A BRIEF PRESENTATION OF ANTIPHOSPHOLIPID ANTIBODIES AND THE PREGNANCY OUTCOME AFTER THERAPY

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Abstract

Antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia. Antiphospholipid antibodies (aPL) are a family of autoantibodies that are associated with pregnancy complications including stillbirth and recurrent miscarriage. APS treatment is essentially preventive; the approach for women with obstetric manifestations of APS is based on the use of aspirin plus low-molecular-weight heparin (LMWH). Laboratory explorations are needed in order to apply appropriate preventive measures. The aim of the present review is focused on who should be tested, what tests and the way tests are to be interpreted, and the pregnancy outcome after therapy.

Rezumat: O prezentare succintă a anticorpilor antifosfolipidici și a prognosticului sarcinii după tratament

Sindromul antifosfolipidic (APS) este cea mai frecventă cauză de trombofilie dobândită. Anticorpii antifosfolipidici (aPL) sunt o familie de autoanticorpi care sunt asociați cu complicații ale sarcinii, inclusiv moarte intrauterină și avorturi spontane recurente. Tratamentul APS este, în esență preventiv; abordarea pentru femeile cu manifestări obstetricale de APS se bazează pe utilizarea de aspirină, plus heparine cu greutate moleculară mică (HGMM). Sunt necesare explorări de laborator în vederea aplicării unor măsuri adecvatate de prevenire. Scopul acestei prezentări este axat pe: cine ar trebui să fie testat, teste specifice, modul în care testele trebuie să fie interpretează și prognosticul sarcinii după terapie.

Cuvinte cheie: anticorpi antifosfolipidici, complicații ale sarcinii, heparine cu greutate moleculară mică (HGMM), aspirină

Antiphospholipid antibodies (aPL) are a family of autoantibodies that are associated with pregnancy complications including stillbirth and recurrent miscarriage. According to data from the literature, the prevalence of aPL in infertile women varies from 4% to 66%. These differences can be explained by the lack of assay standardization, the panel of antibodies tested, and the definition of population of patients [1].

Clinical expression of antiphospholipid syndrome (APS) is the same as vascular placental insufficiency. Therefore, spontaneous evolution could be an acute way leading to in utero death (IUD) associated or not with placenta abruptio (PA) or with pre-eclampsia (PE). It could be also a chronic evolution with fetal growth retardation (FGR) complicated or not by PE [2].

The aim of the present review is focused on...
who should be tested, what tests and the way tests are to be interpreted, and the pregnancy outcome after therapy.

**Antiphospholipid antibodies (aPL), laboratory and clinical challenge**

Women with a history of thrombotic events should be screened for APS possible before pregnancy. Laboratory explorations are needed in order to apply appropriate preventive measures.

Lupus anticoagulant is a medical condition that predisposes to the appearance of thrombi and repeated pregnancy loss. Determination LA is necessary in patients with a high probability of having antiphospholipid syndrome (APS) or a routine check shows unexplained APTT (activated partial thromboplastin time) prolongation. It is important to highlight that the guidelines stress that all three steps (screening, mixing and confirmation) are essential and should be performed. A mixing test with a confirmatory assay can be performed if the confirmatory clotting time is prolonged. This increases the diagnostic efficacy [3]. Paradoxically, LAs prolong clot-based assays in vitro while predisposing to thrombosis in vivo. In fact, approximately 30% of LA patients will experience thrombosis [4]. The diagnosis of LA is suspected mainly based on the difference in clotting times between low and high phospholipid reagents. In patients receiving heparin therapy, LA-insensitive APTT reagents should be used. In patients clinically suspected of lupus inhibitors, LA-sensitive APTT reagents should be used [5].

Regarding other aPL, a huge variety of assays is available with low comparability. To reduce inter-laboratory variation, similar to LA, the choice of assays for anticardiolipin antibodies (aCL) and anti-β2 glycoprotein I antibodies (aβ2GPI) could be restricted in future guidelines. In addition, standardization in the set-up and production process for ELISA (enzyme-linked immunosorbent assay) as well as the application of new technologies will facilitate reproducibility between laboratories [3].

Several studies have reported that “triple positivity” (the combination of positive aCL, LA, and (anti-β2GPI) is strongly associated with adverse clinical outcomes. Lockshin et al. observed that the simultaneous positivity for aCL, anti-β2GPI, and LA was not superior for the prediction of adverse obstetric outcomes than positive LA results alone [6].

Based on the laboratory recommendations for APS, a confirmed positive result of one immunoassay, i.e. aCL or a β2GPI IgG or IgM, is sufficient for classifying patients with vascular thrombosis and/or pregnancy related morbidity as having APS. Of the “criteria” immunoassays for APS, aCL is the most sensitive while aβ2GPI antibodies are considered highly specific with low sensitivity for APS [7]. It has been proposed by some that the Sydney laboratory criteria should be modified such that testing for aβ2GPI should be limited to measurements of IgG aβ2GPI only and testing for aCL should be omitted. Others have argued that it is premature to consider reducing the number of assays used in the diagnosis of APS [8].

It is recommended that both anticardiolipin and β2GPI aPL assays be performed to maximize sensitivity and specificity. Current guidelines include only medium and high levels of antibodies (>99th percentile or >40 IgG or IgM phospholipid units) as diagnostic criteria to improve the test specificity [4]. Patients with LA, aCL IgG at high titers, or anti-β2GPI antibodies plus LA or aCL have the highest thrombotic risk.

Closer clinical and therapeutic monitoring (to ensure a correct International Normalized Ratio) is advisable in patients with thrombosis and any of these immunological profiles [9].

In the clinical practice it is possible to find patients with clinical signs suggestive of APS, who are persistently negative for the routinely used assays to detect aCL, aβ2GPI and LA. The most convincing explanation for the existence of such “seronegative” patients may be that the current range of tests is inadequate. It may depend either on limits of the traditional technical approaches or on the existence of different antigenic targets [10].

β2GPI, the major antigen in the antiphospholipid syndrome, is synthesized by hepatocytes, endothelial cells, and also trophoblast cells. Several studies have shown that aβ2GPI
antibodies may represent the main pathogenic antibodies in obstetrical APS that could cause thrombosis of placental blood vessels, dysfunctions of trophoblasts in the peri-implantation period, or an imbalance of maternal hormones [1]. Placental intervillous thrombosis and infarction were significantly correlated with pregnancy failure in these patients. Some authors have demonstrated, in fact, that placentas from aPL-positive women have histopathological signs of inflammation, supporting the hypothesis that thrombotic events are not the only pathogenic mechanism in APS patients with recurrent fetal loss [11].

Current lines of research are examining the usefulness of testing for new aPL specificities in helping to identify APS in patients with thrombosis and/or pregnancy morbidity, particularly in those who are repeatedly negative for the currently used tests. Moreover, non-criteriaaPL tests, among those antiphrotxrombin antibodies, are proposed to help in assessing the risk for both thrombosis and pregnancy morbidities in patients suspected of APS [12].

Once a test for aPL is repeatedly positive (at least 12 weeks apart), clinical events determine if the individual meets criteria for APS [13]. These criteria include any of the following three different types of pregnancy loss as a clinical criterion for APS: (1) one or more unexplained deaths of a morphologically-normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or direct examination of the fetus, (2) one or more premature births of a morphologically-normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or placental insufficiency, (3) three or more consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic, hormonal abnormalities, and paternal and maternal chromosomal causes excluded. In addition to clinical pregnancy loss, a number of investigators have found that infertility is associated with aPL [14].

Pregnancy losses from APS can occur in the first trimester or as late fetal deaths. Severe placental insufficiency can occur. HELLP syndrome (hemolysis, elevated liver enzymes, low-plateletlets) has been reported in APS as well, but the true relationship between the HELLP syndrome and APS is unclear [15].

### Prophylactic therapy

In spite of conflicting data on the efficacy of heparin and ASA(acetylsalicylic acid) therapies in preventing adverse pregnancy outcomes, pregnant women with APS are routinely treated with LMWH, either alone or in combination with ASA.

LMWH and ASA are both known to have anti-inflammatory properties. LMWH may prevent early loss by altering the inflammatory milieu in APS patients, while setting the foundation for impaired placentation by worsening angiogenesis[16].

Aspirin helps in improving uterine perfusion. Aspirin is useful in many undiagnosed implantation failure patients [17]. Low dose aspirin is established for prevention of FGR and pre-eclampsia and is appropriate to use in women with APS and a history of these complications [18].

Low-molecular-weight heparins are widely used, mainly for thromboprophylaxis [19]. Nadroparin (Fraxiparin®) is dosed weight adapted while Dalteparin (Fragmin®) and Enoxaparin (Clexane®) risk-adapted dosed. From pharmacological kinetic point of view, it is logical LMWH dosing based on actual body weight. From a clinical perspective, a patient with a higher risk of thrombosis (e.g.thrombophilia with a history of thromboembolism) has a higher LMWH doses as a patient at low risk of thrombosis. In vitro studies showed that fondaparinux do not cross the placenta or cross the placenta minimal, so that a clinical application seems to be possible [20].

Published studies indicate that the effective maintenance dose of enoxaparin is 40 mg once daily and of dalteparin, 500 IU once dailyor therapeutic (1 mg/kg SC every 12 hours for enoxaparin) [21, 22]. It has been suggested that levels of enoxaparin, given at 40 mg once daily, are not affected by gestational age, but others report that because of increased renal clearance during pregnancy once daily dose may not be enough[21].

