije

Redukcija rizika od karcinoma jajnika i jajovoda: Studije pokazuju da profilaktička obostrana adneksektomija smanjuje rizik od karcinoma jajnika i jajovoda za 80–96% [5].

Uticaj na karcinom dojke: Ukoliko se operacija sprovede pre menopauze, rizik od karcinoma dojke smanjuje se za 40–70%, naročito kod nosilaca BRCA1 mutacije [6].

Mortalitet: Randomizovane i kohortne studije pokazuju da ova intervencija značajno produžava ukupno preživljavanje kod BRCA nosilaca, pre svega eliminacijom rizika od agresivnih oblika karcinoma jajnika [7].

Hirurški pristup i tehnika

Standardna procedura je laparoskopska obostrana salpingo-ooforektomija.

Tehnički aspekti:

Detaljna inspekcija trbušne duplje zbog mogućih ranih karcinoma.

Uklanjanje jajnika i jajovoda u celosti, sa posebnim naglaskom na fimbrijalni deo jajovoda, jer se smatra da mnogi visokogradusni serozni karcinomi jajnika potiču upravo iz ovog segmenta [8].

Patohistološki pregled prema SEE-FIM protokolu, koji podrazumeva detaljnu serijsku sekciju jajovoda, radi identifikacije seroznog intraepitelnog karcinoma (STIC lezije) [9].

Laparoskopski pristup omogućava brži oporavak, manje postoperativne komplikacije i bolji estetski rezultat u poređenju sa laparotomijom.

Posledice i dileme:

- Hormonske i metaboličke posledice: Prevremena menopauza izazvana operacijom povezana je sa valunzima, poremećajem sna, depresijom, kardiovaskularnim rizikom i osteoporozom. Hormonska supstituciona terapija (HST) može se razmatrati kod žena bez lične istorije karcinoma dojke, do fiziološke menopauze [10].
- Reproduktivne implikacije: Žene koje nisu završile reprodukciju suočavaju se sa dilemom odlaganja operacije, pa se preporučuje savetovanje o mogućnostima očuvanja plodnosti, poput krioprezervacije jajnih ćelija.
- Psihološki aspekt: Operacija značajno umanjuje anksioznost vezanu za rizik od raka, ali istovremeno nosi emocionalne i seksualne posledice zbog gubitka fertiliteta i hormonalnih promena [11].

Alternativne i dodatne strategije

Intenzivan nadzor: transvaginalni ultrazvuk i određivanje CA-125, iako nisu dovoljno senzitivni.

Rizik-adaptirana strategija: razmatra se odložena ooforektomija nakon ranije salpingektomije, sa očuvanjem ovarijalne funkcije, iako dugoročni rezultati još nisu potvrđeni [12].

Zaključak

Profilaktička laparoskopska obostrana adneksektomija je zlatni standard u prevenciji karcinoma jajnika i jajovoda kod BRCA1 i BRCA2 nosilaca. Ova intervencija značajno smanjuje rizik i mortalitet, ali nosi i posledice u pogledu hormonskog statusa, plodnosti i kvaliteta života. Optimalno vreme za intervenciju zavisi od tipa mutacije i individualnih okolnosti pacijentkinje. Neophodan je multidisciplinarni pristup koji uključuje ginekološkog onkologa, genetičara, endokrinologa i psihologa, kako bi se odluka donela na temeljan i individualizovan način.

Reference

1. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317(23):2402-2416.
2. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009;101(2):80-87.
3. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 2.2025.
4. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006;296(2):185-192.
5. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967-975.
6. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346(21):1609-1615.
7. Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all-cause mortality in BRCA1 and BRCA2 mutation carriers. BMC Women's Health. 2014;14:150.
8. Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010;34(3):433-443.
9. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol. 2006;30(2):230-236.
10. Kotsopoulos J, Gronwald J, Karlan B, et al. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers. JAMA Oncol. 2018;4(8):1059-1065.

11. Finch A, Metcalfe KA, Chiang JK, et al. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psychooncology. 2013;22(1):212-219.
12. Daly MB, Dresher CW, Yates MS, et al. Salpingectomy as a means to reduce ovarian cancer risk. Cancer Prev Res. 2015;8(5):342-348.

GYNECOLOGY

FUNCTIONAL MAGNETIC STIMULATION IN THE TREATMENT OF WOMEN'S URINARY INCONTINENCE AND PELVIC DISORDERS

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INTRODUCTION

Urinary incontinence (UI) occurs as a common problem, especially in postmenopausal women, often related to pelvic organ prolapse (POP). Functional magnetic stimulation (FMS) is a novel, effective therapy method for UI based on extracorporeal treatment of pelvic floor with powerful magnetic field. FMS is a convenient, non-invasive treatment inducing automated and standardized pelvic floor muscle training. The other chronic urinary disorders, e.g. chronic or interstitial cystitis, lower urinary tract symptoms (LUTS), etc. could also be successfully treated by the FMS.

MATERIALS AND METHODS

A prospective study has been performed using the FMS device (Magneto Stym, Iskra Medical, Slovenia) with a magnetic field power of 3 Tesla and a frequency range of 1-160 Hz. The patient was seated and dressed on an electromagnetic chair. Magnetic stimulation of the muscles is conducted by an electromagnetic coil built into the seat and controlled by an external unit. The stimulus intensity is gradually increased up to the limit of tolerability as indicated by the patient. All patients were treated with FMS twice a week for 8 weeks (16 therapies in total) using the treatment protocol adequate for the type of urinary incontinence. Each treatment lasted 20 minutes using the preset treatment protocol. The results were obtained using a patient self-evaluation questionnaire (PFDI-20, PFIQ-7) and collected before starting the treatment and after finishing the last therapy. Patients with a history of epilepsy, severe cardiac arrhythmias, a pacemaker or metal implants, as well as concurrent pregnancy, malignancy or acute pelvic infection has not been included in the study.

RESULTS

After the therapy, completely dry were >60% of patients with urgent urinary incontinence (UUI), >70% of patients with mixed urinary incontinence (MUI), >80% of patients with stress urinary incontinence (SUI), and >90% of patients following childbirth. The rest of patients reported moderate to significant improvement, but only <5% patients have not been satisfied as expected. Furthermore, >90% of patients would recommend FMS to their friends. These results approved the FMS as a safe, non-invasive method for SUI or/and POP, with high clinical efficacy and significant improvement of the quality of life in treated patients. FMS treatment showed immediate and effective outcomes in properly chosen patients, especially in the frequency of micturition, episodes of incontinence, and nocturia. Also, frequency and urgency symptoms of patients were significantly improved by this method.

CONCLUSIONS

FMS has been presented as a reliable and repeatable, effective treatment for UI in women with encouraging initials efficacy and a prospective future. FMS is a suitable and compliant treatment option for all types of female UI. Favourable feedback and improvement in urinary incontinence symptoms as presented in our study confirms previous literature reports that magnetic stimulation is an effective, non-invasive therapy for all types of incontinence. However, further studies are required to determine other diagnostic parameters and find out the wider therapy indications.

SLING PROCEDURE AND OTHERS TREATMENTS FOR PROBLEM OF STRESS INCONTINENCE

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Types of urinary incontinence: stress incontinence, urge incontinence, mixed incontinence, enuresis nocturna, continuous incontinence, overflow incontinence. One of four women after 18 years will experience urinary incontinence: 50% of women have a problem of stress incontinence, 36% fall on mixed incontinence, 11% of urge incontinence and 3% are other types of incontinene. In Europe, the prevalence of stress urinary incontinence was estimated at 14.5% in 2022 among individuals aged 30 to 60. The prevalence of stress urinary incontinence in women increases with age (>70 years).

There are well known Risk factors, childbirth: Vaginal deliveries are a significant risk factor, with the risk increasing with the number of vaginal births, obesity: higher BMI is a consistent risk factor for SUI, aging: the risk of SUI increases with age due to physiological changes, smoking and other medical conditions: chronic cough (e.g., from COPD) and other conditions that cause repetitive increases in abdominal pressure can exacerbate SUI, prepartum risk factors: positive family history of the prospective mother, urinary incontinence before and during pregnancy, ethnicity, maternal age at delivery (> 35 years), body-mass index (> 25 kg/m^2), estimated birth weight (> 4000 g), parity and Intrapartum risk factors: prolonged delivery (> 120 min), median or mediolateral episiotomy < 60°, vacuum and forceps delivery and Peripartum pelvic floor protection, adequate perineal protection, warm compresses, upright birth position, pre and postpartum pelvic floor physiotherapy.

Classification systems have been derived based on clinical assessment and diagnostic testing, notably videourodynamics. Modern developments in imaging technology may allow other techniques such as ultrasound to offer additional basis for future developments in classification. Other urodynamic approaches include urethral pressure profilometry and Valsalva leak point pressure; these may offer indicators of thresholds below which ISD is more likely to explain SUI, but they are not generally accepted in routine practice.

Treatment includes: behavioral methods (Bladder retraining- timed voiding, pelvic muscle and pelvic floor muscle training exercises, Biofeedback with visual or audio signals, electrostimulation), insertable mechanical devices (pessaries, bladder vaginal supports), pharmacologic options (anticholinergics, duloxetine, Estrogen, Tricyclic antidepressants) and surgery.

Surgery

The primary goals of surgery for patients with stress incontinence include reinforcing the pubourethral ligaments and the paraurethral connective tissue at the mid-urethra area. Surgical treatment is comprised of abdominal procedures, such as open or laparoscopic; vaginal procedures; and urethral compression devices, such as slings, artificial sphincters, and urethral bulking agents. Urethral slings have become the most common type of surgery to correct stress urinary incontinence. There is no single surgical procedure for the treatment of all patients with stress incontinence. The surgery must be tailored for the patient, not the reverse.

An abdominal approach is indicated in cases where there is a large uterus compressing the bladder, necessitating a concomitant hysterectomy, in the absence of vaginal prolapse, when adnexal pathology is present, or following failed vaginal incontinence surgery. Vaginal surgery should be considered when vaginal prolapse is present, a history of failed abdominal surgery, or the patient is at high risk for abdominal surgery due to factors such as multiple abdominal incisions and morbid obesity. If significant uterine procidentia exists, a vaginal hysterectomy should be performed, followed by retropubic suspension. If pelvic pressure symptoms exist with stress incontinence, the surgeon must assess for and correct associated conditions such as cystocele, enterocele, or rectocele through an anterior repair, enterocele repair, or posterior colpoperineoplasty, respectively.

A prophylactic incontinence procedure should be considered for females with prolapse without stress urinary incontinence, given postoperative voiding dysfunction may occur with an anterior colporrhaphy alone.

Abdominal incontinence surgeries:

Marshall-Marchetti-Krantz (MMK) procedure: This procedure is a retropubic approach elevating and fixating the anterolateral part of the urethra to the posterior pubic symphysis and adjacent periosteum of the pubic bone. The Marshall Marchetti Krantz procedure can be considered either as a primary or secondary treatment for incontinence and may be used as an adjunct to vaginal vault repair for prolapse.

Burch colposuspension: In this procedure, the bladder neck is supported by placing a few stitches on either side of the urethra and securing them to the iliopectineal (Cooper) ligament. This surgery can be performed as an open or laparoscopic procedure and is believed to be especially helpful for patients with demonstrable urethral hypermobility.

Pubovaginal sling: A strip of rectus fascia or fascia lata is placed directly under the bladder neck through the retropubic space and secured at the level of the rectus abdominis fascia. Fayyad et al introduced a new surgical technique, the laparoscopic mid-urethral autologous rectus fascial sling, for patients with stress urinary incontinence. This method offers several advantages, including a minimally invasive approach, precise suture placement under laparoscopic guidance, and the prevention of sling over-tightening.

Vaginal and other surgeries:

Modified Pereyra procedure (MPP): This procedure involves the elevation of paraurethral tissue to the abdominal wall, creating a significant elevation of the urethrovesical angle. The MPP can also be considered either as a primary or secondary treatment and may be an adjunct to vaginal vault repair for prolapse.

Mid-urethral sling procedure: This procedure involves placing a synthetic or autologous material under the mid-urethra, the most critical female continence zone. An open-weave polypropylene mesh was originally used, stabilizing and promoting collagen ingrowth over time. In 2011, the US Food and Drug Administration (FDA) recommended against the use of synthetic vaginal mesh due to rare but serious complications such as chronic pain, mesh erosion, and extrusion.

Amid the FDA recommendation and highly publicized litigation, organic materials and non-mesh options are generally preferred. These concerns regarding synthetic mesh in sling procedures spurred new interest in using autologous tissue.Similar efficacy and complication rates at 12 months were found between patients with autologous slings and those using synthetic materials.

According to a systemic review and meta-analysis, a higher BMI during mid-urethral sling surgery is an apparent risk factor for short- and long-term sling failure compared to individuals with normal weight.

Tension-free vaginal tape: The sling or tape insertion is inserted through the retropubic space and exits out the abdominal wall suprapubically. Advantages of the tension-free vaginal tape sling include rapid procedure completion in as little as 30 minutes with same-day patient discharge, no postoperative urinary catheterization, short recovery time, high success rates, and minimal pain.However, the blind retropubic passage of trocars may cause inadvertent bladder trauma and, rarely, severe injury to the bowel or iliac vessels.

Transobturator tension-free vaginal tape: This technique involves placing the sling from the vagina through the obturator foramen and out through the skin of the groin. Compared to the standard tension-free vaginal tape procedure, it offers a reduced risk of bladder perforation or bowel injury, an even shorter operating time, and a quicker return to routine activities.However, there may be an increased risk of bleeding from the medial branches of the obturator vessels.

A recent meta-analysis comparison of the various tension-free tape-based surgical procedures for stress incontinence found similar success rates, with the standard transvaginal tension-free vaginal tape procedure having the highest subjective cure rate.However, it also produced a higher incidence of dyspareunia postoperatively and more vaginal mucosal perforations.

Injection of urethral bulking agents: This procedure involves inserting various materials, such as autologous fat, cross-linked collagen, ethylene vinyl alcohol copolymer, glutaraldehyde calcium hydroxylapatite, polydimethylsiloxane, and pyrolytic carbon-coated beads, directly into the proximal urethral mucosal layer. These agents support, constrict, coapt, and tighten the bladder neck opening, making the procedure particularly useful for managing intrinsic sphincter deficiency. Multiple bulking agents exist, each with unique biophysical properties, efficacy, and safety issues, and no particular agent has proven superior. Collagen is the most commonly used agent, with a reported success rate exceeding 50%.Improved nonabsorbable, non-migrating agents are now commercially available.Two agents have been removed from the market due to injection site reactions (dextranomer hyaluronic acid) and migration problems (polytetrafluoroethylene).

This procedure is performed in an office setting with local anesthesia, and 2 to 3 injections may be required to improve symptoms. Urethral bulking is generally recommended for patients where less invasive methods have failed and are unwilling or unable to undergo anit-incontinence surgery. Although less invasive than incontinence surgical procedures, the urethral bulking procedure is also less effective. The risks include urinary retention, migration of the bulking agent (locally and to regional lymph nodes), systemic absorption, fibrosis, embolization, abscess formation, vaginal erosion, allergic reactions, and continuing or recurrent leakage.

Urethral bulking is not a first-line option for stress incontinence in men due to limited studies demonstrating efficacy, increased complications, lack of a standardized technique, uncertainty about the optimal volume of bulking material, and an unclear ideal injection site.

Cadaver studies suggest that urethral bulking agents may be effective for men with stress incontinence if these technical issues and other problems can be solved.Currently, bulking agents are not generally recommended for men with stress urinary incontinence outside of clinical trials but may be considered for selected individuals with relatively minimal leakage who understand the risks and are unfit or unwilling to accept more invasive surgery.

References:

1. Lugo T, Leslie SW, Mikes BA, et al. Stress Urinary Incontinence. [Updated 2024 Aug 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539769/
2. Tunn R, Baessler K, Knüpfer S, Hampel C. Urinary Incontinence and Pelvic Organ Prolapse in Women. Dtsch Arztebl Int. 2023 Feb 3;120(5):71-80. doi: 10.3238/arztebl.m2022.0406. PMID: 36647585; PMCID: PMC10080228.
3. Nambiar AK, Arlandis S, Bø K, Cobussen-Boekhorst H, Costantini E, de Heide M, Farag F, Groen J, Karavitakis M, Lapitan MC, Manso M, Arteaga SM, Riogh ANA, O'Connor E, Omar MI, Peyronnet B, Phé V, Sakalis VI, Sihra N, Tzelves L, van Poelgeest-Pomfret ML, van den Bos TWL, van der Vaart H, Harding CK. European Association of Urology Guidelines on the Diagnosis and Management of Female Non-neurogenic Lower Urinary Tract Symptoms. Part 1: Diagnostics, Overactive Bladder, Stress Urinary Incontinence, and Mixed Urinary Incontinence. Eur Urol. 2022 Jul;82(1):49-59. doi: 10.1016/j.eururo.2022.01.045. Epub 2022 Feb 23. PMID: 35216856.
4. Todhunter-Brown A, Hazelton C, Campbell P, Elders A, Hagen S, McClurg D. Conservative interventions for treating urinary incontinence in women: an Overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2022 Sep 2;9(9):CD012337. doi: 10.1002/14651858.CD012337.pub2. PMID: 36053030; PMCID: PMC9437962.

EXPECTANT MANAGEMENT OF ENDOMETRIOMAS

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Introduction

Endometriomas are one of the most common manifestations of endometriosis. They may present with chronic pelvic pain, dysmenorrhea, dyspareunia, or infertility, yet in many cases they are found incidentally in women who are asymptomatic or have only minimal symptoms. The management of ovarian endometriomas has traditionally been surgical, with excision aimed at alleviating symptoms, restoring pelvic anatomy, and sometimes improving fertility outcomes. However, surgical removal carries risks, particularly the potential reduction in ovarian reserve, and may not always prevent recurrence.

