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OBSTETRICA și GINECOLOGIA

REVISTA SOCIETĂȚII ROMÂNE
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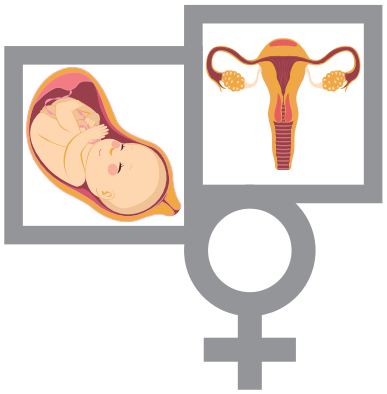

SERIE NOUĂ

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RITMUL LUMII MEDICALE

Respectă Echilibrul Natural[1,2]

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acetat de nomegestrol/estradiol,
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24H PROTECȚIE CONTRACEPTIVĂ.[1]

REGIM MONOFAZIC, *24/4.[1]

IMPACT METABOLIC SCĂZUT.[3]

*24/4 – 24 pilule active și 4 pilule placebo

Referințe:
1. Rezumatul caracteristicilor Zoely;
2. Chabbert-Buffet N et al. Gynecol Endocrinol 2013; 29 (10): 891-6;
3. Lete I et al. Eur J Contracept Reprod Health Care 2015; 20 (5): 329-43.

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ZOELY 2,5 mg/1,5 mg comprimate filmate – INFORMAȚII ABREVIATE DE PRESCRIPȚIE
DENUMIREA COMERCIALĂ A MEDICAMENTULUI - Zoely 2,5 mg/1,5 mg comprimate filmate. **COMPOZIȚIA CALITATIVĂ ŞI CANTITATIVĂ** - Comprimate filmate active albe: Fiecare comprimat filmat conține acetat de nomegestrol 2,5 mg și estradiol (sub formă de hemihidrat) 1,5 mg. Comprimate filmate placebo galbene: Comprimatul nu conține substanțe active. **DATE CLINICE - Indicații terapeutice** - Contracepție orală. Decizia de a prescrie Zoely trebuie să ia în considerare factorii de risc actuali ai fiecărei femei, în special cei pentru tromboembolism venos (TEV)și nivelul de risc de apariție a TEV în cazul administrării Zoely comparativ cu cel al altor contraceptive hormonale combinate (CHC). Doze şi mod de administrare - Se utilizează câte un comprimat pe zi timp de 28 zile consecutive. Fiecare blister începe cu 24 de comprimate active albe urmate de 4 comprimate placebo galbene. Următorul blister se începe imediat după ce este terminat blisterul precedent, fără pauză în utilizarea zilnică a comprimatelor şi indiferent de prezența sau absența sângerărilor de întrerupere. Sângerările de întrerupere încep, de regulă, în ziua 2-3 de la utilizarea ultimului comprimat alb şi este posibil să nu se sfârşească înainte de începerea următorului blister. Grupe speciale de pacienți - Insuficiență renală - Deşi nu sunt disponibile date privind utilizarea la paciente cu insuficiență renală, este puțin probabil ca insuficiența renală să influențeze eliminarea nomegestrolului acetat şi a estradiolului. Insuficiență hepatica - utilizarea Zoely la aceste femei nu este recomandată până când valorile funcției hepatice nu revin la normal. Mod de administrare - Administrare orală. Cum se administrează Zoely - Comprimatele trebuie luate în fiecare zi, în aproximativ acelaşi moment al zilei, indiferent de orarul meselor. Comprimatele trebuie luate cu o cantitate suficientă de lichid şi în ordinea indicată pe blister. Sunt disponibile etichete autocolante cu cele 7 zile ale săptămânii. Femeia trebuie să aleagă eticheta corespunzătoare zilei în care începe să utilizeze comprimatele şi să o lipească pe blister. Pentru informații detaliate despre cum se începe administrarea Zoely, vă rugăm consulați Rezumatul Caracteristicilor Produsului, disponibil la cerere. **Contraindicații** - Contraceptivele hormonale combinate (CHC) nu trebuie utilizate în următoarele condiții. Deoarece nu sunt încă disponibile date epidemiologice referitoare la CHC care conțin 17β-estradiol, în cazul utilizării Zoely sunt considerate valabile contraindicațiile pentru CHC care conțin etinilestradiol. Dacă oricare dintre afecțiuni apare pentru prima dată în timpul utilizării Zoely, administrarea medicamentului trebuie întreruptă imediat: Prezența sau riscul de tromboembolism venos (TEV), Tromboembolism venos –TEV prezent (tratat cu anticoagulante) sau în antecedente (de exemplu tromboză venoasă profundă [TVP] sau embolie pulmonară [EP]), Predispoziție cunoscută ereditară sau dobândită, pentru tromboembolism venos, cum sunt rezistența la PCA (inclusiv Factor V Leiden), deficitul de antitrombină-III, deficitul de proteină C, deficitul de proteină S, Intervenție chirurgicală majoră cu imobilizare prelungită, Risc crescut de tromboembolism venos din cauza prezenței de factori de risc multipli, Prezența sau riscul de tromboembolism arterial (TEA), tromboembolismul arterial – tromboembolism arterial prezent, antecedente de tromboembolism arterial (de exemplu, infarct miocardic) sau afecțiune prodromală (de exemplu, angină pectorală), Boală cerebrovasculară – accident vascular cerebral prezent, antecedente de accident vascular cerebral sau afecțiune prodromală (de exemplu atac ischemic tranzitoriu, AIT), Predispoziție cunoscută ereditară sau dobândită pentru tromboembolism arterial cum sunt hiperhomocisteinemia și anticorpii antifosfolipidici (anticorpi anti-cardiolipină, anticoagulant lupic), Antecedente de migrenă cu simptome neurologice focale, Risc crescut de tromboembolism arterial din cauza prezenței de factori de risc multipli sau a prezenței unui factor de risc semnificativ cum ar fi: • diabetul zaharat cu simptome vasculare, hipertensiune arterială severă, dislipoproteinemie severă, Pancreatită sau antecedente de pancreatită dacă este asociată cu hipertrigliceridemie severă, Prezența sau antecedente de boală hepatică severă cât timp valorile funcției hepatice nu au revenit la normal, Prezența sau antecedente de tumori hepatice (benigne sau maligne), Afecțiuni maligne influențate de hormonii sexuali, suspicionate sau diagnosticate (de exemplu la nivelul organelor genitale sau sânilor), Prezența sau antecedente de meningioma. Sângerări vaginale nediagnosticate, Hipersensibilitate la substanțele active sau la oricare dintre excipienți. **Atenționări şi precauții speciale pentru utilizare** – Atenționări - În cazul prezenței oricăreia dintre afecțiunile sau a oricăruia dintre factorii de risc menționați mai jos, trebuie discutat cu femeia respectivă dacă este adecvată administrarea Zoely. *Risc de tromboembolism venos (TEV)* - Medicamentele care conțin levonorgestrel, norgestimat sau noretisteron sunt asociate cu cel mai scăzut risc de TEV. Nu se cunoaște încă modul în care riscul utilizării Zoely se compară cu aceste medicamente cu risc scăzut. Simptome ale TEV (tromboză venoasă profundă şi embolie pulmonară) - În eventualitatea apariției simptomelor, femeile trebuie sfătuite să solicite asistență medicală imediată şi să informeze profesionistul din domeniul sănătății că iau un CHC. Simptomele trombozei venoase profunde (TVP) pot include: - umflare unilaterală a membrului inferior şi/sau a labei piciorului sau de-a lungul unei vene a membrului inferior; - durere sau sensibilitate la nivelul membrului inferior, care este posibil să fie resimțită numai în ortostatism sau în timpul mersului; - senzație crescută de căldură la nivelul membrului inferior afectat; înroşirea sau decolorarea tegumentului de la nivelul membrului inferior. Simptomele de embolie pulmonară (EP) pot include: - debut brusc inexplicabil al senzației de lipsă de aer sau al unei respirații rapide; - tuse bruscă, care poate fi însoțită de hemoptizie; - durere toracică ascuțită, - vertij sau amețeală severe; - ritm cardiac rapid sau neregulat. *Riscul de tromboembolism arterial (TEA)* - Studiile epidemiologice au evidențiat asocierea utilizării CHC cu un risc crescut de tromboembolism arterial (infarct miocardic) sau de accident cerebrovascular (de exemplu atac ischemic tranzitor, accident vascular cerebral). Evenimentele tromboembolice arteriale pot fi letale. Simptome ale TEA - În eventualitatea apariției de simptome, femeile trebuie sfătuite să solicite asistență medicală imediată şi să informeze profesionistul din domeniul sănătății că iau un CHC. Simptomele de accident cerebrovascular pot include: - amorțire sau slăbiciune bruscă la nivelul feței, brațului sau piciorului, mai ales pe o parte a corpului; - apariția bruscă de probleme la mers, amețeală, pierderea echilibrului sau coordonării; - apariția bruscă a confuziei, problemelor de vorbire sau de înțelegere; - apariția bruscă a problemelor de vedere la unul sau ambii ochi; - cefalee bruscă, severă sau prelungită, fără cauză cunoscută; - pierderea cunoştinței sau leşin, cu sau fără convulsii. Simptomele temporare sugerează că evenimentul este un atac ischemic tranzitor (AIT). Simptomele de infarct miocardic (IM) pot include: - durere, disconfort, presiune, greutate, senzație de constricție sau de plenitudine la nivelul toracelui, brațului sau sub stern; - senzație de disconfort care radiază spre spate, maxilar, gât, braț, stomac; - senzație de suprasaturietate, indigestie sau sufocare; - transpirație, greață, vărsături sau amețeală; - slăbiciune extremă, anxietate, sau dispnee; - ritm cardiac rapid sau neregulat. *Tumori* - În unele studii epidemiologice a fost raportat un risc crescut pentru dezvoltarea neoplasmului de col uterin la femeile care utilizează COC o perioadă îndelungată (> 5 ani), dar continuă să existe controverse în ceea ce priveşte măsura în care această observație este atribuită efectelor comportamentului sexual sau altor factori precum virusul papiloma uman (HPV). *Meningiom* - A fost raportată apariția meningiomului (unic şi multiplu) în asociere cu utilizarea prelungită (mai mulți ani) a nomegestrol în monoterapie în doze de 3,75 sau 5 mg pe zi şi peste. Dacă la o pacientă tratată cu Zoely este diagnosticat un meningiom, tratamentul trebuie oprit. *Hepatita C* - este necesară precauție în cazul administrării concomitente cu schema conținând asocierea medicamentoasă reprezentată de ombitasvir/paritaprevir/ritonavir cu sau fără dasabuvir. Lista completă a Atenționări şi precauții speciale pentru utilizare se regăseşte în rezumatul Caracteristicilor Produsului, disponibil la cerere. **Interacțiuni cu alte medicamente şi alte forme de interacțiune -** Interacțiunile dintre contraceptive orale şi alte medicamente inductoare enzimatic pot duce la metroragie şisau la eşecul contracepției. Metabolizare hepatică: Pot apărea interacțiuni cu substanțele de inducere a enzimelor CYP450, ceea ce duce la scăderea concentrațiilor hormonilor sexuali şi scăderea eficacității contraceptivelor orale combinate, inclusiv a Zoely. Aceste substanțe sunt reprezentate în mare parte de anticonvulsive (de exemplu carbamazepina, topiramatul, fenitoina, fenobarbitalul, primidona, oxcarbazepina, felbamatul), medicamente antiinfecțioase (de exemplu rifampicina, rifabutina, griseofulvina), sunătoarea, bosentanul şi inhibitorii de protează HIV sau a virusului hepatitic C (VHC) (de exemplu ritonavir, boceprevir, telaprevir) şi inhibitorii revers transcriptazei non-nucleozidici (de exemplu efavirenz). După câteva zile de tratament poate apărea inducerea enzimatică. Inducerea enzimatică maximă se observă în general în interval de câteva săptămâni. După oprirea terapiei medicamentoase, inducerea enzimatică poate dura timp de aproximativ 28 zile.Administrarea concomitentă de inhibitori puternici (de exemplu ketoconazol, itraconazol, claritromicină) sau moderați (de exemplu fluconazol, diltiazem, eritromicină) ai CYP3A4 poate determina creşterea concentrațiilor serice de estrogeni sau progestogeni. Utilizarea concomitentă de rifampicină scade ASC0-∞ pentru acetat de nomegestrol cu 95% şi creşte ASC0-tlast a estradiolului cu 25%. Utilizarea concomitentă de ketoconazol (doză unică 200 mg) nu modifică metabolizarea estradiolului, în timp ce au fost observate creşteri ale concentrației plasmatice maxime (85%) şi ASC0-∞ (115%) pentru acetat de nomegestrol, care nu au prezentat relevanță clinică. Rezultate similare sunt anticipate la femeile aflate la vârsta fertilă.Influența Zoely asupra altor medicamente - Contraceptivele care conțin etinilestradiol pot determina scăderea concentrațiilor de lamotrigină cu aproximativ 50%. Trebuie acordată atenție în special la introducerea unui contraceptiv combinat, chiar şi cu estradiol, la o femeie cu stare bine echilibrată căreia i se administrează lamotrigină. **Fertilitatea, sarcina şi alăptarea -** Zoely nu este indicat în timpul sarcinii. Alăptarea - utilizarea COC nu trebuie recomandată până la întârcarea completă a copilului şi trebuie propuse metode contraceptive alternative femeilor care doresc să alăpteze. Fertilitatea - Zoely este indicat pentru prevenirea sarcinii. **Reacții adverse –** reacțiile adverse foarte frecvente: acne, sângerare de întrerupere anormală. Recțiile adverse frecvente: scăderea libidoului, depresie/dispoziție depresivă, modificări ale dispoziției, cefalee, migrenă, greață, metroragie, menoragie, mastodinie, durere pelviană, greutate crescută. Lista completă a reacțiilor adverse se regăseşte în rezumatul Caracteristicilor Produsului, disponibil la cerere. **Supradozaj** - S-au utilizat de către femei doze multiple de până la cinci ori doza zilnică de Zoely şi doze unice de până la de 40 ori mai mari decât doza zilnică de acetat de nomegestrol singur, fără apariția de probleme legate de siguranță. Ținând cont de experiența generală cu contraceptivele orale combinate, simptomele care pot să apară sunt: greață, vărsături şi, la fetele tinere, mici sângerări vaginale. Nu există antidoturi, iar tratamentul trebuie să fie simptomatic. **PROPRIETĂȚI FARMACEUTICE** - Perioada de valabilitate: 3 ani. **DEȚINĂTORUL AUTORIZAȚIEI DE PUNERE PE PIAȚĂ** - Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1, D01 YE64, Irlanda. **NUMĂRUL(ELE) AUTORIZAȚIEI DE PUNERE PE PIAȚĂ EU/1/11/690/001 EU/1/11/690/002 EU/1/11/690/003 EU/1/11/690/004. DATA REVIZUIRII TEXTULUI** – iunie 2020. Acest produs se eliberează pe bază de prescripție tip P6I.

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Prof. univ. dr. Demetra Socolov

Cu aceste două motouri în minte, am organizat Conferința Zilele Medicale „Vasile Dobrovici”, ediția a 15-a, online, între 26 și 28 noiembrie 2020.

Conferința Zilele Medicale „Vasile Dobrovici” este una dintre cele mai longevive manifestări științifice de obstetrică-ginecologie din România. De la prima ediție, organizată în 1992, s-a păstrat o periodicitate de 2 ani, acum ajungând la ediția a 15-a.

Anul 2020 a însemnat o provocare deosebită pentru continuitatea acestei manifestări științifice, în special din cauza pandemiei de COVID-19, care a împiedicat reunirea fizică a multor invitați, numeroși lectori care confirmaseră deja invitația nemaiputând să o onoreze.

Din fericire, cu sprijinul tehnologiei moderne, organizarea, chiar și în aceste condiții grele, a devenit posibilă și, astfel, în perioada 26-28.11.2020, un număr de 439 de participanți s-au conectat online pentru a-și însuși noutățile și experiența lectorilor, legate mai ales de temele propuse pentru conferință:

1. Screeningul în obstetrică, ginecologie și neonatologie.
2. Patologia maternă asociată sarcinii.

Cu sprijinul organizatorilor, a fost posibilă și desfășurarea a două evenimente precongres. Astfel, cursul cu tema „Restricția în creșterea intrauterină” a beneficiat de intervențiile unor experți în acest domeniu din străinătate: profesorul Laurent Salomon de la Universitatea Descartes din Paris, doctorul Christos Ioannou de la Universitatea din Oxford (Marea Britanie), profesorul Greg De Vore de la Universitatea Pennsylvania (SUA), dar și a multor experți din țară. Concluzia este că restricția în creșterea intrauterină nu este încă o problemă obstetricală rezolvată, fiind necesară promovarea de protocoale internaționale pentru screening, diagnostic și decizie obstetricală.

Al doilea curs preconferință, având ca temă noțiuni practice de colposcopie, i-a avut ca lectori pe majoritatea membrilor boardului Societății Europene de Colposcopie, precum: profesorul Pekka Nieminen, din Finlanda, actualul președinte al societății, și profesorul Maggie Kruikshank, din Scoția (viitoarea președintă aleasă a societății), profesorul Xavier Carcopino, din Franța, profesorul Vesna Kesic, din Serbia, profesorul Wiebren Tjalma, din Belgia, și profesorul Murat Gultekin, din Turcia, membru în boardul ESGO (European Society of Gynecological Oncology), care au discutat despre aspectele practice și noutățile în domeniu.

În total, conferința s-a bucurat de prezența online a 92 de lectori, dintre care 11 lectori internaționali, susținând două cursuri preconferință și conferința propriu-zisă, organizată pe trei canale online/sesiuni full-day în paralel.

Lucrările înscrise la conferință, sub formă de prezentări orale și postere, au atins aspecte de practică și actualizări în domeniu, fiind împărțite pe trei sesiuni paralele, cu o largă audiență online (439 de înscriși la conferință, cu o medie de 70% prezenți live, 99 la cursul de IUGR și 85 la cursul de colposcopie). Am primit, de asemenea, un număr de 57 de rezumate care au fost publicate ca supliment al revistei *Ginecologia.ro* și un număr de 17 e-postere.

Un alt atú al conferinței l-a constituit desfășurarea în paralel a Congresului de Uroginecologie, de asemenea cu o prezență internațională de marcă, pentru care dorim să mulțumim Societății Române de Uroginecologie.

În numele comitetului științific de organizare, doresc să exprim profunda recunoștință pentru toți cei care au manifestat un imens interes ca să participe la acest eveniment științific, cu o diversitate atât de largă de lucrări.

Doresc să mulțumesc Societății Române de Obstetrică și Ginecologie și Universității de Medicină și Farmacie „Grigore T. Popa” din Iași, sub egida cărora s-a desfășurat manifestarea, dar și comitetului științific național, partenerilor din industria farmaceutică și firmei Paloma Tours, care ne-au fost alături, dovedind un exemplu de lucru în echipă și planificare excelentă.

Așadar, considerăm că această a 15-a ediție a Zilelor Medicale „Vasile Dobrovici” a reușit îndeplinirea obiectivelor pe care și le-a propus, constituind o obligație și o promisiune pentru edițiile următoare.

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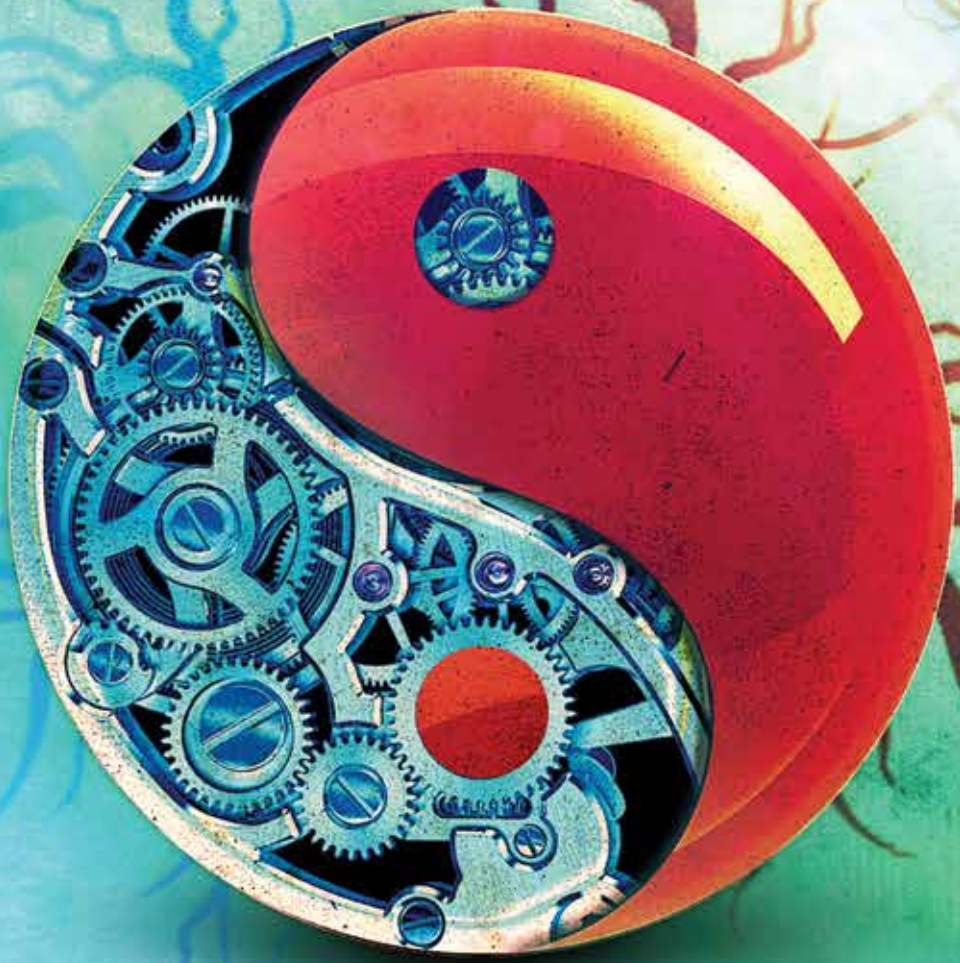

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review articles

Condyloma acuminata during pregnancy

Ana Maria Alexandra Stănescu[1], Ana-Maria Cioti[2], Anca Angela Simionescu[3], Ioana Veronica Grăjdeanu[1]

1. Department of Family Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
2. Private Medical Practice Dr. Ioana Veronica Grăjdeanu, Bucharest, Romania
3. Department of Obstetrics and Gynecology, Filantropia Clinical Hospital of Obstetrics and Gynecology; "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Corresponding authors: Anca Angela Simionescu, e-mail: asimion2002@yahoo.com;
Ana-Maria Cioti, e-mail: ciotiana_maria@yahoo.com

ABSTRACT

Human papillomavirus (HPV) infection is the most common sexually transmitted viral infection. The sexually active individuals will acquire at least one type of HPV infection, frequently with more than one strain, and some people may be repeatedly infected. The patients with HPV infection during pregnancy represent a high-risk group. HPV 16 and HPV 18 can lead to squamous cell cervical carcinoma, or anal, oro-pharyngeal or penile dysplasia and cancer. HPV types 6 and 11 are responsible for over 90% of the genital or cutaneous *condylomata acuminata*. We aim to review the clinical implications for the diagnosis and the management of *condylomas acuminata* associated with pregnancy. The removal of condylomas during pregnancy, especially the larger ones, can be considered in order to minimise the risks during labor and childbirth; the resolution might be incomplete or poor until pregnancy is complete.

Keywords: HPV 6, HPV 11, *condyloma acuminata*, pregnancy

REZUMAT

Infecția cu virusul papiloma uman (HPV) este cea mai comună și răspândită infecție virală transmisă pe cale sexuală. Toate persoanele active sexual vor dobândi cel puțin un tip de infecție cu HPV de-a lungul vieții, cel mai frecvent cu mai mult de o singură tuplină, iar unii vor fi infectați în repetate rânduri. Pacienții cu infecție cu HPV în timpul sarcinii reprezintă un grup cu risc crescut. Infecția cu HPV 16 sau HPV 18 poate duce la carcinom de col uterin scuamos celular sau la displazie ori cancer anal, orofaringian sau penian. Infecția cu HPV 16 sau 18 este răspunzătoare pentru peste 90% din condiloamele acuminate cutanate sau genitale. În acest articol, ne propunem să revedem implicațiile clinice pentru diagnosticul și conduita în condiloamele acuminate descoperite în sarcină. Condiloamele trebuie tratate până la dispariție în timpul sarcinii, mai ales cele voluminoase, pentru a reduce complicațiile acestora în timpul travaliului și al nașterii; dispariția lor poate fi incompletă în timpul sarcinii.

Cuvinte-cheie: HPV 6, HPV 11, *condyloma acuminata*, sarcină

Introduction

As counted by the Centers for Disease Control and Prevention (CDC), anogenital human papillomavirus (HPV) is the most common and widespread sexually transmitted infection. Eight out of 10 sexually active people will be infected with more HPV strains[1]. The prevalence of the identified HPV infection in European women from the general population is estimated to be 14%, with a peak in the age groups represented by adolescents and females in their early 20s, affecting women during their gestational period[2,3].

More than 200 distinct types of human papillomavirus have been identified, and at least 40 subtypes can infect the genital area. In most cases, HPV infection is asymptomatic and resolves spontaneously within two years. In persistent infection, low-risk HPV strains can cause benign proliferative lesions, while high-risk strains infection can progress, over at least ten years, to precancerous lesions and malignancies of the cervical uterus, anal, oropharynx and penile tissue[4].

During pregnancy, external anogenital warts (*condyloma acuminata*) are the most common manifestation of HPV infection. During this period, the proliferation and growth of warts accelerate, being frequently followed by a spontaneous regression of lesions in the puerperium[5]. The mother's immune system is highly adaptative, going through various changes at every stage of gestation, keeping a balance between the allogeneic fetus and immunocompetence against any pathogens. The physiological increase in local estrogen and glycogen in the genitals during pregnancy, in addition to the immune disorders inherent in pregnancy, favors the proliferation of the HPV[5,6].