The British RCOG Guideline for risk stratification recommends that low-risk patients received treatment with oral aspirin 100 mg daily only
throughout pregnancy. Intermediate risk patients received prophylactic treatment with enoxaparin 40 mg subcutaneously daily throughout pregnancy in combination with aspirin 100 mg orally daily in case of the presence of antiphospholipid syndrome, lupus anticoagulant, or SLE. High-risk patients received treatment doses of low molecular weight heparin (LMWH) with enoxaparin as 1 mg/Kg body weight subcutaneously twice daily or 1.5 mg/Kg body weight subcutaneously daily. Anticoagulation was continued for at least 4 weeks postpartum in the intermediate and high-risk groups [23].

Women receiving warfarin before pregnancy should discontinue this therapy because of its teratogenic properties between 6 and 14 weeks of gestation and switch to LMWH at conception [24]. Patients with the APS are at an especially high risk of recurrent thrombosis and are candidates for secondary thromboprophylaxis beyond 6 months [25].

This treatment combination of low dose aspirin and low molecular weight heparin reduces the miscarriage rate by 54%. The consensus is combination of low molecular weight heparin and aspirin is superior to aspirin alone in achieving more live births [17].

LMWH does not cross the placenta and is safe for both mother and fetus [26]. While side effects were minimal, LMWH use among pregnant women with various indications for anticoagulation was associated with successful pregnancy outcomes [22].

CONCLUSIONS

APS treatment is essentially preventive. It is necessary to start it very early in the pregnancy and to prolong it a long time during the postpartum period [2]. The pregnant state may have some effect on tests for aPL, suggesting that investigation should be pursued between pregnancies where possible [18]. Testing for aPL requires skill due to the difficulty of standardization and interpretation of tests. To know when testing should be performed and when to repeat tests are still a matter of debate [27].

REFERENCES


LASER APPLICATIONS IN GYNAECOLOGY

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Abstract

Introduction: The evolution of medical technology has progressed rapidly over the past decades to offer the clinician multiples therapeutic options, apparently similar, for different medical conditions. After the 60’s, continuous improvement of laser technology offered a new alternative of treatment in the surgical field with multiple advantages but also with higher economic costs.

Objective: Identification and understanding of advantages and specific applications of different types of lasers, for a more efficient usage in medical practice.

Material and method: Study of several articles from the PUB MED, MEDSCAPE, COCHRANE LIBRARY and DIRECT SCIENCE databases and also from speciality literature.

Results: Carbon dioxide laser is still used for cervical excisions and vulvar premalignant lesions. The properties of this laser expanded its utility in abdominal and gynecological surgery, proving to be one of the safest methods in endometriosis treatment in all evolution stages and also in adherence syndromes. Disadvantages of carbon dioxide laser are represented by the rigid system of laser beam transmission and the large quantity of smoke released during vaporization.

Argon Laser has proven to be as efficient and safe as carbon dioxide laser but has the added advantages of transmitting the laser beam through a flexible system like fiber optic and a reduced quantity of smoke. The latest technological development - PlasmaJet - whose multiple applications are still in a study phase, led to reconsideration of therapeutic options due to its safety and efficiency. The Nd-YAG Laser has a special application, namely in utero fetal interventions, due to its special property of reduced absorption through liquid mediums. The utility of Nd-YAG laser in hysteroscopic interventions is questionable due to its similar efficiency as conventional methods that have a lower cost.

Conclusions: Laser technology represents a possible treatment method for endometriosis, adherence syndromes and fetal interventions, but still remain a second favorite choice treatment due to its high costs. The utility of lasers and of the new PlasmaJet technology in specialized centers in endometriosis treatment and fetal medicine is justified and necessary considering the present technological level.

Rezumat: Aplicaţiile laserului în ginecologie

Introducere: Evoluţia tehnologică galopantă din ultimele decenii pune clinicianul în faţa unei multitudini de opţiuni terapeutice, aparent similare, destinate anumitor afecţiuni. După anii 60, perfecţionarea continuă a laserelor a oferit ramurilor chirurgicale o nouă alternativă de tratament cu multiple avantaje, dar şi cu un cost economic superior.

Obiective: Identificarea şi cunoaşterea avantajelor şi aplicaţiilor specifice fiecărui tip de laser, pentru o utilizare mai eficienţă în practica medicală.

Material şi metodă: studierea mai multor articole din bazele de date PUB MED, MEDSCAPE, COCHRANE LIBRARY şi SCIENCE DIRECT, şi din literatura de specialitate.


Eficienţa şi siguranţa asemănătoare laserului CO2 a dovedit şi laserul Argon, care are în plus avantajul transmiterii şi emisiiei razei laser prin intermediul unui sistem flexibil ca fibra optică şi o producţie mult mai redusă de fum. Dezvoltarea în ultima perioadă a unei noi tehnologii – plasmajetul, ale cărei multiple aplicaţii sunt în continuare în studiu, a condus la reconsiderarea opţiunilor terapeutice datorită siguranţei şi eficacităţii deosebite pe care aceasta o oferă. Laserul Nd-YAG are, indiscutabil, datorită absolvirii reduse la traversarea mediilor

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KEY WORDS: gynecology, lasers, efficiency, safety
apoase, o întrebuiințare de elecție, și anume, intervențiile fetoscopice in utero. Utilitatea laserului Nd-YAG în histeroscopie, deși dovedită, este discutabilă, datorită eficienței asemănătoare cu cea a metodelor convenționale care au un cost mai redus.

Concluzii: Laserele reprezintă metode de elecție în tratamentul anumitor afecțiuni ca endometrioza, sindromele aderențiale sau intervențiile fetoscopice, dar rămân, în continuare, datorită costurilor crescute, a doua opțiune de tratament în chirurgia abdominală și ginecologică de rutină. Acest fapt este datorat unei eficiențe asemănătoare la un cost mai redus al chirurgiei convenționale. Utilizarea laserelor și a noilor tehnologii, ca plasmajetul, în centre specializate în tratamentul endometriozei și de medicină fetală este pe deplin justificată și absolut necesară în contextul stadiului tehnologic actual.

Cuvinte cheie: ginecologie, lasere, eficiență, siguranță

Brief history

The laser is an optical device that generates a monochromatic beam of light that propagates over large distances with small divergence, very good focusing capacity and a high intensity, which give it the property of dissection and cutting.

The principles of laser were formulated by Albert Einstein after an evaluation of the consequences of the Max Plank radiation by introducing the concepts of spontaneous and stimulated emission.

The first functional laser was built by Theodore Mailman in 1960 and the first gas laser was created by Iranian physicist Ali Javan in 1960, using a mixture of helium and neon. Romania was the fourth country in the world where lasers were created by Ion I. Agârbiceanu (Ion Agârbiceanu’s son) and his collaborators. (1)

The rapid evolution of laser technology in recent years has proved its efficiency and has made it possible to use this technology on a large scale in the surgical field.

The pioneering of laser therapy in gynecology was made in 1973 by Kaplan and his collaborators, when they applied for the first time the treatment with carbon dioxide laser for premalignant cervical lesions, method that has proven and increased its usefulness over the years until the present day. (2)

Further technological development introduced in surgical practice several types of lasers, including neodymium: YAG - Nd (yttrium-aluminum-garnet), KTP (potassium titanyl-phosphate), argon and a derived technology - PlasmaJet. (3)

For a long period of time the use of lasers in medicine has been restricted by the prohibitive cost of this technology and the emergence on the market of other surgical methods with similar efficiency such as electroexcision of cervical lesions, mono and bipolar.

Carbon dioxide laser

The lasers are named after the medium which, following activation, releases energy as monochromatic light waves. Medium (CO2) activation is achieved by applying an electric current which triggers energy absorption at the atomic level and the movement of electrons from their orbits onto higher energy orbits. The electrons which are moved in this way, quickly recoup their previous positions on the atom orbit releasing energy in the form of a photon. This process is called spontaneous emission and leads to the emission of light with different frequencies in different directions.

These released photons further stimulate other activated atoms to release identical photons that have the same wavelength, color and direction (not
suffering from divergence). In carbon dioxide laser case this process occurs within the arm of the machine which contains a system of mirrors that are designed to focus the laser beam and to increase the energy through successive reflections. The laser beam is then released through a mirror which is controlled by the operator via a pedal.

Due to the principle of emission, the laser beam can not be transmitted through a truly flexible system, such as fiber optic, which is a disadvantage for its use in laparoscopy. The intensity of the laser is expressed in watts/cm² (power density) and is directly proportional to its effects on the tissue. Thus, using a laser beam, we obtain tissue effects, inversely proportional to the diameter of the laser beam. For example, doubling the light spot diameter will reduce interaction with the target tissue by 75% (2).

This property is defined as power density. The carbon dioxide laser emits in the infrared wavelength of 10800nm and has a reduced tissue penetration due to the intense water absorption in the tissue because of instantaneous water evaporation and destruction of the cell. It can be used for vaporization, incision and lesion ablation. The carbon dioxide laser penetration is between 0.1 and 0.5mm (therefore can be used safely in procedures such as the more difficult adhesiolysis due to endometriosis which may involve organs such as the bladder, ureters or intestinal loops with a minimal risk of injury and subsequent fistulization). Lateral thermal tissue damage zone due to carbon dioxide laser action does not exceed 0.5mm, making it one of the safest lasers. Its coagulation capacity is limited to blood vessels with a diameter less than 1mm. Due to the vaporization and coagulation, carbon dioxide laser leaves behind minimal necrotic tissue. A disadvantage of carbon dioxide laser in laparoscopy is represented by the release of an increased amount of smoke which limits the visibility in the surgical field and the need for frequent evacuation. Besides its utility in laparoscopy, carbon dioxide laser keeps its utility in cervical resections for severe cervical dysplasia with the disadvantage of the impossibility of obtaining tissue for histopathology examination.