This has prompted a growing interest in expectant (conservative) management, especially for women who have no pressing clinical indication for surgery. Expectant management involves regular monitoring of the lesion without active medical or surgical treatment. The challenge for clinicians has been the limited evidence regarding the natural course of these cysts when left untreated. This chapter examines the background to this approach, reviews current understanding of endometrioma behaviour, and presents findings from a large retrospective cohort study that provides new insight into their natural history.

Background

Endometriosis affects an estimated 2–19% of women in the general population, although its true prevalence is difficult to determine because of differences in diagnostic criteria and the fact that many women may remain undiagnosed. It is defined by the presence of endometrial-like tissue outside the uterus, accompanied by a chronic inflammatory reaction. Endometriotic deposits can be found on the pelvic peritoneum, ovaries, uterosacral ligaments, pouch of Douglas, bowel, bladder, and occasionally in extra-pelvic sites.

Ovarian endometriomas are distinct in that they form within the ovary itself. Several theories have been proposed to explain their origin. Sampson's well-known theory of retrograde menstruation posits that menstrual blood containing endometrial cells flows backward through the fallopian tubes into the pelvic cavity, where the cells implant and proliferate. However, only a minority of women with retrograde menstruation develop endometriosis, suggesting that additional factors—possibly genetic predisposition, altered immune responses, or local tissue susceptibility—are involved. Alternative theories include coelomic metaplasia, where the ovarian surface epithelium transforms into endometrial-like tissue, and the development of endometriomas from haemorrhagic corpus luteum cysts in the presence of pelvic adhesions, leading to invagination of the ovarian cortex and metaplastic change.

Recent molecular studies have illuminated the biological processes that may underlie the development and eventual behaviour of endometriomas. These include epithelial–mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM), processes that together drive fibrosis within the lesion. Increased fibrosis over time may reduce vascularity and limit the lesion's capacity to enlarge, leading in some cases to

gradual shrinkage. This dynamic process may explain why, contrary to common assumptions, many endometriomas do not enlarge.

Diagnosis is most often achieved by transvaginal ultrasound, which is widely regarded as the first-line imaging modality for suspected endometriosis. Endometriomas typically appear as thick-walled cysts with homogeneous low-level internal echoes—described as “ground-glass” echogenicity—on ultrasound. The accuracy of diagnosis is highest when examinations are performed by experienced operators following standardised protocols.

Expectant Management in Context

Historically, surgery was considered the default approach for managing ovarian endometriomas. Over recent decades, however, concerns about the impact of surgery on ovarian reserve have encouraged a shift towards more selective intervention. This has been aided by advances in ultrasound imaging, which allow reliable diagnosis and follow-up without the need for immediate surgical exploration.

Expectant management is now considered a viable option for many women, particularly those with no significant symptoms or in whom fertility preservation is a priority. The potential advantages include avoiding surgical risks, preserving ovarian function, and reducing healthcare costs. However, the main concern has been the fear of cyst progression, rupture, or malignant transformation—risks that, although low, have historically influenced decision-making towards more interventionist strategies. Until recently, the absence of robust longitudinal data has made it difficult to counsel patients accurately about what to expect if they opt for surveillance.

Study Overview

We have performed a retrospective study including all asymptomatic women or women with mild symptoms who have decided for expectant management. Standardised ultrasound techniques were used for all examinations, with cyst size measured in three orthogonal planes and the mean diameter recorded. The annual growth rate was calculated for each patient, and statistical analysis explored whether baseline characteristics could predict cyst progression.

Results

Of the 1,922 women attending the clinics during the study period with moderate or severe endometriosis, 83 met the criteria for inclusion in the final analysis. The median age was 39 years, with follow-up intervals ranging from just over six months to more than eight years. Sixty per cent had a single endometrioma, and the remainder had multiple cysts, with the right ovary slightly more commonly affected than the left.

The overall pattern of change was reassuring for those considering expectant management. Nearly half of the women (47%) experienced a reduction in cyst size over time, and around one-third (31%) had cysts that remained essentially unchanged. Only 22% showed an increase in size. When expressed as an annual growth rate, the median change was –1.7 mm per year per woman, indicating a general trend towards stability or regression. Cysts were significantly smaller at the end of follow-up compared to baseline.

Interestingly, larger cysts at baseline were more likely to shrink than smaller ones, supporting the idea that advanced fibrosis in older lesions may limit growth potential. The study found no demographic or clinical features that reliably predicted progression, meaning that cyst behaviour could not be forecast from age, parity, previous surgery, or coexisting deep endometriosis.

Another notable finding was that more than one in five cysts initially diagnosed as endometriomas disappeared entirely during follow-up. This suggests that a proportion of lesions classified as endometriomas on first scan may in fact be functional haemorrhagic cysts, which are known to be more common in women with endometriosis and can resolve spontaneously.

Interpretation and Clinical Relevance

The study challenges the common assumption that ovarian endometriomas inevitably enlarge if left untreated. Instead, it shows that the majority remain stable or regress, even without medical or surgical intervention. For asymptomatic or minimally symptomatic women, this offers an evidence base for a conservative approach, allowing avoidance of surgery unless symptoms worsen or fertility needs dictate otherwise.

From a diagnostic perspective, the finding that some lesions resolve completely underlines the importance of follow-up imaging before committing to a diagnosis. This is particularly relevant when lesions are newly detected, as repeat scanning after a few months can help distinguish between true endometriomas and haemorrhagic cysts.

The absence of reliable predictors of progression means that management decisions should continue to be individualised. Ultrasound follow-up at appropriate intervals appears to be a safe strategy, enabling timely detection of the minority of cases that do progress. The optimal frequency of monitoring remains to be defined, but annual or biennial review may be sufficient for most women.

Relationship to the Wider Literature

Earlier prospective studies examining the conservative management of benign-appearing adnexal masses excluded most women with endometriomas because of fears about progression risk. The present findings suggest that this caution may not always be warranted, and that the natural behaviour of endometriomas is more heterogeneous than previously assumed. Observations of regression under hormonal therapy, such as with dienogest, are consistent with the spontaneous regression seen in this study, although the mechanisms differ. The concept of late-stage cyst “burnout” due to fibrosis is increasingly supported by both imaging and molecular data.

Future Directions

Further research is needed to refine our understanding of which endometriomas are most likely to progress and which can be safely left alone. Prospective longitudinal studies starting from the earliest detectable stages, ideally with parallel biomarker analysis and serial imaging, could help identify reliable predictors of behaviour. The impact of expectant management on fertility outcomes, quality of life, and healthcare costs also warrants systematic evaluation. There is also scope to explore whether certain ultrasound features—such as vascularity, wall thickness, or internal echotexture—might serve as early indicators of future growth.

Conclusion

The evidence now available supports expectant management as a reasonable and safe option for many women with ovarian endometriomas who are asymptomatic or have minimal symptoms. Most cysts will remain stable or regress over time, and the risk of significant progression is relatively low. This information can help clinicians counsel women more confidently, balancing the benefits of avoiding surgery against the small possibility of cyst enlargement. Regular ultrasound surveillance remains important, but the findings suggest that immediate intervention is not necessary in the majority of cases.

References:

1. Alcázar JL, Castillo G, Jurado M, García GL. Is expectant management of sonographically benign adnexal cysts an option in selected asymptomatic premenopausal women? Hum Reprod. 2005;20(11):3231–3234. doi:10.1093/humrep/dei206.
2. Alcázar JL, Olartecoechea B, Guerriero S, Jurado M. Expectant management of adnexal masses in selected premenopausal women: a prospective observational study. Ultrasound Obstet Gynecol. 2013;41(5):582–588. doi:10.1002/uog.12369.
3. Bean E, Chaggar P, Thanatsis N, Dooley W, Bottomley C, Jurkovic D. Intra- and interobserver reproducibility of pelvic ultrasound for the detection and measurement of endometriotic lesions. Hum Reprod Open. 2020;2020(2):hoaa001. doi:10.1093/hropen/hoaa001.
4. Bean E, Knez J, Setty T, Tetteh A, Casagrandi D, Naftalin J, Jurkovic D. Natural history of endometriosis in pregnancy: ultrasound study of morphology of deep endometriosis and ovarian endometrioma. Ultrasound Obstet Gynecol. Published online July 13, 2023. doi:10.1002/uog.26310.
5. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group. ESHRE guideline: endometriosis. Hum Reprod Open. 2022;2022(2):hoac009. doi:10.1093/hropen/hoac009.
6. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group. ESHRE guideline: endometriosis. Hum Reprod Open. 2022;2022(2):hoac009. doi:10.1093/hropen/hoac009.
7. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril. 2017;108(1):125–136. doi:10.1016/j.fertnstert.2017.05.004.
8. Benagiano G, Guo S. Age-dependent phenotypes of ovarian endometriomas. Reprod Med Biol. 2022;21(1). doi:10.1002/rmb2.12438.
9. Byrne D, Curnow T, Smith P, Cutner A, Saridogan E, Clark TJ; BSGE Endometriosis Centres. Laparoscopic excision of deep rectovaginal endometriosis in BSGE endometriosis centres: a multicentre prospective cohort study. BMJ Open.2018;8(4):e018924. doi:10.1136/bmjopen-2017-018924.
10. Chaggar P, Tellum T, Thanatsis N, De Braud LV, Setty T, Jurkovic D. Prevalence of deep and ovarian endometriosis in women attending a general gynecology clinic: prospective cohort study. Ultrasound Obstet Gynecol. 2023;61(5):632–641. doi:10.1002/uog.26175.
11. Ding D, Wang X, Chen Y, Benagiano G, Liu X, Guo SW. Evidence in Support for the Progressive Nature of Ovarian Endometriomas. J Clin Endocrinol Metab. 2020;105(7):2189–2202. doi:10.1210/clinem/dgaa189.
12. Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29(3):400–412. doi:10.1093/humrep/det457.
13. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997;24(2):235–258. doi:10.1016/s0889-8545(05)70302-8.
14. Fernandez H, Harmas A. [Clinical presentation and natural history of endometriosis]. Rev Prat. 1999;49(3):258–262.
15. Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FPG, Van Schoubroeck D, Exacoustos C, Installé AJF, Martins WP, Abrao MS, Hudelist G, Bazot M, Alcazar JL, Gonçalves MO, Pascual MA, Ajossa S, Savelli L, Dunham R, Reid S, Menakaya U, Bourne T, Ferrero S, Leon M, Bignardi T, Holland T, Jurkovic D, Benacerraf B, Osuga Y, Somigliana E, Timmerman D. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol. 2016;48(3):318–332. doi:10.1002/uog.15955.
16. Guerriero S, Van Calster B, Somigliana E, Ajossa S, Froyman W, De Cock B, Coosemans A, Fischerová D, Van Holsbeke C, Alcazar JL, Testa AC, Valentin L, Bourne T, Timmerman D. Age-related differences in the sonographic characteristics of endometriomas. Hum Reprod. 2016;31(8):1723–1731. doi:10.1093/humrep/dew113.
17. Guo SW. Fibrogenesis resulting from cyclic bleeding: the Holy Grail of the natural history of ectopic endometrium. Hum Reprod. 2018;33(3):353–356. doi:10.1093/humrep/dey015.
18. Holland TK, Yazbek J, Cutner A, Saridogan E, Hoo WL, Jurkovic D. Value of transvaginal ultrasound in assessing severity of pelvic endometriosis. Ultrasound Obstet Gynecol. 2010;36(2):241–248. doi:10.1002/uog.7689.
19. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E; ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698–2704. doi:10.1093/humrep/dei135.
20. Knez J, Bean E, Nijjar S, Tellum T, Chaggar P, Jurkovic D. Natural progression of deep pelvic endometriosis in women who opt for expectant management. Acta Obstet Gynecol Scand. Published online May 15, 2023. doi:10.1111/aogs.14491.
21. Nisenblat V, Bossuyt PMM, Farquhar C, Johnson N, Hull ML. Imaging modalities for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;2(2):CD009591. doi:10.1002/14651858.CD009591.pub2.
22. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril. 1997;68(4):585–596. doi:10.1016/S0015-0282(97)00191-X.
23. Piketty M, Chopin N, Dousset B, Millischer-Bellaische AE, Roseau G, Leconte M, Borghese B, Chapron C. Preoperative work-up for patients with deeply infiltrating endometriosis: transvaginal ultrasonography must definitely be the first-line imaging examination. Hum Reprod. 2009;24(3):602–607. doi:10.1093/humrep/den405.
24. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I; International Ovarian Tumor Analysis (IOTA) Group. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol. 2000;16(5):500–505. doi:10.1046/j.1469-0705.2000.00287.x.

25. Vallvé-Juanico J, Houshdaran S, Giudice LC. The endometrial immune environment of women with endometriosis. Hum Reprod Update. 2019;25(5):565–592. doi:10.1093/humupd/dmz018.
26. Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Fedele L. 'Blood On The Tracks' from corpora lutea to endometriomas. BJOG. 2009;116(3):366–371. doi:10.1111/j.1471-0528.2008.02055.x.
27. Vinatier D, Orazi G, Cosson M, Dufour P. Theories of endometriosis. Eur J Obstet Gynecol Reprod Biol. 2001;96(1):21–34. doi:10.1016/s0301-2115(00)00405-x.
28. Wenger JM, Loubeyre P, Marci R, Dubuisson JB. [Endometriosis: review of the literature and clinical management]. Rev Med Suisse. 2009;5(222):2085–2086, 2088–2090.
29. Xholli A, Filip G, Previtera F, Cagnacci A. Modification of endometrioma size during hormone therapy containing dienogest. Gynecol Endocrinol. 2020;36(6):545–549. doi:10.1080/09513590.2019.1703942.

SUBTOTALNA HISTEREKTOMIJA: IMA LI OPRAVDANJA U MODERNOJ GINEKOLOŠKOJ PRAKSI?

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Subtotalna (supracervikalna) histerektomija (SH) podrazumeva uklanjanje tela uz očuvanje grlića materice, sa ili bez adneksektomije. Iako se u današnje vreme ova procedura retko izvodi, neretko se nailazi na mišljenje da je ova procedura praćena nižim stopama morbiditeta, u prvom redu manjim stopama seksualne disfunkcije i disfunkcije karličnog dna, što se povezuje sa očuvanjem potpornih struktura karličnog dna. S druge strane, noviji podaci ukazuju da su „teoretske prednosti“ subtotalne histerektomije minimalne ili neosnovane, dok očuvanje cerviksa zahteva redovne kontrole i može biti praćeno dugoročnim komplikacijama.

Iako postoje dokazi da se histerektomija izvodila u antičkim vremenima, relevantniji dokazi sa kompletnim opisima slučajeva datiraju iz 19. veka. Procedura je bila praćena visokom stopom mortaliteta koja je iznosila do 70% i većina žena je umirala zbog iskrvarenja ili razvoja sepse. Do tridesetih godina 20. veka uobičajen pristup histerektomiji je bila subtotalna procedura koja je nosila manji rizik od pelvične infekcije i povreda mokraćne bešike i uretera. Nakon otkrića antibiotika koji su rešili problem ascedentne infekcije, peritonitisa i fatalnog ishoda u tim slučajevima, SH ostaje praktično rezervisana za slučajeve u kojima se odustaje od totalne histerektomije zbog tehničkih poteškoća.

Moderna medicina podrazumeva informisani pristanak pacijenta za svaku hiruršku proceduru, kao i aktivno učešće pacijenta u izboru pristupa (laparotomija ili laparoskopija) i obima hirurške intervencije (poštedna ili radikalna procedura). U razvijenim zemljama je krajem prošlog i početkom ovog veka uočen porast broja subtotalnih procedura, pri čemu nije jasno koliki udeo u ovom porastu imaju sami pacijenti, a koliki udeo imaju lekari.

Analizom dostupne literature, pokušaću odgovoriti na pitanje iz naslova: ima li opravdanja za izvođenje subtotalne histerektomije u modernoj ginekološkoj praksi.

Operativni i kratkoročni ishodi SH u odnosu na TH

Prezervacija cerviksa omogućava bržu proceduru, jer je potrebno ligirati ascedentne grane uterine arterije i vene, čime se izbegava disekcija vaskularizovanog paravaginalnog tkiva. Prema Kohrejnovoj analizi iz 2022. godine koja je obuhvatila 11 studija, abdominalna SH traje kraće u odnosu na abdominalnu TH (prosečno -11 minuta), dok je u slučaju laparoskopskog pristupa ta razlika manja (prosečno -5 minuta) i nije statistički značajna, pri čemu nema razlike u dužini hospitalizacije i vremenu potrebnom za pun oporavak. Gubitak krvi tokom abdominalne SH je manji u odnosu na abdominalnu TH (-57ml krvi), dok razlika kod laparoskopskog pristupa nije prisutna. Nije uočena razlika u potrebi za transfuzijom krvi bez obzira na pristup.

Febrilni morbiditet i urinarna retencija su značajno niže kod SH u odnosu na TH (OR 0,48 i 0,23). Nije uočena razlika u drugim kratkoročnim komplikacijama kao što su učestalost hirurških povreda, pelvičnih hematoma, vaginalnog krvarenja, infekcija rane ili opstrukcije creva između grupa sa SH i TH.

U retrospektivnoj analizi kanadskih autora ukupna stopa uroloških komplikacija je iznosila niskih 0,6%, pri čemu je rizik od urološke komplikacije bio značajno veći kod TH u odnosu na SH (OR 1,49).

Funkcija urinarnog i digestivnog trakta

U studiji koja je obuhvatila 279 pacijentkinja nije uočena razlika u incidenciji urinarnih tegoba između ispitanica randomizovanih u SH i TH grupu. Procena urinarne funkcije je obavljena preoperativno, nakon 6 meseci i nakon 2 godine od operativnog zahvata primenom standardizovanih upitnika i urodinamskih merenja. Nije uočena razlika u prevalenciji stres inkontinencije, nepotpunog pražnjenja bešike i urinarne urgencije u navedenim grupama. Takođe nije uočena razlika u odnosu na pristup operativnog zahvata (laparotomija/laparoskopija). Druga studija je došla do rezultata da je brzina protoka urina prilikom pražnjenja veća u SH grupi u odnosu na TH grupu. Takođe, SH grupa je imala veći prosečni funkcionalni kapacitet mokraćne bešike u odnosu na TH grupu (526 ml naspram 443 ml).