Condyloma acuminata (anogenital warts)

HPV types 6 or 11 are the etiologic factor for the majority of anogenital warts. Other types of human papillomavirus that have been isolated in genital warts are HPV 2, 40, 42, 43, 54, usually as co-infections with HPV 6 or 11. The infection with one type of HPV does not prevent the infection with a different type, 5% to 30% out of mucosal HPV infections being caused by multiple strains of the virus. HPV types 6 and 11 have also been associated with conjunctival, nasal, oral and laryngeal warts[7,8].

Anogenital warts present as flat, papular, pedunculated or cauliflower-like growths of pink, grey or brown colouring, on perineal and anogenital skin and/or mucous membranes. Anogenital warts are frequently multiple, asymmetric and polymorphic and can occasionally cause bleeding, pruritus, increased vaginal secretions, obstruction of the birth canal and neonatal infections. These type of skin lesions decrease the quality of life, as they can be intractable to treatment, may regenerate spontaneously or remain in remission for a long period[9].

During pregnancy, *condyloma acuminata* can have a rapid development of the perineal and anogenital lesions, especially during weeks 12 and 14 of gestation. HPV seems to actively replicate due to the rising estrogen levels, decreased cellular immunity and increased vascularisation and blood flow in the genital area due to pregnancy. Anogenital warts that develop during pregnancy are usually located near the vaginal opening, cervix and the vaginal wall, and are more difficult to treat because of ulceration and infections risks. Furthermore, they are fragile and pruriginous and can easily cause bleeding[7,10]. They may sometimes become very large, particularly when new warts develop during pregnancy. There have been cases of giant condylomas – also known as Buschke-Löwenstein tumors – reported during pregnancy, that grow to such an extent, that they obstruct the birth canal. Caesarean delivery is indicated for women who may suffer from labor dystocia or excessive bleeding during vaginal delivery associated with *condyloma acuminata*[11-13].

Risk of vertical transmission

The transmission of HPV from mother to offspring has been reported by several studies. The virus may infect the fetus during pregnancy, through transplacental or perinatal transmission, or by nursing after delivery[14,15]. The vertical transmission is due to the microtears in fetal membranes or through the placenta if the mother has genital HPV infection. Studies have demonstrated that HPV (low- and high-risk) can cross the placenta and reach the fetus, with a detection rate of HPV-DNA in the placental samples varying from 0% to 42.5%[14]. HPV-DNA has been detected both in amniotic fluid and the umbilical cord[15]. The risk of transmission of the same HPV type present in the maternal genital tract is four times higher when the umbilical cord blood tests positive for the same HPV[16].

The way of delivery (vaginal or caesarean section) does not seem to influence the neonatal infection rate. Caesarean delivery may be considered when the birth canal is obstructed, in case of premature rupture of membranes or when high viral load is suspected. Breastfeeding should not be restricted if the mother is found to be infected with HPV[10,17].

Generally, the newborn becomes clear of the HPV infection after the first year of life; nevertheless, neonatal anogenital, oral or conjunctival HPV lesions can develop. The infection with mucosal HPV 6 and 11 may cause recurrent respiratory papillomatosis in children, which is a rare and severe respiratory disease[18].

Therapeutic options

There is currently no curative antiviral treatment available for HPV infection. Most treatment options for *condyloma acuminata* require physical destruction of the infected cells. The surgical or medical treatment choice depends on the location, number, dimension, type of wart and on the compliance to treatment. During pregnancy, the treatment options are limited, as the standard systemic treatment is teratogenic[8].

The preferred method to treat anogenital warts during pregnancy is the surgical treatment, that consists of electrocautery excision, curettage, scalp excision under general or local anaesthesia, cryotherapy, and using a CO_2 laser. Cryotherapy is considered the first line of treatment; it uses nitrous oxide or liquid nitrogen directly on the lesions. Small lesions can be treated during pregnancy with trichloroacetic acid (TCA) applied sparingly, with limited efficacy[10,19].

Podofilox® (podophyllotoxin) and sinecatechins are topical treatment options that should not be used during pregnancy. Podophyllotoxin is an antimitotic drug, toxic to the mother, but also teratogenic; it can cause malformations of the ear, heart and extremities of the fetus. Despite the low risk of teratogenicity, the use of imiquimod should be avoided, as the current data are insufficient.

The removal of warts during pregnancy can be considered, despite the fact that the resolution might be incomplete or poor until pregnancy is complete[10,20].

Discussion

Condyloma acuminata during pregnancy poses a dilemma for the clinician; untreated it may affect the fetus, whereas the treatment options are limited due to lack of eloquent clinical trials.

Researchers have recently discovered a link between the strains of beta HPV in the oral cavity and the increased risk to develop head and neck cancer. Also, it is very important to understand if viral DNA of HPVs is pathogenic for infants or if it is only a transient infection and without the possibility to cause a real disease in the future[21].

Prevention plays a key role. Achieving high vaccination rates among young girls and implementing a programme of gender-neutral vaccination can help reduce the vertical HPV transmission and, implicitly, the incidence of juvenile recurrent respiratory papillomatosis. In Australia, the national vaccination programme started in 2007 and extended to boys in 2013[22,23], while in the 19 EU countries, the national vaccination programme was introduced from 2012[24]. HPV vaccines that prevent HPV 6 and HPV 11 related anogenital warts are available in Romania from 2008 (Gardasil/Silgard® – Merck & Co., Inc., tetravalent vaccine) and from 2020 (Gardasil 9® – 9-valent vaccine). The Romanian Ministry of Health promotes a school-based immunization campaign, providing free vaccines for 10- to 11-year-old girls[25,26]. ■

Conflict of interests: The authors declare no conflict of interests.

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Difficult diagnosis in gastrointestinal endometriotic lesions with ileal localization

Alexandra Radu[1,2,3], Cătălin Coroleucă[1,2,3], Elvira Brătilă[1,2,3]

1. "Prof. Dr. Panait Sîrbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania
2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
3. Doctoral School of the "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author: Alexandra Radu, e-mail: dralexandrabruja@gmail.com

ABSTRACT

Endometriosis is characterized by the presence of endometrial tissue, consisting of glands and stroma, outside the uterine cavity. The diagnosis of endometriosis remains an issue due to the nonspecific nature of symptoms and the difficulty in distinguishing between the pelvic pain caused by endometriosis and the pelvic pain caused by other medical conditions such as pelvic infection or various nongynecological medical conditions. Endometriosis of the ileum represents less than 7% of all gastrointestinal endometriosis cases. The presurgical diagnosis of ileal endometriosis is extremely difficult because the medical results obtained following the clinical examination and the imagistic methods are nonspecific. Many of the ileal endometriosis cases remain undiagnosed, causing real surgical emergencies, such as intestinal obstruction.

Keywords: ileal endometriosis, diagnosis, nonspecific

REZUMAT

Endometrioza se caracterizează prin prezența țesutului endometrial, format din glande și stromă, în afara cavității uterine. Diagnosticarea endometriozei rămâne o problemă din cauza naturii nespecifice a simptomelor și a dificultății de a distinge între durerea pelviană datorată endometriozei și cea cauzată de o infecție pelviană sau de diverse afecțiuni nonginecologice. Endometrioza ileală reprezintă mai puțin de 7% din totalul cazurilor de endometrioză gastrointestinală. Diagnosticul preoperatoriu al endometriozei ileale este extrem de dificil, întrucât rezultatele obținute în urma examenului clinic și a investigațiilor imagistice radiologice sunt nespecifice. O parte dintre cazurile de endometrioză ileală rămân nediagnosticate, determinând adevărate urgențe chirurgicale, precum obstrucția intestinală.

Cuvinte-cheie: endometrioză ileală, diagnostic, nespecific

Introduction

Endometriosis is a gynecological disease with a chronic evolution, being common among women of reproductive age, affecting up to 15% of patients. The incidence of this pathology increases in cases of patients with chronic pelvic pain and infertility. Despite its high prevalence, this disease remains enigmatic, being called the "disease of theories". With an incompletely elucidated etiology, endometriosis is defined by the presence of functional endometrial tissue outside the uterine cavity[1,4].

Over time, several theories have been developed that justified the ectopic location of endometrial tissue, including the theory of retrograde menstruation. According to this, during an abundant menstrual flow, viable fragments of endometrial tissue are transported along the fallopian tubes, causing the implantation of endometrial cells and the secondary development of endometriotic lesions in the serosa of the intraabdominal or pelvic organs[1,3].

Other theories that explain the appearance of endometriotic lesions are: endometrioid metaplasia of mesothelial cells in the peritoneum, hematogenous or lymphatic dissemination of viable endometrial cells[1].

The most common locations of endometriotic lesions are represented by: ovaries, fallopian tubes, pelvic peritoneum, Douglas posterior sac and, last but not least, uterosacral ligaments. On the other hand, the gastrointestinal tract, vagina, rectovaginal septum or round ligaments are rarely affected. Regarding the extraabdominal locations of endometriosis, such as the lung, urinary tract, skin or central nervous system (CNS), they are very rarely mentioned in the specialized literature[1,6].

Regarding the involvement of the ileum, this type of endometriotic lesion is very rare and represents less than 7% of all endometriotic lesions with gastrointestinal (GI) localization[1].

Deep infiltrative endometriosis (DIE) is defined by the presence of endometrial implants, fibrosis and muscle hyperplasia under the peritoneum (>5 mm) and involves, in descending order of frequency, the uterosacral ligaments, the rectosigmoid colon, vagina and bladder[2].

Etiopathogenesis of gastrointestinal endometriosis

The gastrointestinal tract is the most common site of extrapelvic endometriosis. Gastrointestinal tract endometriosis affects both women of childbearing age and adoles-

cents or menopausal women in a proportion up to 37%[3]. The most affected segment of the GI tract is the sigmoid colon, followed by the rectum, ileum, appendix and cecum. Small bowel lesions mostly involve the terminal ileum and represent 5-16% of the cases of GI endometriosis. Other locations of endometriosis in the GI tract, described in the literature but to a lesser extent, include the gallbladder, Meckel's diverticulum, stomach, pancreas and liver[3].

The increased incidence of endometriotic lesions in the GI tract segments that are close to the uterus justifies the theory of retrograde menstruation[3]. The superficial endometriotic implants in the serosa of the colon are often asymptomatic. On the other hand, DIE lesions cause severe gastrointestinal symptoms. Depending on the degree of invasion of the endometriotic lesion in the intestinal wall, endometriosis is classified histopathologically into four stages: stage 0 – the endometriotic lesion is found in the peritoneum and subserosal connective tissue, without reaching the plexus; stage 1 – the endometritic foci are located in the subserosal adipose tissue or adjacent to the neurovascular branches (subserosal plexus), rarely involving the external muscular layer; stage 2 involves the damage to the muscle wall and of the Auerbach plexus; stage 3 – the submucosal nerve plexus or even the mucosa is invaded[3].

Clinical picture of gastrointestinal endometriosis

Most cases of GI endometriosis are symptomatic[4]. When present, the symptoms of intestinal endometriosis depend on the location of the disease and also the depth of the invasion. When the lesions are limited to serosa, the symptoms are similar to those encountered in pelvic endometriosis[3]. These include dysmenorrhea, dyspareunia and infertility. Other symptoms may be present, usually those that complete the clinical picture of an intestinal obstruction, especially when the endometriotic lesion of the intestinal wall causes a narrowing of the intestinal lumen, which will cause distension or stretching during peristalsis. However, the severity of the symptoms does not always correspond to the extent of the disease[3].

Establishing a solid preoperative diagnosis can be difficult due to the nonspecific symptoms. Many of the symptoms can mimic a wide range of diseases, including irritable bowel syndrome, infectious diseases, ischemic colitis, inflammatory bowel disease, ileocolonic intussusception, appendicitis and even malignancy[3,5,6]. Symptoms generally include abdominal cramps, dyskinesia, rectal tenesmus, flatulence, constipation, melena, diarrhea, vomiting, defecation pain etc. The traditional cyclical pattern of symptomatology has not been confirmed by recent studies, which postulate that chronic noncyclic pelvic pain is the persistent symptom[3,7]. Cyclic symptoms that worsen during menstruation have also been reported in a small number of patients[3,8]. Because the intestinal mucosa is rarely affected, rectal bleeding may be an unusual symptom. Bleeding can also occur due to severe intestinal obstruction and ischemia[3,9]. Acute intestinal obstruction due to stenosis is a rare complication, reported only in cases of severe small bowel involvement, or in the presence of dense pelvic adhesions[10]. Also, the perforation of the intestine caused by endometriosis is an extremely rare entity, along with appendix rupture and intussusception[3,12].

Diagnosis of gastrointestinal endometriosis

The clinical suspicion of ileal endometriosis is important for optimizing the diagnostic imaging. In symptomatic patients, the surgical treatment is effective in resolving symptoms, laparoscopy being considered of choice. During surgery, a thorough examination of the abdominal cavity is essential for the detection of ileal endometriotic lesions, especially in patients with rectosigmoid colon involvement, as they are frequently associated with other lesions, which are often not detected by imaging diagnostic methods[13].

Often, the diagnosis of ileal endometriosis is delayed, because its clinical picture, often suggestive of an intestinal obstruction, is erroneously attributed to an inflammatory bowel disease, such as Crohn's disease. Thus, the histopathological diagnosis is the one that attests the presence of the endometriotic lesion[1].

The general examination is very rarely useful in differentiating intestinal endometriosis from other intestinal diseases or pelvic endometriosis. In fact, many women with intestinal endometriosis are treated for irritable bowel syndrome before the final diagnosis is made[3,14].

At the clinical examination of the vagina or rectum, the presence of a knot of hard consistency can be detected, either at the level of the posterior vaginal fornix or on the rectal wall, which indicates an involvement of the intestine[3].

The accuracy of the diagnosis depends on the imaging technique used, the location and size of the lesion, as well as the expertise of the observer[3].

Radiological studies are often performed due to the nonspecific nature of patients' symptoms and signs. However, there are no radiological or clinical results specific to endometriosis[3,15].

According to the latest studies, compared to surgery, it seems that, so far, there is no sufficiently accurate imaging method for the diagnosis of endometriosis[3]. However, ultrasonography has demonstrated its value in this direction. The literature recognizes the importance of transvaginal and endorectal ultrasound in the diagnosis of rectosigmoid submucosal lesions[3].

Through transvaginal ultrasound (TVU), deep endometriotic lesions can be diagnosed, usually located in the anterior wall of the colon. The suggestive ultrasound image describes an irregular hypoechoic formation that often involves the left uterosacral ligament[3].

Transvaginal ultrasonography is considered a routine noninvasive diagnostic investigation, which can detect intestinal endometriosis with a sensitivity and specificity of 91% and 98%, respectively[3,16]. Intestinal endometriotic nodules are in the form of heterogeneous, hypoechoic, rarely spiculated masses[16].

TVU with or without bowel preparation is effective in the noninvasive and preoperative detection of deeply infiltrative endometriosis of the rectosigmoid, and less of the ileum[17].

Ileal endometriosis usually involves the terminal ileum, 10 cm away from the ileocecal valve. In the diagnosis of this pathology, barium enema was also used. Following this investigation, the following aspects were found: extrinsic mass effect, annular lesions with spiky folds and steep edges, filling lesions etc. Therefore, the diagnosis of ileal endometriosis should also be considered when we detect something like this, after a barium enema in young, nulliparous women with abdominal or pelvic pain[18]. Enteroclysis is a diagnostic imaging method used for small bowel analysis[3].

Although traditional computed tomography (CT) has been shown to be valuable in assessing pelvic endometriosis, it is limited in diagnosing the intestinal form of this pathology. Multidetector CT (MCTe) enterography appears to be useful in highlighting intestinal endometriosis[3]. Moreover, MCTe can accurately identify the location of endometriotic nodules, as well as the degree of invasion of the endometriotic lesion in the intestinal wall[19].

However, MRI is considered the most useful means of imaging diagnosis of intestinal endometriosis. MRI is useful for the diagnosis of multifocal endometriotic nodules and for defining anatomical relationships, with a sensitivity and specificity of approximately 90%. The endometriotic lesion can be visualized as a mass with high contrast, hyperintense focus on T1-MRI weighted images. Fat suppression on T1-weighted sequences is also suggestive of endometriosis, as it designates either hemorrhagic foci or secondary hyperintense cavities. On T2-weighted images, endometriotic nodules can be seen as hypointense masses with a signal close to that of the pelvic muscles[16]. On both T1 and T2 MRI sequences, the ileum appears thickened, with the appearance of hyperintense round images[13].

Pelvic MRI or sonography may not show lesions beyond the visual field. Thus, the main challenge for the treating medical team is to determine the best diagnostic imaging method for deeply infiltrative intestinal endometriotic lesions. In the assessment of endometriosis located in the colon, there are several diagnostic techniques that use the retrograde distension of the colon. These include: Hydro Colo-CT, barium enema with double contrast and MRI colonography, all demonstrating a good accuracy[20]. However, retrograde filling through the ileocecal valve is not constant. Therefore, none of these techniques is satisfactory for the analysis of the ileal intestinal segment. A combination of CT and enteroclysis has been attempted that may force the opening of the ileocecal valve to improve the diagnosis of terminal ileal endometriosis. However, this technique is invasive and requires ionizing radiation. This is an important disadvantage, especially for young patients interested in preserving fertility[20].

MRI enterography, which uses anterograde opacification, is a radiation-free examination technique that is widely used to investigate various pathologies associated with the small intestine[20].

3.0-T MRI enterography is useful in the preoperative diagnosis, as well as in mapping deep endometriotic intestinal lesions located above the rectosigmoid junction. The ability of MRI to map lesions can guide the surgeon during laparoscopic surgery, as some lesions may be camouflaged by adhesions and others may be erroneously considered superficial in the serosa[20].

3.0-T MRI enterography allows the obtaining of images with high spatial resolution and high contrast resolution, accurately illustrating the presence of deeply infiltrative endometriotic intestinal lesions. 3.0-T MRI enterography is a method that does not use radiation, allowing

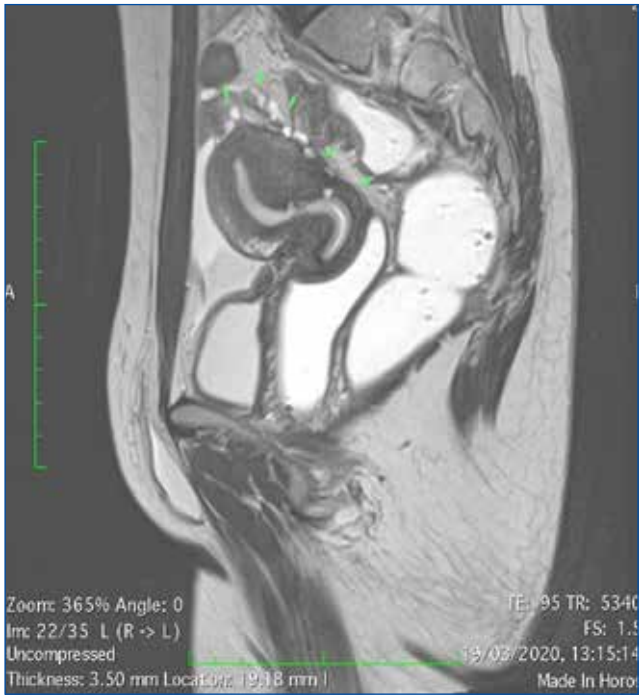

Figure 1. Sequence T2 – MRI

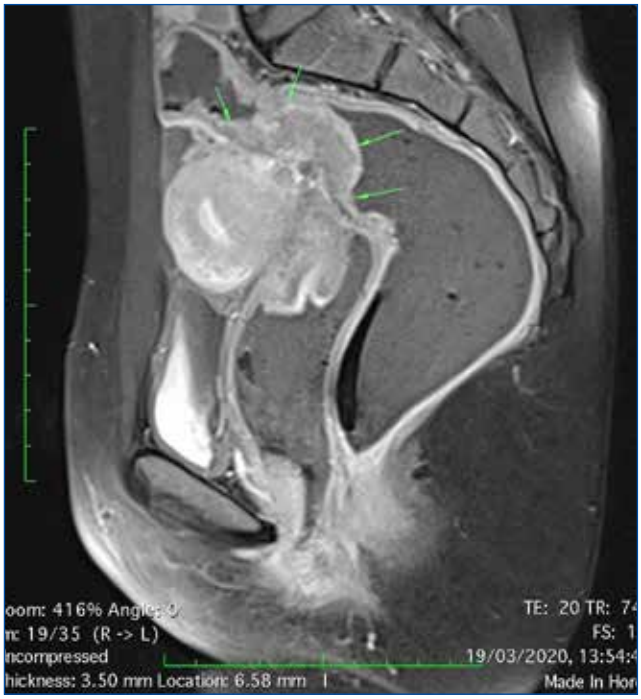

Figure 2. Sequence T1 – MRI

the mapping of endometriotic lesions and being well tolerated by patients[20].

Recent studies in the field support the utility of virtual colonoscopy based on computed tomography (CTC) for the diagnosis of intestinal endometriosis and have compared its usefulness with other diagnostic techniques. The CTC provides accurate information about endometriotic lesions located in both the large intestine and small intestine, providing a multiplanar and anatomical correlation between the lesion and a reference point (anal distance or ileocecal valve). Moreover, the accuracy in obtaining the image is higher compared to MRI, distinguishing very clearly the movements of the intestinal walls or feces[26].

However, the association of the two imaging investigations, MRI with CTC, improves the preoperative evaluation of the colorectal endometriosis, as well as the surgical therapeutic conduct[26].

In the study we performed from 2018 until present on 130 patients, aged between 20 and 41 years old, with planned surgeries for deep endometriosis, interventions performed by the same operating team, we assessed the sensitivity of imaging methods in the diagnosis of ileal endometriosis and multiple sigmoid endometriotic nodules.

Among the imaging methods used during the study, we mention transvaginal ultrasonography, MRI and CTC.

Of the 130 patients included in the study, seven patients were diagnosed with ileal endometriosis. In six cases, the diagnosis was made following scheduled surgery for another location of endometriosis. Of the seven patients, only one refused intestinal segmental resection, and in the remaining cases, ileal segmental resection was performed with ileo-colic anastomosis on the tapeworm of the cecum. These surgical procedures were performed minimally invasive: laparoscopic (five cases), robotic (one case).

It is worth mentioning that the seven patients performed both MRI and CTC. In only one case, the MRI raised the suspicion of ileal lesion, by visualizing an adhesive block formed by intestinal loops and omentum, as seen in Figures 1 and 2.

Also, the CTC detected only the endometriotic lesion with rectosigmoid colon localization.

Discussion

The preoperative diagnosis of intestinal endometriosis offers an advantage to the surgeon, but also a safety for the patient. Thus, surgical emergencies, such as intestinal obstruction, can be prevented[21].

The nonspecific results obtained after the clinical examination and preoperative imaging investigations postpone the diagnosis of this pathology and make the differential diagnosis more difficult. Although rare, ileal endometriosis should be considered when making the differential diagnosis of intestinal obstruction in women of reproductive age[22].

MRI is considered the most useful imaging diagnostic tool for intestinal endometriosis. The data present in the literature argue for a higher sensitivity and specificity of MRI, in terms of diagnosis of endometriotic lesions with rectosigmoid localization, compared to those located in the ileum[3,26].

Although most ileal endometriotic lesions involve the terminal ileum at a distance of 10 cm from the ileocecal valve, endometriosis is a multifocal disease, therefore several lesions with ileal or jejunal localization may occur. Because MRI enterography allows the complete exploration of the small intestine, this method may be more accurate than CT enterography in the diagnosis of ileal intestinal endometriosis[20].

No specific aspects are detected in multidetector helical CT enterography for an intestinal endometriotic lesion, but this imaging method, through its discoveries, can help diagnose ileal endometriosis, in a suitable clinical context[24,25].

However, MRI enterography and CT enterography are not routine investigations among women with gastrointestinal endometriosis, because multiple locations of deep endometriosis often coexist, and the clinical picture is nonspecific. Therefore, the suspicion of ileal endometriosis is low. Rarely, the clinical manifestations suggest an obstructive small bowel syndrome. In reality, there are subocclusive crises that are treated in emergency departments surgery as being caused by another pathology. It should be noted that, in the cases included in our study, the simultaneous presence of endometriotic lesions with ileal and rectosigmoid location was confirmed, as shown in Figure 3.

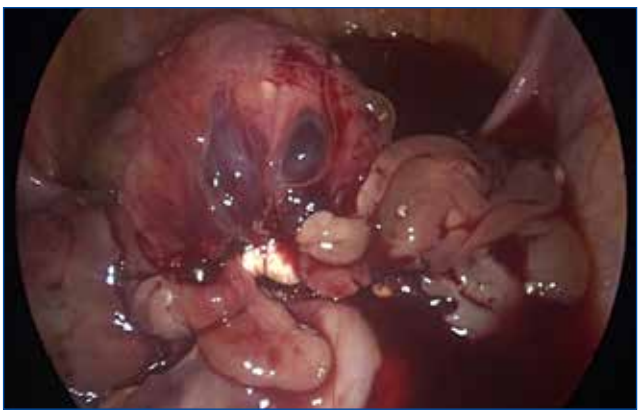

Figure 3. Endometriotic lesion

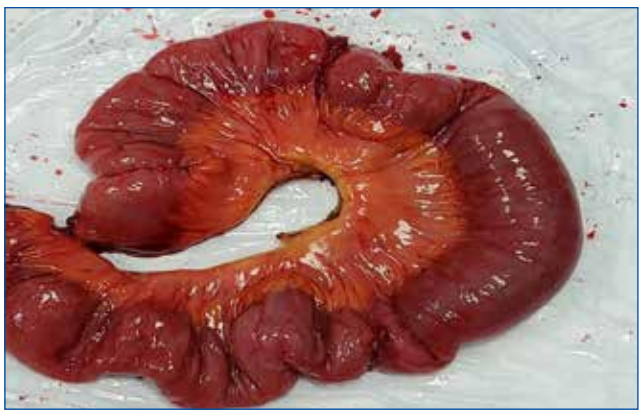

Figure 4. Surgical piece – small intestine

Therefore, following the intraoperative findings, the surgical team decided to perform the rectosigmoid resection simultaneously with the ileal segmental resection. The surgical piece is shown in Figure 4. Because endometriotic nodules which are located in sigmoid colon generate a higher degree of stenosis compared to rectal nodules, it has been found that CTC has a higher diagnostic accuracy than MRI. However, the combination of the two investigations, MRI and CTC, leads to an increased sensitivity in the detection of rectal and sigmoid colonic nodules[26].