2. Indication for carbon dioxide laser vaporisation in cervical dysplasia

After the vaporization of carbon dioxide, in case of impossibility of complete excision or endocervical extension suspicion, the intervention can be completed by electric conization and histopathology examination.

The carbon dioxide laser can be successfully used for the treatment of vulvar intraepithelial neoplasia and vulvar warts. With the vaporization of the lesion, there is a significant amount of smoke which may contain intact fragments of papilloma virus DNA that can be inhaled by the operator, thus wearing appropriate protective equipment is welcomed.

Types of lasers used in Gynecology

a. KTP and Argon Lasers

KTP and argon lasers have similar wavelengths, 532nm and 514nm respectively. In contrast to the carbon dioxide laser, argon and KTP laser beams are directed and released through a flexible fiber optic system. The resulting light is in the blue or green color spectrum, with selective absorption, increased by hemoglobin and its pigments (foci of endometriosis). Using this type of laser

<table>
<thead>
<tr>
<th>Table 1. Indication for carbon dioxide laser vaporisation in cervical dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no suspicion of endocervical extension of dysplasia;</td>
</tr>
<tr>
<td>There is no suspicion of stromal invasion;</td>
</tr>
<tr>
<td>There is no PAP smear results that is not relevant with the colposcopy;</td>
</tr>
<tr>
<td>Satisfying colposcopy examination.</td>
</tr>
</tbody>
</table>
releases only a small amount of smoke, so it does not disturb the intraoperative visualization. Tissue penetration is deeper when using KTP laser reaching 2mm depth and more superficial for argon laser with approximately 0.5 mm. (4)

Due to its reduced tissue penetration and flexible optical system, argon laser was proven to be safe and easy to use. The disadvantage of using these lasers is the necessity of the operators having to wear some special protection glasses which may distort the colors and may decrease the visibility of endometriosis foci.

b. Nd-YAG Laser

Nd-YAG Laser is a solid medium crystal which by electrical stimulation emits lasers beams similar with ruby laser.

Nd-YAG laser emits a beam outside the visible spectrum of the human eye, with a wavelength of 1,064nm, and is guided into the apparatus similar to the dioxide carbon beam by a helium-neon spot.

In tissues rich in water the absorption is very low, unlike the carbon dioxide laser. Tissue penetration is deeper, about 3-4mm. (5)

Since absorption through the liquid medium is very low, Nd-YAG laser is ideal for hysteroscopy or fetoscopic interventions inside the amniotic cavity. The laser beam can be released by two methods. The first method is represented by a simple quartz fiber which, in contact with the tissue creates a coagulation area of 3-5mm in depth and peripheral extension. A second method is represented by a quartz fiber with a sapphire tip which has the ability to focus the beam and vaporize the tissue (through the intensive local heat release), without extensive tissue coagulation. Quartz fiber with the sapphire tip, due to the intense heat released, needs a cooling system with dioxide carbon that may cause air embolism and this is the reason why it is a contraindication in hysteroscopy but found its utility in abdominal surgery.

Lasers applications in gynecological and obstetrical surgery

Out of all lasers, carbon dioxide laser remains the safest, because of low tissue penetration and is the elective treatment in laparoscopic surgical treatment of endometriosis in all stages of development. It can be used safely around the intestines, bladder or rectum. (6)

Ovarian drilling in the anovulatory polycystic ovary with resistant ovarian stimulation is achieved by creating “craters” in ovarian cortical tissue with lasers with deeper penetration such as KTP, Nd- YAG or argon lasers. This procedure is, however, questionable due to thermal destruction of the follicular ovarian reserve at the cortical level and the relatively short term benefits (maximum 1 year after surgery). (5)

Laser interventional hysteroscopy is preformed with Nd-YAG or KTP lasers which are using easy to handle flexible fiber optic that ease the excision of septa, submucosal and intracavitary fibroids, endometrial polyps or endometrial ablation. To facilitate the intervention, GnRH agonist treatment is indicated preoperative in endometrial ablation or

<table>
<thead>
<tr>
<th>Type</th>
<th>Wavelength (nm)</th>
<th>Color</th>
<th>Fiber Optic</th>
<th>Depth of penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argon</td>
<td>488–512</td>
<td>Blue green</td>
<td>Yes</td>
<td>0.5mm</td>
</tr>
<tr>
<td>KTP/532</td>
<td>532</td>
<td>Green</td>
<td>Yes</td>
<td>1–2 mm</td>
</tr>
<tr>
<td>Nd:YAG</td>
<td>1,064</td>
<td>Infrared</td>
<td>Yes</td>
<td>3–4mm</td>
</tr>
<tr>
<td>CO2</td>
<td>10,600</td>
<td>Infrared</td>
<td>No</td>
<td>0.1-0.5mm</td>
</tr>
<tr>
<td>Plasma-jet</td>
<td>-</td>
<td>White</td>
<td>No</td>
<td>0.1mm</td>
</tr>
</tbody>
</table>

Table 2. Types of lasers used in Gynecology
intracitary/submuncosal myomectomy. (7) However, for hysteroscopic myomectomy, the technique of choice remains the one through resectoscope (conventional method). Laser hysteroscope myomectomy should be reserved only for large intracavitary fibroids to get a good cost-benefit ratio. Septal resection and intrauterine adhesions resection is performed effectively with Nd-YAG laser, with the benefit of reduced bleeding compared to conventional techniques.(5)

Another Nd-YAG laser use in oncology is represented by the laser thermal ablation of secondary determinations or intrahepatic or abdominal primary tumors.(5)

Endometrial cysts ablation can be performed by removing the cyst wall with a low power laser (10 watts) and subsequent coagulation of the remaining ovarian tissue.

Salpingostomy in obstruction or tubal pregnancies can be easily performed with a high power carbon dioxide laser beam (30 watt) and also with minimal loss of blood.

Tubal pregnancy can be excised with laser surgery, with results simila to using scissors and electrocautery.

Peritubal adhesions can be vaporized with a very small carbon dioxide laser spot diameter. Uterine fibroids, which develop at the rate of about 30% in fertile age women are sometimes accidental findings. In most cases they are asymptomatic, but bulky intramural fibroids (> 5cm) and submucosal fibroids are a cause of recurrent miscarriage and infertility. The surgical excision indication should be made only after full investigation and excluding other causes of infertility. Elective laparoscopic approach is especially chosen for pedicle and subserosal fibroids. Laparoscopic excision of large fibroids in women who wish to conceive may lead to a difficult and insufficient hysteroraphy with subsequent poor quality scar formation, with the risk of uterine rupture in pregnancy or childbirth and this would certainly be conditioned by the surgical team experience. (Harris WJ: laparoscopic myomectomy Uterine dehiscence GMT). Regarding small fibroids obstetrical prognosis is similar regardless of the chosen approach.(7, 8)

Small dimension fibroids may be successfully vaporized with carbon dioxide laser with the advantage of reducing postoperative bleeding and adhesions formation.

Nd-YAG laser has multiple applications in fetoscopy, such as cutting the amniotic bands, vascular anastomosis coagulation in severe forms of twin-to-twin transfusion syndrome or selective feticide by coagulation of umbilical cord. A usual technique involves the use of a fetoscope with a length of 20-30cm and diameter of 1,3-3mm which is inserted into the uterine cavity under ultrasound guidance through a trocar with a diameter of 1,3-5mm.(9)

The fiber optic which leads the laser beam is inserted through the operative channel of the fetoscope. The Nd-YAG laser has the advantage of absorption tropism for the color spectrum of hemoglobin, meaning for the anastmosis that need to be coagulated. Ringer’s solution at 38p C is used as distention medium. Penetration with fetoscope is performed under ultrasound guidance in the twin amniotic sac with hydramnios. The laser is operated at an angle of 90p from a distance of about 1 cm to give a 1-2cm long clotting of the vessel concerned.

![Figure 2. Instruments in laser technique](image-url)

Indications for laser coagulation of placental anastomoses include moderately severe forms of twin-to-twin transfusion syndrome in monochorionic...
twin pregnancies and in twin-to-twin transfusion syndrome with an onset before 28 weeks of gestation in which mortality in case of waiting exceeds 80%.(10)

Arterial-venous anastomoses responsible for twin-to-twin transfusion syndrome are located deep into the placenta and are represented by placental cotyledons, not the proper vascular anastomosis as many would think. The artery that comes into the cotyledon comes from the donor blood and the drainage is made through the vein that is departing to the transfused twin. The vessels that supply common cotyledons are viewed on the chorionic surface of the placenta and can be coagulated.

The vessels that supply the common cotyledons prevent blood transfusion between the twins. Amniotic fluid drainage during the intervention improves the visibility. At the end of the operation, the amniotic fluid may be drained until a normal amniotic index is obtained. After coagulation of anastomoses, fetal survival rate is 55-69 % and the survival rate of at least one of the twins is 82 %, death of the donor being recorded in 20-25% of cases. (11). 0.6% of the newborns from these pregnancies develop neurological impairment and 5% suffer premature rupture of membranes. (12)

Twin-to-twin Transfusion Syndrome has an average recurrence after laser coagulation of 11% of which 43-45 % in stage 2 and 3 and only 1% in stage 4.(9). From all the treatment methods for twin-to-twin transfusion syndrome, fetal anastomosis coagulation is the only option that addresses the pathophysiological mechanism and was proven to have the best results.

Coagulation of the umbilical cord using Nd-YAG laser is the treatment of choice in twin pregnancies with TRAP (twin reversal arterial perfusion sequence) - acardiac twin, structural or genetic abnormalities of one fetus and death in utero of one of the twins, to avoid bleeding and hypovolemic shock and fetal death. Overall, the survival rate after coagulation of the umbilical cord is 72 %, but premature rupture of membrane is recorded in 20-30% of cases.(11)

 Fetoscopy may be complicated by bleeding at the trocar insertion, bleeding into the amniotic cavity, chorioamnionitis, premature rupture of membranes, DPPNI, amniotic embolism, intestinal perforation or sepsis.