U navedenoj studiji nije uočena razlika u funkciji digestivnog trakta pre i posle operativnog zahvata. Stope opstipacije, urgencije, napora prilikom defekacije, upotrebe laksativa, inkontinencije i flatusa su bile slične u obe grupe.

Seksualna funkcija

Naučni dokazi o uticaju histerektomije na seksualnu funkciju su kontraverzni, što može biti posledica razlika u indikacijama za hiruršku intervenciju, razlika u ispitivanoj populaciji i upotrebi nestandardizovanih parametara za procenu seksualne funkcije. Preoperativne tegobe, kao što su mentrualna krvarenja, pelvični bol, dispareunija i dismenoreja mogu negativno uticati na seksualnu funkciju i histerektomija može poboljšati seksualnu funkciju u ovim slučajevima. S druge strane, histerektomija može štetno uticati na inervaciju u smislu smanjenja genitalne osetljivosti što dovodi do seksualne disfunkcije koja se tada može pripisati i razlikama u hirurškom pristupu, mada se ovo prvenstveno odnosi na radikalnu histerektomiju. Teoretski, SH bi trebala biti superiornija u odnosu na TH, jer se prilikom SH štedi se parasimpatička i simpatička inervacija male karlice i genitalnog regiona, dok bi očuvanje grlića moglo smanjiti rizik od dispareunije. Međutim, autori meta-analize, koja je obuhvatila 32 studije sa 4000 pacijentkinja, su zaključili da nema dokaza da je ijedan modalitet (SH ili TH) bolji ili lošiji u smislu promena seksualne funkcije ili pelvičnog bola nakon histerektomije. Histerektomija sa konyervacijom adneksa je bila praćena boljom lubrikacijom i intenzivnijim orgazmima u odnosu na procedure sa obostranom adneksektomijom, ali očuvanje cerviksa nije uticalo na ove ishode.

Mala retrospektivna norveška studija je procenila stavove partnera žena kod kojih je prethodno načinjena SH ili TH u smislu frekvencije seksualnih odnosa i stepena zadovoljstva. Većina partnera u obe grupe prilikom odnosa nije osećala da je uterus uklonjen, bez obzira da li se radilo o SH ili TH. Interesantno, oni partneri koji su prijavili da osećaju promenu su to prijavili kao pozitivno iskustvo, proporcionalno više u TH grupi.

Rizik od prolapsa pelvičnih organa (POP)

Danski autori su analizirali nacionalni registar u višedecenijskom periodu. Nakon isključivanja pacijentkinja koje su rađale, zaključili su da histerektomija povećava rizik od prolapsa pelvičnih organa za oko 60%, odnosno da uterus per se predstavlja protektivni faktor za prolaps pelvičnih organa. Do sličnih rezultata su došle i studije koje su ispitivale populacije žena koje su rađale.

Dugoročno praćenje pacijentkinja koje su prethodno randomizovane u SH i TH grupu je pokazalo da je rizik od prolapsa pelvičnih organa uporediv u obe grupe. Iako je TH grupa bila praćena nešto većim rizikom od spada, posebno u prednjem kompartmanu, prisustvo simptomatologije je bilo uporedivo u obe grupe.

Druge dugoročne komplikacije

Ciklično krvarenje kod SH se kod mlađih pacijentkinja može uslovno smatrati komplikacijom obzirom da je u većini slučajeva oskudno (u vidu spotinga) i ne zahteva dalji tretman. Obično se javlja kod pacijentkinja kod kojih je indikacija za SH bila intraoperativna komplikacija, što podrazumeva nestandardizovan pristup kojim se štedi deo tela materice, odnosno endometrijuma koji reaguje na ciklične hormonske varijacije. Perzistentno krvarenje iz očuvanog grlića (i dela materice) se može javiti u 10-20% slučajeva i tada predstavlja indikaciju za sekundarnu hirurgiju.

Očuvanje grlića podrazumeva dugoročni nastavak skrininga na cervikalnu patologiju kod pacijentkinje sa SH i povremeno sekundarnu ekstirpaciju grlića materice. U retrospektivnoj analizi koje je obuhvatila 137 pacijentkinja sa sekundarnom ekstirpacijom grlića indikacije za proceduru su bile prolaps u 31,4%, spoting u 19% i cervikalna displazija u 18,2% slučajeva. Neočekivani histološki nalazi (premaligne ili maligne promene) nakon SH su bile praćene ponovnom hirurgijom u proseku nakon mesec dana u 11 slučajeva. Kod 4 pacijentkinje indikacija za ekstirpaciju grlića je bilo maligno oboljenje koje se javilo nakon više od 5 godina u odnosu na subtotalnu histerektomiju. Sekundarna resekcija cervikalnog patrljka je izvedena u 75% slučajeva vaginalno (često sa prednjom kolporafijom), u 20% slučajeva laparoskopski, dok je u preostalim slučajevima procedura izvedena laparotomijom. Ukupna stopa komplikacija je iznosila 5% i obuhvatala je intraoperativno i postoperativno krvarenje i teškoće prilikom mokrenja kod pacijentkinja kod kojih je načinjena prednja kolporafija.

Preporuke

Većina preporuka koje se odnose na histerektomiju se bazira na preporukama koje se odnose na indikacije i izbor pristupa, preporučeno minimalno invazivnom hirurgijom (vaginalni pristup ili endoskopija). Stručna udruženja ne preporučuju rutinski izbor SH u odnosu na TH i SH je rezervisana za određene kliničke situacije, kao što su hirurške poteškoće, želja pacijentkinje za očuvanjem cerviksa ili određena stanja odnosno kontraindikacije za uklanjanje grlića.

Posebno pitanje predstavlja laparoskopska SH koja podrazumeva i morselaciju preparata, a time i rizik od diseminacije neprepoznate maligne bolesti (karcinom endometrijuma, sarkom uterusa).

Odluku o izvođenju SH treba doneti nakon detaljnog razgovora sa pacijentkinjom, koju treba informisati o nastavku redovnih ginekoloških kontrola, ali i o mogućim sekvelama ovakve procedure. Suspektna cervikalna citologija (Papa bris), ultrazvučno suspektne promene endometrijuma ili miometrijuma su apsolutne kontraindikacije za subtotalnu histerektomiju.

Zaključak

Subtotalna histerektomija nudi manje perioperativne prednosti, ali ove prednosti nisu praćene funkcionalnim ili dugoročnim prednostima u odnosu na TH. Dva osnovna faktora koja ograničavaju širu upotrebu ove procedure su perzistentno krvarenje iz očuvanog dela materice i rizik od cervikalnog kancera. U modernoj ginekološkoj praksi, SH može biti opravdana samo u selektovanoj grupi dobro informisanih pacijentkinja kod kojih postoje ili su naglašeni perioperativni rizici za izvođenje TH, ili kod pacijentkinja koje imaju želju da očuvaju grlić materice.

Reference

1. Lethaby A, Mukhopadhyay A, Naik R. Total versus subtotal hysterectomy for benign gynaecological conditions. Cochrane Database Syst Rev. 2012 Apr 18;(4):CD004993.
2. ACOG Committee Opinion No. 701: Choosing the route of hysterectomy for benign disease. Obstet Gynecol. 2017;129.
3. Husby KR, Gradel KO, Klarskov N. Pelvic organ prolapse following hysterectomy on benign indication: a nationwide, nulliparous cohort study. Am J Obstet Gynecol. 2022; 226(3): 386.e1-386.e9.

4. Aleixo GF, Fonseca MCM, Bortolini MAT, Brito LGO, Castro RA. Total Versus Subtotal Hysterectomy: Systematic Review and Meta-analysis of Intraoperative Outcomes and Postoperative Short-term Events. Clin Ther. 2019 Apr;41(4):768-789.
5. Neis F, Reisenauer C, Kraemer B, Wagner P, Brucker S. Retrospective analysis of secondary resection of the cervical stump after subtotal hysterectomy: why and when? Arch Gynecol Obstet. 2021 Dec; 304(6):1519-26.

MINIMALLY INVASIVE GYNECOLOGICAL SURGERY

PERSPECTIVES AND ALTERNATIVES TO LAPAROSCOPIC HYSTERECTOMY

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The development of minimally invasive gynecological surgery is also changing perceptions in the field of laparoscopic hysterectomy. We are proud to mention the fact that in 1994., in Zabok, we performed the first laparoscopic hysterectomy in Southeast Europe, led by Prof. Kopjar, just five years after Prof. Reich published the same work as the first in the world in 1999. We celebrated the thirtieth anniversary of the first laparoscopic hysterectomy and now, with the experience of over a thousand performed surgical procedures, we can responsibly claim that this is truly a revolutionary operation that has fundamentally changed paradigms that have been in place for decades and even centuries.

Today, as we enter the fourth decade of performing laparoscopic hysterectomy, we can very objectively look at all the significant elements of the aforementioned procedure. First of all, we must emphasize the truly minimal invasiveness of the aforementioned procedure, so that a truly extensive procedure has become truly acceptable in many areas, and in accordance with the indication postulates. Laparoscopic hysterectomy is established in clinical practice, and robotic hysterectomy is also gaining an increasing share today, as it has significant advantages over conventional laparoscopic hysterectomy. The introduction of robotic hysterectomy ensures additional quality of the procedure itself, its minimal invasiveness and precision, as well as numerous benefits for patients, primarily in terms of faster recovery and achieving work and functional ability. The only current disadvantage of robotic hysterectomy today is still the high price of the technology itself and consumables, but current findings that speak of new devices and manufacturers that offer increasingly cheaper devices on the market are encouraging.

The public health system with the use of laparoscopic hysterectomy has numerous benefits, especially with the fastest possible postoperative inclusion of patients in the working environment and with a far lower incidence of comorbidities. Since hysterectomy, including laparoscopic hysterectomy, is still one of the most frequently performed surgical procedures in gynecology, it is to be expected that the same will be true in the future. We can hope that the introduction of the most modern technological systems and their practicality and accessibility will ensure their soon and much wider application for the benefit of the entire public health system and our patients.

Keywords: total laparoscopic hysterectomy, minimally invasive gynecological surgery, robotic surgery

Recent findings on laparoscopic hysterectomy

It is undeniable that the concept of minimally invasive gynecological surgery imposes a different philosophy in the approach to gynecological pelvic diseases. The above also applies to the frequency and indication area for performing laparoscopic hysterectomy. Although hysterectomy is still one of the most common gynecological operations today, we have had to redefine and update our previous knowledge in many areas. [1-5]

Numerous considerations have also been redefined, and for a long time now the issue of laparoscopic morcellation has been approached in a different and strictly indicated manner, primarily in accordance with modern gynecological oncological and endoscopic settings. [6]

In many other areas, laparoscopic hysterectomy is no longer approached in the same way as it once was, and alternative methods that exclude hysterectomy are increasingly being used. Today's environment is primarily focused on the wishes of our patients, their primary well-being, but also on the quality of life and patient satisfaction. [7,8]

On these foundations, scientific and professional knowledge and procedures regarding laparoscopic hysterectomies themselves are evolving. Thus, in benign pathology, there are centers that do not use uterine manipulators in their surgical technique, as well as those for which their use is still mandatory. [9] Numerous other technical settings also determine the indication areas and techniques of laparoscopic hysterectomies themselves today. Will the patient undergo laparoscopically assisted vaginal hysterectomy, total laparoscopic hysterectomy, supracervical laparoscopic hysterectomy or robotic hysterectomy? We must also include in our considerations the field of gynecological oncology with total radical laparoscopic hysterectomy, where in modern times it has a very strong place, especially in the treatment of endometrial cancer. [10,11]

The prospects of laparoscopic hysterectomy in the future will certainly be directed towards its minimally invasive component. The continuous progress of science, technology, experience, as well as the change of paradigm related to laparoscopic hysterectomy, are fundamentally changing the atmosphere in which we live and work. Since the world never stands still, and scientific research and the amount of new knowledge is multiplied immeasurably, the aforementioned aspirations do not bypass pelvic medicine, and therefore the issue of laparoscopic hysterectomies. Surgical techniques, given the development of technology and modern surgical techniques as well as instrumentation, are today much more advanced and provide our patients with a very safe and acceptable alternative for further consideration and making the best decisions. By promoting and adopting modern knowledge, educating a large number of endoscopists, today we have a positive atmosphere with a large number of centers where endoscopic techniques are applied in minimally invasive gynecological surgery. The prospects today are much better than they were ten, twenty or thirty years ago. Many centers use laparoscopic surgery methods, including laparoscopic hysterectomy, in routine practice. Since today, in accordance with strictly indicated cases, we have very precise decision-making capabilities and patient selection, making decisions about the type of surgical endoscopic procedures becomes much easier and more defined. Whether one of the many possible types of hysterectomy, especially laparoscopic, will be applied today must be considered multidisciplinary, first and foremost accepting strict indication frameworks and the well-being of the patient. We must also include in our considerations the field of gynecological oncology with total radical laparoscopic hysterectomy, where in modern times it has a very strong place, especially in the treatment of endometrial cancer. It is undeniable that the development and success of laparoscopic hysterectomy depend to a large extent on

the education and training of the operator, which is why continuous education and training of endoscopists are of exceptional importance. [12-15]

Development, research and perspectives of laparoscopic hysterectomy

We must proudly point out that the development of minimally invasive gynecological surgery is changing the perception in the field of minimally invasive gynecological surgery, including laparoscopic hysterectomy. We must once again recall the pioneering successes of gynecological endoscopy in the areas of Southeast Europe, which had an unstoppable course. We must remember the year 1994 when the first laparoscopic hysterectomy in Southeast Europe was performed at the Zabok General Hospital. The team that included Prof. Miroslav Kopjar and Dr. Nikša Knezović truly performed a revolutionary operation at that time, bypassing the spatial, technological and organizational circumstances. However, after a great deal of effort, education and experience spanning more than three decades, today we must proudly say that the process that we have gone through and brought to life, truly has no alternative. The facts that speak of the historical truth, that in Zabok and Croatia, the first laparoscopic hysterectomy was performed only five years after the pioneering one performed in 1999 by Prof. Harry Raich, are truly something we should be proud of. The passage of time is the best way to see the achievements of the aforementioned pioneering steps, which changed paradigms that have existed for decades, and even centuries, which is very difficult to change.

It is undeniable that today, as we enter the fourth decade of performing laparoscopic hysterectomy, we can see all the significant elements of laparoscopic hysterectomies much more objectively. We should always emphasize the most important component related to the surgical procedure itself, which is its minimal invasiveness. With strict indication postulates, laparoscopic hysterectomy is now established in clinical practice. Robotic hysterectomy is also entering routine clinical practice in a big way, which today truly represents the highest stage in the development of technology and brings our patients numerous benefits, while offering the additional component of minimal invasiveness. The high price of the device and consumables is still associated with the aforementioned technique, but even today we have much cheaper and more sophisticated systems on the market. It is undeniable that a complete public health system using laparoscopic hysterectomy has numerous advantages. In doing so, we must always emphasize the much faster postoperative inclusion of patients in the working environment and with a much lower incidence of comorbidities. The fact is that even today, hysterectomy, including laparoscopic hysterectomy, is one of the most frequently performed surgical procedures in gynecology. We expect that millions of laparoscopic hysterectomies in the world and thousands of laparoscopic hysterectomies performed in Croatia will be the best guarantee for the implementation of the method even in the few centers where the aforementioned methods are still not implemented. We should certainly hope that the aforementioned changes will take place in the near future and that the introduction of the most modern technological systems and knowledge, as well as their practical application and accessibility, will ensure additional quality for patients, healthcare workers, and the entire public health system. We are convinced that the continuous and unprecedented development of minimally invasive gynecological surgery, including the development of laparoscopic hysterectomy techniques, cannot be stopped. On these postulates, it is still necessary to invest significant efforts aimed at continuously raising the level of education, training and continuous improvement of new generations of gynecological endoscopists, as well as maintaining the level of training of the existing staff. To the extent that we will succeed in our efforts, and we see no reason why it would not be so, it is certain that the future of minimally invasive gynecological

surgery is indeed guaranteed in our region. And the role of laparoscopic hysterectomy in that process will continue to be in the center of interest. [16-18]

Literature:

1. Vargas M, Arora Y, Alejandro Bueno M, Gerardo Rodriguez C. Adverse outcomes related to morcellation in Total Laparoscopic Hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2024;294:231-237.
2. Del Boca G, Damiani GR, Zagni R, Guglielmi D, Malvasi A, Vimercati A, Pellegri AM, Biffi A, Vitagliano A, Cicinelli E. Total laparoscopic hysterectomy four-handed ergonomic technique: description of an original surgical procedure for the reduction of learning curve. Minerva Obstet Gynecol. 2023;75(3):298-306.
3. Bahall V, Singh K, De Barry L. Day case total laparoscopic hysterectomy in a low resource setting: A descriptive analysis. Womens Health (Lond). 2025 Jan-Dec;21:17455057251331766. doi: 10.1177/17455057251331766. Epub 2025 Apr 21. PMID: 40258131; PMCID: PMC12034970.
4. Tercan C, Gunes AC, Bastu E, Blockeel C, Aktoz F. The comparison of 2D and 3D systems in total laparoscopic hysterectomy: a systematic review and meta-analysis. Arch Gynecol Obstet. 2024;310(4):1811-1821.
5. Januszek SM, Barnas E, Skret-Magierlo J, Sokolowski J, Szczerba P, Januszek R, Domka W, Malinowski KP, Kalandyk-Osinko K, Kluza M, Bolanowska A, Kluz T. Obesity as a risk factor of in-hospital outcomes in patients with endometrial cancer treated with laparoscopic surgical mode. Ginekol Pol. 2020;91(10):573-581.
6. Rosales Delgado JA, González-Sicilia Cotter E, González Vergara R, Aedo Ocaña O. Histerectomía laparoscópica por morcelación tipo CASH (Classical, Abdominal, Semm, Histerectomy) [Morcellation laparoscopic hysterectomy of the CASH (Classical, Abdominal, Semm, Hysterectomy) type]. Ginecol Obstet Mex. 1994;62:378-80.
7. Lobão A, Ferruzzi CM, Ohara F, Lima RF, Abdalla-Ribeiro H, Kuteken FS, Aldrighi JM, Ribeiro P. Assesment of the Intrafascial Total Laparoscopic Histerectomy in the Academic Environment. J Minim Invasive Gynecol. 2015 Nov-Dec;22(6S):S164-S165. doi: 10.1016/j.jmig.2015.08.615. Epub 2015 Oct 15. PMID: 27678914.
8. Mieli MPA, Grell AMSM, Simões RDS, de Mattos LA. Parasitic myoma after supracervical laparoscopic histerectomy. Autops Case Rep. 2013;3(2):45-49.
9. Zygouris D, Chalvatzas N, Gkoutzioulis A, Anastasiou G, Kavallaris A. Total laparoscopic hysterectomy without uterine manipulator. A retrospective study of 1023 cases. Eur J Obstet Gynecol Reprod Biol. 2020;253:254-258.
10. Popa A, Copaescu C, Horhoianu V. Laparoscopic total hysterectomy still not routinely chosen Operative description and available instruments. J Med Life. 2019;12(3):301-307.
11. Del Boca G, Damiani GR, Zagni R, Guglielmi D, Malvasi A, Vimercati A, Pellegri AM, Biffi A, Vitagliano A, Cicinelli E. Total laparoscopic hysterectomy four-handed ergonomic technique: description of an original surgical procedure for the reduction of learning curve. Minerva Obstet Gynecol. 2023;75(3):298-306.
12. Bahall V, Singh K, De Barry L. Day case total laparoscopic hysterectomy in a low resource setting: A descriptive analysis. Womens Health (Lond). 2025 Jan-Dec;21:17455057251331766. doi: 10.1177/17455057251331766. Epub 2025 Apr 21. PMID: 40258131; PMCID: PMC12034970.
13. Tercan C, Gunes AC, Bastu E, Blockeel C, Aktoz F. The comparison of 2D and 3D systems in total laparoscopic hysterectomy: a systematic review and meta-analysis. Arch Gynecol Obstet. 2024;310(4):1811-1821.
14. Giglio-Ayers T, Zullo F, Hersey A, Ranaweera I, Ouellette L, Di Mascio D, Foley CE, Wagner SM. Impact of Simulation Exercises on Total Laparoscopic Hysterectomy Surgical Outcomes: A Systematic Review and Meta-Analysis. R I Med J (2013). 2024;107(6):19-23.
15. Reich H. Total laparoscopic hysterectomy: indications, techniques and outcomes. Curr Opin Obstet Gynecol. 2007;19(4):337-44.
16. Leal Ghezzi T, Campos Corleta O. 30 Years of Robotic Surgery. World J Surg. 2016;40(10):2550-7.
17. Lobão A, Ferruzzi CM, Ohara F, Lima RF, Abdalla-Ribeiro H, Kuteken FS, Aldrighi JM, Ribeiro P. Assesment of the Intrafascial Total Laparoscopic Histerectomy in the Academic Environment. J Minim Invasive Gynecol. 2015;22(6S):S164-S165.
18. Mereu L, Berlanda V, Surico D, Gardella B, Pertile R, Spinillo A, Tateo S. Evaluation of quality of life, body image and surgical outcomes of robotic total laparoscopic hysterectomy and sentinel lymph node mapping in low-risk endometrial cancer patients - A Robotic Gyne Club study. Acta Obstet Gynecol Scand. 2020;99(9):1238-1245.

HYSTEROSCOPY IN EVERYDAY CLINICAL PRACTICE - OUR EXPERIENCES

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Introduction

Hysteroscopy is the gold standard in the diagnosis and treatment of intrauterine pathologies. As a minimally invasive method, it enables direct visualization of the inside of the uterus and the simultaneous performance of therapeutic procedures, which significantly shortens the time of diagnosis and treatment, reduces the need for more procedures and improves the quality of patient care. In daily clinical practice, hysteroscopy occupies a central place in the treatment of abnormal uterine bleeding, infertility, suspected intrauterine malformations, polyps, fibroids, as well as tissue retention after childbirth or abortion. [1]

Indications for hysteroscopy

In daily practice, hysteroscopy is used as the first step in the diagnosis of patients with intermenstrual and postmenopausal bleeding. Also, it is an indispensable tool in the evaluation of the intrauterine cavity in women facing the problem of infertility or repeated spontaneous abortions. It enables accurate detection and immediate resolution of intrauterine pathologies that negatively affect implantation or pregnancy. [2, 3]

Types of hysteroscopy

Therapeutic hysteroscopy is most often used for the removal of endometrial polyps, submucosal myomas, uterine septum, intrauterine synechiae (Asherman's syndrome), as well as for the extraction of residual tissues. In many cases, it is possible to solve both diagnostics and therapy with one procedure, which leads to a more efficient and economical approach to treatment. [4]

Our experiences

In our clinic, approximately 2,000 patients undergo hysteroscopic interventions per year (Department of Minimally Invasive Surgery, Department of Fertility Preservation and Oncofertility, and Department of General Gynecology). Indications, types of interventions as well as intraoperative findings were analyzed.

In addition to numerous advantages, hysteroscopy requires appropriate doctor education, experience, and proper selection of patients. Potential complications, although rare, include uterine perforation, infection, and complications related to the use of distension media.

In conclusion, hysteroscopy is an irreplaceable diagnostic and therapeutic method in modern gynecological practice. Its wide application, minimal invasiveness and high degree of efficiency make it a key tool in the treatment of a large number of gynecological conditions. The introduction of ambulatory hysteroscopy additionally contributes to the improvement of women's health care, making diagnostics faster, more precise and more comfortable for patients. [5, 6]

References

1. Carugno J, Grimbizis G, Franchini M, Alonso L, Bradley L, Campo R, Catena U, Carlo A, Attilio DSS, Martin F, Haimovich S, Isaacson K, Moawad N, Saridogan E, Clark TJ. International Consensus Statement for Recommended Terminology Describing Hysteroscopic Procedures. J Minim Invasive Gynecol. 2022 Mar;29(3):385-391.

2. Yen CF, Chou HH, Wu HM, Lee CL, Chang TC. Effectiveness and appropriateness in the application of office hysteroscopy. J Formos Med Assoc. 2019 Nov;118(11):1480-1487.
3. The Use of Hysteroscopy for the Diagnosis and Treatment of Intrauterine Pathology: ACOG Committee Opinion, Number 800. Obstet Gynecol. 2020 Mar;135(3):e138-e148.
4. ACOG Technology Assessment No. 13: Hysteroscopy. Obstet Gynecol. 2018 May;131(5):1.
5. Yin X, Cheng J, Ansari SH, Campo R, Di W, Li W, Bigatti G. Hysteroscopic tissue removal systems for the treatment of intrauterine pathology: a systematic review and meta-analysis. Facts Views Vis Obgyn. 2018 Dec;10(4):207-213.
6. Agostini A, Cravello L, Bretelle F, Shojai R, Roger V, Blanc B. Risk of uterine perforation during hysteroscopic surgery. J Am Assoc Gynecol Laparosc. 2002 Aug;9(3):264-7.

FREE COMMUNICATIONS

A RARE CASE OF CYSTIC ARTERY THROMBOSIS IN 24-WEEK GESTATION

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Introduction: Cystic artery thrombosis is extremely rare, but potentially severe disease with gallbladder necrosis and perforation leading to biliary peritonitis as surgical emergency. Clinical presentation is alarming since the patients are critically ill with sepsis and multiorgan failure. The diagnosis in pregnancy is challenging because diseases associated with gall bladder also mimic pregnancy related conditions.

Case presentation: A 20-year-old female presented with sepsis and multiorgan dysfunction four days after spontaneous abortion in 24th gestational week. Polymicrobial antibiotic therapy and supportive therapy was started and uterine curettage was performed. Since the clinical response was poor, she underwent explorative laparotomy. At laparotomy, gangrenous gall bladder and thrombosis of cystic artery with subhepatic peritonitis and pericholecystitis were found. There were no signs of gastrointestinal perforation so cholecystectomy was performed. Postoperatively, the patient was under intensive care unit monitoring with multidisciplinary team including gynaecologist, anaesthesiologist, abdominal surgeons, infectious disease specialist, haematologist, nephrologist, neurologist. After 24 days the patient was discharged recovered.

Conclusion: There are only few cases in literature describing this condition but not pregnancy related. Since it is a life-threatening condition, timely diagnosis followed by surgery and adequate supportive therapy is very important.

Key words: cystic artery thrombosis, pericholecystitis, pregnancy, surgical emergency

References

1. Brown KE, Hirshberg JS, Conner SN. Gallbladder and Biliary Disease in Pregnancy. Clin Obstet Gynecol. 2020;63(1):211-225.
2. Mahjoubi MF, Dhaou AB, Maatouk M, et al. Acute cholecystitis in pregnant women: A therapeutic challenge in a developing country center. Ann Hepatobiliary Pancreat Surg. 2023;27(4):388-393.
3. Masroor M, Sarwari MA. Spontaneous common bile duct perforation in full term pregnancy: a rare case report and review of literature. BMC Surg. 2021;21(1):239.
4. Liu YL, Hsieh CT, Yeh YJ, Liu H. Cystic artery pseudoaneurysm: A case report. World J Clin Cases. 2023;11(1):242-248.

PROGRESIVNI HIPERANDROGENIZAM U POSTMENOPAUZI: PRIKAZ SLUČAJA TUMORA JAJNIKA STEROIDNIH ĆELIJA KOJI SE NE MOŽE DRUGAČIJE KLASIFIKOVATI

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Uvod

Period postmenopauze povezan je sa promenama u hormonskom miljeu koji se karakteriše smanjenjem nivoa estrogena, povećanjem gonadotropina i blagim porastom nivoa testosterona. Kao posledica toga, nije neuobičajeno da žene u postmenopauzalnom periodu imaju blago izražene simptome uzrokovane višim koncentracijama androgena. Međutim, naglo nastali i progresivni hirzutizam, akne i androgena alopecija kod postmenopauzalnih žena zahtevaju detaljno ispitivanje u pravcu postojanja tumora jajnika ili nadbubrežne žlezde koji luči androgene [1].

Neepitelni karcinomi jajnika su retki i čine približno 10% svih karcinoma jajnika, a obuhvataju prvenstveno tumore germinativnih ćelija, tumore polnih vrpci i specijalizovane strome jajnika, kao i nekoliko izuzetno retkih tipova tumora. Steroidni ćelijski tumori jajnika predstavljaju retke oblike tumora polnih vrpci i strome jajnika koji čine manje od 0,1% svih tumora jajnika. Mogu se javiti kod žena svih starosnih dobi i izazvati simptome poput virilizacije, izoseksualnog preranog puberteta kod adolescentkinja, Kušingovog sindroma i infertiliteta. Prema ćelijskom poreklu, ovi tumori se dele na tri podtipa: stromalne luteome, tumore Lajdigovih ćelija i tumore koji se ne mogu drugačije klasifikovati (engl. NOS; not otherwise specified) [2]. Predstavljamo slučaj progresivnog postmenopauzalnog hiperandrogenizma uzrokovanim retkim tipom tumora jajnika – tumora steroidnih ćelija koji se ne može drugačije klasifikovati.

Prikaz slučaja

Pacijentkinja stara 62. godine, upućena je na endokrinološku obradu zbog progresivnih znakova virilizacije koje su se intenzivirale u prethodne dve godine. U anamnezi je navela da je u menopauzi već više od deset godina, ima jedno dete i nikada nije bila pušač. U 56. godini dijagnostikovana joj je Parkinsonova bolest zbog koje se leči levodopom, pramipeksolom i amantadin sulfatom. Poslednjih godina u terapiju je uključen i metformin zbog poremećaja glikoregulacije.

Pacijentkinja je počela da primećuje značajno pogoršanje telesne konstitucije i telesne mase — ugojila se 15 kg u periodu od dve godine — uz izraženu maljavost po licu i telu, androgeni tip gubitka kose, promenu boje glasa i opštu slabost. S obzirom da su svi simptomi uoućivali na posledice hiperandrogenizma, sprovedena detaljna laboratorijska i radiološka obrada.

Laboratorijski nalazi pokazali su izrazito povišene vrednosti ukupnog testosterona (11.36 nmol/L) i slobodnog testosterona (5.27 pg/mL), uz blago povišen DHEAS (125.7 µg/dL), dok su vrednosti FSH, LH i estradiola bile neuobičajene za ženu u postmenopauzi, sa relativno visokom koncentracijom estradiola (216 pmol/L). Kortizol, prolaktin, TSH i FT4 bili su u opsegu referentnih vrednosti. Tumorski marker CA-125 bio je uredan.

Radiološka evaluacija započeta je CT pregledom abdomena koji nije ukazao na patološke promene na nadbubrežnim žlezdama. Nakon toga je urađena magnetna rezonanca male karlice, kojom je u loži levog jajnika detektovana jasno ograničena, ovalna formacija dimenzija 20 mm, sa osobinama koje su ukazivale na stromalni tumor jajnika. Ostale strukture abdomena i male karlice bile su urednog izgleda

Pacijentkinja je upućena na ginekološki pregled gde je transvaginalnim ultrazvukom uočena tumorska formacija u predelu levog jajnika dimenzija 27x24mm, sa indeksom rezistencije (engl. Resistance index, RI) od 0,73 uz hiperehogenu formaciju u predelu kavuma uterusa, suspektna na endometrijalni polip. Ostali ultrazvučni i ginekološki nalaz nisu ukazali na postojanje drugih promena.

Zbog kliničke slike i laboratorijskih nalaza koji su ukazivali na aktivno lučenje androgena, uz isključenje tumora nadbubrežnog porekla i radiološkim dokazima o postojanju tumorske promene u predelu levog jajnika doneta je odluka o hirurškoj eksploraciji. Urađena je histeroskopska polipektomija uz jednostranu adneksektomiju.

Patohistološkom analizom potvrđena je dijagnoza tumora jajnika steroidnih ćelija koji se ne može drugačije klasifikovati. Histološki, tumor je bio izgrađen od traka i plaža poligonalnih, krupnih ćelija eozinofilne i vakuolizovane citoplazme, okruglih jedara sa upadljivim jedarcem. U citoplazmi ćelija uočena su zrnca lipofuscina. Nisu nađeni Reinke kristali, kao ni fibrinoidna nekroza krvnih sudova. Nisu uočene mitoze, krvarenje niti ćelijska atipija.

Nakon operacije došlo je do brze normalizacije vrednosti testosterona, uz kliničko povlačenje simptoma hirzutizma i stabilizaciju telesne mase. Na kontrolama u narednih 6 i 12 meseci nije bilo znakova recidiva bolesti, a hormonski status ostao je u granicama za postmenopauzu. Paralelno, simptomi Parkinsonove bolesti ostali su stabilni uz prethodno prepisanu neurološku terapiju.

Diskusija

Kod postmenopauzalnih žena, progresivno pojačavanje maljavosti na licu i telu, androgeni tip alopecije i promena tonaliteta glasa zahtevaju ozbiljnu endokrinološku evaluaciju. U našem slučaju, pacijentkinja je u šestoj deceniji života primetila izraženu maljavost po licu i telu, androgeni tip gubitka kose, promenu boje glasa, opštu slabost i značajan porast telesne težine, što je značajno narušilo njen kvalitet života. Nije imala simptome hiperandrogenizma u reproduktivnom periodu, što je isključilo druge uzroke i hronične endokrinopatije, poput sindroma policističnih jajnika ili kongenitalne adrenalne hiperplazije. Takođe, nije bilo podataka o egzogenom unošenju testosterona, što je važno isključiti kod svake pacijentkinje sa povišenim vrednostima androgena.

Tumori jajnika steroidnih ćelija, podtip koji se ne može drugačije klasifikovati predstavljaju retke tumore polnih vrpci i specijalizovane strome jajnika i čine manje od 0,1% svih ovarijalnih tumora. Iako se mogu javiti u bilo kom životnom dobu, najčešće se dijagnostikuju kod žena reproduktivne dobi. U pregledu literature iz 2024. godine koji je uključio 73 opisana slučaja (3), uzrast pacijentkinja varirao je od 3 do 93 godine, sa medijanom od 34 godine. Klinička slika gotovo isključivo zavisi od hormonske aktivnosti tumora, pri čemu oko 56–77% pacijentkinja pokazuje znake hiperandrogenizma: hirzutizam, akne, produbljenje glasa, klitoromegaliju, amenoreju i infertilitet. Manifestacije viška estrogena (npr. krvarenje u postmenopauzi) prisutne su kod 6–23% pacijentkinja, dok oko 10% može razviti simptome Kušingovog sindroma. U oko četvrtini slučajeva tumor je asimptomatski i otkriva se tek akcidentalno, nakon hirurške eksploracije, nekada zbog potpuno druge indikacije.

Laboratorijski nalazi karakteristično pokazuju povišene vrednosti testosterona i androstendiona, uz uredan DHEAS, što kliničare navodi na ovarijalno poreklo androgena. Tumorski markeri CA-125 i HE4 su uglavnom u opsegu referentnih vrednosti i nisu korisni za preoperativno postavljanje dijagnoze. Transvaginalni ultrazvučni pregled obično prikazuje unilateralne, solidne, ovalne ili okrugle tumorske mase sa bogatom vaskularizacijom i niskim otporom protoka. Međutim, osetljivost ultrazvuka je ograničena, te je magnetna rezonanca često preciznija. Ovi tumori se na magnetnoj rezonanci prikazuju kao izointenzne solidne mase ili mase sa blago povišenim signalom na T1, visokim signalom na T2 i difuzionim sekvencama, uz jasno pojačanje signala nakon primene kontrastnog sredstva. Diferencijalna dijagnoza uključuje epitelne tumore jajnika, granuloza ćelijske tumore, ali i ređe tipove tumora, kao što su liposarkomi.