Our study shows, so far, that none of the diagnostic imaging methods we used is effective in diagnosing ileal endometriotic lesions.

Conclusions

Given the nonspecific clinical picture of ileal endometriosis, as well as the low sensitivity of the imaging methods used, we can conclude, at least partial, that the diagnosis of this gynecological pathology is a real challenge for the medical team. An imaging method considered the gold standard in the diagnosis of endometriosis with ileal location has not yet been identified.

Therefore, further studies in this area of expertise are needed. In the specialized literature, we can find studies that support an increased concordance between intraoperative and preoperative findings on the presence of rectosigmoid endometriotic nodules, when in the preoperative diagnosis are associated two imaging methods, such as CTC and MRI, compared to each imaging diagnostic technique used individually[26].

The detection rate of ileal endometriosis is low, regardless of the imaging method used. However, in most cases, ileal endometriosis coexists with rectosigmoid endometriosis. Knowing this detail becomes an extremely useful tool for the operating team, that will carefully explore the ileum in order to discover possible endometriotic lesions. ■

Conflict of interests: The authors declare no conflict of interests.

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review articles

Acute CMV infection in pregnancy

Iulian Goidescu[1], Cerasela Mihaela Goidescu[2], Georgiana Nemeti[1], Iulia Popa[1], Mihai Surcel[1], Gheorghe Cruciat[1], Daniel Mureșan[1]

1. First Department of Obstetrics and Gynecology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
2. First Medical Clinic, Department of Internal Medicine, Cardiology and Gastroenterology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
Corresponding author: Cerasela Mihaela Goidescu, e-mail: ceraselagoidescusava@yahoo.com

ABSTRACT

Primary cytomegalovirus (CMV) infection is still a major problem in developing countries despite screening programs. Due to nonspecific symptoms and reduced therapeutic possibilities, the morbidity of this infection may be increased. The confirmation of this infection in the first part of pregnancy requires careful imaging surveillance and, possibly, a confirmation of fetal impairment using invasive methods. Even in the context of normal fetal imaging, the postnatal impairment cannot be completely ruled out, therefore the follow-up of these children in the first years of life is mandatory.

Keywords: CMV, cCMV, neurological impairment, MRI

REZUMAT

Infecția primară cu citomegalovirus (CMV) este încă o problemă importantă în țările în curs de dezvoltare, în ciuda programelor de screening. Din cauza simptomelor nespecifice și a posibilităților terapeutice reduse, morbiditatea acestei infecții poate fi crescută. Confirmarea infecției în prima parte a sarcinii impune o supraveghere imagistică atentă și, eventual, o confirmare a afectării fetale prin metode invazive. Chiar și în contextul unei imagistici fetale normale, afectarea postnatală nu poate fi complet exclusă, motiv pentru care supravegherea acestor copii în primii ani de viață este obligatorie.

Cuvinte-cheie: CMV, cCMV, afectare neurologică, RMN

Introduction

Cytomegalovirus (CMV) is a member of the *Herpesviridae* family, which belongs to DNA viruses, and is common in the general population[1]. The rates of seropositivity in adult women are ranging from 40% (in most European countries) to 90% (in African and Asian countries)[2,3].

Congenital cytomegalovirus infection (cCMV) is the most common non-genetic cause of sensorineural hearing loss (SNHL), accounting for 25-30% of cases of childhood sensorineural deafness[4], and one of the congenital infections that cause significant neurological impairment in children from USA and Northern Europe[5].

Several factors contribute decisively to the underdiagnosis of CMV in childhood, which leads to an increased rate of morbidity and mortality in these infants. These include limited awareness of the CMV infectious risk in both parents and doctors[6,7], lack of recognition of the infection (due to nonspecific symptoms in both pregnant women and newborns), lack of screening programs in some countries, and low effective vaccines and treatment regimens[8].

Epidemiology

Primary CMV infection occurs as a result of close personal contact and is transmitted through fluids, body secretions or vertically (transplacental), leading to congenital infection in the fetus[3].

CMV infection is the most common intrauterine infection, affecting 0.3-2% of live births[9], being defined as active CMV infection when detected in the first three weeks of life[10].

The overall prevalence of cCMV has been estimated around 0.7%, but it varies widely worldwide, being estimated between 0.48% and 1.3% in the United States[10], 0.54% in The Netherlands[11], and 1.08% in Brazil[12].

In the past, symptomatic cCMV infection was considered to occur only after the mother's primary infection during pregnancy, and preexisting maternal immunity prevented the fetus from being at risk for infection in recurrent maternal infection[3]. These assumptions led to the conclusion that populations with high rates of seroprevalence may have a lower risk of primary maternal CMV infection and therefore lower risks of cCMV, which is not entirely true[3]. This assumption was questioned because it was observed that populations with low socioeconomic status and high seropositivity rates in women of reproductive age usually have higher overall rates of cCMV infection (1-2%), compared to the global average (0.4-0.7%)[3].

These observations led to the hypothesis of secondary CMV infections in pregnant women immunized for CMV at conception (either by reactivation of the latent virus or reinfection with a new CMV strain). These infections can also lead to cCMV and fetal infection[13], but with a lower risk rate, around 1.4%[14].

Furthermore, some authors hypothesized that reinfection with a new strain of CMV can lead to a higher risk

of cCMV compared with the viral reactivation, but this has not been clearly established[15].

The incidence of primary CMV infection in pregnant women varies between 0.5% and 4%[1], but only about one third (30-39%) of these infections will result in transmitting the virus to the fetus[3]. The risk of fetal CMV infection is higher with primary maternal infection and less likely with recurrent infection[3].

Also, the severe forms of disease occur more commonly among fetuses whose mothers suffer from a primary infection in the first half of pregnancy, although the viral transmission rate is 8.3%[16], up to 8.8%[17] in the first 18 weeks of pregnancy, compared to the third trimester, when CMV transmission varies between 40% and 70%, but when newborns are more commonly asymptomatic[17,18].

For these reasons, the Society of Maternal-Fetal Medicine recommends explaining to the pregnant women with primary CMV infection that the risk of congenital infection varies, on average, between 30% and 50%, but the severity of the disease cannot be anticipated[19].

What is certain is that determining the timing of CMV infection is important in order to determine the risk of fetal infection[19], the primary infection having a 20-fold higher risk of vertical transmission compared to CMV reactivation or reinfection (30% versus 1.4%)[3].

Maternal diagnosis of CMV infection

1. Clinical

In pregnant women, CMV infection is asymptomatic or usually appears with mild clinical symptoms, and therefore this condition is difficult to recognize if the serology testing on CMV is not done as a routine screening in the first trimester of pregnancy[1]. For these reasons, the CMV infection can be easily overlooked, leading to fetal infection and to congenital CMV[1].

Most studies have shown that less than 5% of pregnant women with primary CMV infection have flu-like syndrome, defined by simultaneous occurrence of fever, pharyngitis, cervical lymphadenopathy, fatigue, malaise, myalgia, headache, hepatosplenomegaly or rash[20,21].

2. Laboratory

Changes in laboratory tests, such as lymphocytosis and increased transaminases, may indicate the presence of CMV infection in 12% to 36% of pregnant women affected by this condition, but these are nonspecific and may be caused by other viral infections[22].

3. Serology

Infectious serological screening is essential for the early detection of CMV infection, but in some countries, such as Australia, New Zealand or USA[3], it is no longer performed, while in other countries (Austria, Belgium, France, Germany, Israel, Italy, Portugal, Spain and The Netherlands) it is carried out only for certain risk groups[23].

However, in Romania, the screening is mandatory in the first trimester of pregnancy, being added to the TORCH profile, along with hepatitis B, C, VDRL and syphilis.

Usually, the presence of IgM antibody indicates an acute infection, but this antibody can be produced during secondary infections, or may be false positive in response to other viral infections, such as Epstein-Barr virus, herpes simplex virus (HSV) or varicella-zoster virus (VZV)[19,24]. IgM can also persist for several months following the primary infection, potentially predating pregnancy by a significant period of time[19]. Therefore, the presence of IgM alone should not be used for diagnosis[19].

The diagnosis of primary CMV infection is made by documenting seroconversion and the appearance of virus-specific IgG antibodies in the pregnant woman serum, previously known as seronegative. The presence of IgG antibodies indicates a past infection, but the time interval from this infection, especially if IgM are also positive, varies from two weeks to one year[25]. Approximately 1-4% of the seronegative women will have a primary infection during pregnancy, and the majority of these women will be asymptomatic[19].

If the IgM CMV antibodies are detected without specific IgG CMV antibodies, the primary infections diagnosis is clear[26]. Unfortunately, this clinical situations is rare, because of the rapid increase of IgG antibodies after the acute infection and due to a decreased of CMV screening in many countries[26].

For this reasons, in countries without CMV screening programs or when we have both the IgM CMV and IgG CMV present, the IgG CMV avidity test is considered essential to establish the infection time or to differentiate a primary infection from the secondary one[3,27,28].

The IgG antibodies produced as a response for the primary CMV infections usually have low avidity, evolving in time for a better bond with the CMV antigens[27,28].

The avidity levels are mentioned as an avidity index, described as the IgG percent bonded to the antigens as a result of the agents distortion treatment, and can be a sensitive marker for a primary CMV infection in the last 4 months[19].

For these reasons, the Society of Perinatal Medicine recommends that for women suspected of primary CMV infection during pregnancy, the diagnose should be made using IgG seroconversion, or by IgM CMV +, IgG CMV + and low IgG avidity[19].

4. Polymerase chain reaction (PCR) testing is a fast and sensitive method in detecting CMV, which has become widely available in recent years and has as its mechanism the amplification of nucleic acids. This technique examines either the well preserved genetic antigens fragments, or some specific DNA fragments – showing a high sensibility in pathogen agent detection[29].

Molecular methods can be used for CMV nucleic acids detections, as well as for viral replication diagnosis from specific cells culture[24].

The CMV may be isolated from several biological samples, including blood, urine, saliva, semen, vaginal discharge and amniotic fluid[24]. Viremia may persist for up to one month after the primary infection, but detectable viremia has also been reported in seropositive women with recurrent infections usually at lower values[30,31].

PCR identification of CMV DNA can be qualitative or quantitative. Quantitative PCR (real-time PCR) allows both the diagnosis and the treatment surveillance in

the severe forms of the disease, but a threshold above which the risk of vertical transmission is higher could not be established[32,33].

The prenatal diagnosis of CMV infection

Only 10-20% of the fetuses exposed to CMV *in utero* will show signs of infection at birth, such as: intrauterine growth restriction, microcephaly, hepatosplenomegaly, thrombocytopenia, parenchymal calcifications of the brain, ventriculomegaly, cerebellar hypoplasia[34]. Furthermore, neurodevelopmental sequelae such as mental retardation and motor/auditory or visual impairment may occur later in life, even in asymptomatic newborns[34].

In case of a primary maternal CMV infection, but without a confirmed fetal infection, the risk of severe fetal sequelae is approximately 3% and the overall risk of fetal impairment is around 8%[19].

The methods used for assessing primary infection are invasive (amniocentesis, cordocentesis) and noninvasive (imaging techniques), the disadvantage of the latter being that some changes may not be visible in the early stages of the infection and also that it cannot assess the severity of the lesions, especially the neurological lesions[35].

1. Invasive prenatal diagnostic techniques: amniocentesis or cordocentesis

The most common method used for prenatal diagnosis of CMV fetal infection is amniocentesis[36,37]. The cordocentesis may be performed, having a sensitivity and specificity similar to those of amniotic fluid CMV testing, but with a higher complications rate compared to amniocentesis[36,37], which is why the usefulness in cCMV prenatal diagnosis is disputed[24].

The prenatal diagnosis of cCMV can be made either by viral cell culture or by detecting CMV DNA in an amniotic fluid sample using PCT or real time PCR[24]. The molecular diagnosis by PCR is currently preferred to CMV culture, due to a higher sensitivity (90% to 100%)[5].

Although the amniotic fluid CMV-PCR is a test with increased sensitivity and specificity, it depends on when the amniocentesis is performed[22,24]. The amniotic fluid taken before 21-22 weeks of pregnancy or less than 6 weeks after the primary maternal infection may have an undetectable CMV load due to the time required for CMV to be excreted by the fetal kidney, which is the primary site of viral shedding[22,24].

As a result, the Maternal-Fetal Medicine Association recommends carrying out amniocentesis for CMV detection after 21 weeks in pregnancy or more than 6 weeks since the primary maternal infection[19].

The use of real-time PCR allows a quantitative determination of the viral load, but currently there are differences of opinion regarding its value due to an increased risk of fetal complications. Some authors claim that a CMV viral load of more than 10^3 copies/ml in amniotic fluid correlates with fetal infection, and that viral loads higher than 10^5 copies/ml are associated with more severe forms of the disease[38]. Other groups of investigators claim that a viral load in the amniotic fluid of more than 10^5 copies/ml was associated with symptomatic infection in the newborn or fetus[38,39], while others failed to establish a clear link between the viral load and the degree of fetal/neonatal impairment[40,41].

For this reasons, the professional forums recommend caution in assessing the degree of fetal impairment only on the basis of the CMV viral load from the amniotic fluid[5].

2. The imagistic/imaging investigations

The imagistic studies in cCMV have two main objectives: detecting the fetal structural abnormalities for confirming the fetal impairment, and providing information on fetal prognosis[42].

However, certain sequelae of cCMV, such as chorioretinitis, petechiae and neurodevelopmental disorders, are not detectable by prenatal imaging methods, so the absence of imaging abnormalities does not rule out fetal impairment[43].

At a cellular level, CMV is able to affect multiple cell lines, nonetheless his action is targeted on the fetal brain and kidney[2,44,45]. In neurons, astrocytes, glial cells and endothelial cells, CMV causes a number of changes in the neuronal proliferation and migration, as well as in the organization of cortical cells[44,45].

While ultrasound is the method of choice for fetal imaging, being easy and more accessible, MRI can bring additional information especially in the detection of fetal brain abnormalities, both structural and functional (metabolic)[46].

■ Ultrasound examination

Fetal structural changes identifiable through prenatal ultrasounds are: cerebral abnormalities, such as ventriculomegaly, brain calcifications, microcephaly, occipital horn variations, and non-cerebral abnormalities, such as echogenic bowel, intrauterine growth restriction, hepatosplenomegaly, ascites and cardiomegaly[35,47], growth in placental width (enlarged placenta – due to placental inflammation)[48], oligohydramnios and, seldom, polyhydramnios[2]. Rare lesions, such as subependymal cysts or intrahepatic calcifications, have also been reported, but these changes need to be confirmed by other studies[47].

The neurological ultrasound examination in the cCMV-confirmed cases is essential, because the cranial abnormalities like ventriculomegaly and microcephaly are associated with a poor neurocognitive prognosis[49].

The intracranial calcifications are a classic sign found in cCMV, usually described by ultrasound, being observed in the basal ganglia, as a manifestation of lenticular vasculopathy, but also in the cerebral parenchyma[50]. Furthermore, according to Doneda et al., the suspicion of cCMV should be raised when these intracranial calcifications are detected in the anterior temporal lobe, also called "polar temporal lesion"[51].

The hyperechoic intestine is a classic ultrasound sign of cCMV, although it is sometimes overestimated[52], being caused either by direct injury of the virus to the intestine, or by intraamniotic hemorrhage[53].

cCMV is associated with an increased risk of fetal death *in utero*, even in the absence of suspicious ultrasound changes[43].

Magnetic Resonance Imaging (MRI)

Fetal MRI can be used especially in the detection of neurological abnormalities, particularly if the ultrasound has detected abnormalities at this level[54].

Fetal MRI is complementary and often superior to ultrasound in detecting abnormal gyration and myelination[51,55].

The timing to perform fetal MRI in cCMV is not well established, being preferred at the beginning of the third trimester (27-33 weeks of gestation), because some lesions, such as neuronal migration, are more difficult to detect in the first two trimesters[50,54].

The lesions identified by MRI in cCMV are often nonspecific, the most common abnormalities observed being ventriculomegaly and white matter (WM) signal abnormalities or cerebellar hypoplasia[42,56]. Other brain lesions that can be seen on MRI are cerebral cysts, dilation of the temporal horns, ventriculitis and intracranial calcifications[50,51].

Congenital CMV infection affects the germinal matrix, leading to the loss of neurons and their disruption of migration when the infection occurs before 16-18 weeks of gestation[2,50]. Lissencephaly and polymicrogyria can be seen in infections that occur between 18 and 24 weeks, while fetuses exposed to CMV in the third trimester usually have a normal gyral pattern[2,50].

Polimicrogyria occurs mainly in the frontal and perisilvic regions, due to a neural migratory disorder[57].

Hoffman et al.[58] found, using MRI examination, that the volume of the brain is smaller in fetuses with cCMV, an observation also confirmed by Grinberg et al.[9] One possible explanation of these MRI modifications could be the loss of neuronal stem cells, the disruption of migration and the differentiation of brain stem cells, as well as accentuated local inflammation and hypoxia[44].

Furthermore, Grinberg et al. found on MRI examination that there is a correlation between low cerebellar volume and neurobehavioral disorders in childhood, especially for daily activities and communication skills[9]. There is an association between cerebellar lesions and the presence of some cognitive disorders, such as speech, behavioral, social and motor deficiencies[9,59].

Cerebellar abnormalities are a common feature in postnatal MRI for cCMV[60], but are less common in fetal MRI, either due to the fact that they occur later in pregnancy, or to the fact that children with symptomatic cCMV undergo more detailed imaging examinations[51,61].

Cerebellar hypoplasia and dysplasia can affect the vermis, cerebellar hemispheres, or both, and are associated with a high risk of childhood sequelae[2,51].

Other abnormalities of cCMV identifiable on MRI are: hepatomegaly, splenomegaly, intrauterine growth restriction (FGR), hyperechoic bowel, cutaneous edema, ascites, pleural and pericardial effusion, hydrops, oligo-/polyhydramnios and placentomegaly[48,62].

The isolated cases of hyperechoic bowel detected on ultrasound without other organic lesions are associated with normal MRI and a good prognosis[43].

In situations where both MRI and ultrasound are normal, the fetal prognosis is good and the rate of major complications in childhood is low[63].

However, normal brain imaging does not completely rule out the presence of neurodevelopmental disorders in childhood, especially since hearing loss is frequently progressive in cCMV.

The postnatal diagnosis of CMV infection

Congenital cytomegalovirus infection is the most common non-genetic cause of sensorineural hearing loss, accounting for 25-30% of cases of childhood sensorineural deafness[4].

Between 5% and 10% of the newborns with congenital cytomegalovirus infection are symptomatic, mainly the central nervous system being affected[64]. On the other hand, the majority of the asymptomatic infants remain unidentified due to the lack of clinical manifestations[5].

The most common symptoms in the cCMV infection are jaundice, petechiae, hepatosplenomegaly and neurological anomalies, such as microcephaly and intracranial calcifications, which are found in up to 75% of cases[3,65]. Less frequent signs that can also be observed are cataract, microphthalmia, myocarditis and cardiac defects[3,65].

Hepatobiliary abnormalities, confirmed by increased transaminases and conjugated hyperbilirubinemia, can be seen in 23-80% of symptomatic newborns, but they are only transient, with normalization in a few weeks[3,65].

The congenital CMV infection diagnostic can be confirmed by identifying the virus or the viral antigens in the newborns' urine or saliva in the first two weeks of life[5]. The presence of the virus or viral antigens after three weeks alone cannot confirm cCMV, because after this interval the CMV infection can be one acquired at birth or postnatal[5].

The serological methods are not very accurate for the postnatal confirmation of the diagnosis of cCMV, because the detection of CMV-IgG antibodies in fetal blood may be due to transplacental transfer of maternal antibodies, and the detection of CMV-IgM antibodies do not have a high level of sensitivity and specificity[66].

Treatment

The effectiveness of antiviral treatment during pregnancy is still a hot topic, due to the questionable efficacy and potential teratogenic risk of drugs. The clinical benefits of CMV-specific hyperimmune globulin treatment are also disputed, due to the discordant results obtained from various studies[16,67].

The treatment options for cCMV infections are still limited, because most drugs act by inhibiting CMV viral replication, but cannot remove the virus from the human body. It has also been observed that, after stopping antiviral therapy, the viral load in the blood tends to increase[68].

Studies have shown that a six-week course of ganciclovir, started in the neonatal period, is effective in reducing the severity of neurological sequelae and hearing loss in both symptomatic and asymptomatic infants[69,70], but unfortunately there is no benefit of a long-term use[68].

Regarding the antenatal use of CMV hyperimmune globulin (CMV HIG) to prevent infection in newborns, in a study published in 2014, the authors found no benefit

of treatment, but there were a number of side effects in those who received CMV HIG[67].

The American College of Obstetricians and Gynecologists (ACOG) does not currently recommend the prenatal treatment with ganciclovir or valaciclovir because it has not been shown to be effective[71]. These observations are also reinforced by the Society of Maternal-Fetal Medicine, which does not recommend the prenatal treatment with ganciclovir or valaciclovir or the antenatal therapy, either with antivirals or with CMV HIG[19].

Conclusions

CMV remains the leading infectious cause of birth defects in both the fetus and the newborn.

An increasing number of evidence indicates that the CMV reinfection during pregnancy contributes to a much larger proportion of symptomatic cCMV than was previously supposed.

For this reason, avoiding exposure of pregnant women to CMV or serological screening should be recommended for both seronegative and seropositive pregnant women.

In cases of confirmed or suspected primary maternal CMV infection, amniotic fluid viremia obtained by amniocentesis, as well as prenatal ultrasound and, possibly, MRI evaluation are required to determine the risk of cCMV and to assess the possible fetal damage.

MRI can bring additional information especially in the case of brain abnormalities and can achieve a better assessment of the neonatal prognosis. ■

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review articles

Elective oocyte cryopreservation: can we expand the women's reproductive lifespan?

Carina Ragea[1], Nicolae Gică[1,2], Radu Botezatu[1,2], Gheorghe Peltecu[1,2], Anca Maria Panaitescu[1,2], Corina Gică[1]

1. Filantropia Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania
2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Corresponding author: Nicolae Gică, e-mail: gica.nicolae@umfcd.ro

ABSTRACT

Objective. Oocyte cryopreservation is being offered to women who wish to defer childbearing. Elective oocyte cryopreservation provides women the possibility to prevent involuntary childlessness due to age-related infertility. The purpose of this review is to summarize recent data regarding the outcomes and economic implications of elective oocyte cryopreservation. **Recent findings.** Oocyte vitrification has comparable *in vitro* fertilization (IVF) outcomes as fresh oocytes. Although evidence about the outcomes of IVF cycles in the population who undergoes elective oocyte vitrification is limited, new studies are starting to emerge. The age at retrieval and the number of available oocytes are the most important factors that improve a woman's chance of having a baby. Biologically, the ideal age of cryopreserving is <35 years old. However, the majority of studies show that elective fertility preservation is more cost-effective at 37-38 years old. When counseling women who take into consideration postponing motherhood, they should be informed of the complications associated with pregnancy at an advanced maternal age. **Conclusions.** Elective oocyte cryopreservation is a strategy that helps women gain the reproductive autonomy they need for deferring childbearing. Given the increasing interest toward elective oocyte cryopreservation, clinicians need to properly counsel and inform women about the limitations of this procedure. Oocyte vitrification does not guarantee success, but increases the likelihood of having a child later in life.

Keywords: oocyte cryopreservation, reproductive lifespan, oocyte vitrification

REZUMAT

Obiectiv. Femeile care doresc să amâne concepția au posibilitatea de a crioprezerva ovocite. Acestea pot fi utilizate la o vârstă mai înaintată, atunci când femeile decid să obțină o sarcină. Crioprezervarea electivă de ovocite le oferă femeilor șansa de a preîntâmpina infertilitatea cauzată de vârsta maternă avansată. Această recenzie a literaturii are ca scop sintetizarea celor mai recente studii privind ratele de succes ale crioprezervării elective de ovocite, respectiv implicațiile financiare inerente. **Constatări recente.** Procedurile de fertilizare *in vitro* (FIV) cu ovocite vitrificate au rezultate similare cu ale procedurilor efectuate cu ovocite proaspete. Informațiile privind succesul ședințelor de FIV la pacientele care au crioprezervat ovocite electiv sunt limitate, însă noi studii despre acest subiect încep să apară. Cei mai importanți factori care influențează șansele unei femei de a avea un copil sunt vârsta la momentul prelevării de ovocite și numărul de ovocite vitrificate. Din punct de vedere biologic, vârsta ideală pentru crioprezervare este sub 35 de ani. Cu toate acestea, din punctul de vedere al cost-eficienței, majoritatea studiilor arată că vârsta indicată pentru prezervarea electivă de ovocite este de 37-38 de ani. Atunci când clinicienii consiliază o femeie privind amânarea concepției primului copil, este necesar ca aceasta să fie informată despre complicațiile asociate unei sarcini la o vârstă înaintată. **Concluzii.** Crioprezervarea electivă de ovocite este o procedură strategică prin care femeile își pot exercita autonomia reproductivă, oferindu-le posibilitatea de a-și extinde fertilitatea. Având în vedere tendința tot mai mare a femeilor de a-și dori copii la o vârstă mai târzie, cât și interesul crescut pentru crioprezervarea de ovocite, clinicienii au datoria să consilieze și să informeze femeile privind limitările acestei proceduri. Deși vitrificarea de ovocite nu garantează succesul concepției, aceasta crește șansele unei femei de a avea un copil la o vârstă mai înaintată.