**Plasma-Jet**

Compared with conventional surgery that uses cutting and elective coagulation, the PlasmaJet system has a neutral electrical energy source that offers a safer alternative.

It is a multi electrode system, built to release a high-temperature plasma jet through an outflow of gas. Compared to conventional surgery, pure plasma emitted by the system does not bear any electricity. Therefore, there is no risk of reflection or transmission through instruments nor any consecutive organ injuries with which they are in contact.

As in the case of carbon dioxide laser, there is a minimal tissue penetration of about 0.15 mm, with a lateral extension of the lesion of 0.22mm.(13,14)

PlasmaJet uses the energy from argon gas heating and its transformation into plasma. The resulting plasma jet is focused as an extremely thin beam with dissection, coagulation or cutting, properties, depending on the distance at which it is used. Although this system has a better coagulation capacity than carbon dioxide laser, for vessels larger than 1-2mm diameter it is necessary to use electrocoagulation for a better hemostasis result. The main advantage of PlasmaJet consists in extremely low penetration and lateral diffusion in the tissue, which makes it an ideal method of treatment for severe adherence syndrome in endometriosis in advanced stages and malignancies without risk of damage to the surrounding organs.(11)

Also resection of the endometriosis located on the ovaries using PlasmaJet, results with minimal follicle loss, preserving a good ovarian reserve, because of very superficial tissue destruction.

Recurrence of endometriosis after intervention with PlasmaJet has been reported in some studies to only 10.9 % and with a spontaneous conception rate of 59 %. (15)

PlasmaJet has proven its many advantages and benefits is gynecological and oncology surgery field and also the potential for application in other
are as such as plastic surgery, general surgery, thoracic surgery, neurosurgery or orthopedics.

CONCLUSIONS

Due to the collective effort of medical researchers, physicists, engineers and surgeons to overcome the technical difficulties which led to practical implementation lasers have become very useful tools in the treatment of multiple gynecological conditions and not only.

Carbon dioxide laser and PlasmaJet are the safest lasers and have in common the superficial tissue penetration with minimal side destruction and can be used in difficult adhesions syndrome involving organs such as the bowel, rectum, bladder or ureters.

Nd-YAG laser has a deeper tissue penetration, but compared to the carbon dioxide laser has a very low absorption in the liquid medium so is ideal for interventions in utero and hysteroscopic interventions and it represents the treatment of choice for twin-to-twin transfusion syndrome or selective coagulation of umbilical cord in monochorionic twin pregnancies.

Although they have proved their effectiveness, usage of carbon dioxide laser, KTP or argon lasers is still limited by high costs and the need of postgraduate training of the operating team. However, lasers have been eclipsed by the emergence of cheaper and with similar efficiency technologies such as electroexcision, monopolar and bipolar. However, in some centers specialized in the treatment of endometriosis, the use of carbon dioxide laser technology, argon laser or PlasmaJet was proven necessary and with a good cost efficiency ratio. Unlike abdominal surgery or hysteroscopic interventions, where the choice between conventional and laser surgery is left at the decision and experience of the operator, in fetoscopic interventions in utero, Nd-YAG laser is certainly the option of choice, being the only treatment method which directly addresses the cause of the twin-to-twin transfusion syndrome in monochorionic twin pregnancies. In case of death of one of the fetus or
TRAP syndrome, although it does not treat the cause, laser coagulation of the umbilical cord was proven to be life saving and is the only treatment method that makes possible the continuation of pregnancy that could be compromised by extreme prematurity or death in utero of the surviving, normal twin.

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MANAGEMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION DURING PREGNANCY AND DELIVERY

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Abstract

According to Matei Bals Institute of Infectious Disease, Romania has reported in the first trimester of the year 2015, 0.25% of new cases of HIV infection in the population age 20 to 29 year older. Prenatal screening and diagnosis for HIV infection during pregnancy is available and become a part of a prenatal diagnosis. The use of highly active antiretroviral therapy (HAART) during the last decade has significantly reduced the rates of mother-to-child transmission and the HIV mortality. The aim of this article is to review the point of view of the obstetrician in 2015, regarding the optimal management of HIV infection during pregnancy and time delivery based on the data of clinical literature.

INTRODUCTION

In Romania, prenatal screening and diagnosis for HIV infection during pregnancy or in postpartum period has been available for nearly 20 years. Upon diagnosis of HIV infection during pregnancy or postpartum, a multidisciplinary team of healthcare professionals is essential for the selection of the treatment approach; including an obstetrician, an infectious disease specialist, a nurse, a hematologist, a neonatologist and a psycho specialist. The widespread use of highly active antiretroviral therapy (HAART) during the last decade has significantly reduced the rates of mother to child transmission and the HIV mortality.

In 2014, World Health Organization have reported 36.9 million of people living with HIV infection, 17.4 million of women and 2 million of new infection (1). In Romania, in the first trimester of the year 2015, 0.25% of new cases of the population age 20 to 29 year older was found to be seropositive for HIV infection (2).
Nowadays, for female, the most common mechanism of transmission of infection is intravenous drug use; multiple sex partners and unprotected intercourse may represent another mechanism of HIV transmission.

In the communist period before 1989, a nosocomial epidemic HIV infection was reported; among 10,000 orphans and hospitalized children was infected, due to the use of contaminated needles, inappropriate sterilized equipment and through blood transfusion with infected blood (3).

Since 2002, Romania have declared HIV/AIDS a top health priority and launched the Action Plan for Universal Access to antiretroviral treatment. Romania became the first country in Europe to benefit from facilities for the treatment, standard guidelines and universal coverage to all HIV-positive persons (4).

Transmission of the human immunodeficiency virus from mother to child can occur in utero via placenta, during labor or from breastfeeding. Perinatal HIV transmission occurs, without any treatment, at rates to 14 to 42%; one third of transmissions occur during gestation and two thirds during delivery (5).

Many clinical trials have demonstrated that, with the combination of antiretroviral treatment, the highly active antiretroviral therapy and the optimal management of delivery, the perinatal transmission was reduced to 1-2% (6, 7, 8).

The aim of this article is to review the point of view of the obstetrician in 2015, regarding the optimal management of HIV infection during pregnancy and time delivery based on the data of clinical trials.

Human Immunodeficiency Virus (HIV) infection in pregnancy

HIV infection is due by a single-stranded, enveloped RNA, retrovirus who attacks the immune system, destroys white CD4+ T lymphocytes and has a high rate of mutation and recombination. Two major strains of the virus have been identified: HIV-1 and HIV-2; with different geographical distribution of genotypes and subtypes. In Romania HIV-1 infection is more common. This diversity of HIV virus has impeded the progress of a vaccine against HIV.

There are the following situation in the clinical practice: a pregnant woman who is HIV positive and take her treatment, a HIV infection discovered during pregnancy or in postpartum period.

In Romania, the universal screening for HIV infection in pregnancy is recommended; testing is free and it is routinely performed at the first antenatal visit. The screening test is done by the enzyme immunoassay for HIV1 and HIV 2. If the screening is positive, a Western blot or immunofluorescent assay should be done. All positives cases will be reported at Directia de Sanatate Publica and an epidemiologic questionnaire will be done.

A rapid screening tests is available for the patients with unknown status of HIV infection.

The rate of mother-to-child-transmission of HIV infection is increased with viral load, very premature delivery and short duration of optimal therapy (9).

The optimal time to start antiretroviral therapy in pregnancy may influence the risk to mother-to-child transmission.

Opportunistic infections and HIV infection

Before highly active antiretroviral therapies (HAART) were available for the treatment of persons with HIV infection, the most common opportunistic co-infections were: *Pneumocystis Jiroveci* and *Pneumocistis pneumonia*, *Mycobacterium avium-intracellularare infection*, *non-Hodgkin lymphoma*, tuberculosis, toxoplasmosis, *Candidiadis*, CMV-infection. Lifelong prophylaxis for disease recurrence has been recommended for those with a history of opportunistic infection. HIV positive pregnant women will be vaccinated for pneumococcal infection, influenza, hepatitis A and B, meningococcal infections, tetanus, diphtheria and pertussis. She should be tested for tuberculosis and may receive prophylaxis taking into account her blood tests and her previous infections. The infectious disease specialist will decide the optimal treatment.
Prenatal invasive procedures in women with human immunodeficiency virus infections (10,11,12)

For women infected with human immunodeficiency virus, the use of non-invasive methods of prenatal risk assessment is strongly recommended. In case of prenatal invasive procedures indications due to the high risk for aneuploidies or to the structural abnormalities, every effort should be made to avoid placenta or inserting the needle through, or very close to, the placenta. Chorionic villus sampling and chordocentesis are not indicated.

Amniocentesis in women infected with human immunodeficiency virus on combination antiretroviral therapy does not appear to significantly increase the risk of vertical transmission, particularly if the viral load is undetectable, but women should be counselled that data on this issue is limited. For women not on combined antiretroviral therapy, the risk of vertical transmission is increased by performing an amniocentesis. When possible, combined antiretroviral therapy should be initiated and the procedure postponed until the viral load is undetectable.

Management of HIV infection during pregnancy

The risk of the perinatal transmission of HIV infection is increased in the absence of the treatment. In Romania, this cases may occur in case of unknown HIV infections status or in the diagnosis of this in the postpartum period.

After the establishment of the HIV diagnosis, a CD4+ T cell count and viral load measurement is done. The pregnant woman should be screened for all sexual transmitted diseases, including syphilis, gonorrhea, chlamydia, trichomonias; tests for hepatitis B and C and screening tests for tuberculosis, toxoplasmosis and cytomegalovirus will be recommended.