Patohistološki pregled predstavlja zlatni standard u postavljanju definitivne dijagnoze tumora jajnika steroidnih ćelija koji se ne može drugačije klasifikovati. Ovi tumori su jednostrani u oko 94% slučajeva, a makroskopski su najčešće solidni i jasno ograničeni od ostatka tkiva jajnika. Veličina tumora varira od 1,2 do 45 cm, sa prosečnom veličinom od 6,5 cm.

Mikroskopski, ovi tumori se sastoje od velikih poligonalnih ćelija sa vakuoliziranom citoplazmom i manjih ćelija sa bogatom, granuliranom eozinofilnom citoplazmom. Ćelije su obično difuzno raspoređene ili formiraju manja gnezda unutar vaskularne strome. Odsustvo Reinkeovih kristala u citoplazmi je važan kriterijum za razlikovanje ovih tumora od tumora Lajdigovih ćelija. Tumori jajnika steroidnih ćelija koji se ne može drugačije klasifikovati može sadržati fibromatozne komponente slične onima koje se viđaju kod tekoma, ali one čine manje od 10% tumorske mase. Nedostatak vretenastih ćelija i fibromatozne pozadine pomaže u razlikovanju tumora jajnika steroidnih ćelija koji se ne može drugačije klasifikovati od luteinizovanih tekoma [4].

Ovi tumori su u većini slučajeva benigni. Međutim, između 25% i 43% ovih tumora može imati maligni potencijal. Metastaze van jajnika zabeležene su u oko 20% slučajeva. Hayes i Scully su identifikovali pet histopatoloških karakteristika koje su bile povezane sa malignim ponašanjem ovih tumora: prisustvo više od dve mitoze na 10 polja velikog uveličanja (92% slučajeva), nekroza tumora (86%), tumorska masa veća od 7 cm (78%), krvarenje u tumoru (77%) i nuklearna atipija drugog i trećeg stepena (64%) [5].

Trenutno ne postoje jasno definisani terapijski protokoli za lečenje tumora jajnika steroidnih ćelija, što je posledica njihove niske incidencije. Lečenje je individualno i zavisi od nekoliko faktora, uključujući starost pacijentkinje, stadijum bolesti, histopatološke karakteristike tumora, prisustvo malignih karakteristika, kao i želje za daljom reprodukcijom.

Kod pacijentkinja sa benignim oblicima, hirurška resekcija predstavlja terapiju izbora. Kod žena koje žele očuvanje fertiliteta i kod kojih je tumor dijagnostikovan u ranom stadijumu, preporučuje se jednostrana adneksektomija ili ciljana ekscizija tumora sa očuvanjem materice i kontralateralnog jajnika. Sa druge strane, totalna histerektomija sa obostranom adneksektomijom najčešće se sprovodi kod postmenopauzalnih pacijentkinja i onih koje nemaju želju za daljom reprodukcijom. Budući da kod određenog broja pacijentkinja sa ovim tumorima može biti prisutna hiperplazija endometrijuma, a u pojedinim slučajevima i endometrijalni karcinom, preporučuje se dijagnostička kiretaža i analiza endometrijalnog tkiva [3, 4].

Naš slučaj sadrži nekoliko karakteristika koje smatramo značajnim za kliničku praksu. Najpre, tumor jajnika steroidnih ćelija, NOS je izuzetno redak entitet koji čini manje od 0,1% svih tumora jajnika. Iako se najčešće javlja kod žena reproduktivne dobi, kod ove pacijentkinje se razvio u u periodu postmenopauze. Izražen hiperandrogenizam u šestoj deceniji života, uz značajnu progresiju u

kratkom vremenskom periodu, ukazivao je na neophodnost diferencijalne dijagnoze između tumora ovarijalnog i adrenalnog porekla. Dodatnu dijagnostičku kompleksnost predstavljao je komorbiditet u vidu Parkinsonove bolesti, koja je mogla da zamaskira neke od nespecifičnih simptoma, kao što su dobitak na telesnoj težini, opšta slabost ili promena raspoloženja, potencijalno odlažući sumnju na endokrinološki poremećaj. Takođe, iako je poslednje publikovanim pregledima literature utvrđeno da je prosečna veličina ovih tumora oko 6 do 7 cm, tumor jajnika je u našem slučaju bio promera od nešto više od 2cm. To ukazuje da nekada i radiološki mali tumori, naizgled bez kliničkog značaja, mogu dovesti do izraženih simptoma viška androgena. Ovo dodatno potvrđuje značaj detaljnog ispitivanja pacijentkinja i pravovremeno postavljanje dijagnoze.

Zaključak

Zbog niske učestalosti tumora jajnika steroidnih ćelija koji se ne može drugačije klasifikovati i odsustva velikih multicentričnih studija ne postoje univerzalno prihvaćene preporuke za lečenje ovih pacijentkinja. Ovi tumori predstavlja retku podvrstu tumora jajnika, koja se može javiti u bilo kom životnom dobu. S obzirom da su virilizacija, povećanje telesne mase, uz povišene vrednosti testosterona česti nalazi kod ovih tumora, svaka od navedenih karakteristika kod postmenopauzalnih pacijentkinja, pogotovo progresivnog karaktera, treba navesti lekare da detaljno tragaju za tumorima jajnika steroidnih ćelija jer pravovremeno prepoznavanje i hirurško uklanjanje ovih tumora može dovesti do potpunog povlačenja simptoma i značajno poboljšati kvalitet života pacijentkinja.

Literatura:

1. Hirschberg AL. Approach to Investigation of Hyperandrogenism in a Postmenopausal Woman. J Clin Endocrinol Metab. 2023;108(5):1243-1253.
2. Hanley KZ, Mosunjac MB. Practical Review of Ovarian Sex Cord-Stromal Tumors. Surg Pathol Clin. 2019;12(2):587-620.
3. Sun Y, Tian L, Meng C, Liu G. Ovarian steroid cell tumors, not otherwise specified: three case reports and literature review. Front Oncol. 2024;14:1400085.
4. Lin M, Bao K, Lu L, Xu S, Liang Y, Cheng X, Wang F. Ovarian steroid cell tumors, not otherwise specified: analysis of nine cases with a literature review. BMC Endocr Disord. 2022;22(1):265.
5. Hayes MC, Scully RE. Ovarian steroid cell tumors (not otherwise specified). A clinicopathological analysis of 63 cases. Am J Surg Pathol. 1987;11(11):835-45.

NEONATALNI ISHOD NAKON PRIMJENE MAGNEZIJUM SULFATA ZA FETALNU NEUROPROTEKCIJU

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Uvod: Prijevremeni porođaj je glavni faktor rizika za cerebralnu paralizu, a rizik se značajno povećava sa smanjenjem gestacijske dobi. Novorođenčad iz grupe ekstremnog i vrlo ranog prematuriteta imaju povećan rizik od smrtnosti ili preživljavanja sa cerebralnom paralizom ili drugim neurosenzornim oštećenjima i invaliditetom. Intraventrikularno krvarenje (IVH) je poznati faktor rizika za cerebralnu paralizu, sa rizikom od IVH koji se povećava što je niža gestacijska starost pri rođenju. U prvim opservacionim studijama primjena magnezijum sulfata kod majke je bila povezana sa naknadnim smanjenjem rizika od IVH, cerebralne paralize i pedijatrijskog mortaliteta. Nekoliko studija krajem 20-og vijeka potvrdilo je značaj antenatalno primjenjenog magnezijum sulfata kod prijevremeno rođene djece kad je MgSO4 korišten kao antikonvulziv ili tokolitik. Cohrane 2024 (pregledane studije gdje se MgSO4 koristio samo za neuroprotekciju, ne kao tokolitik ili antikonvulziv) navodi da trenutno dostupni dokazi ukazuju da magnezijum sulfat za žene sa rizikom od prijevremenog porođaja radi neuroprotekcije fetusa, u poređenju sa placebom, smanjuje cerebralnu paralizu i smrt ili cerebralnu paralizu kod djece do dvije godine korigovanog uzrasta, vjerovatno smanjuje teška intraventrikularna krvarenja kod novorođenčadi i da magnezijum sulfat može dovesti do male ili nikakve razlike u ishodima kod djece u školskom uzrastu.

Cilj rada: Ispitati značaj davanja magnezijum sulfata za fetalnu neuroprotekciju kod žena sa rizikom od prijevremenog porođaja.

Metodologija i rezultati rada: U ovom radu su praćena prijevremeno rođena djeca gestacijske dobi od 24 do 32 nedelje koja su primila MgSO4 za fetalnu neuroprotekciju (eksperimentalna grupa) i djeca porođena iste gestacijske dobi kojoj nije ordiniran MgSO4 (kontrolna grupa). Djeca iz obe grupe se praćena za korigovani uzrast od dvije godine. Eskperimentalna grupa je uključivala 58 žena porođenih u periodu 2022-2023 godine u Univerzitetskom kliničkom centru republike Srpske kojima je ordiniran MgSO4, a kontrolna grupa je uključivala 50-oro djece koja nisu primila MgSO4 i porođena su u periodu od 2019-2021.godine. Rezultati pokazuju da je u eksperimentalnoj grupi 35-oro (60,3%) djece je imalo intraventriklularnu hemoragiju uključujući 7-oro nedonoščadi sa IVH gradus III i IV. U kontrolnoj grupi 26-oro (52%) djece je imalo intraventrikularnu hemoragiju od kojih je 4-oro djece imalo IVH gradus III ili IV. U kontrolnoj grupi 7-oro djece (14%) je oboljelo od cerebralne paralize, a u eksperimentalnoj grupi cerebralna paraliza je potvrđena kod dvoje djece (3,44%).

Zaključak: MgSO4 koji se koristi u fetalnoj neuroprotekciji je tercijarna intervencija za smanjenje morbiditeta i mortaliteta koji je povezan sa prijevremenim porođajem i daje se kad je porođaj već započeo sa ciljem boljeg ishoda za nedonoščad, prvenstveno u cilju smanjenja neuroloških komplikacija i cerebralne paralize. Pošto je cerebralna paraliza rezultat više faktora rizika u interakciji, a ne jednog uzroka, malo je verovatno da antenatalna primjena magnezijum sulfata sama po sebi može spriječiti sve slučajeve ove bolesti kod nedonoščadi, ali uzimajući u obzir manji broj djece sa dijagnostikovanom cerebralnom paralizom nakon antenatalne primjene magnezijum sulfata glavni zaključak je da je primjena ovog relativno jeftinog tretmana neophodna.

Ključne riječi: prematuritet, neuroprotekcija, cerebralna paraliza

ABRIKOSSOFFOV TUMOR (GRANULAR CELL TUMOR) VULVE – PRIKAZ SLUČAJA

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Uvod

Abrikossoffov tumor ili granular cell tumor (GCT) je rijetka benigna neoplazma porijekla Švanovih ćelija. Najčešće se javlja u usnoj duplji (na jeziku), dok je lokalizacija na vulvi izuzetno rijetka, čineći svega 5-10% svih GCT-ova. Zbog nespecifične kliničke slike, često imitira druge benigne, ali i maligne lezije vulve (poput ciste Bartolinijeve žlijezde, hidradenoma, lipoma ili karcinoma). Pravilna dijagnostika i adekvatna histopatološka potvrda imaju ključnu ulogu u planiranju liječenja.

Cilj

Prikazati rijedak slučaj benignog GCT-a vulve i naglasiti značaj uključivanja ove dijagnoze u diferencijalnu dijagnozu vulvarnih lezija.

Prikaz slučaja

Pacijentkinja stara 51 godinu se javila na pregled zbog čvrste, dobro ograničene, nodularne promjene u donjoj trećini desne velike labije. Klinički je promjena imponovala kao cista Bartolinijeve žlijezde. Učinjena je biopsija u lokalnoj anesteziji. Histopatološki nalaz je pokazao solidne nakupine velikih ćelija sa granularnom citoplazmom i malim okruglastim, pravilnim, uniformnim jedrima. Rijetke ćelije su imale uvećana jedra, mitoze su bile rijetke, bez znakova nekroze. Imunohistohemijski su ćelije bile pozitivne na S-100 protein, što je potvrdilo dijagnozu benignog granular cell tumora (Abrikossoffov tumor). Po pristizanju nalaza biopsije da se radi o benignom tumoru, učinjena je kompletna hirurška ekscizija sa slobodnim marginama u uslovima opšte anestezije. Postoperativni tok je protekao uredno, a pacijentkinja je bila bez znakova recidiva na kontrolnim pregledima tri i šest mjeseci nakon operacije.

Diskusija

Abrikossofov tumor (granular cell tumor – GCT) prvi put je opisao Abrikossoff 1926. godine. Danas se zna da nastaje iz Schwannovih ćelija, što potvrđuje pozitivnost na S-100 protein i neuron-specifičnu enolazu (NSE).

GCT se najčešće javlja na jeziku (40–60% slučajeva), zatim u dermisu i subkutisu glave, vrata i ekstremiteta. Urogenitalna lokalizacija je rijetka, a vulva čini svega 5–10% svih slučajeva. Najčešće se javlja kod žena starosti 30-60 godina, sa većom prevalencijom među afroameričkom populacijom.

Abrikossofov tumor vulve je izuzetno rijetka lokalizacija granular cell tumora (GCT) i zbog nespecifične kliničke slike često se klinički pogrešno procjenjuje kao cista Bartolinijeve žlijezde, hidradenom, lipom ili čak karcinom. U najvećem broju slučajeva, pacijentkinje se javljaju zbog bezbolne, spororastuće nodularne promjene čvrste konzistencije, jasno ograničene, ali u pojedinim slučajevima može doći do ulceracije, što dodatno komplikuje diferencijalnu dijagnozu.

Diferencijalna dijagnoza uključuje cistu Bartolinijeve žlijezde, epidermoidnu cistu, lipom, hidradenom, fibrom, neurofibrom, ali i karcinom vulve.

Zato je definitivna dijagnoza moguća samo histopatološki, uz primjenu imunohistohemije.

Standardno liječenje je kompletna hirurška ekscizija sa slobodnim resekcionim marginama, zbog mogućnosti lokalnog recidiva u 15–20% slučajeva ako je ekscizija nepotpuna.

Većina GCT-ova su benigni, ali otprilike 1–2% može pokazivati znake maligne transformacije. Maligni GCT se odlikuje invazivnim rastom, izraženim ćelijskim atipijama, visokim mitotskim indeksom, nekrozama i metastazama. U tim slučajevima, prognoza je loša, sa preživljavanjem od svega nekoliko godina nakon dijagnoze.

Zaključak

Prikazom ovog slučaja želimo da naglasimo značaj uključivanja Abrikossoffovog tumora u diferencijalnu dijagnozu svake solidne, bezbolne, nodularne lezije vulve. Konačna dijagnoza se postavlja histopatološki, a kompletna ekscizija je terapija izbora, sa dobrom prognozom i rijetkim recidivima.

FOREIGN BODY IN THE VAGINA LEADING TO VESICOVAGINAL FISTULA – A CASE REPORT

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Introduction: Vesicovaginal fistulas (VVF) represent a major clinical problem that significantly impairs quality of life. The most common causes in developing countries include prolonged obstructed labor and pelvic surgery, while fistulas caused by intravaginal foreign bodies are extremely rare and mostly described through isolated case reports [1]. Patients who self-insert foreign objects into the vagina often conceal this fact, which prolongs the diagnostic process and increases the risk of complications [2].

Case Report: A 25-year-old female presented to the surgical department with abdominal pain, nausea, and vomiting lasting for three weeks. She reported two febrile episodes up to 38°C during this period. The pain was localized under the left costal arch with irradiation to the left lumbar region. Bowel movements were regular, but she described dysuria and discomfort during urination. After exclusion of acute abdominal pathology, she was referred to both urologist and gynecologist. Urological assessment and abdominal ultrasound revealed multiple calculi in the left renal pelvis with grade II–III dilatation, as well as a large calculus in the urinary bladder measuring approximately 4 cm, associated with a suspected inflammatory process. CT scan of the abdomen and pelvis confirmed an obstructive left renal calculus with hydronephrosis, as well as a bladder formation almost entirely filling the posterior wall, initially interpreted as an obstructive calculus. At the gynecological clinic, after detailed anamnesis, the patient admitted that one year earlier she had inserted a cosmetic bottle cap into her vagina, which she was unable to remove. She denied any history of sexual intercourse and stated that this was her first gynecological examination. Menstrual cycles were reported as regular and normal.

Bimanual and speculum examination revealed a foreign body measuring approximately 5×3 cm in the vagina, partially calcified and adherent to the anterior vaginal wall and right anterior fornix. Manipulation of the object caused intense pain, and copious purulent, blood-stained discharge with a strong odor drained from the vagina. A vaginal swab was obtained for microbiological analysis. The patient was admitted for full clinical and laboratory evaluation. Blood tests revealed leukocytosis and elevated CRP, while urinalysis showed pyuria and bacteriuria. Empirical dual antibiotic therapy (Ceftriaxone and Metronidazole) was initiated.

The foreign body was removed transvaginal under general anesthesia. Post-procedural digital rectal examination confirmed intact rectal wall. Through a urinary catheter, methylene blue solution was instilled into the bladder, while a vaginal gauze pack was placed. After two hours, removal of the gauze demonstrated staining with methylene blue, raising suspicion of a vesicovaginal fistula. The patient was transferred to the urology department, where targeted antibiotic therapy was continued according to culture and sensitivity, along with management of

hydronephrosis. Following infection control, cystography confirmed the presence of a VVF, and the patient subsequently underwent successful reconstructive surgery for fistula repair.

Discussion: While prolonged obstructed labor and iatrogenic pelvic injuries remain the predominant causes of VVF, vaginal foreign bodies represent a rare but important etiology. Only a few dozen such cases have been reported worldwide [3,4]. In our case, the object remained in situ for one year, leading to calcification, secondary infection, and fistula formation.

The diagnostic process was delayed due to the patient's initial omission of the history of foreign body insertion. This underlines the importance of thorough anamnesis and speculum examination in all women presenting with nonspecific abdominal or urinary complaints. Early recognition and prompt intervention are crucial to prevent further complications.