Cuvinte-cheie: crioconservarea ovocitelor, perioada de viață fertilă, vitrificarea ovocitelor

Introduction

Elective oocyte cryopreservation (EOC), also known as social egg-freezing, was defined by the ANZSREI consensus as a "a strategy to improve a woman's longitudinal fertility potential with her own oocytes in the absence of a medical diagnosis of infertility or contraindication to pregnancy"[(1)].

Originally, cryopreserved oocytes were used for women with a medical need for these procedures, such as patients diagnosed with premature ovarian insufficiency, endometriosis, or those who underwent oophorotoxic cancer treatment. Subsequently, the opportunity rose to cryopreserve oocytes solely for elective fertility preservation (EFP) purposes. This seems to overcome the age-related infertility issue, a growing problem in our current society.

Elective oocyte cryopreservation offers women the possibility to prevent involuntary childlessness due to

age-related infertility. Furthermore, women can have children who are biologically related to them, in contrast to the other options that are available such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with donor oocytes.

In the past years, there has been an increasing number of women who wished to delay childbearing because of different personal reasons. The main problem which occurs for these women is the decreasing fertility that comes with aging. EOC is a strategy that helps women gain the reproductive autonomy they need for deferring childbearing. This is both an opportunity and a challenge for the healthcare provider because these women need proper counseling. This strategy is costly and can raise false hopes. For this reason, women should be accurately informed and have realistic expectations before taking a decision.

The average age of women who have their first child is increasing. Women choose to defer childbearing because of the following reasons: the absence of a partner (this being the main reason), seeking higher education, career prioritization, financial reasons, or psychological reasons such as not being prepared for parenthood[2].

It is known that both ovarian reserve and oocyte quality decrease with age. Fertility in women starts to decrease gradually beginning with the age of 32 years old and declines steeply after the age of 37[3]. Simultaneously, the risk of miscarriage increases abruptly, from approximately 11% in the third decade of life to 93% over the age of 45 years old[4]. This results in a rise of involuntary childlessness. The risk of involuntary childlessness increases from 2% to 3% for women younger than 30 years old, to 36% for women of 40 years or older[5].

Habbema *et al.* created a simulation that took into account the age-related fertility decline and the IVF success rates as a means to determine the ideal age of starting a family for a couple to achieve their desired family size. The simulation proposed that, in order to have a chance of at least 90% to conceive, couples should start trying to conceive when the female partner is 35 years old or younger, in case IVF is an acceptable option. To conceive two or three children, the conception should begin when the female partner is 31 or 28 years of age, respectively. If the couple does not accept IVF, they should start no later than the age of 32 years old for a one-child family, at 27 years old for a two-child family, and at 23 years old for having three children[6].

After slow freeze protocols of oocytes have been replaced with vitrification, emerging evidence has shown that IVF with cryopreserved oocytes is both safe and has comparable pregnancy rates as IVF/ICSI with fresh oocytes[7-9]. In 2013, this led the American Society for Reproductive Medicine to remove the experimental status of oocyte cryopreservation when this procedure is medically indicated for fertility preservation. However, they report a lack of data supporting the "safety, efficacy, ethics, emotional risks, and cost-effectiveness of oocyte cryopreservation" when it is used for the sole purpose of deferring childbearing[10]. On the other hand, the European Society of Human Reproduction and Embryology stated that "oocyte cryopreservation should not just be available for women at risk of premature pathogenic or iatrogenic fertility loss, but also for those who want to protect their reproductive potential against the threat of time"[11].

Currently, oocyte cryopreservation is receiving increasing promotion and public acceptance. Therefore, this review has the purpose to evaluate the existing data regarding the birth outcomes, efficiency and the costs of elective oocyte cryopreservation, and aims to guide clinicians working with women considering elective oocyte cryopreservation.

Outcomes of elective oocyte cryopreservation

Most data available today regarding the outcomes of IVF derive from IVF using donor oocytes, which come from young women and have a survival rate of over 95%[9]. This is not the case for EOC, because women choosing EOC are usually over 35 years old at the time of oocyte retrieval. The oocytes have a poorer quality and are less resistant to the freeze-warming process than oocytes from the younger oocyte donor population. Therefore, women choosing to cryopreserve oocytes electively need a higher number of oocytes per pregnancy achieved than donor oocytes[12].

The evidence is scarce in literature about the outcomes of IVF cycles in the population who undergoes elective oocyte vitrification. On one hand, this is a relatively new concept and, on the other hand, women who cryopreserved their oocytes haven't yet decided to return and use them.

Table 1 and Table 2 present the success rates of IVF conducted with cryopreserved oocytes for elective nonmedically-indicated fertility preservation in three studies[12-14]. They all concluded that the age at retrieval and the number of available oocytes are the most important factors that increase a woman's chance of having a baby.

Cobo *et al.*[13] reported that the age at retrieval and the number of oocytes are the main factors that influence the success rate of achieving a pregnancy. The study showed that women ≤35 years old who used 10 mature oocytes had twice the success rate to achieve a live birth (60.5%) than women ≥36 years old who used the same number of oocytes and had a 29.7% likelihood of live birth. Regarding the number of oocytes which needed to be cryopreserved, they concluded that at least 8-10 metaphase II (MII) oocytes should be vitrified to obtain a reasonable success rate. Additionally, the cumulative live birth rate (CLBR) was higher and increased faster in younger women. The CLBR of women <35 years old raised from 15.4% for five oocytes to 40.8% for eight oocytes, reaching a plateau of 85.2% above 15 oocytes. For women older than 36 years old, the increase in CLBR was slower from 5.1% to 19.9% for five and eight oocytes, respectively. The CLBR plateau for this group was reached with 11 oocytes (35.6%).

Doyle *et al.*[14] compared the outcomes of IVF with both fresh and frozen oocytes to assess the likelihood

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	No. of patients who returned for IVF (% of total patients with co)	Mean time of storage	Mean age at cryopreservation	CLBR	
				≤35y/38y*	>35y/38y*
Cobo *et al*. (2016)	137 (9.3%)	2.1 years	37.7	50%	22.4%
Doyle *et al*. (2015)	117 (9.9%)**	2 years	34.9	60.2%	43.9%
Cobo *et al*. (2018)	641 (12.1%)	2.1 years	37.2	68.8%	25.5%

** 38 years in Doyle et al. (2015)*
*** 31 patients electively cryopreserved oocytes for nonmedically-indicated fertility preservation*
co = cryopreserved oocytes
CLBR = cumulative live births rate

	CLBR for at least 1 baby		No. of oocytes
	≤35y/38y*	>35y/38y*	
Cobo *et al*. (2016)	60.5%	29.7%	10
	85.2%	35.6%	15
Doyle *et al*. (2015)	55-60%	25-40%	10
	68-70%	30-50%	15
Cobo *et al*. (2018)	42.8%	25.2%	10
	69.8%	38.8%	15

** 38 years in Doyle et al. (2015)*
NS - not specified
CLBR = cumulative live births rate

of live birth per each oocyte depending on the age of the patient at retrieval. They suggested that 15-20 MII oocytes should be cryopreserved for women aged <38 years old (with approximately 70-80% chance of at least one live birth) and 25-30 MII oocytes for women aged 38-40 years old (with approximately 65-75% chance of at least one live birth). They found that women under 38 years old at oocyte retrieval have better chances of achieving a pregnancy than those over 38 years old (60.2% compared with 43.9%, respectively).

This study also concluded that using warmed vitrified oocytes has similar outcomes as using fresh oocytes, proving that oocytes cryopreservation is an effective method and confirming what other studies already revealed[8,9].

The study of Cobo *et al.*[12] is the largest study published to date and presents the outcomes of IVF cycles of 641 patients who cryopreserved oocytes for elective fertility preservation purposes. According to this study, women aged under 35 years old who cryopreserved 8-10 oocytes have a CLBR of approximately 30% and 45%, respectively. Furthermore, with 15 oocytes, the success rate can reach 70%. On the other hand, older patients (>35 years old) need more oocytes to achieve the same chances of having a baby as younger women, but the CLBR plateau is reached much earlier (50%). The CLBR of patients aged ≤35 year old was 68.8%, while the CLBR of patients aged >35 year was 25.5%. They emphasize the fact that the most important factor that impacts the success rate of IVF is the age at retrieval, proposing that, ideally, women should cryopreserve oocytes when aged ≤35 years old. Moreover, improved outcomes are reached when a higher number of oocytes are available, 10-15 oocytes being an indicated number.

Cost-efficiency

From a biological point of view, it is clear that the earlier a woman cryopreserves oocytes, the more chances she has for a successful IVF at the moment she decides to have children. However, these oocytes are less likely to be needed when women cryopreserve at very young ages, because they have a high probability of spontaneously conceiving a pregnancy. To determine the optimal timing for elective oocytes cryopreservation, one must balance the costs and benefits of this procedure.

Devin *et al.*[15] designed a model to determine whether cryopreserving oocytes at the age of 35 years old with the intention of using them for IVF at the age of 40 is more cost-effective than attempting pregnancy and, if needed, undergoing conventional IVF at the age of 40 years old. They concluded that oocyte cryopreservation before 38 years of age reduces the cost to obtain a live birth. Moreover, oocyte cryopreservation at the age of 35 years old in women intending to delay pregnancy until 40 years old would decrease the cost per live birth from around $55,000 to roughly $40,000 (with the likelihood of live birth increasing from 42% to 62%).

Another model[16] analyzed the optimal timing for cryopreserving oocytes from the cost-efficiency point of view. They found that performing oocyte cryopreservation at ages <34 years old ensures the highest probability of live birth (>74%). Instead, cryopreserving at the age of 37 years old compared to taking no action offers women the best chances of having a baby while being also the most cost-effective.

Van Loendersloot *et al.* demonstrated that, for a woman deciding to have a child at the age of 40 years old, cryopreserving oocytes at the age of 35 is the most cost-effective solution. They took into account three strategies: strategy 1 – women cryopreserve oocytes at the age of 35 and then at the age of 40 use these oocytes; strategy 2 – women at the age of 40 years old try to conceive without treatment; strategy 3 – women at the age of 40 years old attempt to conceive and, if not pregnant after one year, undergo IVF using freshly obtained oocytes. The results were as follows: strategy 1 had a live birth rate of 84.5% at an average cost of € 10,419; strategy 2 had a live birth rate of 52.3% at an average cost of € 310 per birth; strategy 3 had a live birth rate of 64.6% (31.4% after IVF and 33.2% after natural conception) at an average cost of € 7798. As they concluded in determining the success and cost-effectiveness of oocyte cryopreservation, the best results were achieved with strategy 1.

We can observe that a dilemma is emerging when considering the ideal age of cryoperserving oocytes. On one hand, biologically, the ideal age of cryopreserving is <35 years old and, on the other hand, the majority of studies show that elective fertility preservation is more cost-effective at 37-38 years old. Taking this into account but considering also that the chances of having a baby decrease when women vitrify at 36 years old or over, Cobo *et al.*[17] advise women to cryopreserve at the age < 36 years old. The Australasian ANZSREI consensus recommends that the best age to undertake oocyte cryopreservation is before 36 years old, although this would not be as cost-efficient as cryopreservation at the age of 37 years old. They state that at a younger age oocytes are of higher quality and of a greater number, which increases the likelihood of a live birth[1].

Obstetrical considerations

Elective cryopreservation of oocytes offers the opportunity to expand the reproductive lifespan of women, meaning that women who defer childbearing will become pregnant at a later age. We cannot disregard the remaining complications associated with pregnancy at an advanced maternal age (defined as >35 years old). When counseling women who take into consideration postponing motherhood, they should be informed about these risks. Advanced maternal age presents risks such as gestational diabetes, fetal growth restriction, preterm birth, labor complications and operative delivery. Additionally, women over the age of 40 have a higher prevalence of hypertensive disorders of pregnancy and almost twice the risk of developing preeclampsia[2,18]. Nevertheless, these risks are the same as those in older women using conventional IVF[19].

The American Society for Reproductive Medicine committee advises that woman over 45 years old considering IVF with donor oocytes should be counseled regarding the obstetrical risks, the state of health of both parents, the physical and emotional challenges of raising a child, the possible impact on the child of having older parents, and the possibility of parental death before the child reaches adulthood[20]. The same counseling should be given to women who are considering to cryopreserve oocytes and use them at an advanced age[18].

Conclusions

In today's society, women are driven to postpone motherhood at the expense of losing their reproductive capacity. Oocyte cryopreservation provides the opportunity to extend fertility beyond a woman's natural reproductive lifespan. In comparison with IVF, with donor oocyte vitrifying, their oocytes give the woman the possibility to have genetically linked children. With these new emerging topics and increasing interest toward it, healthcare providers have the responsibility to counsel women about the optimal time, success rates, the number of cryopreserved oocytes sufficient to achieve live birth and financial costs of cryopreservation, but also about the health risks arising with an advanced maternal age. It is important not to raise false hopes, especially because these women are undergoing a medical procedure only as a form of insurance against future declines in their fertility potential. The message of ESHRE remains that women should be primarily advised that the best chance of having a child is through natural reproduction at a relatively early age. They emphasize the need for official protocols to regulate elective oocyte cryopreservation[11]. However, for women who do not have the option of naturally conceiving and wish to delay childbearing, oocytes cryopreservation offers a reasonable alternative. ■

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Myasthenia gravis and pregnancy

Crisanda Vîlciu[1], Bogdan Marius Istrate[2]
1. "Mareș-Bulandra" Neurology Clinic, Fundeni Clinical Institute, Bucharest, Romania
2. University Hospital Antwerp, Belgium

ABSTRACT
A chronic neuroimmunological disorder of the neuromuscular synapse, caused by the direct attack of antiacetylcholine receptor antibodies at the end of the motor plate, *myasthenia gravis* can be a diagnostic trap and a great challenge for any clinician. Being a multifaceted disease that affects the muscular system on different muscle groups, dramatically exhausting the patient, this disease makes its impact felt also in the obstetric practice. The expectant mothers with *myasthenia gravis* have their anxieties and insecurities about the various aspects of the manifestation of the disease during pregnancy and then on the newborn. At present, in our country, there are no official publications dedicated exclusively to this issue, which is why, through this article, we try to point out important aspects of *myasthenia gravis*, meant to support young mothers, neurologists, anesthetists and obstetricians.
Keywords: *myasthenia gravis*, pregnancy, obstetrics, newborn

REZUMAT
Afecțiune cronică neuroimunologică a sinapsei neuromusculare, cauzată de atacul direct al anticorpilor antireceptor pentru acetilcolină la nivelul terminațiilor plăcii motorii, *myasthenia gravis* poate fi o capcană de diagnostic și o mare provocare pentru orice clinician. Fiind o boală cu multe fațete, care afectează sistemul muscular la nivelul unor diferite grupe de mușchi, epuizând dramatic pacientul, această maladie își face simțit impactul și în practica obstetricală. Viitoarele mame miastenice au angoasele și nesiguranța lor, cu privire la diversele aspecte ale manifestării miasteniei pe parcursul sarcinii și apoi asupra nou-născutului. În prezent, la noi în țară nu există publicații oficiale consacrate și dedicate exclusiv acestei problematici, tocmai de aceea încercăm, prin intermediul acestui articol, să punctăm unele aspecte importante ale *myastheniei gravis*, menite să vină în sprijinul tinerelor mame, medicilor neurologi, anesteziștilor și obstetricienilor.
Cuvinte-cheie: *myasthenia gravis*, sarcină, obstetrică, nou-născut

What is *myasthenia gravis* and how can it be diagnosed?

Myasthenia gravis (MG) is an autoimmune disorder affecting nearly 1 million individuals worldwide[1], being diagnosed typically in the second and third decades of life. *Myasthenia gravis* is defined by muscle weakness caused by defective function of the acetylcholine (AChR) receptors at the neuromuscular junction[1,2] as a consequence of a direct autoantibodies attack against the AChR receptors[3]. Tumors and thymus hyperplasia can cause an aberrant synthesis and production of these autoantibodies. The clinical severity of MG varies from pure ocular muscle involvement (ocular MG) to generalized muscular weakness (generalized MG).

The diagnosis of MG is made following clinical and physical examination and is confirmed by serum immunodiagnose to measure autoantibody levels. The diagnosis of myasthenia should be made carefully, by corroborating the clinical aspect and the clinical outcome of the patient.

The stages of the clinical diagnosis include the following aspects:

- physical examination (myasthenic score QMG, adapted in our clinic after Cincă and Ion, in 1974);
- electromyogram (repetitive nerve stimulation/single fiber electromyography);
- laboratory tests – immunoserology, in order to detect the antibody titer;
- chest computer scan for thymus.

Myasthenia gravis treatment and management during pregnancy

Generally, MG does not affect pregnancy to a considerable extent. There is no increased risk of low birth weight, spontaneous abortion or a given prematurity degree of the newborn, although an increased risk of premature rupture of membranes does exist in myasthenic women, the reason of which is not very clear enough and documented[4].

The pharmacologic treatment for MG is commonly centered on increasing the levels of AChR and decreasing the production of autoantibodies.

The medical treatment should not be interrupted during pregnancy; anyhow, it might need to be influenced depending on disease severity or exacerbations[5].

The ideal management of MG during pregnancy requires a multidisciplinary team participation, including obstetrician, anesthesiologist, neonatologist/pediatrician, also by assuring a good contact by the patient and relatives.

Other aspects that must be considered, but without detailing them in this article, are:

- prenatal counseling;
- antenatal care;
- specific drugs- and pregnancy-related problems;
- breast feeding (the impact and the effects of MG medication on lactation and breastfeeding safety).

Myasthenic crisis in pregnancy

Myasthenic crisis in the context of pregnancy is rare and requires unique management challenges for emergency physicians. In general, if the treatment of myasthenia during pregnancy is well dosed and administered, there are no complications. In case of a myasthenic crisis during hospitalization for childbirth or during labor (rarely), the means of intensive care are used. In the following, we will point out this important aspect for both intensivists and gynecologists. The histological constitution of the uterus is defined by the presence of smooth muscle, not being affected by the presence of ACh receptor antibodies, and vaginal delivery is desired and recommended[6,7]. A possible myasthenic crisis during the hospitalization of the pregnant woman can be announced by the following pathophysiological features: acute onset cough, increased secretions, dyspnea, nasal congestion, sore throat, dysphagia, resting dyspnea and generalized weakness, increasing difficulty clearing her secretions. Generally, these symptoms worsen in the evening, being followed by the alterations of the specific vital signs given to this clinical context: blood pressure (sometimes), heart rate, respiratory rate, oxygen saturation/fraction of inspired oxygen by facial mask, arterial blood gasometry. Testing for rhinovirus/enterovirus can be useful, as well.

The respiratory testing is a helpful tool for the intubation prognostic, and should be taken seriously into account, given that early intubation is critical[8]. There are unforeseen, emergency situations when plasmapheresis is needed. After the pregnancy plasmapheresis sessions, the patient must be transferred and supervised in an antepartum service. There is also an increased risk of preterm birth concerning congenital myasthenic syndrome, although this is the resultant of a polyhydramnios caused by the loss of fetal swallowing[9]. Myasthenia has not been found to increase the risk of fetal death, growth restriction or preeclampsia[10]. Still, as it happens, in preeclampsia or eclampsia, magnesium sulfate is contraindicated, as it affects the motor endplate, blocking acetylcholine release and worsening myasthenia.

The effects of myasthenia on labor and delivery

One aspect that raises questions is the impact of labor and expulsion of the fetus, due to "the myasthenic muscle" contractions related to this physiological act. Pregnancy with *myasthenia gravis* is known to be correlated with an increased caesarean section rate, doubtless due to maternal fatigue in the course of labor. Even though the uterine muscles, which consist of smooth muscles, are barely affected in *myasthenia gravis*-complicated pregnancies, the voluntary muscle weakness can be aggravate due to the expulsive efforts during the second stage of labor, and fatigability can lead to respiratory distress[11]. The patients can lose strength after the third expulsive effort. There are particular cases when the administration of oxytocic drugs and vacuum-assisted delivery are a beneficial option. The apparition of respiratory distress, bulbar symptoms and muscle weakness must be carefully checked during labor. Briefly, vaginal delivery in pregnant myasthenic woman should be encouraged. Caesarean delivery shall be carried out only for obstetrical reasons, as surgery might often associate the worsening of the disease and can even precipitate myasthenic crisis.

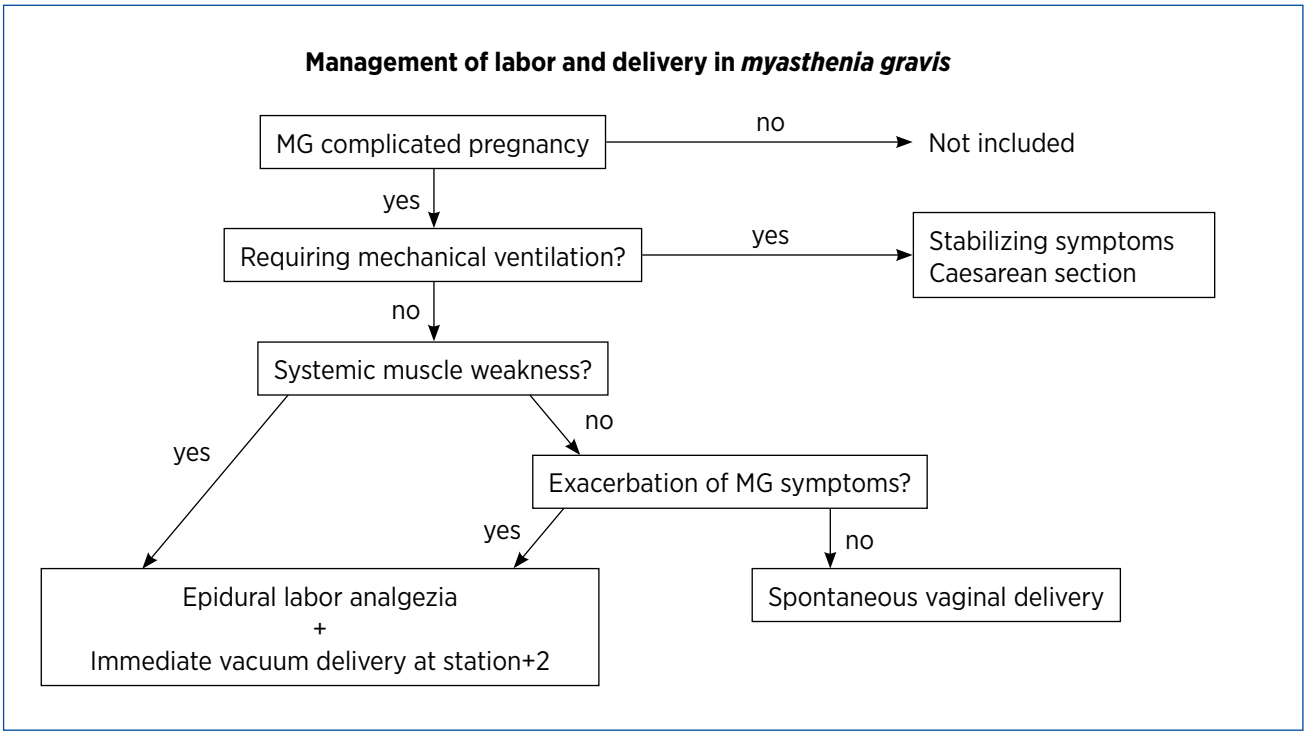

Figure 1. Obstetrical management protocol in myasthenic women (adapted after the guidelines of Japan Society of Obstetrics and Gynecology, 2019)

Anesthetic remarks

The preoperative evaluation of the myasthenic patient aims at reviewing the severity of the patient's myasthenic condition and the treatment control. Specific consideration should be attributed to voluntary and respiratory muscle strength. During labor, epidural analgesia should be used to diminish pain. The use of narcotic/neuromuscular blocking agents should be avoided. Local anesthetic agents might be avoided (as much as possible), as these can block the neuromuscular transmission. Non-depolarizing neuromuscular blocking drugs should be avoided. Sedatives and opioids need to be avoided, as these may accelerate the respiratory depression[12]. The potential for respiratory alterations in these patients obliges the anesthesiologist to be up-to-dated with the underlying disease stage, as well as the impact of anesthetic and non-anesthetic drugs on patients with *myasthenia gravis*. Inhaled anesthetics also exert muscle relaxation, but in the case of myasthenic ill, it acquires a special sensitivity. Sevoflurane and isoflurane impair the neuromuscular function, with a sensitivity close to 90% in myasthenic patients. It seems that the anesthetic opioids detected in the plasma concentrations of these patients do not weaken the neuromuscular transmission[13]. Also, the most tolerated short-acting intravenous anesthetics, such as propofol, do not affect neuromuscular function.

Neonatal considerations

Regarding the review of some neonatological features of *myasthenia gravis*, attention should first be paid to the mother-to-child *myasthenia gravis* antibodies transfer. Autoantibodies *per se* do not seem to give infertility. The placental transfer of maternal IgG antibodies to the fetus is a primordial mechanism that grant protection to the neonate while his/her humoral response is ineffective. IgG is the only antibody class that significantly crosses the human placenta[14]. In nearly all patients, the antibodies bind to acetylcholine receptors (AChR), but on the other hand, it was shown that other incriminated target is the muscle-specific tyrosine kinase (MuSK) and lipoprotein-related peptide 4 (LRP4)[15]. Around 10% of the babies of myasthenic mothers have a transient muscle weakness. This is due to antibodies against AChR or MuSK that are carried from the mother's circulation, across placenta, to the fetus. In the neonate, these antibodies may bind to their respective antigens and induce muscle weakness, which nearly always appear in the course of the first 24 hours after birth. As mother's IgG antibodies are impaired in the baby and gradually disappear, the muscle weakness improves, and the normal function recover[16]. The weakness usually lasts for up to 4 weeks, but is most noticeable during the first week.