In order to prevent opportunistic infections, this patients will be vaccinated since mentioned anteriorly. In case of recurrent herpes simplex infection a therapy with Acyclovir is recommended after the first trimester.

Toxoplasmosis infection is difficult to diagnose during pregnancy in HIV infected population due to the lack of specific IgM and IgA. In HIV-infected patients, most cases of toxoplasmosis result from the reactivation of a latent infection of Toxoplasma gondii; this co-infection may manifest clinically with eye and brain damage affected the children. The treatment use sulfametoxazol and trimethoprim(13).

Immunological changes during pregnancy and HIV infection make the activation of latent Tuberculosis infection or de novo infection more likely than among non-pregnant women (14). The diagnosis is difficult and a chest radiograph with abdomen protection may exclude the tuberculosis. Treatment with Isoniazid may prevent tuberculosis among HIV infected women with tuberculin test positive and chest radiograph with no evidence of tuberculosis(14,15).

Recurrent Candidiasis may necessitate orally antimicotics.

The use of highly active antiretroviral therapy (HAART) significantly reduces transmission of HIV from mother to child. Pharmacokinetics of antiretroviral during pregnancy requires special consideration because pregnancy-associated changes in the pharmacokinetics of drugs. Understanding antiretroviral placental transfer may offer additional insight into each drug’s potential role in preventing HIV transmission in utero and may also have implications regarding viral resistance in cases where transmission does occur and the understanding of the adverse birth outcomes.

The standard treatment consists of a combination of at least three drugs (often called “highly active antiretroviral therapy” or HAART) that suppress HIV replication.

The combination of Zidovudine (ZDV), Lamivudine (3TC, Epivir), Ritonavir and Lopinavir is the optimal treatment during pregnancy.

Vannappagari V et al, showed that no difference in prevalence of birth defects in pregnancy with Zidovudine treatment; the risk of low birth weight was statistically significantly higher among ZDV-containing regimens versus non-ZDV ARV regimens (16). In a series of more than 12000 children, ZDV
Management of human immunodeficiency virus (HIV) infection during pregnancy and delivery

exposure in the first trimester of pregnancy was associated with anomalies in cardiac function (17).

The World Health Organization consolidated 2013 HIV guidelines have simplified antiretroviral therapy (ART) regimens by the introduction of an inexpensive fixed-dose combination utilizing tenofovir disoproxil fumarate, lamivudine/emtricitabine and efavirenz (TDF+3TC/FTC+EFV)(1,2).

Management of HIV infection during labor

VAGINAL DELIVERY:
If the patient’s viral load in the third trimester is less than 1000 copies/ml, a vaginal delivery is acceptable. During labor should be avoided: amniotomy, fetal scalp monitoring, episiotomy or instrumental delivery in order to reduce the contamination with maternal blood and secretions. A minimal of number of vaginal examinations should be recommended after chlorhexidine application. Intrapartum intravenous Zidovudine administration (2mg/kg for 1 hour, than 1 mg/kg/hour until delivery) was proved to reduce viral load (18).

CESAREAN DELIVERY:
If the patient’s viral load is greater than 1000 copies/ml, a Cesarean section is recommended at 38 weeks of gestation, before the onset of labor. For women who term delivered by elective cesarean delivery, the transmission rate was five-fold higher without than with intravenous ZDV (19).

The ZDV intravenous infusion should begin 3 hours before C-section.

Management of HIV infection in postpartum period

The breastfeeding is avoided. The patient will continue the treatment. In our clinic, the patient is not necessary separated from another patients.

CONCLUSIONS

In conclusion, screening for HIV infection during pregnancy is recommended. In case of HIV positive women, the use of highly active antiretroviral therapy (HAART) during the last decade has significantly reduced the rates of mother-to-child transmission to less than 2% and the HIV mortality. A multidisciplinary team will be involved.

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THE AGE OF MENARCHE AND FRAX USE IN MENOPAUSE: A CROSS-SECTIONAL STUDY IN ROMANIAN POPULATION

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Abstract

Introduction: FRAX algorithm provides the 10-year probability of hip fracture (HF), and 10-year probability of major osteoporotic fractures (MOF). The menopause is a sensitive period of time regarding the increased risk fracture. We aim to analyse the menarche/menopause and FRAX profile in menopausal women with and without osteoporosis.

Material and Methods: A transversal study in previously untreated Romanian women (who had a DXA and osteoporosis or normal lumbar DXA was found) was started.

Results: Out of 319 subjects 108 (group 1) had T-score >/=2.5 and 211 (group 2) had T-score >/=-1, </=1. Age was 59.96 vs. 44.26 yrs (p<0.0005); body mass index was 26.39 vs. 29.78 kg/m² (p<0.0005). The age of menarche was 13.85 vs. 13.42 yrs (p=0.06); the number of births was 1.86 vs. 1.59 (p=0.11), the age of menopause was 46.69 vs. 46.66 yrs (p=0.97); the years since menopause (YSM) were 13.19 vs. 1.17 (p<0.0005). HF was 1.74 vs. 0.69% (p<0.0005); MOF was 5.72 vs. 3.59% (p<0.0005). No correlations between FRAX risk and age of menarche was found.

Conclusion: The menopausal subjects with osteoporosis versus those with normal DXA have higher FRAX risk and a larger period of time since menopause independently of menarche age or number of births.

Rezumat: Menarha şi utilizarea FRAX în menopauză: un studiu transversal pe populaţia din România

Introducere: Algoritmul FRAX furnizează riscul pe 10 ani de fracură de şold (HF), respectiv de fractură majoră osteoporotică (MOF). Menopauza reprezintă o perioadă importantă privind riscul de fractură. Scoalul nostru este să analizăm profilul de menarhă/menopauză şi FRAX la femei aflate în menopauză cu şi fără osteoporoză.

Material şi Metode: Acesta este un studiu transversal realizat pe femei române anterior netratate (care au efectuat DXA şi s-a găsit osteoporoză sau DXA normal la nivel lombar).

Rezultate: Din 319 subiecţii 108 (grup 1) au avut T-score >/=2.5 şi 211 (grup 2) au avut T-score >/=-1, </=1. Vârsta a fost 59.96 vs. 44.26 ani (p<0.0005); indicele de masă corporală a fost 26.39 vs. 29.78 kg/m² (p<0.0005). Vârsta la menarhă a fost 13.85 vs. 13.42 ani (p=0.06); numărul de naşteri a fost 1.86 vs. 1.59 (p=0.11), vârsta la menopauză a fost 46.69 vs. 46.66 yrs (p=0.97); perioada în menopauză a fost 13.19 vs. 1.17 (p<0.0005). HF a fost 1.74 vs. 0.69% (p<0.0005); MOF a fost 5.72 vs. 3.59% (p<0.0005). Nu s-au găsit corelaţii între riscul conform FRAX şi vârsta menarhă.

Concluzie: Subiecţii în menopauză cu osteoporoză versus cei cu DXA normal au avut un risc FRAX mai mare şi o perioadă de timp mai mare de la instalarea menopauzei independent de vârsta la menarhă sau numărul de naşteri.

Cuvinte cheie: FRAX, menarhă, menopauză
INTRODUCTION

Menopause represents a serious turn in bone status due to the risk of osteoporosis or osteopenia in the surrounding context of estrogens lack. The need for economic efficient tools in order to have the fracture risk assessment increased the levels of using mathematical algorithms that are derived from large meta-analysis. FRAX is a model coming from clinical risk factors of bone loss which may be applied after the age of 40 for both men and women. (1) The model provides the 10-yr probability of hip fracture (HF) and 10-yr probability of major osteoporotic fractures (MOF) based on parameters as age, secondary causes of osteoporosis, smoking, alcohol consume, glucocorticoids use, etc. (1) The estimated risk is basically provided with or without femoral neck bone mineral density (BMD) as showed by central Dual-Energy X-Ray Energy, also called DXA. (1) Since the calculation of the fractural risk is based on several databases the inputs in the model are different with the geographical area. (2,3,4,5,6) In Romania the risk calculator is available since 2011. (7,8) The FRAX use did not overwhelm the golden standard represented by DXA which is the only tool providing us the diagnosis of normal BMD, osteopenia or osteoporosis by cut offs of T-score. (9) DXA is correlated with traditional parameters as quantitative ultrasound especially for heel assessment mostly to DXA hip results. (10,11,12) The correlation with bone remodelling markers (classical as alkaline phosphatase or osteocalcin or atypical as serum serotonin) still associates some limits based on their high variations from one individual to another. (13,14)

In this study we aim to analyse patients with normal DXA and diagnosis osteoporosis exclusively based on central T-score of less/or equal to -2.5 at lumbar site regarding the menarche age and the FRAX risk.

MATERIAL AND METHODS

This is a cross-sectional study. The including criteria were Romanian menopausal women who had interpretable data at central (lumbar) DXA. The exclusion criteria were osteopenia at lumbar DXA, previous anti-osteoporotics, inadequate data related to age of menarche or menopause. Student ttest considered statistical significance at p<0.05.

RESULTS

319 subjects met the inclusion and exclusion criteria. Group 1 had osteoporosis and included 108 females and group 2 had normal DXA (N=211). (Figure 1) The osteoporosis group had statistically significant higher age, lower body mass index, lower bone mineral density (p<0.0005). (Table 1) The mean values of age are within the six decades of life. The mean values of body mass index are within the overweight area for each group. (The body mass index was calculated based on formula weight in kilogram divided to squared height in squared meters.)