Conclusion: Continuous efforts are needed to improve sexual education among young women, as lack of knowledge and unsafe practices related to sexual behavior may lead to serious urogenital complications. Comprehensive anamnesis and gynecological examination remain essential for diagnosis. Infection control, careful planning, and reconstructive surgery are fundamental for successful management and recovery.

References

1. Mengistu Z, Ayichew Z. Large vesicovaginal fistula after vaginal insertion of a plastic cap healed with two weeks of catheterization: a case report. Int Med Case Rep J. 2022;15:437-441.
2. Veselinović A, Vasić J, Jovanović V, Mihajlović S. Neglected intravaginal foreign body and possible complications. J Pediatr Adolesc Gynecol. 2023;36(3):e1-e3.
3. Bansal A, Kumar M, Goel S, Aeron R. Vesicovaginal fistula following insertion of a foreign body in the vagina for sexual gratification: could it be catastrophic? BMJ Case Rep. 2016;2016:bcr2016214705.
4. Elia CD, Curti P, Angela M, Carmelo C. Large urethro-vesico-vaginal fistula due to a vaginal foreign body in a 22-year-old woman: case report and literature review. Urol Int. 2015;95(1):120-124.

GENETIC BASES OF RECURRENT ISOLATED FETAL ANOMALIES

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Prenatal exome sequencing, as endorsed by the International Society for Prenatal Diagnosis in the context of recurrent fetal anomalies with a presumed genetic etiology, constitutes a transformative modality for enhancing diagnostic precision and elucidating underlying genetic mechanisms. In this report, we describe three illustrative cases in which exome sequencing identified pathogenic gene variants associated with recurrent, isolated fetal anomalies detected via prenatal ultrasound.

In the first case, recurrent isolated microcephaly was detected at the 18 th week of gestation. Clinical exome sequencing pinpointed pathogenic mutations (c.7324C>T, p.Arg2442Ter) and likely pathogenic mutations (c.101248delC) in the ASPM gene, associated with autosomal recessive forms of microcephaly.

The second case involved recurrent isolated hydrocephalus observed at the 22nd week of gestation. Exome sequencing identified mutations in the MPDZ gene (c.3508C>T, p.Arg1170Ter and c.1197dup, p.Leu400fs) linked to autosomal-recessive congenital hydrocephalus.

The third case revealed recurrent isolated fetal omphalocele detected at the 15th gestational week. Exome sequencing uncovered a mutation in the CDKN1C gene (c.835C>T, p.Arg279Cys), associated with Beckwith-Wiedemann syndrome, a rare overgrowth disorder characterized by omphalocele among other clinical features.

These cases underscore the critical role of exome sequencing in elucidating the genetic underpinnings of recurrent fetal anomalies identified through prenatal ultrasound. Prioritizing comprehensive genetic evaluation is essential for achieving diagnostic accuracy, enabling precise risk stratification, and facilitating informed genetic counseling—thereby enhancing the quality of prenatal care and guiding clinical decision-making.

OPTIMIZACIJA ANTENATALNE KORTIKOSTEROIDNE TERAPIJE KOD PRIJEVREMENOG PORODAJA

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Uvod: Antenatalni kortikosteroidi (AKS) dokazano umanjuju rizik od peripartalne i neonatalne smrti, kao i od respiratornog distres sindroma (RDS), a vjerovatno i od intrakranijalnog krvarenja. Primena AKS-a predstavlja standardnu terapiju kod trudnica sa visokim rizikom od skorijeg prijevremenog porođaja. Preporuke Svjetske zdravstvene organizacije iz 2015. godine ističu da AKS imaju potvrđenu kliničku korist kada se primjenjuju u odgovarajućim uslovima, ali i da mogu izazvati značajne neželjene efekte ukoliko se indikacije i kriterijumi ne ispune u potpunosti.

Cilj rada: Prikazati tok i ishod trudnoće, te neonatalne rezultate kod žena koje su primile AKS prema protokolu, uz analizu razloga hospitalizacije i vremenskog intervala do porođaja, definisanog kao optimalni i suboptimalni(≥24sata i ≤7 dana)

Metodologija: Istraživanje je sprovedeno retrospektivnom analizom podataka iz informacionog sistema Klinike za ginekologiju i akušerstvo. Kriterijumi uključenja bili su svi prijemi na Odjeljenje reproduktivne ginekologije i Perinatologije sa dijagnozom prijetnje prijevremenim porođajem. Podaci koji su analizirani obuhvatili su razlog prijema, dužinu grlića materice, datum porođaja i Apgar skor.

Rezultati: U periodu od šest mjeseci 2024.godine ukupno 141 trudnica je primila AKS, 56 do 28. ng i 85 do 34.ng. Analizom indikacija za prijem, 56 (39,7%) je bilo zbog skraćenog grlića, od toga 16 sa već plasiranim serklažom, 42 (29,7%) zbog verifikovanih kontrakcija, te 16 (11,3%) zbog krvarenja, PPROM-a 9 (6,3%) i 15 (10,6%) su činile ostale. Od 141 trudnice koje su primile AKS 29 se porodilo van Klinike. Od 112 porođenih u Klinici 52 (46,4%) su rodile prijevremeno, 60 (53,5%) terminskih porođaja. Sa indikacijom skraćen grlić od ukupnog broja (56) 22 je rodilo prijevremeno, 20 terminski, 14 van klinike. Sa indikacijom prijevremene kontrakcije od ukupnog broja (42) 10 je rodilo prijevremeno, 24 terminski, 8 van klinike. Ukupan broj prijevremenih porođaja u tom periodu u protokolu odjela porodilišta bilo je 193, do 34 ng 78 (40%). Rezultati pokazuju da je 52 (66,6 %) primilo AKS i porodilo se prijevremeno, te da kod 24 (33,3%) trudnice koje su rodile prijevremeno AKS nije ordiniran.

Zaključak: Poboljšanje stope preživljavanja prijevremeno rođenih uglavnom se zasniva na unaprjeđenju i racionalnoj primeni antenatalnih kortikosteroida (AKS).

Dobijeni podaci ukazuju na potrebu za opreznijim pristupom pri izradi kliničkih protokola i donošenju odluka, naročito u sredinama sa ograničenim resursima.

Iako strategija intenzivnog podsticanja upotrebe AKS-a kod trudnica sa rizikom od prijevremenog porođaja može povećati njihovu primjenu u ciljnoj populaciji, ona istovremeno nosi rizik od nepotrebnog izlaganja lijeku kod žena kod kojih ne postoji jasna indikacija [1]. Buduća istraživanja trebalo bi da se usmjere na razlike u terapijskim režimima, procjenu djelotvornosti u nedovoljno ispitanim grupama kao što su trudnice sa više plodova i druge visokorizične akušerske kategorije, kao i na odnos koristi i rizika u slučajevima veoma rane ili kasne prijevremene trudnoće.

Takođe, potrebno je pratiti dugoročne efekte AKS-a kroz rezultate postojećih studija koje uključuju posmatranje ispitanika u djetinjstvu i zrelom dobu. Poseban značaj treba dati promišljenoj i svrsishodnoj upotrebi AKS-a, uz oslanjanje na pažljivu kliničku procenu.

Reference:

1. Anke 2020

PRELOM I ZAOSTAJANJE FRAGMENTA HIRURŠKE IGLE TOKOM APLIKACIJE SERKLAŽA: PRIKAZ SLUČAJA RIJETKE AKUŠERSKE KOMPLIKACIJE

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Cervikalna insuficijencija predstavlja nesposobnost grlića materice da održi trudnoću u drugom trimestru, uz karakterističnu bezbolnu dilataciju cerviksa bez kontrakcija, krvarenja ili rupture plodovih ovojaka. Serklaž je terapijska intervencija namijenjena produženju trudnoće kod pacijentkinja sa pozitivnom anamnezom preterminskog porođaja ili ultrazvučnim nalazom skraćenog cerviksa. Iako se serklaž rutinski sprovodi u akušerskoj praksi, te je opšteprihvaćen kao bezbjedna intervencija, komplikacije procedure su rijetke, ali moguće. Tehničke komplikacije intervencije, u koje spada i prelom igle tokom intervencije, su izuzetno rijetke i slabo dokumentovane u literature.

Prikazujemo slučaj pacijentkinje stare 29 godina, u 15. nedelji druge, spontano ostvarene trudnoće, hospitalizovane na Klinici za ginekologiju i akušerstvo Kliničkog Centra Crne Gore radi planirane aplikacije serklaža zbog prethodnog preterminskog porođaja i ultrazvučno verifikovanog skraćenja grlića materice.

Tokom pokušaja plasiranja serklaža McDonald tehnikom došlo je do preloma hirurške igle, pri čemu je fragment dužine oko 12 mm zaostao u stromi prednje usne grlića materice. Fragment nije bilo moguće vizualizovati niti palpirati, te su pokušaji uklanjanja obustavljeni zbog rizika od dodatne traume. Intervencija je odložena, a pacijentkinja je nastavila profilaktičku antibiotsku i gestagenu terapiju. Transvaginalnim ultrazvukom je konstatovano da se zaostali fragment igle nalazi na 18 mm od OEU i 17 mm od OIU.

Dvije sedmice kasnije, u 17. nedelji gestacije, uspješno je plasiran serklaž korišćenjem istog tipa hirurškog materijala. Dalji tok trudnoće je protekao uobičajeno, bez znakova infekcije, kontrakcija ili krvarenja, bez daljih pokušaja uklanjanja zaostalog fragmenta. Na redovnim ultrazvučnim pregledima nije konstatovana migracija zaostalog fragmenta.

U 39. nedelji gestacije, trudnoća je završena hitnim carskim rezom, kada je pokušana intraoperativna ekstrakcija fragmenta, ali bez uspjeha. Nakon završetka puerperijuma, urađen je CT male karlice radi preciznog određivanja lokalizacije stranog tijela. Tehnika markacije pomoću igala postavljenih u prednju usnu cerviksa na 11h i 1h, uz RTG skopiju, omogućila je minimalno invazivnu i kompletnu ekstrakciju fragmenta. Postoperativni tok protekao je uredno.

Komplikacije prilikom plasiranja serklaža uključuju krvarenje, infekciju, rupturu plodovih ovojaka, kao i tehničke poteškoće. Prelom igle tokom intervencije predstavlja izuzetno rijetku komplikaciju, veoma oskudno opisanu u literaturi, sa svega nekoliko pojedinačnih opisa iz oblasti drugih hirurških disciplina. Potencijalni uzroci uključuju loš kvalitet materijala, neadekvatnu tehniku ili izmijenjenu strukturu tkiva. Iako metalni fragmenti mogu predstavljati rizik od infekcije, migracije ili bola, u ovom slučaju nije bilo komplikacija tokom trudnoće. Ekspektativni pristup, uz brižljivo praćenje, pokazao se opravdanim kada uklanjanje fragmenta u ranoj fazi nosi preveliki rizik.

Markacija iglama i radiološko pozicioniranje, iako češće korišćeni u onkološkoj hirurgiji, pokazali su se kao efikasna metoda i u ginekološkoj hirurgiji, omogućivši preciznu ekstrakciju bez većih komplikacija. Odlaganje intervencije za postporođajni period bilo je klinički opravdano da bi se izbjeglo potencijalno ugrožavanje trudnoće, u skladu sa strategijama primjenjivanim kod prisustva drugih stranih tijela u graviditetu.

Ovaj prikaz ističe važnost spremnosti na neočekivane kliničke situacije u svakodnevnoj praksi, značaj individualizovanog pristupa pacijentkinji, te primjenu multidisciplinarnih rješenja kako bi se uspješno riješila komplikacija bez ugrožavanja trudnoće, uz očuvanje reproduktivnog zdravlja pacijentkinje.

KLINIČKI ZNAČAJ ANTI-C ANTIERITROCITNOG ANTITELA U TRUDNOĆI: PRIKAZ SLUČAJA

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Uvod: Anti-D aloimunizacija predstavlja najčešći uzrok teške hemolitičke bolesti fetusa i novorođenčeta (HBFN). Međutim i druga antieritrocitna antitela, iako ređe zastupljena, mogu dovesti do značajnih komplikacija u trudnoći, sa potencijalno ozbiljnim posledicama po plod. Praćenje ovih trudnoća predstavlja poseban klinički izazov, dok su podaci o perinatalnim ishodima ograničeni i nedovoljno opisani u literaturi. Anti-c antitelo može se javiti usled izlaganja fetalnih eritrocita antitelima majke, tokom fetomaternalnog krvarenja, abrupcije placente, spontanog ili terapijskog pobačaja, carskog reza, vanmaterične trudnoće ili usled primene transfuzione terapije. Razaranje fetalnih eritrocita može izazvati akutne ili odložene hemolitičke reakcije.

Cilj: Ovaj rad ima za cilj da, kroz prikaz slučaja, prikaže klinički značaj anti-c antieritrocitnog antitela u trudnoći, kao i da naglasi važnost sprovođenja skrininga antitela, kako kod RhD -(negativnih), tako i kod RhD + (pozitivnih) trudnica.

Prikaz slučaja: Pacijentkinja, četvorotka, starosti 28 godina, primljena u KGA UKCS, ml IX/X, zbog bolova. Nema anamnestičnih podataka o vođenju aktuelne trudnoće, niti o toku prethodnih trudnoća. Krvna grupa pacijentkinje je B RhD + (pozitivna). Pacijentkinja je sutradan porođena prirodnim putem. Rođeno je živo žensko dete, sa merama na rođenju: dužina 50.0 cm, težina 3350.0 g, obim glave 34.0 cm. Apgar skor je bio 9. Po rođenju dete je uredne rane postnatalne adaptacije. U prvom danu počinje da žuti, ukpni bilirubin 265. Premešteno u Odeljenje poluintenzivne nege (PIN). Započeta antibiotska terapija, hidratacija i intenzivna fototerapija.

U našu laboratoriju donet je uzorak krvi deteta. Krvna grupa novorođenčeta je 0 RhD + (pozitivna), DAT 4+, IAT 2+, fenotip CcDee. Dete prevedeno na Odeljenje intenzivne nege (OINN). Tražen je uzorak krvi majke i identifikovano je anti-c antieritrocitno antitelo. Fenotip majke je CCDee. U dogovoru sa neonatolozima pripremljena je krv za eksangvinotransfuziju (EST). Učinjena je dvovolumenska EST, zamenjeno je 445 ml krvi, koja je ponovljena dan kasnije, kada je zamenjeno 450 ml krvi. U daljem toku dete je bilo stabilnog opšteg stanja.

Zaključak: Pošto je pacijentkinja krvne grupe B RhD + (pozitivna), pretpostavljamo da antitela nisu praćena tokom trudnoće. Ovim prikazom želimo da ukažemo na značaj praćenja antitela u trudnoći i kod RhD - (negativnih) i kod RhD + (pozitivnih) žena, kao i međusobne saradnje ginekologa/akušera, neonatologa i transfuziologa.

Ključne reči: antieritrocitna antitela, inkompatibilija, senzibilizacija u trudnoći, hemolitička bolest novorođenčeta, eksangvinotransfuzija

PERIPARTUM CARDIOMYOPATHY IN PREGNANCY: CASE REPORT

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Introduction: Peripartum cardiomyopathy (PPCM) is a disorder in which initial left ventricular systolic dysfunction and symptoms of heart failure occur between the late stages of pregnancy and the early postpartum period.

The acute form of PPCM is a clinical syndrome with reduced cardiac output, tissue hypoperfusion, and increase in the pulmonary capillary wedge pressure. Monitoring of the patient with the acute form of PPCM should be initiated as soon as possible. The syndrome carries a high morbidity and mortality and diagnosis is often delayed.

Case report: Our patient is 32 year old women in 27th week of second pregancy. Patient had one prior pregnancy 4 years ago, terminated naturally without complications, but was diagnosed with hypothyreosis after delivery and since then is on substitution therapy with levothyroxine. Cardiac symptoms began 2 years earlier, when she was diagnosed with left fascicular block and advised to do heart ultrasound wich she never did. First symptoms were fatigue, cough and dyspnea, which were misread as respirathory infection, she was examined by pulmologist and cardiologist but sent home with antibiotics.

A week later patient was admitted to hospital with signs of acute heart failure. Heart ultrasound showed extremely decreased ejection fraction (15%), dilatation of left ventricle, decreased systolic function and mitral regurgitation. Patient was treated with diuretics, cardiotonics, beta blockers and heparine and it was conciliarly decided to terminate pregnancy by performing Caesarean section on vital indications. Post operative therapy included inotropes, vasopressors (Noradrenaline, Dobutamine), diuretics, antibiotics, heparine, bromokriptine, fluids. Inothropic support was excluded form therapy on sixth postoperative day and the rest of recovery went without complications. However, patient is still a candidate for heart transplant.

Conclusion: The exact cause of PPCM is still unknown. There is data underlying the hypothesis of a multifactorial cause which includes nutritional deficiencies, genetic disorders, viral or autoimmune causes, hormonal imbalances, volume overload, alcohol, physiologic stress of pregnancy, abnormal immune response to pregnancy, unmasking of latent idiopathic dilated cardiomyopathy and inflammation. Numerous risk factors have been summarized recently, but only a few have been confirmed in epidemiological studies. Several authors have suggested that multiparity, multifetal pregnancies, older maternal age, pregnancy-induced hypertension or preeclampsia, and prolonged use of tocolysis may be risk factors for PPCM.