The characteristic symptoms are slight general hypotonia and poor sucking due to reduced muscle tonus. Dysphagia and a weak cry are other symptoms noticed in neonates. Insufficient respiration, meconium aspiration and pneumonia are not so often reported, but these make the neonatal ward monitoring necessary for those infants, and lately difficulty breast feeding by ineffective sucking. Breast feeding is very important in the development and well-being of every infant, therefore we will point out a relevant aspect from this point of view. Fetal dysphagia result in association to polyhydramnios in some pediatric neonatal disorders, which is very important to detect, observe and relate to possible swallowing difficulties.

Feeding problems installed at birth, with a neonatal onset, are often related to weak/poor sucking. In most neuromuscular diseases, excepting spinal muscular atrophy, the triggering and timing of swallowing in the bulbar region appear normal[17], therefore dysphagia is mainly associated to weakness of the oral muscles rather than to incoordination of sucking, swallowing and breathing. At the beginning, neonates suckle from the breast (or bottle), but after about 3 months, the brainstem reflexes – for instance, the sucking reflex – disappear, and by about 6 months the infants begin eating foods of diverse consistencies. The oral anatomy modifies as a result of the advance of the oral cavity and the downgrade of laryngeal structures. Between 6 and 12 months, infants' reflexes for chew and swallow appears, so the infants will start to learn to eat pureed or solid food[18], which necessitate better strength of the oral muscles. For example, the muscular weakness at the level of orbicularis of the lips leads indirectly to reduced pharyngeal pressure, leading to post-swallow residue and indirect aspiration (the risk to aspirate the regurgitated material), thus the careful introduction to small quantities of liquids and food might be taken in consideration[19]. Without going into detail about congenital myasthenic syndromes, we have chosen only to enumerate them, their exposure broadly being the subject of strict concerns of neonatologists. The types of pediatric myasthenic syndromes:

1. Congenital *myasthenia gravis*.
2. Transient neonatal *myasthenia gravis*.
3. Juvenile autoimmune *myasthenia gravis*.
4. Arthrogryposis multiplex congenita (as a persistent sequela in child).

Conclusions

We hope that this article will support, first and foremost, the neurologists and gynecologists who face the great challenges that this multifaceted disease brings to our attention. All babies by myasthenic mothers should be observed and monitored in the hospital for at least 72 hours. The obstetrical and neurological follow-up during pregnancy should be an important prerequisite in order to prevent unpleasant events. From the long experience of our clinic, myasthenic women are recommended to get pregnant 3-5 years after thymectomy, when the disease stabilizes. Before pregnancy, patients undergo a complete biological and infectious assessment to avoid antibiotic treatment in the first semester of pregnancy. During pregnancy until the seventh month, it is recommended to continue the maintenance treatment with Medrol® and Mestinon® until another neurological reevaluation, by increasing the dose of Medrol® until they return to control after birth. All these steps are necessary in order to avoid the aggravation of myasthenia in the last tri-

mester of pregnancy, during pregnancy and after that. During pregnancy, myasthenic crises set in and manifest in the first trimester of pregnancy, and we encountered situations in which patients had to be curetted in the ICU department, a life-saving workforce. In our activity, myasthenic crises have also been reported after birth, borderline situations in which plasmapheresis has proven to be effective and life-saving for both mother and newborn. The neonatal myasthenic phenomena (transient neonatal myasthenia) improved 3-4 weeks after the Mestinon® administration. ■

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Ways of improving the diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13 weeks of gestation

C.A. Ispas
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Corresponding author: C.A. Ispas, e-mail: Alexandru.Ispas@umfcd.ro

ABSTRACT

The 11-13-week scan is gaining a greater importance with the passing of time, as the diagnosis of more and more birth defects can be achieved at this time in pregnancy. The available guidelines for this scan are increasing, including new pieces of information that can be obtained on this occasion, and the diagnosis of open *spina bifida* and cleft lip and palate could be among them. The accuracy of the first-trimester detection of these two conditions has significantly increased during the past 10 years, and some of the views available for their diagnosis seem to offer a better performance in this instance.
Keywords: intracranial translucency, cleft lip and palate, first-trimester scan

REZUMAT

Ecografia de screening de prim trimestru devine, cu timpul, tot mai importantă, odată cu posibilitatea diagnosticării a tot mai multe defecte fetale cu această ocazie. Ghidurile disponibile includ în mod progresiv tot mai multe informații care se pot obține cu ocazia acestei examinări, iar diagnosticarea *spina bifida* deschise și a cheilopalatoschizisului ar putea face parte dintre acestea. Acuratețea diagnosticului ecografic de prim trimestru în aceste două patologii a crescut semnificativ în ultimii 10 ani, iar unele dintre secțiunile utilizate în diagnosticul lor par a fi mai utile pentru a crește rata de detecție pentru fiecare caz în parte.
Cuvinte-cheie: translucență intracraniană, cheilopalatoschizis, ecografie de prim trimestru

Introduction

Many years ago, the routine ultrasound (US) scans performed during the first trimester of pregnancy used to be dedicated mainly to the diagnosis of pregnancy, its location, the viability of the pregnancy, the gestational age and, of course, to the number of fetuses[1]. The technological advances of the past decades led to an impressive increase in diagnostic possibilities, making the first-trimester scan one the most important exams performed during pregnancy.

In 2013, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) issued a guideline on the performance of the first-trimester fetal ultrasound scan and, in 2014, the Romanian Society of Ultrasound in Obstetrics and Gynecology (SRUOG) issued the first Romanian guideline on the subject.

The last revision of the Romanian guideline was in 2019[2,3].

Birth defects detectable as early as the first-trimester scan

There is a growing number of birth defects that can now be detected at the early scans of the pregnancy. Out of these, some have proven to be so accurate in detection and easy to obtain, that they could be introduced in the routine of performing this scan.

Open *spina bifida* (OSB)

Intracranial translucency (IT) was first described in midsagital view in 2009. It is now widely used as an early diagnosis tool for OSB[4,5]. The assessment of the IT can be performed in a sagital view of the fetus, the same view used for the assessment of the nuchal translucency (NT), but the view needed for the IT visualisation is rather less strict than the one for the NT, as this view doesn't have to be perfectly midsagital in order to have a good IT assessment[4,5]. The IT can also be assessed in an axial view, but with less acuracy for an unexperienced sonographer[5].

The IT is actually the fourth ventricle, but visualised in the NT view between the image of the brain stem (BS) and the one of the future *cisterna magna* (CM)[4,5]. The translucency is bordered superiorly (or on the anterior) by the echogenic posterior edge of the BS and inferiorly (or on the posterior) by the choroid plexus of the 4th ventricle[4,5]. It has normally a median size ascending from 1.5 to 2.5 mm in the period the crown-rump length (CRL) increases from 45 to 84 mm[4]. It is abnormal or appears to be absent in cases with OSB, as the 4th ventricule, the choroid plexus of the 4th ventricle and the developing *cisterna cerebellomedullaris* are compressed by the caudal displacement of the brain[4,5]. Common abnormal signs of an OSB are represented by the BS, which appears

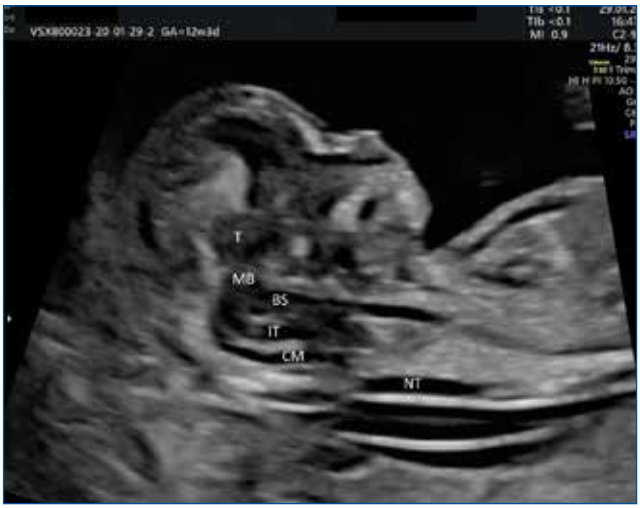

Figure 1. IT – intracranial translucency; T – thalamus; MB – mid brain; BS – brain stem; CM – *cisterna magna*; NT – nuchal translucency

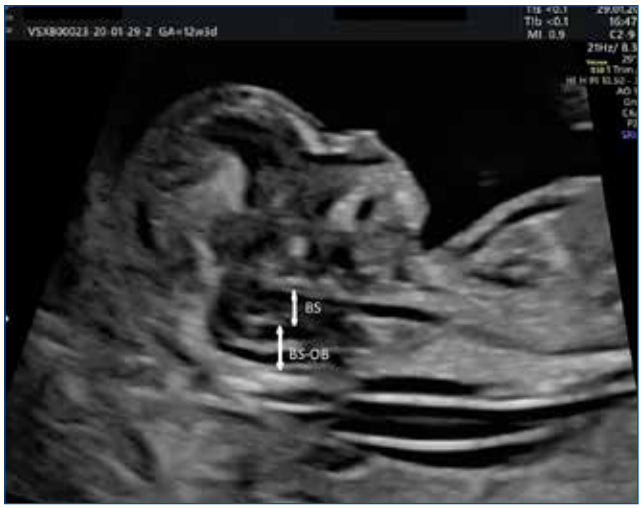

Figure 2. The ratio of the BS to the BS – OB distance (BS – brain stem; OB – occipital bone)

thickened, and the ratio of the brainstem to the brainstem – occipital bone (OB) distance, which is increased (>1)[5]. In a recent meta-analysis, this ratio showed a high accuracy in detecting OSB[6] (Figures 1 and 2).

Cleft lip and palate (CLP)

Another birth defect that can be diagnosed today during the first trimester is the CLP. This diagnosis was initially detected at the time of the 11-13-week US examination using a coronal view, called the retronasal triangle[5], but it was also later detected using a sagital view, the maxilary gap[6], and then using a transverse view[7], which seems to be the most accurate view for detection at this time during pregnancy[8].

When we want to obtain the axial view of the lips and palate, we need to start from the view checking the fetal eyes and lenses and move slightly inferior until we reach the desired view and we should see the entire anterior part of the palate and the superior lip without any gaps. The fetal head should be oriented towards 12 o'clock (Figure 3).

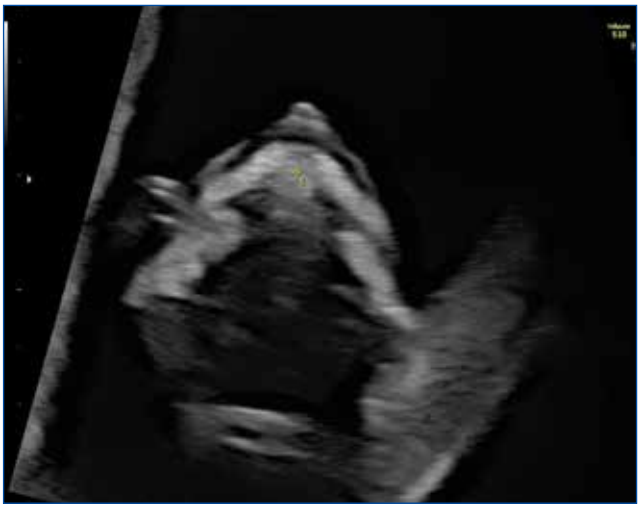

Figure 3. Axial view of the upper lip and maxilla

Discussion

In 2011, A. Syngelaki analyzed the performance of the first-trimester screening for non-chromosomal abnormalities in a group of over 45,000 patients scanned between 2006 and 2009, and discovered a detection rate of only 5% for facial clefts and 15% for open *spina bifida*, a result which confirmed the findings for CLP from other previously published studies that were also showing a detection rate smaller than 10% at the 11-13-week scan[9]. At the time, the author suggested placing all anomalies in three different categories, based on the possibility of detection during the first-trimester scan: anomalies that should always be detected, anomalies that are undetectable, and anomalies that are potentially detectable at this stage[9]. Both open *spina bifida* and CLP fell in the third category at the time[9].

Following the publishing of different ways of diagnosing the open *spina bifida* and the CLP in the recent years, in 2019 A. Syngelaki has repeated the performance analysis for over 100,000 patients scanned between 2009 and 2018 and discovered a detection rate of 59% for open *spina bifida* and of 35% for CLP, with a major increase in the diagnosis rate since the last assessment.

In 2018, M.M. Zheng reported a detection rate of 100% for abnormal axial view of the maxilla in a smaller group of 2982 fetuses (including 315 twins), with 8 confirmed cases of CLP[8].

The variations in the severity of the condition will, however, keep these diagnoses in the third category, as the most severe cases are more likely to be discovered, while the less severe ones could pass undetected, but on the other hand, the severe cases are the ones that we are most interested in finding, as they pose the bigest threats to the fetus.

It is important to mention that the cleft lip only and the cleft palate only were not included in these numbers in the Syngelaki studies, as they are more difficult to be diagnosed, and they aren't good candidates for routine check in the first trimester.

Conclusions

The abundance of anatomical elements that can be assessed today during the first-trimester screening scan created the need of guidelines on performing this exam and maximising its findings.

Based on a view that is already recommended in today's guidelines, an important finding such as OSB could be detected just by recognising a pattern or by applying a measurement together with another measurement collected from that view anyway, so the assessment of OSB could be implemented as a routine check during the 11-13-week scan.

The CLP can also be detected during this scan, but for this diagnosis there is another view that might be necessary, as the palate in an axial view is not a standard view at this time, but it is fairly easy to obtain if we start from the view checking the fetal eyes and lenses. ■

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review articles

Uterine microbiota – a new possible culprit in infertile patients

Mihai Surcel[1], Iulia Neamțiu[2], Georgiana Nemeti[1], Dan D. Axente[3], Alina Surcel[4], Iulian Goidescu[1], Daniel Mureșan[1]

1. First Obstetrics and Gynecology Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
2. Environmental Health Center – Health Department, Cluj-Napoca, Romania
3. Fifth Surgery Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
4. "Regina Maria" Private Healthcare Network, Romania
Corresponding author: Iulia Neamțiu, e-mail: iulianeamtu@ehc.ro

ABSTRACT

Current knowledge asserts that microbial structures are present in niches considered traditionally sterile and, consequently, the functions assigned to the human microbiota are to be reanalyzed. When considering the uterine segment of the microbiome, the data reported by the authors who studied this subject differ greatly, especially in terms of germ weight, even though there is agreement for the presence of the main actors, *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*. The exploration of the uterine flora and the identification of some pathology at this level are mandatory in infertile patients with repeated implantation failure. The alterations of the uterine microbiota can create the premises for the development of chronic endometritis and uterine dysbiosis.

Keywords: uterine microbiota, endometrium, dysbiosis, chronic endometritis

REZUMAT

Date recente au permis identificare florei saprofite în teritorii considerate în mod tradițional sterile. În acest context, se impune reevaluarea funcțiilor atribuite microbiotei umane. Există discrepanțe majore între autori în privința ponderii diferiților germeni, acceptându-se totuși faptul că actorii principali aparțin familiilor *Firmicutes*, *Bacteroidetes*, *Proteobacteria* și *Actinobacteria*. Explorarea florei bacterine uterine și identificarea anomaliilor de la acest nivel sunt obligatorii la pacientele sterile cu eșec repetat de implantare. Alterarea microbiotei uterine creează premisele pentru dezvoltarea disbiozei uterine, respectiv a endometritei cronice.

Cuvinte-cheie: microbiotă uterină, endometru, disbioze, endometrită cronică

Introduction

Idiopathic infertility is an extremely exciting and equally frustrating subject for practitioners. In recent years, the research space has focused mainly on the study of oocytes/embryos and endometrium.

The term non-receptive (refractory) endometrium has been used more and more often for patients with repeated good quality embryos implantation failures, in which no organic uterine pathology has been identified[1,2]. During endometrial explorations by hysteroscopy, forms of clinically unapparent chronic endometritis have often been identified. Moreover, hysteroscopy experts observed a certain endometrial pattern (stromal oedema, micropolyps, polypoid endometrium, and diffuse hyperaemia) which they also included in the category of chronic endometritis despite negative endometrial cultures. In these patients, a major improvement in post-antibiotic pregnancy rates was observed[3].

In the last decade, the study of the human microbiota has developed a lot. A great gain of this research was the identification of saprophytic cultures in areas long considered sterile, such as the placenta, uterus or fallopian tubes. However, the small volume of these commensal germs was a major impediment to their identification in standard cultures.

The new techniques – next-generation sequencing – coupled with insertion sequencing allowed the exhaustive examination of the genes of bacterial origin proteins, by using mobile DNA elements (transposons)[4]. This new approach allowed access to a territory that was virtually uninterrupted by standard technical resources and, thus, opened a new door to understand in intimacy the functionality of the endometrium[4].

The present study aims to review the possible impact of the microbiota in the fertility equation and to examine the data we currently have.

Endometrium dysfunction

The role of the endometrium in reproduction is extremely important. At the moment of maximum receptivity of the endometrium, the implantation process implicates the involvement of numerous actors and the development of extremely sophisticated phenomena, culminating in embryo-maternal cross-talk[1]. The factors responsible

for endometrial preparation are very diverse. Attempts have been made over time to detach several functional levels directly involved in the preparation of the endometrium: the immune system, the interleukin system, adhesion molecules and barrier structure compartments system, the local metabolic system and free-radical oxidation system. In this paradigm, any uterine pathology with an impact on reproduction is explained by the alteration of some of these factors. The most intensively studied were organic diseases such as fibroids, polyps or adenomyosis, and their implications on the systems described before[5]. More recently, practitioners have identified a new type of pathology defined generically as the refractory endometrium. Behind this condition, there are the traumas after curettage/myomectomy/embolization or after radiotherapy, infections, but also a segment that does not seem to fall into any obvious category – idiopathic alteration. Especially for the latter segment, the vast majority of researchers agreed either on the existence of a primary genetic alteration in some of the systems that control endometrial development, or on subtle aggressors unapparent to standard tests, such as chronic infections or, more recently, uterine dysbiosis[6].

Unfortunately, despite some special efforts, which included testing many parameters, such as leukaemia inhibitory factor, dv/ß3 integrin (ß3), cyclin E, products from homeobox/wnt genes, B cell lymphoma 6, and advancing a significant number of functional tests (Receptive Dx, E tegrity, Endometrial Function Test)[7,8], there could not be identified recurrent changes present in all patients with this diagnosis (or at least in a sufficiently large group), a reason for which it was concluded that under this title (idiopathic refractory endometrium) there are found a lot of subentities.

In this context, the exploration of the uterine flora and the identification of some pathologies at this level can constitute such a subsegment.

Human microbiome

The human microbiome is the totality of microorganisms, as well as the related genetic material located on and in the human body. Although the term microbiome was advanced long ago, it was not until the early 2000s that the framework of the Lederberg definition was established[9].

The special attention that this subject enjoys at present has its origin, first of all, in the rethinking of the relationship humans – saprophytic flora, through the neo-Darwinian concept proposed by the biologist Lynn Margulis ("Symbiosis as a Source of Evolutionary Innovation"). In this paradigm, humans appear as a holobiont – a host organism that coexists with other species – bionites. The combined genome is called a hologenoma[10].

It is currently considered that the number of germs belonging to the microbiome exceeds 100 trillion, including bacteria, archaea, protists and fungi. This structure can be associated with a vital superorgan to maintain the health of the host organism. The functions of this body have proven to be extremely diverse. In a schematic manner, a series of major levels can be distinguished: maintaining energy homeostasis, preventing colonization with pathogenic opportunistic germs, developing a degree of tolerance to non-self substances and the formation of intestinal architecture.

The association of commensal bacteria located in the digestive tract has proven to be extremely important in the management of components of nutrients that the host organism was unable to metabolize[11].

In terms of immunity, the microbiota is attributed a major role in inducing and developing its many branches. The constant microbiota – host organism dialogue involves an elastic feedback between the microbiota and the various congenital or acquired components of immunity. The immune system controls the shape and type of microbiota (favouring certain types of colonies), while the microbiota induces fine calibrations of the immune system. The imbalances that appear in this equation open the door to the respective infections, in the opposite direction to minor diseases or allergies[12].

The development of molecular techniques for exploring the microbiota – next-generation sequencing (NGS) technologies, after 2007, combined with the development of homicidal concepts have greatly broadened the horizon of understanding the microbial flora. Thus, microbial structures were identified in niches considered traditionally sterile and, consequently, the functions assigned to the microbiota were reanalyzed, obtaining data that offer additional dimensions. Starting from these elements, the definition of the microbiota has been recently subjected to a constant process of refining. In a joint effort, a group of experts redefined in 2020 the microbiome "as a characteristic microbial community occupying a reasonable well-defined habitat which has distinct physiochemical properties". "*The microbiome not only refers to the microorganisms involved, but also encompass their theatre of activity, which results in the formation of specific ecological niches. The microbiome, which forms a dynamic and interactive micro-ecosystem prone to change in time and scale, is integrated in macro-ecosystems, including eukaryotic hosts, and here crucial for their functioning and health. The microbiota consists of the assembly of microorganisms belonging to different kingdoms (prokaryotes [bacteria, Archaea], eukaryotes [e.g., protozoa, fungi, and algae]), while «their theatre of activity» includes microbial structures, metabolites, mobile genetic elements (e.g., transposons, phages, and viruses), and relic DNA embedded in the environmental conditions of the habitat*"[13].

Uterine microbiome and its pathology

The genital tract is probably one of the segments that has benefited mostly from the findings regarding the microbiome.

The arguments in favour of colonizing the upper genital area are diverse. First of all, we have a solid documentation in support of the existence of an ascending current induced by uterine peristalsis in the follicular phase[14]. Secondly, the cervical mucus functions only as a barrier to germs in the vagina. At the time of ovu-

lation, the consistency of the mucus becomes very low, which further reduces the efficiency of this protection mechanism. In addition, the semen has its own microbiota that will be engaged in the ascension process, simultaneously with the sperm[15].

The disposition of the bacterial flora on the genital tract differs, however, during the four major stations (vagina, endometrium, fallopian tubes, Douglas sac), both in terms of type and volume.

Thus, at the level of the vagina, the order of size of the flora is 10^{11}, in which the lactobacilli represent >99% of the flora, while at the level of the uterus, the bacterial flora decreases to 10^{7}, and is much more diverse. At the level of the fallopian tubes/Douglas sac, the flora is very low and *Lactobacillus* represents <1%. Including at the level of the intrafollicular environment, commensal germs such as *Lactobacillus*, *Actinomyces*, *Bifidobacterium*, *Propionibacterium*, *Staphylococcus* and *Streptococcus* are described[16].

From the practitioner's perspective, the uterine segment of the microbiome is the area of greatest interest. Unfortunately, the data reported by the authors who studied this subject differ greatly, especially in terms of germ weight, even though there is agreement for the presence of the main actors, *Firmicutes* (lactobacilli, *Streptococcus*, *Staphylococcus*), *Bacteroidetes* (*Enterobacter – E. coli*), *Proteobacteria* and *Actinobacteria*[17].

The main shortcomings are represented, on the one hand, by the physiological variations of the flora related to ethnicity, race, eating habits, but also by changes induced by age (the microbiota is probably the organ with the greatest capacity for change over time) or periods of the cycle. The technical difficulties of harvesting, respectively the accessibility, cannot be neglected either, being extremely important in the context of the massive examinations in the general population necessary for a more realistic mapping.

The volume of information on the action of the uterine microbiota on the endometrium is still too small to document which segments are affected in the endometrial preparation process. The peculiarities of the uterine area – low germ volume (compared to other situses), the proximity of a region with extremely rich flora (vagina) and relatively difficult to access (requiring minimally invasive manoeuvres) are important obstacles in the consistent analysis of uterine flora.

However, relatively recent studies in immunology confirm the potential of genital epithelial cells to express a wide range of pattern recognition receptors (PRRs) capable of responding differently and individually to non-self-agents[18]. In this sense, Toll-like receptors (TLRs) and NOD-like receptors, essential in both the immediate cellular immune response and in tissue adaptive reactions, are described. The activation of TLR receptors *via* the microbacterial metabolites will control the size of the bacterial cohort, while the activation of NOD receptors will induce changes in the endometrial cell from its metabolism to its communication systems to modulate gene expression *via* the underlying transcriptomic modulations, representing grounds for epigenetic inductions.

In the practitioner's registry, the alterations of the uterine microbiota can create the premises for the development of chronic endometritis and uterine dysbiosis, respectively.

Chronic endometritis is a clinical entity that is difficult to diagnose in the context of a frustrating condition. The examinations imposed by infertility (hysteroscopic balance + cultures + endometrial biopsies) allowed the diagnosis of a much larger number of cases[19].

At present, the most reliable means of diagnosis is considered to be the identification of plasma cells in the endometrium using immunohistochemistry for plasma marker CD138 (also known as syndecan-1, a transmembrane-type heparan sulphate proteoglycan)[20]. The bacterial agents involved in the development of corneal endometritis are sensitive to different acute infections – *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Mycoplasma*. Most often, chronic endometritis has common bacteria, such as *Streptococcus* species, *Escherichia coli*, *Enterococcus faecalis* and *Staphylococcus* species), *Mycoplasma*/*Ureaplasma* species (*Mycoplasma genitalium*, *Mycoplasma hominis* and *Ureaplasma urealyticum*), *Pseusonia aerosa*, *Proteus* species, *Gardnerella vaginalis*, *Corynebacterium*, and to a much lesser extent *Chlamydia trachomatis*[3]. The actual mechanisms by which the implantation process is altered revolve around the structural alterations of the endometrial test or at least of its functional expression (production of interleukins/adhesins/mucins), respectively of the immune changes. Unlike other territories in the endometrial area, natural killer (NK) cells have a much more consistent role in modulating the receptivity of endometrial cells to progesterone[2].

Starting from the massive involvement of bacteria that make up the microbiota in the process of nutrition by metabolizing many products that are unaffordable to human enzymes, it is easy to speculate that a possible uterine dysbiosis could affect the nutrition of the endometrium.

Clinical data that associate the alteration of the vaginal and uterine microbiome with infertility

The first studies that explored the relationship between uterine microbial flora and infertility used cultures to document infection. The systematic identification of germs at the tip of the catheter used for embryo transfer has been associated with much lower pregnancy rates[21].