The age of menarche, the age at first birth, the number of births or abortions (spontaneous or not), the age of menarche were not statistically significant different. The years since menopause (YSM) were higher if the subjects were osteoporotics (YSM in group 1 of 13.19 vs. 1.17 years in group 2, p<0.0005). (Table 2) The 10-year risk of hip (HF) fracture based on FRAX model (for Romania) is 1.74 +/- 2.41% in patients with DXA according to osteoporosis score, respective 0.69 +/-1.61% in subjects with normal DXA (p<0.0005). The 10-year probability of major osteoporotic fractures (MOF) is 5.72 +/- 4.01% in group 1 and 3.59 +/- 1.93% in group 2 (p<0.0005).

![Figure 1. The Romanian population distribution according to the study (N=319); group 1 with osteoporosis based on lumbar T score of d”-2.5 (N=108), and group 2 with normal lumbar DXA meaning T score e”-1, d” 1 (N=211)](image)

Both the parameters are statistically significant. (Table 3) We found no correlation
between the FRAX risk (regardless the type of fracture) and the age of menarche.

**DISCUSSION**

Based on our observations the patients with osteoporosis compare to females with normal DXA are older if DXA scan was performed for the first time in a previously unselected population regarding the bone profile. The BMD and T-score results are statistically significant between the two groups, as expected. The menarche, births and abortions profile was not statistically relevant between the two cohorts but calculating the years since menopause up to the moment of DXA scan the subjects with osteoporosis have a higher period of time (probably associated with the older age). FRAX model includes the early menopause (of less than 40 years old) as an input of secondary osteoporosis but the years since menopause are not quantified into the FRAX model. (15)

As expected the FRAX algorithm is correlated to the risk of fracture based on DXA T-score meaning that the 10-year probability of fracture for both hip and major osteoporotic fractures are statistically significant higher in osteoporotic group (p<0.0005). The relatively low values of fracture risk as predicted by FRAX for the following 10 years are expected for the type of population we applied meaning subjects without specific history of fractures, falls, and osteoporosis. (16)

**CONCLUSION**

The menopausal subjects with osteoporosis versus those with normal DXA have higher FRAX risk and a larger period of time since menopause.
independently of menarche age or number of births.

**Conflict of interest:** none  
**Acknowledgement:** none

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BIRTH – FROM DESTINY TO ARTIFICIAL PROCEDURE

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Abstract

Introduction. The continuous increase of caesarean section rate from about 6% in the 70’s, to about 60% today, due to sometimes unjustified extension of cesarean section indications, forced obstetricians to deal with uterine scar specific pathology and pediatricians with neonatal and long term fetal morbidities, which led to adverse consequences for both mother and child.

Objectives/material and methods. This is a compilation study for creating a critical picture over the existing literature about the incidence and consequences of the cesarean delivery.

Results. At this increased incidence of birth by Caesarean section contributed the consideration of this method more convenient for both physician and patient, continuous CTG monitoring during labor (many false positive for fetal distress occurrence), excessive medicalization and labor induction in the absence of favorable conditions and last but not least, the gradual loss of obstetrical skills. A reconsideration of the birth process approach and limiting cesarean section indications only for cases with real benefits, could lead to morbidity and mortality decrease for both mother and child. The overall rate of late-preterm births is rising, and so are rates of morbidity and mortality, especially among infants delivered by cesarean section in the absence of labor. Immediate consequences of caesarean delivery (CD) includes complications subsequent pregnancies and iatrogenic early delivery, increased incidence rates of the respiratory distress syndrome, neonatal hypoglycemia, hyperbilirubinemia, sepsis and neonatal intensive care unit admission. As a long-term implication, CDs results in a 20–50% higher incidence of autoimmune diseases and obesity in the offspring.

Conclusion. The choice of the delivery path in prematurity, non-cephalic presentation and associated maternal pathology, should be done after proper information, evaluation and individualization of the case for improving obstetrical and fetal outcome.

Rezumat: Naşterea de la destin la artificializare

Introducere. Creşterea continuă a ratei operaţiei cezariene de la aproximativ 6% în anii 70, până la aproximativ 60% în prezent, din cauza extinderii, uneori nejustificată, a unor indicaţii de operaţie cezariană, a pus tot mai frecvent obstetricienii în faţa patologiei specifice uterului cicatricial, iar pe pediatrii în faţa unor morbidităţi fetele neonatale şi pe termen lung, cu consecinţe nefaste asupra mamei şi copilului.

Scop/material şi metoda: Aceasta este o lucrare de compilaţie care încercă crearea, în mod critic, a unei viziuni asupra literaturii existente cu privire la incidenţa şi consecinţele naşterii prin operaţie cezariană.

Rezultate. La această creştere a incidenţei naşterii prin operaţie cezariană a contribuit considerarea acestei metode mai comodă atât pentru medic şi pentru pacientă, monitorizarea CTG continuă în timpul travaliului, (cu multe alarame fals pozitive pentru apariţia suferinţei fetale), medicalizarea şi declanşarea excesivă în condiţii nefavorabile a naşterii şi nu în ultimul rand, pierderea treptată a abilităţilor obstetricale a practicienilor. O reconsiderare a abordării procesului de naştere şi a indicaţiilor de operaţie cezariană, cu limitarea acestora doar la cazurile cu un beneficiu real, ar putea conduce la scăderea morbidităţii şi a mortalităţii atât maternă cât şi fetale. Incidenţa naşterii premature fiind în creştere, se constată o morbidade şi mortalitate importante în rândul acestor copii născuţi prin operaţie cezariană, în afara travaliului.

Consecinţele fetale imediate ale naşterii prin operaţie cezariană includ complicaţiile inerente ale naşterii premature induse iatrogen, creşterea incidenţei sindromului de detresă respiratorie, a hipoglicemiei, a hiperbilirubinemiei, a sepsisului şi a spitalizării prelungite în cadrul secţiilor de terapie intensivă neonatală.

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KeY WORDS: caesarian section, birth, bad outcomes, prematurity, consequences
INTRODUCTION

The continuous growth of the rates of caesarian section, due to the extension of its indications, forced obstetricians to deal with uterine scar specific pathology, which leads to dire consequences for the mother and child. Also, neonatologists and pediatricians warn about the increasing neonatal morbidity and some diseases such as autoimmune diseases, asthma, celiac disease, obesity etc, developing especially in the childhood of newborns delivered by caesarian section. There are many studies that demonstrate the direct relationship between the rising number of deliveries by caesarian sections and the pathologies mentioned above and this is the main reason to reconsider the indications and eligibility of performing this type of delivery.

The incidence of caesarian section

The percentage of deliveries by caesarian section varies between 14% in Northern Europe and 50% In South-Eastern Europe, with an increased proportion of 70% in Latin America (see fig 1.a,b.). In Romania, the incidence of delivery by caesarian section is about 40%, which is similar to most of the countries from South Eastern Europe.

The increased incidence of caesarian section in some areas of the world, is probably more related to poor obstetrical abilities, continuous monitoring and misinterpretation of CTG, induction of labor in improper conditions or with legal medical issues than it is related to proof-based medicine. Moreover, the caesarian section increases direct maternal morbidity, exposing the patient to scarred uterus issues in future deliveries, may induce preterm delivery, leads to bacterial colonization in the newborn intestine with consequences for the immune system and increasing the risk of obesity during childhood. Even though caesarian section became a routine intervention in time, the incidence of cerebral palsy did not decrease [17].
The main factors that increased the usage of caesarian section

In the ‘70s the caesarian birth was practiced in about 6% of deliveries, but with the evolution of technology and the antibiotics this maneuver became routinely practiced and also became a very safe one. This led to a change of the patients’ perspective regarding long, difficult deliveries or for deliveries with potential risks for the mother or for the newborn.

Although continuous CTG monitoring has not proved to be more efficient than the intermittent auscultation, it led to a caesarian section rate increase [1,18]. Gradually, even doctors began to either induce labor in adverse conditions, with minimum chances for vaginal delivery, motivated by economic reasons and self-sufficiency or to recommend to patients the idea of caesarian section delivery as a safer procedure. Thus, the general perception changed as far as natural delivery is concerned and the patients formed the false idea that the caesarian section is a risk-free procedure and much safer than vaginal delivery. Choosing this artificial method of delivery, an easier and time-saving method for many obstetricians, leads to poor obstetrical abilities and further increases the incidence of caesarian section, with negative outcomes for the mother and newborn.

The increasing incidence of scarred uterus in the population forced the obstetrician to perform caesarian sections in the future deliveries because of the high risk of uterine rupture.

Another factor that increases the incidence of caesarian delivery is the insufficient numbers of qualified personnel and improper monitoring during labor. A good medical and psychological support during labor may reduce the frequency of caesarian delivery [19].

Last but not least, legal medical issues caused by natural delivery lead to a defensive type of medical practice, this being one of the main causes for the increase of the practice of caesarian section.

### Understanding maternal risks

Short, medium and long-term complications

- Short, medium and long-term complications

  Regarding caesarian section, there are short term and medium/long-term complications.

  Compared to caesarian section practiced during labor, the elective caesarian section is safer and carries a lower risk of:

  - hemorrhage
  - obstetrical shock
  - vaginal or cervix lacerations
  - the intensity of pain in the first 3 days is lower[1,20].