SIGNIFICANCE OF EMPIRICAL ANTIBIOTIC SELECTION IN POSTPARTUM INFECTIONS

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Introduction: The incidence of postpartum infections ranges between 5% and 7%, representing a significant socioeconomic and medical issue even in developed countries. Most postpartum infections can be prevented through timely identification and management of risk factors and common causative pathogens. Risk is significantly elevated in obese patients, those with diabetes, hypertension, and immunocompromised individuals. A positive vaginal swab for bacterial vaginosis, Group B Streptococcus infection, premature rupture of membranes, an excessive number of vaginal examinations during labor, manual removal of the placenta or retained placental tissue are all factors that increase the risk of developing postpartum infections. Endometritis is the most common postpartum infection, occurring in 1–3% of vaginal deliveries, increasing to 5–6% in the presence of risk factors, and up to 10–20% in cesarean deliveries compared to vaginal births. The primary symptom of endometritis is fever >38°C, appearing between postpartum days 2 and 10, either in early or late puerperium. Additional symptoms include lower pelvic pain, uterine tenderness, subinvolution of the uterus, foul-smelling lochia, and general systemic symptoms such as fatigue, malaise, and headache. One of the major challenges in treatment is the increasing resistance of bacteria to commonly used antibiotics. Antimicrobial resistance is considered a "silent pandemic" and, according to the World Health Organization (WHO), was responsible for approximately 1.27 million deaths globally. The Infectious Diseases Society of America (IDSA) introduced the acronym ESKAPE, which refers to the bacteria most likely to develop antibiotic resistance: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. These pathogens are particularly dangerous due to their ability to adapt and persist even within modern healthcare systems. Special attention should be paid to Enterococcus-related infections, as these organisms are innately resistant to commonly used antibiotics such as cephalosporins, monobactams, meropenem, and clindamycin. Inappropriate use of antibiotics has led to the emergence of vancomycin-resistant enterococci (VRE), which are particularly difficult to treat. VRE-related sepsis carries a high mortality rate, reaching up to 58% in some cases.The gold standard for the treatment of postpartum endometritis is a combination of clindamycin (900 mg every 8 hours) and gentamicin (5 mg/kg every 24 hours), with or without ampicillin (2 g loading dose followed by 1 g every 6 hours). This recommendation is based on a meta-analysis conducted in 2015, which included 40 randomized controlled trials.

Objective: To identify the most common pathogens responsible for postpartum infections at our clinic and compare these findings with the literature, in order to apply appropriate empirical antibiotic therapy based on the prevalent etiological agents.

Methodology and Results: A total of 218 women diagnosed with postpartum infection and treated at the "Narodni Front" Obstetrics and Gynecology Clinic in 2024 were included in the study. The overall incidence was 4.24% relative to the total number of deliveries during the observed period. The most frequently isolated pathogens were: Escherichia coli 35%, Enterococcus spp. – 30%, Klebsiella pneumoniae 18%, Staphylococcus spp. 10%, other bacteria 9%.

Conclusion: The cornerstone of postpartum infection management involves thorough assessment of risk factors and a solid understanding of the most common causative organisms. This allows for the appropriate use of empirical antibiotic therapy, followed by targeted treatment based on culture results.

DISTRIBUCIJA KOMORBIDITETA U TRUDNOĆAMA NASTALIM NAKON MIOMEKTOMIJE: UPOREDNA ANALIZA SPONTANIH I IVF TRUDNOĆA

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Uvod: Miomektomija je preferirana hirurška opcija za žene reproduktivnog uzrasta koje žele očuvati fertilitet. U zavisnosti od lokalizacije i karakteristika mioma, može se izvoditi laparoskopski ili laparotomijski. Trudnoća nakon takve intervencije može nastati spontano ili putem asistirane reprodukcije (IVF). S obzirom na porast broja žena koje planiraju trudnoću nakon miomektomije, važno je ispitati njen uticaj na perinatalni ishod i prisustvo komorbiditeta tokom trudnoće Cilj: Cilj studije bio je da se proceni kako prethodna miomektomija utiče na perinatalni ishod i da se uporede komorbiditeti u trudnoćama nastalim spontano i IVF-om.

Materijal i metod: Analizirane su 51 pacijentkinje praćene na Klinici za ginekologiju i akušerstvo UKCS u periodu 2020–2024. godine. Od toga je 37 žena bilo starije od 35 godina, dok su 24 bile mlađe. Uključene su trudnice koje su imale hirurško uklanjanje jednog ili više mioma, putem laparoskopije ili laparotomije. Validacija slučajeva izvršena je na osnovu operacionih izveštaja, ultrazvuka i akušerskog praćenja. Prikupljeni su podaci o prethodnim trudnoćama, hroničnim oboljenjima, telesnoj težini i primenjenim terapijama. Analizirani su i relevantni komorbiditeti tokom trudnoće: hipertenzija, dijabetes melitus, trombofilija, hipotireoza, kao i laboratorijski parametri uključujući hemoglobin i nalaze anemije. Podaci su dobijeni iz elektronskog kartona uz poštovanje etičkih standarda.

Rezultati: Od ukupno 51 trudnoće, 33 su nastale spontano, a 18 putem IVF-a. Žene sa IVF trudnoćom bile su starije (prosek 41,9 godina) u poređenju sa spontanim začećem (35,6 godina). Vremenski razmak od miomektomije do začeća bio je duži u IVF grupi (6,7 vs. 5,6 godina). Hi-kvadrat test pokazao je značajnu povezanost između načina izvođenja miomektomije i tipa porođaja ($\chi^2 = 7{,}94$; $p = 0{,}0048$), pri čemu je laparotomija češće dovela do carskog reza. Trombofilija je bila češća u IVF grupi ($\chi^2 = 11{,}77$; $p = 0{,}0006$), kao i dijabetes melitus ($\chi^2 = 5{,}46$; $p = 0{,}0194$). HTA i hipotireoza nisu pokazale značajne razlike. Anemija je bila prisutna kod 61% IVF trudnoća naspram 42% spontanih. Srednje vrednosti hemoglobina bile su niže u IVF grupi (109,7 g/L vs. 111,5 g/L), bez statističke značajnosti.

Diskusija i zaključak: Rezultati pokazuju da IVF trudnoće nakon miomektomije karakterišu starije pacijentkinje sa češćim komorbiditetima kao što su trombofilija, dijabetes i anemija. Starosna struktura i hormonski protokoli IVF-a mogu doprineti ovim nalazima. Laparotomijska miomektomija je češće povezana sa carskim rezom, što ukazuje na potrebu za pažljivim planiranjem porođaja kod žena sa ovom hirurškom anamnezom. Produžen period od operacije do trudnoće u IVF grupi verovatno odražava duži proces lečenja infertiliteta. Rezultati naglašavaju važnost personalizovanog pristupa u vođenju ovih trudnoća, uz posebno praćenje u IVF populaciji.

TREATMENT OF A PATIENT WITH INVASIVE MUCINOUS OVARIAN CARCINOMA WITH INTESTINAL DIFFERENTIATION

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Introduction: The approach to epithelial ovarian cancer must be individualized based on histological subtype, disease stage, and the patient's fertility status. Mucinous adenocarcinomas are relatively rare making 3-5 % of all primary ovarian cancers and pose a particular challenge, as they often originate from the gastrointestinal tract. ESGO guidelines clearly state that fertility preservation is not recommended in cases of invasive mucinous tumors with intestinal differentiation, due to their biological aggressiveness and diagnostic uncertainty.

Case report: A 35-year-old nulliparous woman presented with a complex multilocular cyst of the left ovary observed on pelvic MRI. She underwent cystectomy of the left ovary with omental biopsy. Histopathological findings indicated a well-differentiated mucinous adenocarcinoma ignota (at least stage IC2) with intestinal differentiation. Gastroscopy and colonoscopy were normal. The diagnosis was confirmed by expert slide review in Germany. Postoperative abdominal and pelvic MRI and tumor markers were normal. She was referred to a fertility preservation board, which, in accordance with ESGO guidelines, advised against fertility preservation and recommended radical surgery. The patient refused radical treatment, and a conservative procedure was performed: left adnexectomy and staging surgery. Final histopathology was a well-differentiated mucinous adenocarcinoma IC2 with intestinal differentiation. The board recommended adjuvant chemotherapy (MONO CBDCA), but the patient did not initiate treatment. At last visit, 18 months after initial diagnosis, the patient was disease-free.

Conclusion: This case illustrates the complexity of therapeutic decision-making in young patients with mucinous ovarian tumors, especially when fertility preservation is desired. Adherence to current guidelines, multidisciplinary collaboration, and patient education are crucial in achieving optimal treatment outcomes aligned with tumor biology and individual priorities.

References

1. Ledermann JA, Matias-Guiu X, Amant F, Concin N, Davidson B, Fotopoulou C, González-Martín A, et al. ESGO–ESMO–ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease. Ann Oncol. 2024 Mar;35(3):248–266.
2. Prat J, D'Angelo E, Espinosa I. Ovarian mucinous tumors: controversies in the diagnosis and origins of borderline and invasive variants. Histopathology. 2015 Jan;66(1):118–132.
3. Kajiyama H, Shibata K, Mizuno M, Yamamoto E, Kawai M, Nagasaka T, et al. Long-term survival of young women with epithelial ovarian cancer after fertility-sparing surgery. Br J Cancer. 2011 Oct 25;105(10):1288–1294.
4. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011 Jul;43(5):420–432.
5. Morice P, Denschlag D, Rodolakis A, Schneider A, Kesic V, Viarisio D, et al. Fertility-sparing strategies in epithelial ovarian cancer: a European perspective. Int J Gynecol Cancer. 2010 Jul;20(5):1044–1051.
6. Shih IM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004 May;164(5):1511–1518.

CANCER TREATMENT DURING PREGNANCY

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Malignancy during pregnancy is relatively rare, with an estimated incidence of approximately 1 in 1,000 to 1 in 2,000 pregnancies, but its frequency is rising due to delayed childbearing and increased cancer detection in younger women. Malignancy during pregnancy is a highly demanding clinical scenario requiring simultaneous attention to maternal cancer treatment and fetal well-being. The global trend of postponing motherhood and the rising incidence of certain cancers at a younger age contribute to the increasing occurrence of these cases.

Treatment selection and timing must be carefully tailored to achieve an optimal balance between effective oncologic management and pregnancy safety. According to registry data and multicenter studies, the most frequently diagnosed malignancies during pregnancy include breast cancer (the most common single tumor in pregnancy), cervical cancer, hematologic malignancies (lymphomas, leukemia) and melanoma, with less frequent cases of ovarian cancer, colorectal cancer, and thyroid tumors. Distribution varies by region and screening coverage. Decision-making requires a team including obstetricians, medical oncologists, surgeons, neonatologists, anesthesiologists, psychologists, and ethicists when appropriate. The choice of therapy depends on the type and stage of the tumor.

Cancer treatments in pregnancy are developing rapidly, but numerous obstacles remain. The decision regarding the optimal therapeutic management should balance both maternal and fetal interests. The patient's desire for pregnancy preservation complicates the treatment choices thereby imposing the necessity of a multidisciplinary team approach that will follow the recommended guidelines.

Symptoms of malignancy (fatigue, nausea, localized pain) often overlap with physiological pregnancy changes, leading to diagnostic delays. The team will evaluate the gestational age, viability, and growth of the fetus as soon as possible, along with simultaneously defining a diagnostic strategy that is best for the pregnant woman. Instead of postponing cancer treatment until the postnatal period or inducing a preterm delivery, modern strategies represent a shift toward individualized oncological and surgical treatment based on the type of cancer and gestational age

Safe imaging- ultrasound and non-contrast MRI are first-line modalities during pregnancy. CT and plain radiography are reserved for situations where diagnostic yield is critical for management, with fetal shielding. Biopsy is safe in all trimesters and is indicated when histological confirmation is required.

First trimester carries the highest teratogen risk (organogenesis); exposure to cytotoxic agents markedly increases the risk of congenital anomalies. Second and third trimesters: most can

be administered after the first trimester with acceptable fetal risk, although there is a higher incidence of intrauterine growth restriction, low birth weight, and preterm delivery. Chemotherapy should be avoided in the 2–3 weeks before delivery to reduce neonatal toxicity risk.

Pregnancy alters drug distribution volume, renal and hepatic clearance, and protein binding — all of which can modify cytotoxic drug exposure. Doses are generally calculated by body surface area, but individual monitoring is essential. Contemporary evidence indicates that pregnancy does not inherently worsen cancer prognosis when treatment is administered according to oncologic principles. However, delaying therapy (e.g., out of concern for fetal safety) can adversely affect outcomes, especially for aggressive tumors.

The most frequent adverse outcome is preterm birth, often iatrogenic (planned early delivery to initiate or intensify maternal therapy). Preterm delivery, rather than chemotherapy itself, is the major driver of neonatal complications. Systematic reviews show markedly increased perinatal complication rates compared to the general population. Longitudinal studies suggest that children exposed to chemotherapy after the first trimester generally have normal neurocognitive and cardio metabolic development in early and mid-childhood.

Surgical and chemotherapeutic interventions, when carefully selected and optimally timed, can be well tolerated with minimal fetal risk. A primary goal in managing such pregnancies is to prolong gestation to the safest possible term without compromising maternal health, thereby optimizing neonatal outcomes. Achieving this balance requires close collaboration among obstetricians, oncologists, and neonatologists within tertiary care centers equipped with specialized facilities and expertise.

In a presented series of 94 patients referred to the Clinic of Gynecology and Obstetrics, University Clinical Centre of Serbia, collected from 2001 until the end of 2024, the most common malignancies were hematologic cancers, particularly Hodgkin lymphoma, followed by gynecologic tumors. The most malignancies were diagnosed and confirmed in the second trimester, while the number of cancers diagnosed in the first and second trimesters was similar. In our cohort, the most frequent cases were pregnant woment with hematologic malignancies who underwent chemotherapy. Chemotherapeutic interventions, when carefully selected and timed, can be well tolerated with minimal fetal risk. Conversely, the time of diagnosis did not significantly impact the outcomes for either the mother and or her child. Advances in multidisciplinary care have enabled many of these pregnancies to progress safely to delivery, with birth weights appropriate for gestational age, even when oncologic treatment was administered during pregnancy. All pregnant women were monitored with expert ultrasound examinations, in close collaboration with specialist of perinatology, ensuring continuous assessment of fetal well-being.

The indications for cesarean section were primarily obstetrical, while only malignancies that compromise vaginal delivery—such as cervical cancer and some abdominal tumors—were considered oncologic indications for cesarean section. However, since postpartum cancer therapy is more often delayed after cesarean section compared to vaginal delivery, vaginal birth should be preferred whenever possible. Surgical and chemotherapeutic interventions, when carefully selected and timed, can be well tolerated with minimal fetal risk.

Experience to date demonstrates that with individualized planning and coordinated care, even pregnancies complicated by malignancy can result in favorable outcomes for both mother and child. This requires a multidisciplinary approach involving obstetricians, oncologists, neonatologists, expert pathologists, and other specialists, carefully balancing effective cancer

treatment with fetal safety. Early diagnosis, timely intervention, and ongoing monitoring are essential to optimize maternal health while minimizing risks to the fetus. Expert pathological evaluation is of utmost importance for precise diagnosis and selection of the most appropriate therapeutic strategy.

Despite the inherent complexities and challenges, modern advances in oncologic and obstetric care have significantly improved the prognosis for both mothers and neonates in these high-risk pregnancies.

References:

1. Barzilai M, Avivi I, Amit O. Hematological malignancies during pregnancy. Mol Clin Oncol. 2018 Jan;10(1):3–9.
2. Avilés A, Díaz-Maqueo JC, Talavera A, Guzmán R, García EL. Hematological malignancy and pregnancy: a single-institution experience with 21 cases. Cancer. 1985;55(9):1913–1916.
3. Avilés A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma. 2001 Mar;2(3):173–177.
4. Pavlidis NA. Cancer and pregnancy: a narrative review. J Adv Res. 2015 May;6(3):391–402.
5. Pereg D, Koren G, Lishner M. Hematological malignancies and pregnancy: a review of the literature. Ann Oncol. 2009 Mar;20(3):473–479.
6. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004 May;5(5):283–291.
7. Azim HA Jr, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. Cancer Treat Rev. 2010 Jun;36(2):110–121.
8. Atienza-Mateo B, et al. Guidelines for Cancer Treatment during Pregnancy: Ethics-Related Content Evolution and Multidisciplinary Approach. J Clin Med. 2022 Aug;11(16):4854.

TRUDNOĆA SA PRISUSTVOM HORMONSKOG INTRAUTRINOG ULOŠKA (IUD) –PRIKAZ SLUČAJA

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Trudnoća sa intrauterinim uloškom predstavlja retku, ali klinički značajnu situaciju koja može nositi povećan rizik od komplikacija za majku i plod. Iako je spirala jedan od najefikasnijih oblika kontracepcije, sa pouzdanošću preko 99 %, mogućnost začeća ipak postoji, naročito ukoliko je došlo do pomeranja ili u ovom slučaju isteka roka IUD. Prikazujemo slučaj četvrtorotke straosti 45 godina, kod koje je došlo do začeća sa prisustvom IUD.

Uvod

Kada dođe do trudnoće sa IUD to predstavlja veliki klinički izazov i sa sobom nosi povećan rizik od brojnih komplikacija, kao što su vanmaterična trudnoća, spontani pobačaj, infekcije, prevremeni porođaj i abrupcija posteljice.

Prikaz slučaja

Pacijentkinja strosti 45 godina, javlja se na pregled zbog izostanka mentrualnog ciklusa unazad 3 meseca, ciklusi su do tada bili uredni na 28 dana i oskudni. S obzirom na godine života misli da ulazi u menopauzu. Daje podatak da ima aplikovan hormonski IUD unazad 7 godina. Poslednji ginekološki pregled obavljen pre godinu dana. IUD je bio u materici, savetovana je ekstrakcija i aplikovanje drugog IUD, što pacijentkinja nije učinila. Na ginekološkom pregledu pod spekulumom konac od IUD se ne vizualizuje. Pacijentkinja ne daje podatak da je primetila da je spirala ispala. Nakon ginekološkog pregleda obavljen je ultrazvučni pregled na kome je ustanovljena monofetalna vitalna trudnoća, koja po biometriji ploda odgovara za 20 nedelja gestacije. Pacijentkinji je urađen morfološko- anatomski ultrazvuk, kojim nije utvrđeno prisustvo fetalnih anomalija. Trudnoća je do kraja praćena na redovnim kontrolama, protekla je uredno i porođaj je završen prirodnim putem spontano u terminu, plod je bio eutriofičnog rasta. S obzirom na situaciju u kojoj nismo znali da li je spirala ispala ili nije nakon porođaja učinjena je manuelna revizija materice i tom prilikom je ekstrahovana.