The development of molecular techniques for identifying bacterial microflora has greatly broadened the horizon of examination, thus identifying pathogenic germs that could not be identified by classical tests due to low biomass.

Kyano examines the uterine microbiota in 92 patients on the ART protocol according to the dominant (>90%) versus non-dominant (<90%) type of *Lactobacillus*. The pregnancy rate was higher in the dominant *Lactobacillus* group (58.9% versus 47.2%), but without reaching the threshold of statistical relevance[22]. Morena, in turn, reports a higher implantation rate in the dominant *Lactobacillus* group versus non-dominant *Lactobacillus* lot (60.7% versus 23.1%; $p<0.001$)[19].

Hashimoto reports a higher pregnancy rate and a lower miscarriage rate in patients who had eubiotic flora in the endometrium compared to patients with dysbiotic flora, but without the results being statistically relevant[23].

Brecewell evaluates, in a systematic review, 26 studies focused on the role of the vaginal and uterine microbiota on ART. The results of studies based on vaginal cultures did not identify any negative effects of vaginal dysbiosis. In contrast, studies in which the vaginal microbiota was examined by metagenomics sequencing techniques documented an adverse effect of vaginal flora imbalances on ART outcomes. However, the authors of the review draw attention to the very large discrepancies between the studies and urge caution in interpreting the results[24].

Cicinelli aims to improve implantation rates by administering antibiotics to the group of patients with repeated implantation failures diagnosed with chronic endometritis. Pregnancy rate was 76.3% versus 20% ($p<0.0001$), while the live birth rate was 65.8% versus 6.6% ($p<0.0001$). It should also be noted that in the group without chronic endometritis (probably, another cause of repeated failure) the respective live birth rates were 9.5% and 4.5%[25].

It is worth mentioning that, unfortunately, the value of all these studies has been greatly diminished (according to their authors) both by technical problems and by the small number of cases and, consequently, the results must be analyzed with caution.

Practical arguments

In sterile patients with resistant endometrium, there is a subgroup in which the alteration of the microbiota may be the central element. In this regard, chronic endometritis is described, histologically confirmed by the presence of plasma cells in the endometrium presenting an altered but nonspecific flora, respectively endometrial dysfunction characterized only by dysbiosis of the uterine microbiota.

Regarding the diagnosis of chronic endometritis, although relatively laborious, the diagnosis is standardized. Unfortunately, the diagnosis of uterine dysbiosis is still in the evaluation stage. At present, there are two molecular tests based on sequencing but which are still being tested: Endometrial Microbiome Metagenomics Analysis – Ingenomix, respectively Endometrial Microbiome Test – Varinos. Both tests are limited to establishing the dominant or non-dominant character of the *Lactobacillus* flora, without making distinctions related to the rest of the flora.

The treatment of chronic endometritis focuses on the use of antibiotics as opposed to the treatment of dysbiosis in which their use will aggravate the existing imbalance.

In the context of disputes over the germs involved, several formulas are discussed. Starting from the frequent presence of *Mycoplasma*, most authors propose an initial monotherapy type based on ofloxacin. In case of persistent infection (documented by a new biopsy after one month of treatment), a broad-spectrum combination, such as ofloxacin + metronidazole or cephalosporin + doxycycline + metronidazole and amoxicillin + clavulanic acid, is used[26]. The route of administration was oral for most authors, but there were also voices for local administration, such as intrauterine instillation. The reported results were generally optimistic, ranging from very good results (92% curability after monotherapy and 99% after combination therapy) to modest results (28% curability after the first cure, 23% after the second cure, 25% after the third cure, respectively 25% resistant after all three cures)[27].

The adjuvant administration of dexamethasone was tested, but the results were unconvincing.

The use of probiotics has proven, at least so far, to be useful only in vaginal dysbiosis. The administration of lactobacilli is problematic, considering that the share it should have in the uterine flora is not very clear.

Equally, the idea of transferring uterine microflora from a healthy patient (with documented fertility) is viewed with great scepticism in the context of the often very large discrepancies that exist even between healthy women.

Conclusions

We currently have compelling arguments to give the uterine microbiota a significant role in the functionality of the endometrium. Under these conditions, its systematic research in patients with repeated implantation failure becomes mandatory.

The hysteroscopic examination with endometrial biopsies (to confirm chronic endometritis), doubled by the evaluation of the microbiota by molecular techniques, seems to be the most consistent direction for a complete diagnosis.

There is an urgent need for the development of a profile of the physiological uterine microbiota adapted to the age, ethnicity, parity or period of the uterine cycle. It is also necessary to develop reliable tests that are widely applicable for monitoring the uterine flora in different circumstances. In addition, the intervention with probiotics or prebiotics must be refined according to the particularities of the endometrium.

Even though in the short term these desiderata seem to be exaggeratedly optimistic, it is indispensable that the subject play an important role in the agenda of both researchers and practitioners. ■

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A retrospective study regarding early pregnancy loss in the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital

Oana Mihaela Teodor[1], Diana Ioana Voicu[1], Delia Maria Grădinaru Fometescu[1], Octavian Munteanu[1,2], Ioana Rotar[3], Monica Mihaela Cîrstoiu[1,2]

1. Department of Obstetrics and Gynecology, Bucharest University Emergency Hospital, Romania
2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
3. Department of Obstetrics and Gynecology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
Corresponding author: Octavian Munteanu, e-mail: octav_munteanu@yahoo.com

ABSTRACT

Vaginal bleeding in the first trimester is a common occurrence, but the majority of the pregnancies have a normal outcome. The careful assessment is yet important, given the possibility of complications. The patients with a threatened abortion should be monitored for progression to pregnancy failure. The most common type of spontaneous abortion is early pregnancy loss, defined as death of an embryo or fetus within the first 13 weeks of pregnancy. The clinical manifestations have low specificity, neither the duration of bleeding, nor the presence of lower abdominal cramping in the first trimester being reliable indicators of pregnancy outcome, thus the special attention has turned to ultrasonography for the evaluation of early pregnancy complications. The therapeutic approach (expectant management, medication or surgical interventions) should be tailored based on the gestational age, clinical and ultrasound findings. Severe hemorrhage requires urgent treatment, the surgical evacuation of the products of conception being often necessary. In this paper, we present the incidence and prevalence of early pregnancy loss and threat of abortion in the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital, for a two-year period, discussing the impact of the advanced maternal age as a risk factor for spontaneous abortion.
Keywords: early pregnancy loss, spontaneous miscarriage, threatened abortion, incomplete abortion, transvaginal ultrasound

REZUMAT

Sângerarea vaginală în primul trimestru de sarcină este frecvent întâlnită, dar majoritatea sarcinilor au o evoluție normală. Evaluarea atentă este totuși importantă, având în vedere posibilitatea complicațiilor. Cazurile diagnosticate ca amenințări de avort pot avea ca rezultat oprirea în evoluție a sarcinii. Cel mai comun tip de avort spontan este avortul precoce, definit ca decesul produsului de concepție survenit în primele 13 săptămâni de sarcină. Manifestările clinice sunt nespecifice, sângerarea vaginală sau durerile abdominale apărute în primul trimestru nefiind indicatori fiabili ai evoluției sarcinii. În acest context, examinarea ultrasonografică joacă un rol esențial în evaluarea complicațiilor sarcinii incipiente. Abordarea terapeutică (expectativă, tratament medicamentos sau tratament chirurgical) trebuie adaptată în funcție de vârsta gestațională și de constatările clinice și ecografice. Hemoragia severă necesită tratament urgent, evacuarea chirurgicală a produselor de concepție fiind adesea necesară. În această lucrare, prezentăm incidența și prevalența pierderii precoce a sarcinii și amenințarea de avort în cadrul Departamentului de obstetrică și ginecologie al Spitalului Universitar de Urgență din București, pe o perioadă de doi ani, discutând impactul vârstei materne avansate ca factor de risc pentru avortul spontan.
Cuvinte-cheie: avort precoce, avort spontan, amenințare de avort, avort incomplet, ecografie transvaginală

Introduction

Abortion is the termination of pregnancy before 20 weeks of gestation[(1)]. Spontaneous abortion or miscarriage is a naturally occurring event, unlike induced medical or surgical abortions[(1)]. It is difficult to properly estimate the incidence of spontaneous abortion, as many miscarriages are mistaken as heavy, late menses before clinically recognized pregnancy, but the total incidence is as high as 31%[(1)].

Most spontaneous abortions occur during the first trimester of pregnancy and, although there is no consensus over the terminology for nonviable pregnancies, usually the term "early pregnancy loss" (EPL) refers to such nonviable intrauterine pregnancy within 12+6/7 days of gestation, including the anembryonic pregnancies[(1)]. There are several subtypes of spontaneous abortion based on clinical and ultrasound findings (Table 1), including missed, threatened, inevitable, incomplete and complete abortion.

Regarding the etiology of early pregnancy loss, the exact mechanisms involved cannot always be specified. In about half of the cases, chromosomal abnormalities are a direct cause[(2)].

Other etiologies refer to maternal infections, uterine anomalies, coagulation and immunological disorders, chronic diseases, unhealthy lifestyle (alcohol or heavy caffeine use, cigarette smoking), and extreme weight. Advanced maternal age and prior pregnancy loss are important risk factor[3].

The most common signs of EPL are vaginal bleeding and pelvic cramping in patients with positive pregnancy test or abnormal menstrual cycle. Given the nonspecific clinical manifestations, transvaginal or transabdominal ultrasound and quantitative human chorionic gonadotropin (hCG) levels are important diagnostic tools[3]. The physical examination has limitations as the uterine size and patient's estimated gestational age can be misleading. A visibly dilated cervix and conception products at the os are suggestive signs, but the cervix can appear dilated in parous women even in the case of a viable pregnancy. On the contrary, a closed cervix and no active bleeding does not rule out EPL[4]. The combination of ultrasound scan and serial hCG measurements is considered the optimal evaluation strategy[5]. Transvaginal ultrasound criteria for the diagnosis or just suspicious of pregnancy loss are well established and widespread used[6].

Threatened abortion is defined, according to World Health Organization, as pregnancy-related bloody vaginal discharge or frank bleeding during the first 20 weeks of pregnancy without cervical dilatation. About 10% of the cases are caused by subchorionic hemorrhage and subchorionic hematoma, which increase the risk of pregnancy loss (if the hematoma accounts for 25% or more of the volume of the gestational sac, it is located retroplacental versus marginal[16], if is identified earlier[17]).

In this paper, we present the incidence and prevalence of early pregnancy loss and threat of abortion in the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital, for a two-year period.

Materials and method

We retrospectively evaluated the cases admitted in the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital between the 1st of January 2018 and the 31st of October 2020 with diagnosis of abortion (according to International Statistical Classification of Diseases and Related Health Problems 10th revision; search by ICD-10 codes O02.1; O03, O04 and O05 with subdivisions 0-9), in order to analyze the rate of early pregnancy loss. The ectopic and molar pregnancies were not included. Another incidence analyzed rate refers to the threat of abortion (ICD-10 code O20.0).

The diagnosis for the patients included in the study was based on clinical examination and on transvaginal/abdominal ultrasound. Serial quantitative hCG measurements were included into the approach to care for the patients presenting with a pregnancy of unknown location.

The informed consent was obtained from each patient and the statistical analysis was performed using Microsoft Excel and SPSS 9.5.

Results

Between the 1st of January 2018 and the 31st of October 2020, 1849 patients were admitted in the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital for abortion or threat of abortion.

Table 1. Types of abortion

Spontaneous abortion	Missed abortion	asymptomatic death of the embryo without sufficient uterine contractions to open the cervical os and eliminate the products of conception[7]
	Threatened abortion	vaginal bleeding in early pregnancy but closed cervix and ultrasound detection of a viable fetus[8,9]
	Inevitable abortion	vaginal bleeding and open cervical os, the ultrasound showing either a viable fetus or not[10]
	Incomplete abortion	there are products of conception retained within the uterus, after partial evacuation of pregnancy tissue through the cervix[11]
	Complete abortion	complete evacuation of fetal and placental tissue through the cervix[12]
	Recurrent abortion	three or more consecutive pregnancy losses (primary – when all pregnancies ended in loss, or secondary – at least one pregnancy has proceeded to viability)[13]
Induced abortion	Woman's personal choice	in case of unwanted pregnancy[14]
	Therapeutic	in case of maternal health at risk[14]
Septic abortion		spontaneous or induced abortion complicated by intrauterine infection[15]

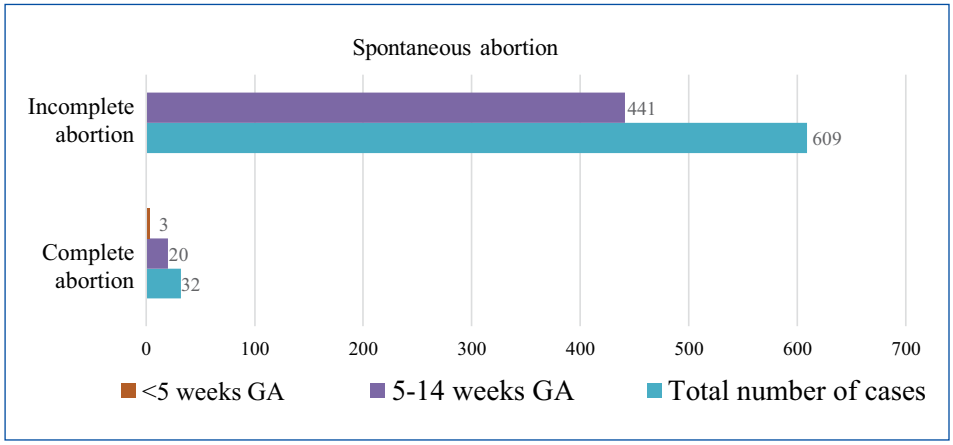

Figure 1. The incidence of early pregnancy loss

The average age of the patients was 30.5 years old, the average weight was 68.2 kg, the average height was 163 cm, and the average Body Mass Index was 24.3.

Among these patients, 1155 women were hospitalized for threat of abortion or inevitable abortion, out of which 47.01% were pregnancies under 14 weeks of gestation (exemplified in Figure 3 and Figure 6). Our records identified 2.6% of all cases in this category eventually ending in early pregnancy loss despite treatment.

We also identified 641 cases of spontaneous abortion, 71.91% of them occurring in the first trimester (Figure 1). The most common type of spontaneous abortion in our clinic is incomplete abortions (95%) – exemplified in Figure 7. Usually, the complete evacuation of gestational tissue does not require further surgical or medical intervention, unless complications occur. Thus, we had only 32 patients with complete abortion, hospitalized for urgent treatment of complications, such as hemodynamic instability due to heavy bleeding, or severe anemia. The mean maternal age among women with spontaneous abortion was 30 years old, range: 13-48, with 31.51% of miscarriages happening in women over 35 years old (Figure 2). Sixteen patients experienced two spontaneous abortions during the selected period.

In the study interval, 53 medical, therapeutic abortions were performed in our clinic and only 40% of them addressed pregnancies less than 14 weeks.

There were two cases of septic abortion, both after surgically induced abortion in a different medical center, and no cases of EPL complicated by embolism in the selected period.

Discussion

The evaluation of early pregnancy loss might be problematic since ICD-10 available codes for this category are not easily aligned with the clinically relevant EPL types in use. For instance, threat of abortion and inevitable abortion are reunited under the same code. Furthermore, the code for the first trimester includes pregnancy duration up to 13 weeks and 6 days.

First-trimester bleeding in a pregnant woman has an extensive differential diagnosis. Apart from spontaneous abortion, it can be caused by ectopic pregnancy, hydatidiform mole, subchorionic hemorrhage (Figure 3), cervical pathology, infection of the vagina or cervix, vaginal trauma or idiopathic bleeding in a viable pregnancy[18].

It is estimated that approximately 20% of pregnant women will have some bleeding before 20 weeks of gesta-

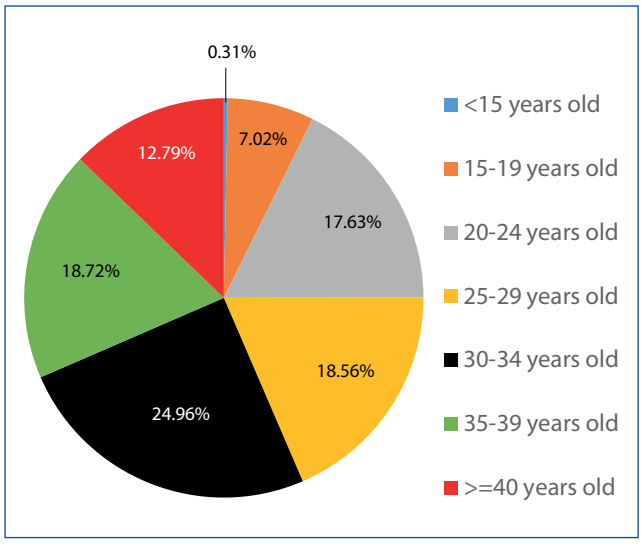

Figure 2. Spontaneous abortion rate by maternal age groups

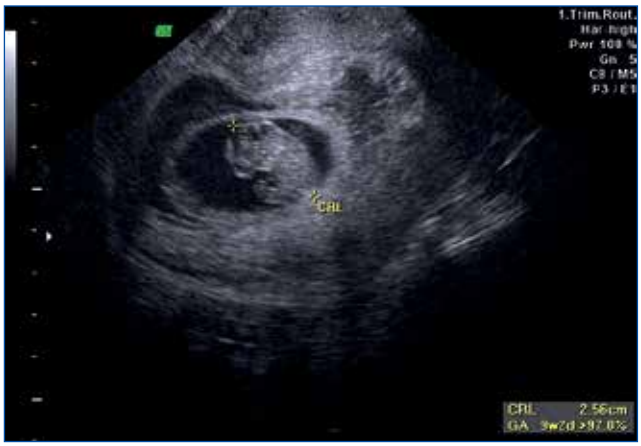

Figure 3. Ultrasound examination in a 34-year-old patient with 9 weeks of amenorrhea diagnosed with threatened abortion, admitted for important metrorrhagia – note a hypoechoic crescent-shape area defining a subchorionic hematoma behind the fetal membranes

tion, and roughly one half of these pregnancies will end in spontaneous abortion[19]. Despite the great number of threat of abortions in our study, we found that 2.6% of them returned to our clinic for EPL (exemplified in Figure 4).

Pregnancy loss is most common in the first trimester and our study revealed about 72 percent of the spontaneous abortions occurring before 14 weeks of gestation (exemplified in Figure 5). The risk of miscarriage varies with maternal age, and there is a strong association between increased maternal age and fetal chromosomal abnormalities[2]. In our study, most patients admitted for spontaneous abortion were aged between 30 and 34 years old. In a national prospective cohort study in the Norwegian population, in which 421,000 pregnancies were included, the risk of miscarriage (after excluding induced abortions) was the lowest in women aged between 25 and 29 years old (10%), and rose rapidly after the age of 30, reaching 53% in women aged 45 years old and over[20].

The clinical evaluation can show cervical dilatation and intracervical conception products, being diagnostic for inevitable abortion (exemplified in Figure 6), but ultrasonography is more reliable for distinguishing between complete and incomplete abortion, with 100% sensitivity and 80% specificity for finding products of conception[21].

Although most cases of EPL have mild clinical manifestations, the complications such as severe hemorrhage or infection require a prompt treatment[18]. The main reason for hospitalization of patients addressing to our emergency room was moderate or heavy vaginal bleeding, with only two cases of septic abortion.

In case of hemorrhage, severe anemia, cardiovascular disease, bleeding disorders, hemodynamic instability or signs of infection, the surgical evacuation through sharp or suction curettage is the preferred treatment option of early pregnancy loss[22]. While the success rates for surgical evacuation reach 99%[23], the risk of complications among the treatment options (expectant, medical or surgical) remains low and is equivocal in women without comorbid conditions or contraindications to one form or another. The patients admitted to our clinic usually required surgical treatment due to severe symptomatology, and had good outcome after treatment.

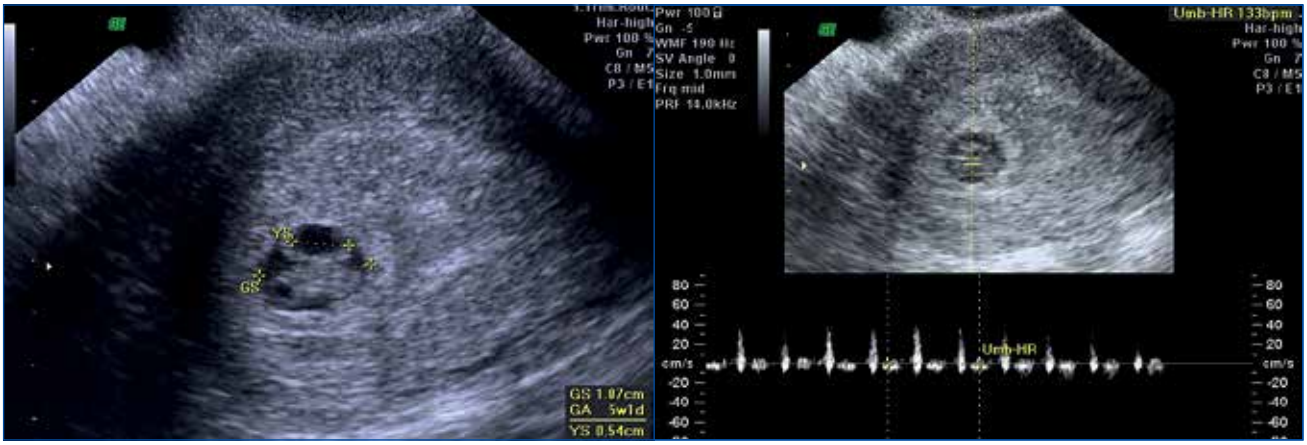

Figure 4. The ultrasound performed for a 29-year-old patient with a history of recurrent abortion, experiencing vaginal bleeding, shows a small gestational sac in relation to the size of the embryo (crown rump length was 9.7 mm, corresponding to 7 weeks of pregnancy) and an enlarged yolk sac. The follow-up scan objectified the pregnancy failure a week later

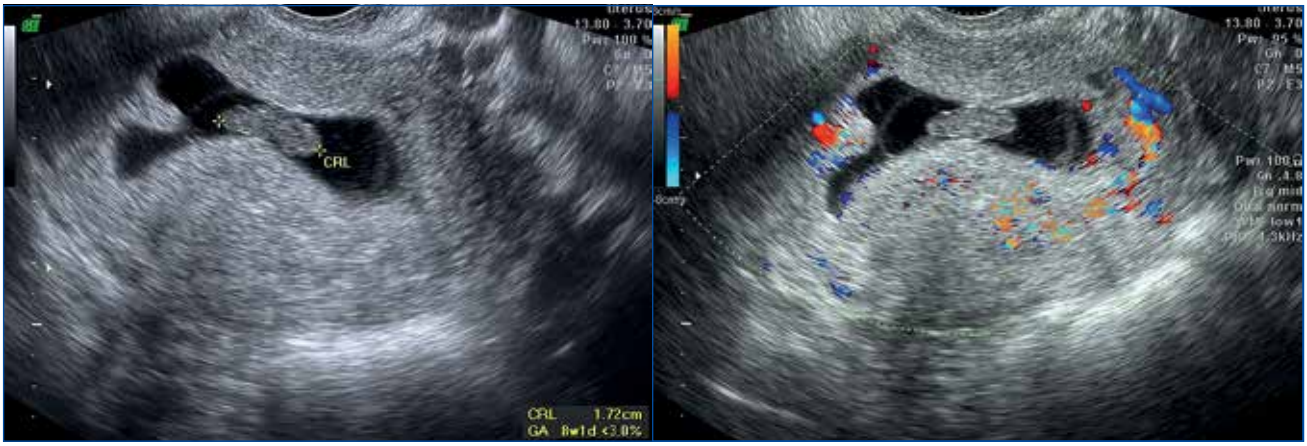

Figure 5. Early pregnancy loss in the case of a 34-year-old woman with 10 weeks of amenorrhea who presented moderate vaginal bleeding and abdominal cramping, the transvaginal ultrasound scan revealing intrauterine irregular gestational sac, crown rump length of the embryo of 17 mm and no cardiac activity

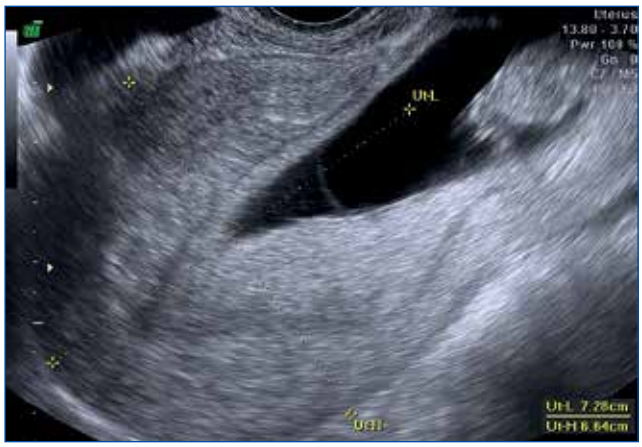

Figure 6. Inevitable abortion in the case of a 7-week pregnancy. The 28-year-old patient presented for rhythmic pelvic pain and moderate vaginal bleeding and the ultrasound scan showed an open internal os and the presence of intracervical conception products

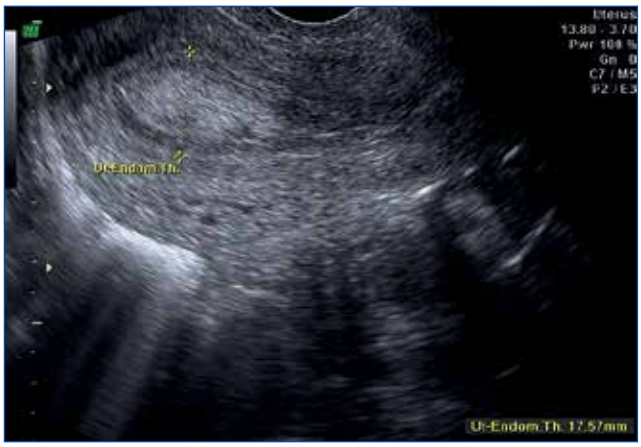

Figure 7. Sonographic examination done for a 26-year-old patient presenting with mild uterine bleeding, fever and uterine tenderness, two weeks after a medically induced abortion for a 6-week pregnancy. The ultrasound scan reveals residual gestational tissue, confirmed later by pathologic reports of numerous trophoblasts

Conclusions

Vaginal bleeding is a common first-trimester complication and in our clinic we had more than 1000 cases of threat of abortion during the two-year study period. Among the cases of spontaneous abortion requiring hospitalization, incomplete abortions were the most frequent. Ultrasonography plays a crucial role in the evaluation of early pregnancy loss for a highly certain diagnosis. ■

Conflict of interests: The authors declare no conflict of interests.