  Even though the possible complications have a low incidence, the phenomenon should be analyzed

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Table no.1  Main factors to determine the growth of Caesarian sections

<table>
<thead>
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<th>Continuous CTG monitoring</th>
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<tr>
<td>Induction of labor in improper conditions based on socioeconomic reasons and self-sufficiency</td>
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<tr>
<td>Patient misinformation and fear of vaginal delivery</td>
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<td>Low obstetrical skills</td>
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<td>Scarred uterus pathology - risk of uterine rupture in future pregnancies</td>
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<td>Insufficient trained personnel for correct labor monitoring</td>
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<td>Legal medical issues involved in vaginal delivery</td>
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</tbody>
</table>
with respect to the whole fertile female population, in which the percentage of scarred uterus may be higher than 50% and for whom the risks are amplified 15-20 fold. As an example, we can review the indication for caesarian section in breech presentations where it was proven that the incidence of mortality and morbidity decreased with this practice but for each saved newborn there will be one in ten uterine ruptures leading to neonatal death. For each 80 saved newborns, one mother will die following placenta praevia complications or uterine rupture. In consequence, the indication for caesarian section should take into consideration the patient’s desire for future pregnancies. In multiple pregnancies with the first fetus in cephalic presentation, the caesarian section has not been shown to improve the neonatal outcome[1,4,16,22,23].

As far as preterm delivery is concerned, caesarian section has a real benefit in pregnancies under 25 weeks of gestation and with an estimated weight under 750g [12,27,28].

In the weight category between 500g and 750g there is a decreasing incidence of mortality and morbidity in cases where caesarian section is performed compared vaginal delivery cases. In gestational age between 26 and 32 weeks the newborn outcome is not influenced by the delivery method the choice being based on the maternal pathology and wellbeing of the fetus [12,27,28].

In normal pregnancies without any risks, between 32 and 36 weeks of gestation, caesarian section increases the morbidity and mortality rate (12) - see table no.3

Still, in preterm pregnancies, caesarian section is preferred when the following complications are present(see table no.4):

- Uterine leiomyomatosis and caesarian section

Nowadays, with the increasing of the age of the first pregnancy in the female population, there is a more frequent association between uterine leiomyomatosis and pregnancy. In consequence, the

<table>
<thead>
<tr>
<th>Table no. 3 The advantage of Caesarian section in preterm pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Under 25 weeks of gestation</strong> Decreasing the morbidity and mortality rates in (weight between 500 g and 750 Caesarian section deliveries g)</td>
</tr>
<tr>
<td><strong>Between 26 and 32 weeks of gestation</strong> Fetal outgoing is not influenced by the type of delivery, rather than mother pathology and fetal wellbeing[12,27,28].</td>
</tr>
<tr>
<td><strong>Between 32 and 36 weeks of gestation</strong> In no risk pregnancies, Caesarian section increases the rates of morbidity and mortality [12]</td>
</tr>
</tbody>
</table>
Table no.4 Indication of Caesarian section in preterm pregnancies [13,14,15,16]

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal growth restriction,</td>
</tr>
<tr>
<td>Placental insufficiency,</td>
</tr>
<tr>
<td>Fetal distress,</td>
</tr>
<tr>
<td>Non cephalic presentation, multiple</td>
</tr>
<tr>
<td>pregnancy with the first fetus in non cephalic</td>
</tr>
<tr>
<td>presentation</td>
</tr>
<tr>
<td>Twin to twin transfusion syndrome (TTTS)</td>
</tr>
<tr>
<td>DPPNI</td>
</tr>
<tr>
<td>placenta previa, etc</td>
</tr>
</tbody>
</table>

Table no.5. Uterine leiomyomatosis-risks

<table>
<thead>
<tr>
<th>Uterine leiomyomatosis-risks</th>
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</thead>
<tbody>
<tr>
<td>Caesarian section delivery 70,3%</td>
</tr>
<tr>
<td>Placental detachment 7,5%</td>
</tr>
<tr>
<td>Placenta previa 2,5%</td>
</tr>
<tr>
<td>Preterm delivery 10%</td>
</tr>
<tr>
<td>Neonatal mortality 2,2%</td>
</tr>
</tbody>
</table>

incidence of uterine leiomyomatosis in pregnancy reaches up to 3%, of which voluminous leiomyomas with diameter larger than 5 cm with real obstetrical consequences, represents 1%.

There is a high obstetrical risk for women with leiomyomas larger than 5 cm diameter, and there are a couple of associated conditions (Fig. no. 2)

The caesarian section incidence exceeds 50% in pregnant women with leiomyomas with the diameter larger than 5 cm, and the main causes are fetal malpresentation and dysfunctional labors with low efficiency uterine contractions.

Nevertheless, for a uterus with leiomyomatosis, caesarian section rises the risk of postpartum haemorrhage and secondary anaemia, requiring secondary blood transfusions and even hysterectomy (25). In this case, the indication for caesarian section should be carefully reconsidered, even voluminous leiomyomatosis not being a main indication, but only its complications during labor.

**Fetal consequences following caesarian section**

a) **Short-term complications**

It is well known that short-term complications following caesarian section, include respiratory distress, hospitalization in intensive neonatal care units, neonatal sepsis, hypoglycemia, longer hospitalization (more than 5 days) or hyperbilirubinaemia (see table 6) [1,6,7,26].

b) **Long-term consequences**

Recent studies demonstrate that there is a correlation between the caesarian section and long-term consequences for the health of the newborn.

Thus, there is a 22% higher risk for the newborn delivered by caesarian section to develop asthma and autoimmune disorders, a 25% higher risk for diabetes mellitus type I, a 26% to 50% higher risk for childhood obesity and metabolic disorders and a 15% higher risk for developing celiac disease. [1,8,9,26] (see figure 3).
Birth – from destiny to artificial procedure

The mechanisms of increasing long term fetal risks

The absence of normal stress during vaginal delivery leads to the alteration of the function and maturation of the immune system with a delay in normal function between lymphocytes TH1/TH2.

Also, there is a modification of epigenetic regulation of certain genes expression which favors infantile obesity. Delivery by cesarian section prevents the normal colonization with lactobacilli in the fetal intestine that would occur in the case of vaginal delivery. Abnormal intestinal flora favors increasing intestinal absorption of main nutrients, increases intestinal permeability through local chronic inflammation and modulates the immune response by direct activation of certain genes in the liver [9,11]. Given the consequences of intestinal colonization with

| Table no. 6 Neonatal morbidity odd ratio (short-term complications) depending of gestational age |
|---|---|---|---|---|
| Secondary effects or death | 37 weeks | 39 weeks | 40 weeks | ≥42 weeks |
| Respiratory distress | 2.1 [1.7-2.5] | reference | 0.9 (0.7-1.1) | 2.5 [1.5-4.0] |
| Transient tachypnea of the newborn | 4.2 [2.7-6.6] | reference | 2.3 [0.6-9.7] |
| Hospitalization in neonatal intensive care unite | 1.8 [1.2-2.5] | 1.1 (0.6-2.0) | 2.2 [1.0-4.8] |
| Neonatal sepsis | 2.3 [1.9-3.0] | reference | 0.9 (0.6-1.3) | 2.5 [1.5-4.4] |
| Hypoglycaemia | 2.9 [2.1-4.0] | reference | 0.8 (0.6-1.0) | 4.1 [2.2-7.6] |
| Hospitalization ≥5zile | 3.3 [1.9-5.7] | reference | 1.0 (0.7-1.5) | 2.8 [0.7-11.7] |

![Figure No. 3 Long-term consequences](image)

The mechanisms of increasing long term fetal risks

The absence of normal stress during vaginal delivery leads to the alteration of the function and maturation of the immune system with a delay in normal function between lymphocytes TH1/TH2.

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Table no. 6 Neonatal morbidity odd ratio (short-term complications) depending of gestational age

<table>
<thead>
<tr>
<th>Secondary effects or death</th>
<th>37 weeks</th>
<th>39 weeks</th>
<th>40 weeks</th>
<th>≥42 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>2.1 [1.7-2.5]</td>
<td>reference</td>
<td>0.9 (0.7-1.1)</td>
<td>2.5 [1.5-4.0]</td>
</tr>
<tr>
<td>Transient tachypnea of the newborn</td>
<td>4.2 [2.7-6.6]</td>
<td>reference</td>
<td>2.3 [0.6-9.7]</td>
<td></td>
</tr>
<tr>
<td>Hospitalization in neonatal intensive care unite</td>
<td>1.8 [1.2-2.5]</td>
<td>1.1 (0.6-2.0)</td>
<td>2.2 [1.0-4.8]</td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
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</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2.9 [2.1-4.0]</td>
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</tr>
<tr>
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<td>3.3 [1.9-5.7]</td>
<td>reference</td>
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<td>2.8 [0.7-11.7]</td>
</tr>
</tbody>
</table>
abnormal flora, an adjuvant solution should be the postpartum administrating of probiotics and breast feeding.[see fig no.4]

**Fig. no 4** Mechanism of Long-term complications in infants delivered by caesarian section [4].
DISCUSSIONS AND CONCLUSIONS

The increased incidence of caesarian section in some parts of the world has probably more to do with the loss of obstetrical abilities, the continuous monitoring and mis-interpretation of CTG, the induction of labor in improper conditions or with legal medical aspects than it has to do with proof based medicine.

Given the mentioned risks and complications, it is safe to say that until now an improvement of the materno-fetal obstetrical outcome in caesarian section has not been proven.

A reconsideration of the delivery process and of caesarian section indications and restricting these only to the cases with real benefits would lead to a decrease in maternal and fetal morbidity and mortality.

In this context, the choice of delivery method in case of prematurity, of non-cephalic presentations and maternal associated pathology must only be made after correct evaluation and choice of optimum birth timing in order to improve the obstetrical and fetal outcome.

Some measures must be identified and enforced to try to stop the ascending trend of caesarian sections where there are no indications and no benefit for the mother and child which could decrease the percentage of artificial delivery. Following are measures that have proved to be efficient in countries with a low rate of caesarian section:

- ensure sufficient numbers of qualified personnel
- psychological support and good monitoring of labor
- good patient information about the benefits of vaginal delivery
- maintaining and training the obstetrical skills of practitioners

Least but not last, knowledge of legal medical issues could be of help to obstetricians and could help them avoid practicing a defensive and lacking in ethics kind of medicine.