Diskusija

Iako je trudnoća sa IUD izuzetno retka, ipak do nje može doći, češće ukoliko je nadzor nad kontraceptivinim sredstvom zanemaren. U ovom slučaju jako je bitno naglasiti da rok za zamenu IUD treba strogo poštovati. Pravovremeno javljanje ginekologu nakon izostanka i jednog ciklusa sa IUD je od izuzetnog značaja, kako bi se tačan uzrok izostanka ciklusa definisao i na vreme preduzele neophodne kliničko-dijagnostičke procedure.

Zaključak

Iako trudnoća sa IUD nosi povećan rizik od komplikacija, ovaj slučaj potvrđuje da uz pažljivo praćnje i individualizovan klinički pristup trudnoća može proteći uredno i zavtršiti se povoljnim ishodom i za majku i novorođenče. Rano otkrivanje trudnoće i kontinuirana perinatalna nega ključni su faktori za smanjnje komplikacija majke i novorođenčeta. Ovakav ishod uspešne trudnoće sa IUD je redak, ali je ipak moguć.

BREAST CANCER DIAGNOSED DURING PREGNANCY - CASE SERIES OF THREE PATIENTS AND CLINICAL MANAGEMENT CONSIDERATIONS

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Background: Breast cancer diagnosed during pregnancy (BCP) is rare but presents significant clinical challenges, requiring a balance between optimal maternal cancer care and fetal safety. Case presentation: We report three cases of BCP diagnosed during the second trimester. Case 1: A 28-year-old woman at 25 weeks of gestation presented with a palpable left breast mass. Imaging and biopsy confirmed multifocal invasive ductal carcinoma, luminal B subtype. Neoadjuvant chemotherapy with doxorubicin/cyclophosphamide (AC protocol) was initiated during pregnancy, well tolerated, with regular fetal monitoring. At 39 weeks, an elective cesarean section resulted in the delivery of a healthy neonate. Case 2, a 37-year-old woman at 20 weeks was diagnosed with invasive ductal carcinoma, HER2-positive. Four cycles of AC protocol were given during pregnancy; HER2-targeted therapy was deferred until postpartum. At 36 weeks, after corticosteroid prophylaxis, an elective cesarean section delivered a healthy neonate. Case 3: A 37-year-old woman with locally advanced breast cancer (luminal B-like subtype) was found to be pregnant at ~22 weeks during ongoing chemotherapy and ovarian suppression. Given prior oncologic treatment, lack of prenatal care, and need for further systemic therapy, she opted for pregnancy termination after multidisciplinary counseling and ethics committee approval.

Discussion: In the first two cases, anthracycline-based chemotherapy administered during the second and third trimesters was well tolerated, with no acute neonatal complications. HER2-targeted therapy was appropriately delayed to avoid fetal risk. The third case illustrates complex ethical considerations when pregnancy is discovered during ongoing cancer treatment. Conclusion: BCP requires a multidisciplinary approach, individualized therapy, and close maternal-fetal monitoring. Anthracycline regimens can be safely administered in later pregnancy, while HER2-directed agents should be postponed until after delivery. In certain situations, pregnancy termination may be a medically and ethically justified option.

Keywords: breast cancer in pregnancy, gestational breast cancer, chemotherapy during pregnancy, maternal-fetal outcomes, multidisciplinary approach

References:

1. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012;379(9815):570-579.
2. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast cancer diagnosed during pregnancy: Adapting recent advances in breast cancer care for pregnant patients. JAMA Oncol. 2015;1(8):1145-1153.
3. Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: Results from an international collaborative study. J Clin Oncol. 2013;31(20):2532-2539.
4. Peccatori FA, Lambertini M, Scarfone G, Del Pup L, Codacci-Pisanelli G, Azim HA Jr, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(2):141-157.

5. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004;5(5):283-291.
6. Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R, Bergh J, Steger GG, et al. Taxanes for breast cancer during pregnancy: A systematic review. Clin Breast Cancer. 2013;13(1):16-23.
7. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: A literature review. Arch Surg. 2003;138(1):91-98.
8. Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring AE, Giermek J, et al. Treatment of breast cancer during pregnancy: An observational study. Lancet Oncol. 2012;13(9):887-896.
9. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: An 18-year experience from five London teaching hospitals. J Clin Oncol. 2005;23(18):4192-4197.
10. Lambertini M, Peccatori FA, Azim HA Jr. Targeted agents for cancer treatment during pregnancy. Cancer Treat Rev. 2015;41(4):301-309.

HIRURŠKO LEČENJE EVERZIJE VAGINE NAKON HISTEREKTOMIJE: PRIKAZ SLUČAJA

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Uvod: Lečenje vaginalne everzije i dalje predstavlja uroginekološki izazov, a u literaturi postoje različite preporuke za postizanje optimalnog terapijskog ishoda. Ovim prikazom slučaja ističe se hiruška mogućnost individualizovanog pristupa kod potpune vaginalne everzije.

Cilj: Cilj ovog rada jeste da pokaže efikasnost i bezbednost kombinovane hirurške metode u rešavanju kompleksnih vaginalnih prolapsa.

Prikaz slučaja: Pacijentkinja starosti 61 godinu, javila se sa potpunom vaginalnom everzijom, četvrtog stadijuma, sedamnaest godina nakon klasične abdominalne histerektomije sa bilateralnom adneksektomijom. Zbog prolapsa prednjeg vaginalnog zda urađena je prednja kolpoplastika sa podizanjem mokraćne bešike pomoću U šavova po Kelly-ju, dok je za korekciju rektokele/enterokele i prolapsa zadnjeg zida vagine primenjena Nikols-ova bilateralna sakrospinalna fiksacija. Postoperativni tok protekao je uredno, bez komplikacija. Uspešno rešavanje vaginalne everzije potvrđeno je na kontrolnom pregledu šest meseci nakon operacije. Zaključak: Hirurška rekonstrukcija koja obuhvata prednju kolpoplastiku u kombinaciji sa bilateralnom fiksacijom sakrospinalnog ligamenta preporučuje se kod uznapredovalih stadijuma kompleksnih vaginalnih everzija. Ova terapijska opcija predstavlja efikasnu i bezbednu tehniku.

Ključne reči: vaginalna everzija, histerektomija, prednja kolpoplastika, fiksacija sakrospinalnog ligamenta

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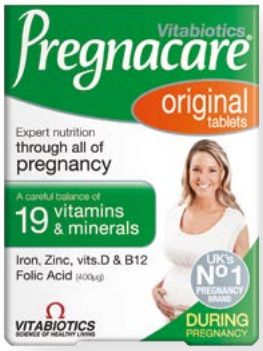

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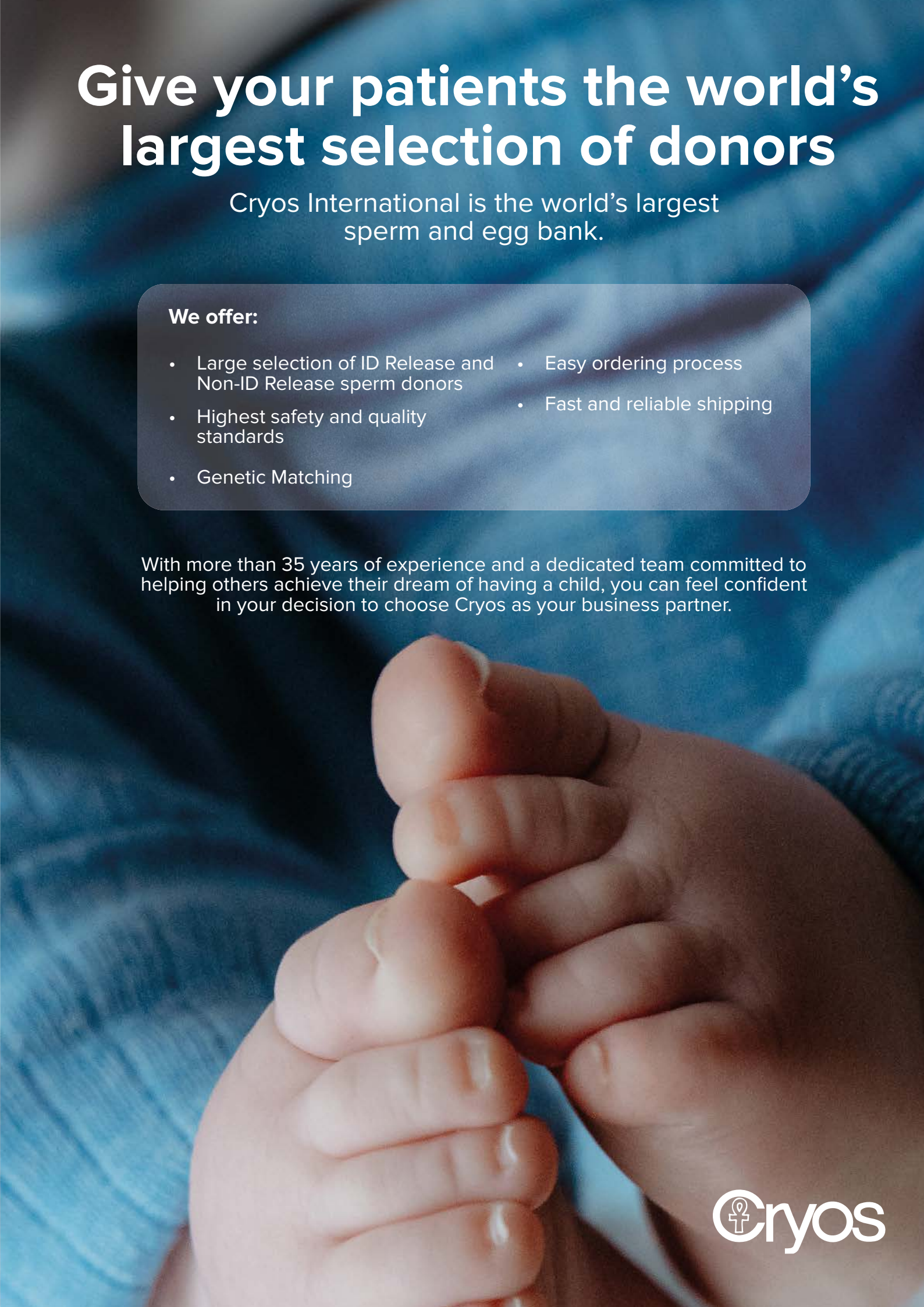

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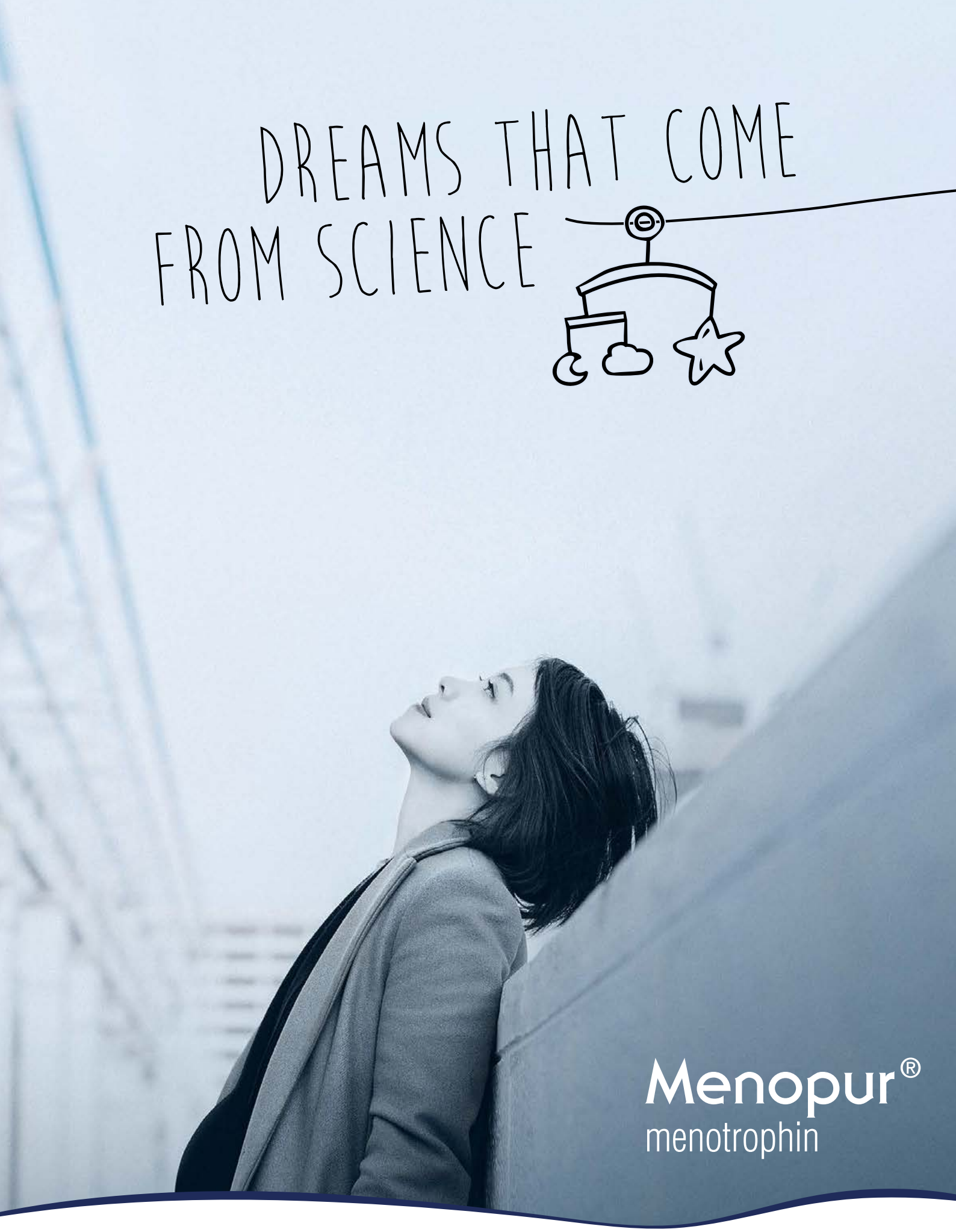

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1. Bonadio RR, et al. Clinics.2018;73(suppl1):e450s

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1. Kozubek A, Gubernator J, Przeworska E, Stasiuk M. Liposomal drug delivery, a novel approach: PLARosomes. Acta Biochim Pol. 2000;47(3):639-49. 2. Kis L, Szüts A, Otomo N, Szabó-Révész P, Deli M. The Potential of Sucrose Esters to be used as Oral Absorption Enhancers. Abstracts of the 8th Central European Symposium on Pharmaceutical Technology (CESPT), Satellite Symposium: 4th International Graz Congress on Pharmaceutical Engineering, September 16th 18th, Graz, Austria; Graz: Scientia Pharmaceutica; 2010. Liver Physiol. 2000;279(4):G767-74. 3. Kiss L, Hellinger E, Pilbat AM, Kittel A, Torok Z, Furedi A, et al. Sucrose esters increase drug penetration, but do not inhibit p-glycoprotein in caco-2 intestinal epithelial cells. J Pharm Sci. 2014;103(10):3107-19. 4. Yamamoto A, Katsumi H, Kusamori K, Sakane T. Improvement of intestinal absorption of poorly absorbable drugs by various sugar esters. Yakugaku Zasshi. 2014;134(1):47-53. 5. LIW, Das S, Ng KY, Heng PW. Formulation, biological and pharmacokinetic studies of sucrose ester-stabilized nanosuspensions of oleanolic Acid. Pharm Res. 2011;28(8):2020-33. 6. Tarantino G, Brilli E, Zambito Y, Giordano G, Eyutani F. Sucrosomial® Iron: A New Highly Bioavaible Oral Iron Supplement. Blood. 2015. 126 (23)4561. 7. Pisani A, Riccio E, Sabbatini M, Andreucci M, Del Rio A, Visciano B. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2014. 8. A. Mafodda. D. Giuffrida, A. Prestifilippo et al. Randomized Phase II Trial of supplementation with oral liposomal iron versus intravenous iron in patients with chemotherapy-related anemia without Iron deficiency treated with Darbepoetin Alfa. Abstract at XVI National Congress of Medical Oncology (AIOM), 2014. 9. Giordano G, Mondello P, Tambaro R, Perrotta N, D'Amico F, D'Aveta A, et al. Biosimilar epoetin alpha is as effective as originator epoetin-alpha plus liposomal iron (Sideral®), vitamin B12 and folates in patients with refractory anemia: A retrospective real-life approach. Molecular and Clinical Oncology. 2015;3(4):781-4. 10. Crawford J, Cella D, Cleeland C, Cremieux P, Demetri G, Sarokhan B, Slavin M, Glaspy J. Relationship Between Changes in Hemoglobin Level and Quality of Life During Chemotherapy in Anemic Cancer Patients Receiving Epoetin Alpha Therapy. Cancer, 2002;95:888-95. 11. Petrungaro A, Mineo G, Cingari R, Crispi F, Uccello G, Santonocito A, et al. Benefit assessment of Liposomal iron (Sideral®) administration to hematologic patients in follow-up after chemotherapy. 3rd Mediterranean Multidisciplinary Course on Iron Anemia; Rome Expert Review of hematology; 2015. p. S18-S9. 12. Campanella MP, Ebbli A, Gaibazzi D, Panunzio V, Tomasini. Effectiveness and compliance of oral liposomal iron (Sideral® Forte) treatment for iron deficiency anemia: a valid alternative to iv. iron therapies. 3rd Mediterranean Multidisciplinary Course on Iron Anemia; Rome, Italy: Expert Review of Hematology; 2015. p. S31-32. 13. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol. 2004;22(7):1301-7. 14. Spivak JL, Gascon P, Ludwig H. Anemia management in oncology and hematology. The oncologist. 2009;14 Suppl 1:43-56.

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