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original articles

Counseling in agenesis of *ductus venosus* secondary to interrupted inferior *vena cava*

Rodica Daniela Nagy[1,2,3], Dan Ruican[1,2], Ana Petrescu[1,2], Anda-Lorena Dijmărescu[1], Sidonia Săndulescu[1], Sidonia Cătălina Vrabie[1], Maria-Magdalena Manolea[1], George Lucian Zorilă[1,2], Dominic Gabriel Iliescu[1,2,3]

1. University of Medicine and Pharmacy of Craiova, Romania
2. County Emergency Clinical Hospital of Craiova, Romania
3. GinEcho Clinic, Medgin SRL, Craiova, Romania
Corresponding author: George Lucian Zorilă, e-mail: zorilalucian@gmail.com

ABSTRACT

Objective. To share our experience in the prenatal diagnosis of agenesis of *ductus venosus* (ADV) secondary to interrupted inferior *vena cava* (IIVC) and how does this affect the outcome. **Methodology.** A prospective study has been conducted in our center regarding the ADV outcome, since October 2016. In all cases, the main features of abdominal fetal circulation were evaluated in all second-trimester ultrasound scans, including the presence of a normal drainage of the umbilical vein, *via ductus venosus*, and the normal location of inferior *vena cava* (IVC). We present an analysis regarding the outcome of the ADV cases secondary to IIVC and we compare our data with those from the literature. **Results.** A total of five cases with prenatally diagnosed ADV and IIVC were identified. The gestational age at diagnosis ranged from 18 to 27 weeks. Karyotyping was performed in all cases but one, with an abnormal result in one case. Two cases were part of left isomerism syndrome and had an unfavorable outcome. Two cases did not present other anomalies and had a good outcome, according to the neonatal and pediatric cardiology follow-up. **Conclusions.** Postnatal outcome in cases with ADV and IIVC mainly depends on the presence of concomitant malformations. In isolated cases, the prognosis is generally good, but counseling is often difficult in such cases, and it is very important to exclude other structural or genetic anomalies.
Keywords: agenesis of *ductus venosus*, interrupted inferior *vena cava*, prenatal diagnosis, ultrasound, counseling

REZUMAT

Obiectiv. Scopul studiului este acela de a prezenta experiența noastră în diagnosticul prenatal al ageneziei de duct venos care apare secundar ageneziei venei cave inferioare, precum și stabilirea modului în care aceasta afectează prognosticul. **Metodologie.** Din octombrie 2016, în centrul nostru se desfășoară un studiu prospectiv cu privire la prognosticul cazurilor cu agenezie de duct venos. În toate cazurile, principalele caracteristici ale circulației fetale abdominale au fost evaluate în toate examinările ecografice efectuate în al doilea trimestru de sarcină, inclusiv prezența unui drenaj normal al venei ombilicale prin ductul venos și localizarea normală a venei cave inferioare. Prezentăm o analiză cu privire la prognosticul cazurilor cu agenezie de duct venos secundară absenței venei cave inferioare și comparăm datele noastre cu cele din literatura de specialitate. **Rezultate.** Au fost diagnosticate prenatal cinci cazuri cu agenezie de duct venos secundară ageneziei de venă cavă inferioară. Vârsta gestațională la diagnostic a variat între 18 și 27 de săptămâni. Cariotiparea a fost efectuată în patru cazuri. S-a identificat un rezultat anormal. Două cazuri au prezentat izomerism atrial stâng și au avut un prognostic nefavorabil. Celelalte două cazuri nu au prezentat alte anomalii asociate și au avut un prognostic bun, potrivit monitorizării cardiologice neonatale și pediatrice. **Concluzii.** Prognosticul postnatal în cazurile cu agenezie de duct venos și agenezie de venă cavă inferioară depinde în principal de prezența malformațiilor concomitente. În cazurile izolate, prognosticul este în general bun, dar consilierea este adesea dificilă și este foarte important să se excludă alte anomalii structurale sau genetice.
Cuvinte-cheie: agenezia ductului venos, venă cavă inferioară întreruptă, diagnostic prenatal, ecografie fetală, consiliere

Introduction

The ultrasound (US) examination of the fetal venous system has exposed a wide spectrum of malformations. These abnormalities of the venous system, especially of the caval system, may be associated with anomalies of the heart, intestinal tract and with anomalies of the symmetry of the body.

Azygos continuation of the inferior *vena cava* (IVC) has a prevalence of about 1.5% in the general population (range: 0.2-3%)[(1)]. Traditionally, this venous anomaly was thought to be strongly associated with congenital heart disease and polysplenia. However, the widespread prenatal diagnosis and postnatal evaluations revealed that interrupted inferior *vena cava* (IIVC) can evolve isolated and asymptomatic[(2)]. As an isolated finding, IIVC with azygos or hemiazygos continuation requires no treatment.

Improved ultrasound technology with the addition of color and spectral Doppler imaging has changed the assessment of fetal circulation and resulted in the increasing number of cases with a prenatal diagnosis of agenesis of *ductus venosus* (ADV). Also, it has been proven the ability of first-trimester (FT) screening in the detection of agenesis of the *ductus venosus*[(3)]. The prognosis of the ADV is also controversial and is related either to the type of the umbi-

lical shunt (intra- or extrahepatic), caliber of the shunt, the association with other fetal abnormalities and the nuchal translucency (NT) measurement[4-7].

The overall aim of fetal anomaly screening is to identify potential anomalies, so that parents can make an informed choice, and to improve the safety of delivery. The increase of ultrasound use highlighted questions regarding the appropriate management in cases with rare anomalies. Unfortunately, the reports regarding agenesis of *ductus venosus* with interrupted *vena cava* are rare and the long-term follow-up is not easy to assess, therefore for further cases the counseling becomes difficult.

Methodology

This is a prospective study conducted in our tertiary center (Prenatal Unit of the County Emergency Clinical Hospital of Craiova), between October 2016 and October 2020. We included the fetuses diagnosed with ADV and interrupted IVC. The examination of the DV was performed with the image magnified, so that the fetal thorax and abdomen occupied the whole screen. The presence of the normal hepatic segment of IVC was confirmed on the abdominal axial planes at the level of circumference biometry plane. In cases with IVC interruption, the azygos or hemiazygos vein were identified and showed in upper planes to drain into the superior *vena cava* (SVC) – Figure 4. Maternal characteristics and medical history along with fetal associated anomalies were noted. The written informed consent was obtained before US examination. The examinations were carried out by several certified sonographers. We compared our results with the ones from published studies, which were identified *via* PubMed and Scopus search, using the keywords: inferior *vena cava* agenesis, ADV outcome.

Results

During the study period, the assessment of the DV and IVC was carried out in 4000 pregnancies. We identified a total of five cases with prenatally ADV and IIVC, with a prevalence of 0.12%. The prenatal findings and outcome of the five cases are summarized in Table 1. Two ADV cases with IIVC were isolated (Figure 1), one case was associated with atrioventricular septal defect and hydrops, and two were part of the left isomerism syndrome. The latter two cases of IIVC presented azygos continuation. From the two isolated cases, one presented hemiazygos continuation (Figures 2-4) and the other with azygos drainage. Genetic evaluation was performed in four cases, and trisomy 13 was found in one case. One couple declined genetic assessment.

Discussion

Agenesis of the *ductus venosus* results from the failure to form the "critical anastomoses" between the portal-umbilical venous system and the hepatic-systemic venous system, shunting the umbilical blood through an aberrant vessel. Two main subgroups can be distinguished: intrahepatic drainage through the portal sinus to the portal venous system (PVS) or a hepatic vein, without giving rise to the DV (umbilicoportal-hepatic shunt). The other group is the one with extrahepatic course of the umbilical vein with liver bypass; the UV does not connect to the PVS and drains into a systemic vein (the inferior *vena cava*, right atrium or, rarely, the left atrium, coronary sinus or iliac vein)[8,9]. Intrahepatic drainage has been reported to have a favorable prognosis, 80-100% of cases having a normal outcome[4,10].

In our study, less than half of the cases with IIVC and secondary ADV were isolated and presented a good outcome. However, the small number of cases, due to the rarity of the disease, did not allow us to draw strong conclusions. In our cases, IIVC associated an umbilical drainage usually into the hepatic circulation – hepatic veins and portal system. One case presented with extrahepatic drainage, into the right atrium, with the subsequent development of hydrops. The poor prognosis seems to be related to the associated abnormalities rather than to the site of umbilical vein drainage.

IIVC is a rare congenital anomaly. This anomaly results from the primary failure of the right subcardinal vein to connect with the hepatic segment of the inferior *vena cava*, shunting its blood directly into the right supracardinal vein. The blood which drains the inferior part of the body reaches the heart by way of the azygos or hemiazygos vein and superior *vena cava*[11]. This anomaly seems to be a good indicator for the presence of atrial isomerism and the polysplenia syndrome[12,13]. We identified a total of five ADV cases with IIVC, out of which 40% were part of the left isomerism syndrome. This study is in line with previous publications, IIVC being usually associated with cardiac and extracardiac malformations, as part of the isomerism

Table 1. Sonographic findings and outcome in five ADV cases secondary to interrupted IVC

Case	GA (weeks)	Drainage	Additional sonographic findings	Outcome	Karyotype
1	19	HV	none	Good	N
2	18	HV	none	Good	N
3	20	HV	Left atrial isomerism	Confirmed postnatally	N
4	18	HV	Left atrial isomerism	Confirmed postnatally	T 13
5	18	Cardiac	AVSD, hydrops	IUFD	Refused

GA: gestational age; N: normal; IUFD: intrauterine fetal death; AVSD: atrioventricular septal defect; HV: hepatic vein; T 13: trisomy 13

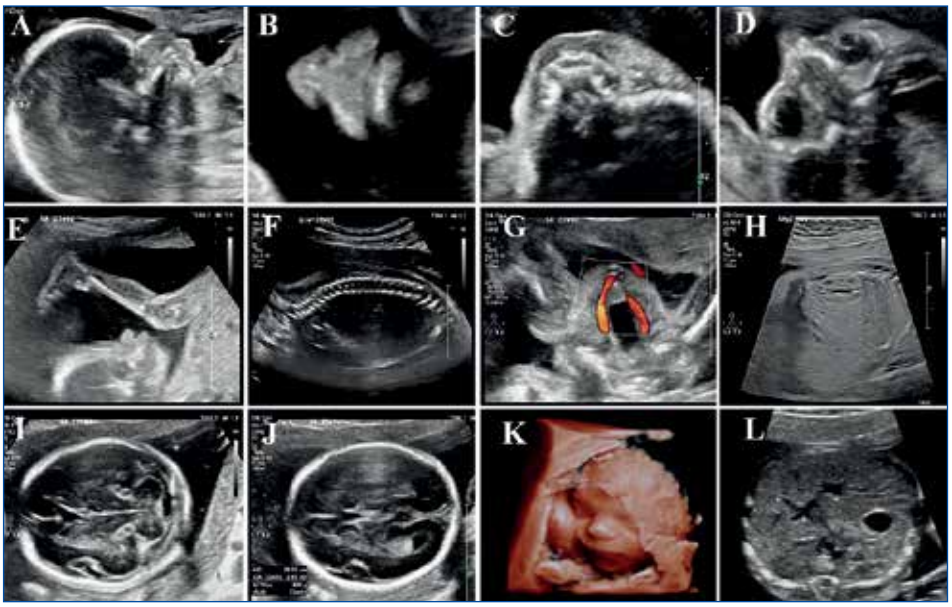

Figure 1. Normal fetal anatomy features. A: Facial profile. B: Fetal face – mouth, lips and nose evaluated in coronal view. C: Upper lip and hard palate alveolar ridge. D: Both fetal orbits appear symmetrical and intact. E: The fetal lower extremities. F: Longitudinal views of the spine and skin line. G: Bladder with surrounding umbilical arteries. H: Longitudinal view of the kidney. I: Cerebellar plane (*cavum septum pellucidum*, cerebellar hemispheres and vermis, *cisterna magna*, nuchal fold, cerebral peduncles, falx, thalami). J: Transventricular plane at the level of the atrium of the lateral ventricles (posterior horn of lateral ventricle, choroid plexus, *cavum septum pellucidum*). K: Fetal face features using 3-dimensional ultrasound volumes. L: Upper abdomen axial plane with stomach, portal confluent of the umbilical vein and aorta

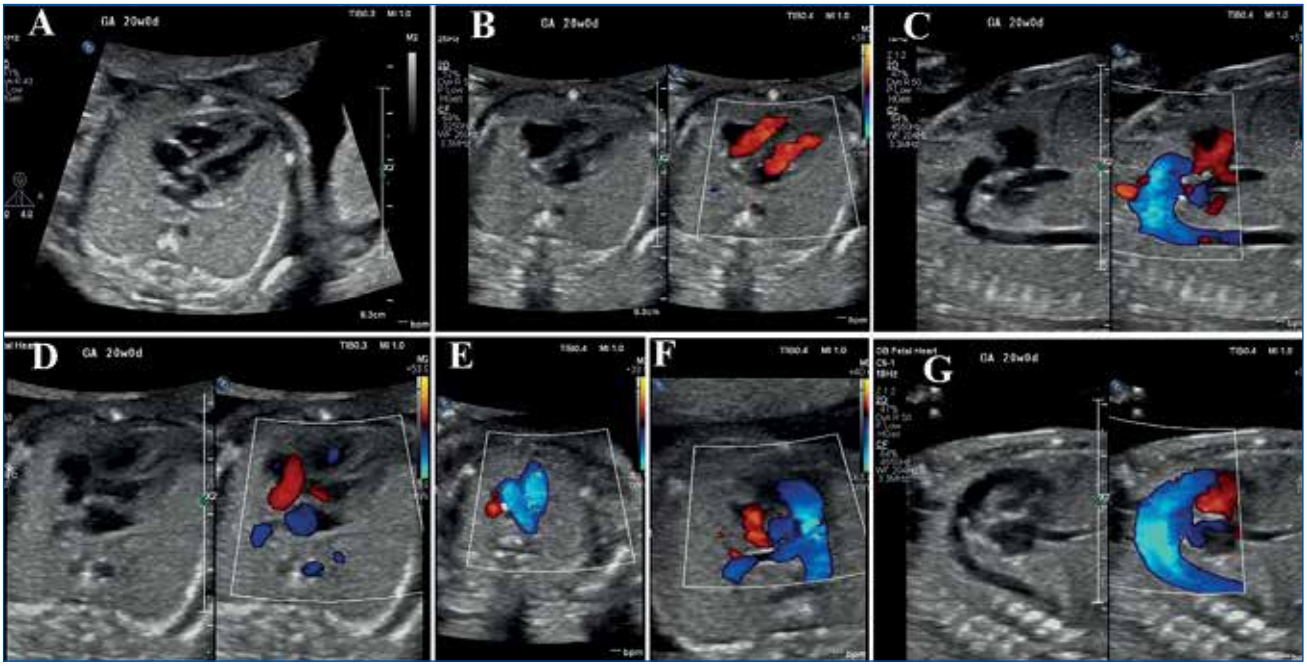

Figure 2. Fetal heart evaluation. A: Four-chamber view: right ventricle with moderator band, left ventricle giving the apex of the heart, left atrium with pulmonary veins, *crux cordis*, foramen ovale, descending aorta and adjacent hemiazygos vein. B: Grey-scale and color Doppler flow evaluation of the four-chamber plane, atrioventricular flows and intact atrioventricular septum. C: Aortic arch. Three head and neck vessels arise from the aorta. Descending aorta. D: Left ventricular outflow tract (aortic root). E: Three-vessel view with the confluence of the ductal and aortic arterial arches and superior *vena cava* present at the right. F: Right ventricular outflow tract, with pulmonary trunk branching in the axial plane with no turbulences across the pulmonary valve and right direction of flow down the *ductus arteriosus*. G: Ductal arch. Doppler assessment demonstrates flow away from the heart with no obvious turbulence or reverse flow and no tributaries directed towards the neck

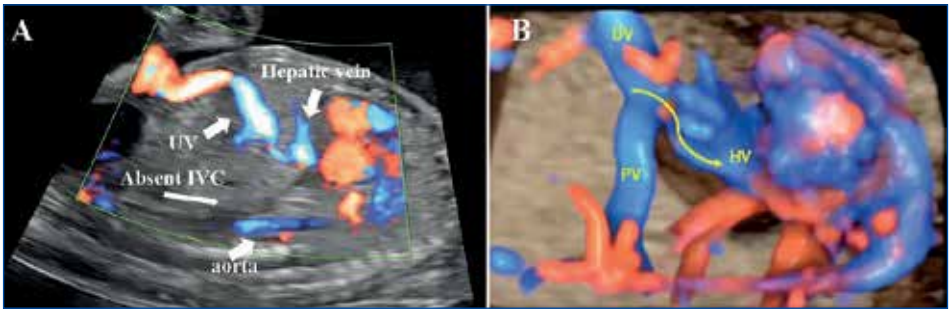

Figure 3. Vascular abnormalities detected in the upper abdomen. A: Color Doppler imaging, showing agenesis of *ductus venosus* with umbilical vein (UV) drainage into a hepatic vein (HV). B: 4D STIC volume presenting interrupted inferior *vena cava* (IVC) and hepatic drainage of the UV (UV: umbilical vein; PV: portal vein; IVC: inferior *vena cava*)

syndrome. The association of IIVC with congenital heart diseases has been reported to be an important marker of symptoms severity and a prognostic factor[14]. The two survivors with left atrial isomerism had a two-year follow-up, with the developing of heart block and surgical correction.

In cases of isolated IIVC, usually there is no treatment regime required. The patients are often asymptomatic, but deep venous thrombosis rate seems to be increased after birth[15,16]. The evaluation of the cases from our study had a multidisciplinary approach along with a fetal cardiologist. 40% of our cases were isolated and had a good outcome at birth and on short-term follow-up. A detailed cardiac evaluation was performed at two-month postnatal age, which confirmed the prenatal diagnosis of inferior *vena cava* agenesis with hemiazygos and azygos continuation to superior *vena cava*. The isolated cases were followed-up on a period of one year postnatally and the development of the infants was according to their age.

Usually, the isolated abnormality of the venous system represents a self-limiting clinical problem. Most of the previous cases of IIVC and hemiazygos continuation have been reported in adults[4], while the few cases reported in fetuses do not have a long-term follow-up. The key finding of this study represents the diagnosis of ADV associated with IIVC, showing a good outcome on the short-term evaluation in isolated cases. Of course, there are limitations of the study, due to the lack of follow-up, which could provide information about the long-term consequences.

The value that the study adds to the current literature is represented by the recognition and description of ADV secondary to IIVC and hemiazygos or azygos continuation and its short-term outcome. We would like to underline the fact that counseling is often difficult in such cases, where a conflict emerges when combining the contradictory prognosis of two rare conditions: the reserved ADV outcome and the well-known overall good development of the IIVC individuals.

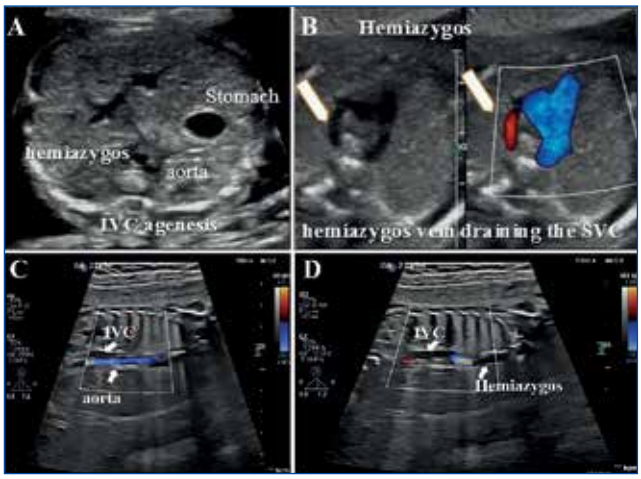

Figure 4. A: Interrupted inferior *vena cava* with hemiazygos continuation confirmed on the abdominal circumference plane. **B:** Superior *vena cava* drainage of hemiazygos vein evident in the three-vessel and trachea view. **C, D:** Coronal view with the absence of the hepatic segment of the inferior *vena cava* and hemiazygos continuation

The postnatal outcome in cases with ADV and IIVC mainly depends on the presence of concomitant malformations. Thus, in such cases, we believe that it is very important to exclude other structural or genetic anomalies. Limited postnatal long-term follow-up does not allow us to draw safe conclusions, but prenatal counseling for this anomaly should include the likelihood of later increased risk for venous thrombosis. ■

Conflict of interests: The authors declare no conflict of interests.

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case reports

The challenges of differential diagnosis between pseudomyxoma peritonei and primary ovarian neoplasia. Case presentation and literature review

Sorin Vasilescu[1], Daniela Meca[1], Natalia Țurcanu[1], Octavian Munteanu[1,2], George Pariza[3], Simion George[4], Oana Pătrașcu[4], Monica Cîrstoiu[1,5]

1. Department of Obstetrics and Gynecology, Bucharest University Emergency Hospital, Romania
2. Department of Anatomy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
3. Department of General Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
4. Department of Pathology, Bucharest University Emergency Hospital, Romania
5. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author: Octavian Munteanu, e-mail: octav_munteanu@yahoo.com

Disclosure: All authors have participated equally in developing this study.

ABSTRACT

Pseudomyxoma peritonei originates from primary mucinous neoplasms of the appendix or from different sites, especially the ovary. The specialized literature emphasizes the possibility of the existence of synchronous primary mucinous tumors of the ovary and appendix involved in the disease's onset. If untreated, the prognosis of the patients diagnosed with pseudomyxoma peritonei is fatal, due to the compression and blockage of the digestive tract. Ascites associates a poor prognosis through the characteristic pharmacoresistance, tumor cells in this context presenting genomic changes of acquired resistance across the whole genome. We report the case of a 61-year-old woman with massive ascites and pleurisy and atypical laboratory and intraoperative aspect, respectively peritoneal carcinomatosis, with infracentimetric disseminations on the epiploon, mesentery and parietal peritoneum. Also, a tumoral pelvic block which included the uterus, the ovaries, the sigmoid colon and ileal loops was detected. The extraabdominal spread of pseudomyxoma peritonei syndrome has a rare occurrence, with only few reports in literature. The differential diagnosis of primary tumor should be well established, because the misdiagnosis of a metastatic mucinous ovarian tumor as a primary neoplasia may adversely affect the surgical management, the complementary treatment and the prognosis.

Keywords: pseudomixoma peritonei, ovarian neoplasia, chylous ascites

REZUMAT

Pseudomixomul peritoneal își are originea, în majoritatea cazurilor, în neoplasmele mucinoase primare ale apendicelui sau în alte structuri, în special în ovar. Literatura de specialitate subliniază posibilitatea existenței tumorilor mucinoase primare sincrone ale ovarului și apendicelui implicate în debutul bolii. Dacă nu este tratat, prognosticul pacienților diagnosticați cu pseudomixom peritoneal este fatal, având ca mecanism principal ocluziile tractului digestiv. Ascita reprezintă un element de prognostic rezervat, prin farmacorezistența caracteristică, celulele tumorale prezentând, în acest context, modificări genomice ale rezistenței dobândite prezente în întregul genom. Raportăm cazul unei paciente în vârstă de 61 de ani, cu ascită masivă și pleurezie și cu aspecte atipice atât paraclinic, cât și intraoperatoriu, respectiv carcinomatoză peritoneală, cu diseminări infracentimetrice epiploneale, la nivelul mezourilor, cât și al peritoneului parietal. De asemenea, a fost remarcat un bloc pelvian tumoral care a inclus uterul, ovarele, colonul sigmoid și ansele ileale. Răspândirea extraabdominală a sindromului pseudomixomului peritoneal este rară, cu numai câteva raportări în literatură. Diagnosticul diferențial al tumorii primare ar trebui să fie clar stabilit, deoarece diagnosticul greșit al unei tumori ovariene mucinoase metastatice ca neoplazie primară poate afecta negativ managementul chirurgical, tratamentul complementar și prognosticul.

Cuvinte-cheie: pseudomixom peritoneal, neoplazie ovariană, ascită chiloasă

Introduction

Pseudomyxoma peritonei, or gelatinous disease of the peritoneum, as Pean described it in 1871[(1)], is a rare condition estimated to occur in 1 to 2 individuals per million[(2,3)]. More than that, only 45 cases were reported until 2018 in the English literature[(2,4)]. It usually originates from primary mucinous neoplasms of the appendix (80% of the reported cases) or it arises from different sites, especially the ovary, with the peculiarity that primary ovarian mucinous adenocarcinomas presenting as pseudomyxoma peritonei were described as low-grade tumors in the majority of cases[(2,5)]. In addition to that, the specialized literature emphasizes the possibility of the existence of synchronous primary mucinous tumors of the ovary and appendix involved in the disease's onset, but this possibility represents the subject of an

important debate[5,6]. It is stipulated that this disease affects most frequently women with the age between 50 and 70 years old[2].

The clinical syndrome's course is characterized by the production of mucine, leading to abundant gelatinous ascites, and not by intracellular mucin accumulation in tumor cells. Also, the rupture or leakage of a mucinous neoplasm within the abdomen was involved in the onset of the disease. It is described as a locoregional disease, with a high propensity for spread to peritoneal surfaces, but almost no lymphatic or hematogenous metastases[7,8]. If untreated, the prognosis of the patients diagnosed with pseudomyxoma peritonei is fatal, due to the compression and blockage of the digestive tract[2].

Ovarian carcinoma remains one of the leading causes of mortality and morbidity from the field of gynecologic-related malignancies[9], and the optimal treatment of these cases can represent a real challenge for the clinician. The International Federation of Gynecology and Obstetrics (FIGO) estimates that two out of three cases of ovarian carcinoma are diagnosed in an advanced stage of the disease[9], this being due to the natural biology of the disease and also to the inexistent efficient screening methods.

Regarding the mucinous ovarian carcinoma, it is estimated nowadays to have an incidence of only 3% because of the recognition of clinical and pathological features of benign mucinous tumors from the invasive ones and between primary and metastatic tumors. The mucinous ovarian carcinoma is described as having a distinct natural history and molecular profile and as not being associated with the known risk factors for epithelial ovarian cancer, excepting tobacco smoking. Eighty percent of mucinous adenocarcinoma of the ovary are metastatic, thus the recognition of immunochemistry profile is essential for the diagnosis and to predict an accurate prognosis[10]. It is revealed that mucinous ovarian carcinoma of intestinal type is associated with an increased level of CA 19.9, with diffusely negative CA 125 and with diffusely positive or focally negative CEA[5].

Severe ascites is a significant indicator of advanced ovarian cancer, but the mechanisms that are responsible for the imbalance existing between peritoneal vascular leakage and lymphatic drainage are still not fully understood. Chylous ascites is the accumulation of peritoneal fluid, rich in triglycerides and with a milk-like aspect, as a response to the disruption of the lymphatic system after a traumatic injury or obstruction from malignant or benign causes. Table 1 summarizes the main causes and the differential diagnosis of chylous ascites.

In developing countries, tuberculosis is the main etiological factor; however, in developed states, cirrhosis and malignancies account for about two thirds of the cases[11]. There is no reported incidence of chylous ascites in Romania, but from the data presented in the specialized literature, this complication is found in 1 out of 20,000 admissions, with an estimated increasing incidence regarding the higher incidence of aggressive cardiothoracic and abdominal surgeries and with prolonged survival rates of cancer patients[11]. However, the mechanism of formation of chylous ascites in pseudomyxoma peritonei consists in the implantation of

Table 1. The main causes of chylous ascites and their characteristic features

Cause of chylous ascites	Characteristic features
Malignancy (lymphoma, breast, pancreatic, colon, renal, testicular, ovarian and prostate cancer, Kaposi's sarcoma, carcinoid tumors, and lymphangiomyomatosis)	Secretory diarrhea is an exclusion criterion. Common in adults[11].
Cirrhosis	Common in adults. It may be an early or late (consequence of hepatocellular carcinoma) symptom[12].
Infection (tuberculosis, filariasis, *Mycobacterium avium* intracellular)	Low-income countries with limited access to medical services. It results from a severe inflammatory reaction. HIV infection is a risk factor[13].
Congenital (primary lymphatic hypoplasia or hyperplasia, Klippel-Trenaunay syndrome, Yellow-Nail syndrome)	Specific to pediatric population. Association with characteristic features of the syndromes. Presence of megalymphatics[14].
Inflammation (radiation, constrictive pericarditis, pancreatitis, sarcoidosis, retroperitoneal fibrosis, celiac sprue, retractile mesenteritis, Whipple's disease)	Fibrosis and obstruction of the lymphatic vessels in the small bowel and mesentery[15].
Postoperative and traumatic (inferior *vena cava* resection, abdominal aneurysm repair, catheter placement for peritoneal dialysis, retroperitoneal node dissection)	It occurs in about one week to one month after the event[16].
Other causes, such as nephrotic syndrome, right heart failure or dilated cardiomyopathy	The underlying pathogenesis is not understood. Some patients may have just opalescent effusions; the triglyceride levels should be measured[17].

mucine of the peritoneal surfaces[1,2]. Several theories have been proposed to explain the pathogenesis of ascites in pseudomyxoma peritonei, including multifocal neoplasia of the peritoneum, ovaries, and appendix[18,19], mucinous metaplasia of the peritoneum[19,20], and metastasis or leakage from a primary mucinous neoplasm of the ovary or appendix[21,22].

Ascites associates a poor prognosis through the characteristic pharmacoresistance, tumor cells in this context presenting genomic changes of acquired resistance across the whole genome[23]. Although the effective palliation of malignant ascites is difficult and challenging, the elimination of the fluid will firstly improve the patient's quality of life and can prolong survival through a better response on targeted therapeutics procedures[24].

Case report

We report the case of a 61-year-old woman, known with psoriasis, who was admitted in the Department of Gastroenterology of the Bucharest University Emergency Hospital, accusing abdominal distention, dyspnea and weight loss, with onset of about two months. The clinical examination revealed psoriatic lesions on the upper limbs, diminished vesicular murmur in the lower third of right hemithorax, increased respiratory rate (26 breaths/minute) and a distended, in tension, painless spontaneously and on palpation abdomen.

The laboratory findings showed elevated values of tumoral markers (CA 125=406.3 U/ml, CEA=5.13 ng/ml), hepatic cytolysis (ALT=125 U/L, AST=70 U/L), hepatic cholestasis (GGT=296 U/L), mild hypoalbuminemia (3.1 mg/dl), mild hyperkaliemia (5.5 mmol/L) and negative hepatic viral markers. Also, a SARS-COV-2 rt-PCR test was performed, given the current epidemiological context.

A pulmonary radiography was performed which showed pulmonary hyperinflation, accentuation of the bilateral basal peribronhovascular interstitial pattern, and small right pleural effusion. Also, the abdominal radiography showed no hydroaeric levels.

The transvaginal ultrasound revealed massive ascites, a uterus with the dimensions of 72/25/51 mm, with nonhomogeneous diffuse myometrium with some calcifications, and small ovaries without cystic tumors. A computed tomography of the abdomen and pelvis was performed, which detected polycystic ovarian measuring 26 mm on the right side and 33 mm on the left side (Figure 1).

On the other hand, the MRI of the abdomen and pelvis showed bilateral adnexal expansive processes, with heterogeneous, mixed cystic-solid consistency, with polycyclic contour, forming a common block with the uterus and measuring 36/40 mm on the right side and 43/27 mm on the left side (Figure 2).

A paracentesis was performed, with the evacuation of 5 liters of ascites fluid (characterized by the laboratory findings as exudate), and the diuretic treatment was initiated.

The patient was referred to the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital for an interdisciplinary consultation. When reevaluating, the patient showed no relief of symptoms, with the persistence of abdominal pain and dyspnea. New laboratory findings showed an increased level of CA 19.9 (86.8 U/ml). The pulmonary radiography revealed bilateral pleural effusion, with a tendency to imprisonment. A right bundle branch block and left axial deviation were discovered during a cardiological evaluation, therefore, additional to the diuretic treatment, a selective beta-blocker treatment was initiated.

Given the patient's low oxygen saturation (SaO_2 94%), an ultrasound-guided thoracentesis was performed, with the evacuation of 400 ml of pleural fluid, which was sent for cytologic analysis.

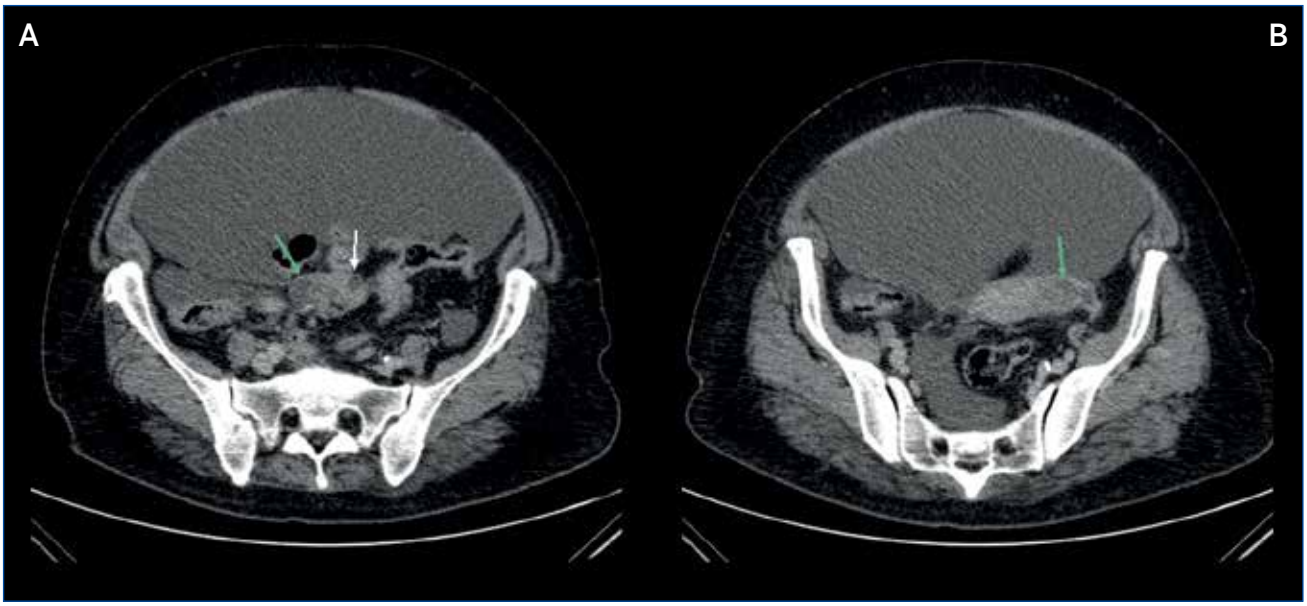


Figure 1. CT of pelvis – postcontrast axial sections. A) Polycystic transformation of right ovary (green arrow) and small leiomyoma of the uterus (white arrow). B) Polycystic transformation of left ovary

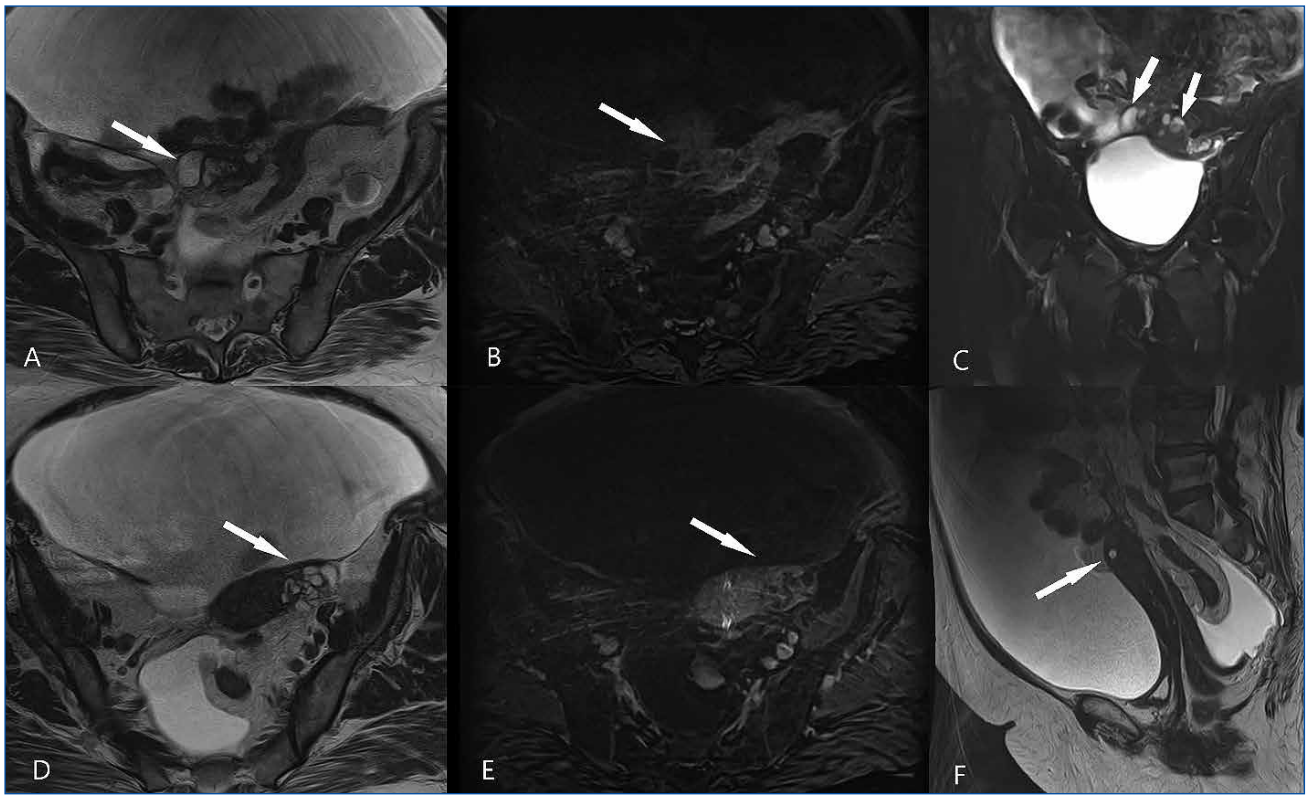
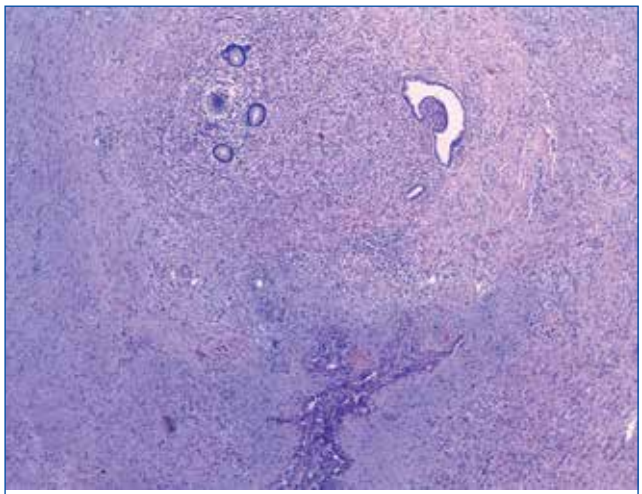
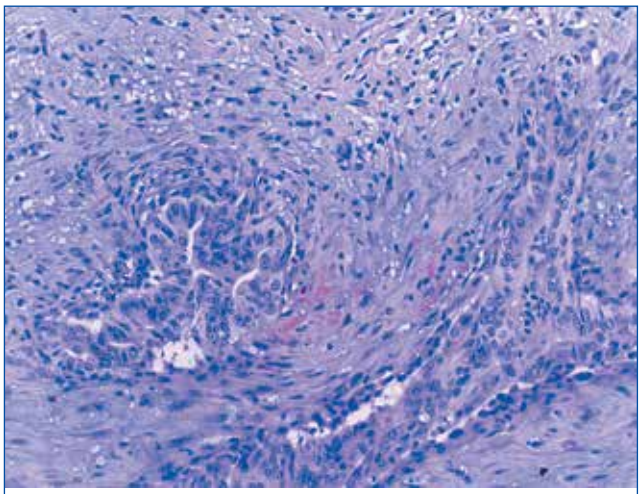


Figure 2. MRI of pelvis. A) Axial section T2 – tumoral transformation of the right ovary. B) Axial section T1 3D fatsat – lower signal intensity in cystic component of the ovary. C) Coronal section T2 fatsat – the high signal intensity suggests the cystic transformation of both ovaries. D) Axial section T2 – cystic transformation of the left ovary. E) Axial section T1 3D fatsat – high signal intensity in the solid component of the ovary; no clear demarcation limit between left ovary and the uterus. F) Sagital section T2 – uterus leiomyoma. All the sections reveal a large amount of ascites fluid



Hematoxylin-eosin staining, ob. 4x



Hematoxylin-eosin staining, ob. 20x

Figure 3. Microscopic images of the appendix – note the colonic glands with goblet cells, with fibrous wall and inflammatory cells with eosinophils, as well as irregular, infiltrative glandular and cribriform structures

Under general anesthesia, an exploratory laparotomy was performed by a multidisciplinary team consisting of gynecologists and general surgeons. We detected peritoneal carcinomatosis, with infracentimetric disseminations on the epiploon mesentery and parietal peritoneum; a tumoral pelvic block which included the uterus, ovaries, sigmoid colon and ileal loops; the ovaries were measuring 3/2/1 cm on the right side and 3/2/2 cm on the left side, with bilateral small cysts and without capsular breakage; also, a 1.5-cm diameter secondary dissemination was detected on mesentery's root. During surgery, 10 liters of ascites fluid with milky appearance were extracted, from which samples for cytology and bacterial culture were collected. Tumor cytoreduction

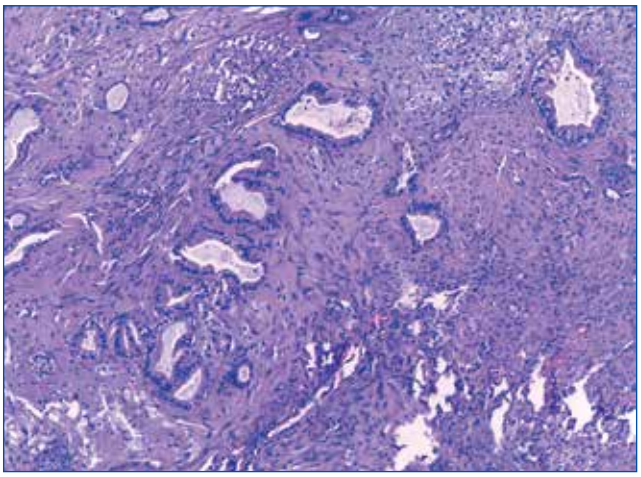


Figure 4. Microscopic images of the greater omentum, hematoxylin-eosin staining, ob. 4x – note the connective-adipose tissue with irregular glandular-cribriform structures, with an infiltrative character and surrounding desmoplastic reaction, and a moderate amount of intraluminal mucus

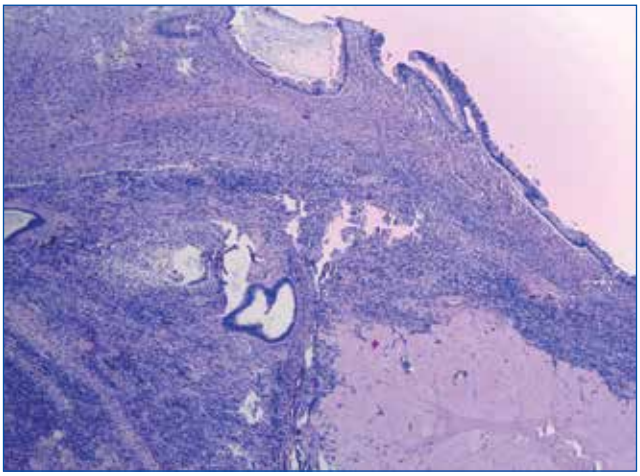


Figure 5. Microscopic images of the ovary, hematoxylin-eosin staining, ob. 4x – note the ovarian structure with *corpus albicans* and mucinous epithelium, with mucous cystic structure

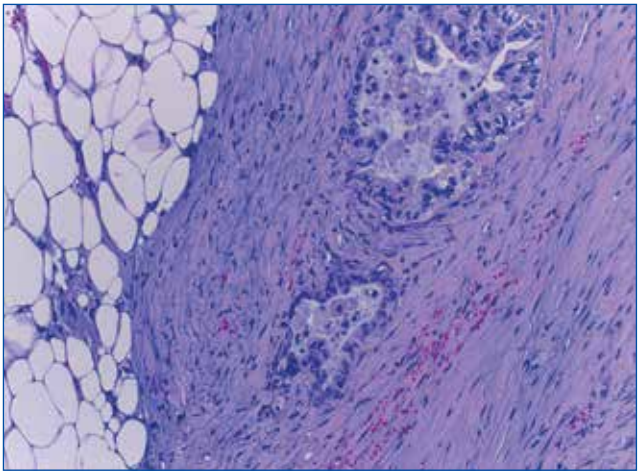


Figure 6. Microscopic images of the ovary, hematoxylin-eosin staining, ob. 20x – note the glands infiltrated in the stroma, near the adipose tissue, having malignant characteristics, with the appearance of mucinous adenocarcinoma and rare intraluminal macrophages

through total hysterectomy with bilateral adnexectomy, peritoneal biopsy and appendectomy (the histopathological extemporaneous examination showed mucinous adenocarcinoma) was performed. The final histopathological result described pseudomyxoma peritonei and metastases of mucinous adenocarcinoma in the ovary and appendix, without the possibility to determine the origin of the primary tumor (Figures 3, 4, 5 and 6). Thus, immunohistochemistry (IHC) test was indicated.

The postoperative evolution was favorable, with the relief of the proeminent symptoms. However, the peritoneal drainage was maintained for 7 days, with the evacuation of approximately 6 liters of ascites fluid during this period, and the patient's oxygen saturation was in a progressive decline (up to 90%). A treatment with Miofilin® and hydrocortisone hemisuccinate was initiated. The patient was discharged after 12 days of hospitalization and was guided to the oncology department for specialized treatment after receiving the IHC results.

Discussion

Pseudomyxoma peritonei defines a very rare condition caused by primary mucinous tumors that arise from different sites, usually the appendix or ovary[5,24]. The pathology involves a hypersecretion of mucine which determines the rupture of the tumor and the dissemination of the mucus in the abdominal cavity[25]. The peritoneal implantation of mucine leads to abundant chylous ascites, which determines multiple recurrences and progressive fibrous adhesions, leading to fatal intestinal obstruction[5,26].

There are no pathognomonic signs to diagnose pseudomyxoma peritonei, as this very rare entity can cover various symptoms, from a simple abdominal pain to subocclusive syndrome. The radiographic features show loculated collections of fluid, along the peritoneal surfaces. The appearance of coated abdominal organs and omental caking is frequent. The CT scan evaluation reveals low attenuation fluid throughout intraperitoneal areas, omentum or mesentery, while the MRI characteristics of the fluid include a low signal in T1 and high signal in T2[27,28].

Tumor markers (CEA, CA 19.9, CA 125) are not useful for the diagnosis of the disease[2]. In our case, all the tumor makers were abnormal. CA 125, a glycoprotein encoded by MUC16 gene on chromosome 19, has been reported to increase in only 12% of ovarian mucinous carcinomas. In our case, the incresead level of this marker can be explained by the presence of ascites fluid[29]. Regarding CA 19.9, a monosialoganglioside secreted by mucinous tumors of the gastrointestinal tract, a limited number of studies sustained that this tumoral marker can predict a primary mucinous ovarian tumor, although in our case its level was slightly increased[30]. Considering a study performed by Numella *et al.* in 2018, of all the tumoral markers analyzed in our case report, only CEA can be exploited to target specialized therapy[31].

Extraabdominal spread of pseudomyxoma peritonei syndrome has a rare occurrence (5.4%), with few reports in literature. The pleural extension of mucinous tumor

in this syndrome was described before cytoreductive surgery in only 17% of these cases[32]. The pleural fluid, besides the ascending of the diaphragm, was associated in our case with dyspnea and a low saturation in oxygen.

The main option in the management, when ovarian neoplastic ascites is highly suspected, is cytoreductive surgery, which in association with chemotherapy has a response rate of up to 70%[33]. Cytoreductive intervention involves hysterectomy, adnexectomy, pelvic and paraaortic lymph node dissection, omentectomy, and excision of all macroscopically visible secondary determinations.

Appendectomy is routinely recommended in mucinous carcinoma. In a group of 269 patients operated for ovarian mucinous carcinoma, in which 172 appendectomies were performed, Rosendhal *et al.* identified micrometastases of mucinous carcinoma on appendix with normal macroscopic appearance. There is always a risk of micrometastasis, therefore routine appendectomy is recommended, especially since this interventional step does not increase the postoperative morbidity and may clarify the difficulties of differential diagnosis regarding the origin of the initial tumor in mucinous carcinoma[34].

The standard therapy for refractory or advanced ascites that have not been able to benefit from surgery consists of repeated paracentesis. The method is minimally invasive and can be performed under ultrasound guidance. Another surgical approach is the radical excision of the peritoneum, which is associated with intraperitoneal administration of chemotherapeutics (cisplatin or paclitaxel) in conditions of hyperthermia. However, this method has not been shown to be effective in mucinous ovarian carcinoma[35-38].

The diuretic treatment has not been shown to be useful in neoplastic ascites and is less effective compared to paracentesis[32]. Spironolactone 100-200 mg/day and furosemide 40-80 mg/day may be administered, but their use is recommended for limited periods, as they may induce hypovolemia, hypotension, renal failure and increase the risk of thromboembolic events in chemotherapy[39].

A new approach in the treatment of neoplastic ascites is monoclonal therapy that addresses directly some of the etiopathogenic factors of ascites, respectively neoangiogenesis. In 2016, bevacizumab (FDA-approved for the treatment of recurrent ovarian cancer) was shown to be effective in relapsed disease associated with ascites[32,40]. The most common complications of monoclonal treatment are thrombocytopenia and neutropenia[40].

Cytoreductive surgery is the gold standard surgical intervention. However, the recurrence rate is high due to the impossibility to remove all the peritoneum surface[32]. In our case, we observed a very accelerated rhythm of formation of ascites, despite the extensive cytoreductive surgery.

Conclusions

Pseudomyxoma peritonei is a very rare disease, described by an indolent and progressive growth pattern, whose diagnosis relies on the histopathological and immunochemistry findings. The differential diagnosis of primary tumor should be well established, because the misdiagnosis of a metastatic mucinous ovarian tumor as a primary neoplasia may adversely affect the surgical management, the complementary treatment and the prognosis. Comparative studies on quality of life and disease progression, between monoclonal therapy and paracentesis associated or not with intraperitoneal chemotherapy as treatment options for refractory ascites, show a better quality of life and longer remission intervals of neoplastic ascites in favor of monoclonal therapies. ■

Conflict of interests: The authors declare no conflict of interests.

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