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THE POTENTIAL ROLE OF PREOPERATIVE SERUM CANCER ANTIGEN CA 15-3 IN THE PROGNOSIS OF BREAST CANCER

I. Juhasz-Böss**, J. Radosa**

*Department of Obstetrics and Gynaecology, University of Ulm, Ulm, Germany
**Department of Obstetrics and Gynaecology, University of Saarland, Homburg / Saar, Germany

Abstract

Background: Serum CA 15-3 has been the most frequently investigated tumor marker in breast cancer. The most important application for CA 15-3 is in monitoring therapy in patients with advanced breast cancer. CA 15-3 levels have also been demonstrated to predict outcome in breast cancer. However, the potential role of CA 15-3 as a prognostic marker for breast cancer was investigated only in a few studies.

Methods: In a retrospective study, we investigated the association of the serum levels of CA 15-3 with tumor characteristics as prognostic factors of the disease. 586 female breast cancer patients confirmed by histopathological reports were included in the study. Information concerning age, menopausal status, diagnosis, and clinical pathology were collected for each patient. CA 15-3 serum levels were evaluated at time of the primary diagnosis.

Results: Our results suggest that elevated pretreatment serum marker values were correlated with poor prognosis and death from the disease. By comparing CA 15-3 levels in metastatic and non-metastatic disease, we found a statistically significant difference between the two categories. This study demonstrates a correlation between stage of breast cancer and CA 15-3 positivity rates. The higher the breast cancer stage, the more likely the CA 15-3 level will be elevated. The CA 15-3 level was similarly significantly related to death from disease. We found no correlation between CA 15-3 levels and recurrences of the disease.

Conclusion: Elevated preoperative serum level of CA 15-3 is significantly correlated with the presence of distant metastatic disease. Our data supports CA 15-3 as a useful parameter in the management of breast cancer preoperatively as well as in an adjuvant setting.

Rezumat: Rolul potenţial al valorii preoperatorii a antigenului CA 15-3 în prognosticul cancerului de sân


Concluzie: Valorile crescente ale CA 15-3 preoperator se asociază semnificativ cu prezenţa bolii metastatice la distanţă. Datele noastre sprijină folosirea CA 15-3 ca un parametru util în managementul preoperator al cancerului de sân precum şi ca adjuvant.

Cuvinte cheie: Cancer de sân, CA 15-3, marker, prognostic
INTRODUCTION

Breast cancer is the most common cancer in women worldwide [18]. Nearly 1.1 million patients are diagnosed with breast cancer yearly [17]. The number of cases worldwide has significantly increased in the last years. New strategies for managing breast cancer are needed.

CA 15-3 is a high-molecular-weight mucin glycoprotein and is the most widely used serum marker in breast cancer for follow-up care and monitoring the treatment of patients with advanced disease [5,6]. For monitoring the treatment of advanced breast cancer, CA 15-3 levels decrease in approximately 70% of patients with chemotherapy-induced breast cancer regression and increase in 80% of patients with progressive disease [19].

Because of its low sensitivity (15-35%), the routine use of CA 15-3 as a screening or diagnostic tool for primary breast cancer is not recommended [1-4]. Elevated levels of CA 15-3 are found in only 3% of patients with non-metastatic breast cancer and in up to 70% of patients with metastatic disease [16]. Increasing and decreasing levels show correlation with breast cancer progression and regression, respectively.

Nonmammary malignancies in which elevated CA 15-3 levels have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium. Mild increased concentrations were observed in benign conditions, such as: hepatitis, liver cirrhosis, lung, kidney, ovarian, breast (mastopatie, fibroadenom).

The potential role of CA 15-3 in prognosis of breast cancer has been analyzed in a few studies, which came to inconsistent results. It has been reported that patients with elevated preoperative CA 15-3 levels had a worse outcome than patients with low levels [9]. The ASCO guidelines found the data insufficient to recommend the routine use of CA 15-3 measurements for screening, monitoring response to treatment, diagnosis, or staging. The ASCO guidelines recognized that in the absence of readily measurable breast cancer, an increasing CA 15-3 might be used to suggest progression of disease.

Our aim was to investigate the association of CA 15-3 concentrations with clinicopathological parameters and outcomes in patients with breast cancer.

PATIENTS AND METHODS

In a retrospective study, we investigated the association of the serum levels of CA 15-3 with tumor characteristics as prognostic factors of the disease.

The study population enrolled a total of 586 consecutive participants with a histologic diagnosis of breast cancer or carcinoma in situ, treated at the Department of Gynecology of the University of Saarland between January 2010 and December 2012. Information concerning age, menopausal status, diagnosis, and clinical pathology were collected for each patient and are summarized in Table 1. The participants were monitored for tumor recurrence or death during a mean follow-up period of 17.5 months. The breast cancer patients were staged according to TNM-UICC classification. 532 patients were diagnosed histologically with ductal infiltrating carcinoma, while 49 of carcinoma in situ. Tumor size was classified as T1 (less than or equal to 2 cm) in 297 (50.77%), T2 (tumor size between 2 and 5 cm) in 157 (26.84%), T3 (tumor size more than 5 cm) in 27 (4.62%) and T4 (tumor extends to chest wall) in 29 (4.96%) of the cases. There were 400 patients with negative lymph nodes and 162 patients with positive lymph nodes. Main tumor characteristics are shown in Table 1.

Pretreatment serum CA 15-3 measurements were available for 510 participants. CA 15-3 serum levels were evaluated at time of the primary diagnosis and were not used in our study to monitor response to breast cancer treatment. The cut-off level for serum CA 15-3 was established at 30 U/mL.

The statistical analyses were carried out using Statistical Analysis System version 9.2 statistics software. The Kruskal-Wallis test was used for relating CA 15-3 levels to clinicopathological parameters. A p-value of less than 0.05 was considered to be significant.
Table 1: Main clinical-pathological tumor characteristics of 586 breast cancer patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>Percent</th>
<th>Characteristic</th>
<th>Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>122</td>
<td>20.82%</td>
<td>Premenopausal</td>
<td>117</td>
<td>19.97%</td>
</tr>
<tr>
<td>50-70 years</td>
<td>296</td>
<td>50.52%</td>
<td>Perimenopausal</td>
<td>35</td>
<td>5.97%</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>168</td>
<td>28.66%</td>
<td>Postmenopausal</td>
<td>433</td>
<td>73.89%</td>
</tr>
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<td><strong>Histological diagnosis</strong></td>
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<tr>
<td>Ductal infiltrating carcinoma</td>
<td>532</td>
<td>91.57%</td>
<td>G1</td>
<td>61</td>
<td>11.80%</td>
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<tr>
<td>In situ carcinoma</td>
<td>49</td>
<td>8.43%</td>
<td>G2</td>
<td>339</td>
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<td>G3</td>
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<tr>
<td>T1</td>
<td>297</td>
<td>50.77%</td>
<td>N0</td>
<td>400</td>
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<tr>
<td>T2</td>
<td>157</td>
<td>26.84%</td>
<td>N1</td>
<td>123</td>
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<tr>
<td>T3</td>
<td>27</td>
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<td>N2</td>
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<tr>
<td>T4</td>
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<tr>
<td>M0</td>
<td>538</td>
<td>95.05%</td>
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<tr>
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<tr>
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<td>No</td>
<td>574</td>
<td>97.95%</td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>2.56%</td>
<td>Yes</td>
<td>12</td>
<td>2.05%</td>
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<td><strong>Death</strong></td>
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</tbody>
</table>

Adela Stoeneakyu
RESULTS

Relationship between CA 15-3 and tumor characteristics in adjuvant patients

Serum levels of CA 15-3 in patients with carcinoma in situ did not differ significantly as compared with patients with invasive breast cancer (20.85 U/ml vs. 64.58 U/ml, p>>0.05).

There were significant correlations between tumor size and CA 15-3 levels in our analysis. CA 15-3 concentrations were higher in patients with larger tumors; p = 0.0377. However, patients with T4 breast cancer had lower CA 15-3 level (mean 17.72 U/mL) than patients with T1, T2 and T3 tumors.

The CA 15-3 concentrations were independent of grading, nodal burden, local disease recurrence, ER, PgR and Her2 expression. A detailed breakdown of distribution of CA 15-3 levels in relation to tumor characteristics is shown in Figure 1.

Figure 1: Relationship between CA 15-3 and tumor characteristics in non-metastatic patients

Relationship between CA 15-3 and tumor characteristics in patients with metastatic disease

26 patients with available data had already distant metastasis at time of their initial breast cancer diagnosis as follows: 5 patients had lung metastases,
8 bone metastases, 2 liver metastases and the others had more than one location of distant metastasis. Patients with primary metastatic disease had a mean CA 15-3 level of 79.45 U/mL, significantly higher than patients without metastasis; p< 0.0001.

The relationship between tumor marker level and clinical and histopathologic characteristics of the patients is shown in Figure 2. CA 15-3 level seemed to be increased linearly with tumor size in patients with metastatic disease. However, the observed differences of CA 15-3 levels between T1, T2, T3 and T4 tumors are not significant. Although a tendency for increased CA 15-3 levels in patients with axillary metastases was observed, this difference again did not reach statistical significance. Non-significant elevations of CA 15-3 were observed in patients with G2 and G3 tumors.

We evaluated correlation of CA 15-3 level at the time of primary diagnosis with ER, PgR and Her 2 expressions. A mean serum CA 15-3 concentration of 20.64 U/mL was observed.

During the follow-up period, 12 patients (2.05%) died, 11 of which due to breast cancer. For 8 patients with available data, significantly higher CA 15-3 levels were found at time of diagnosis (mean level 671.4 U/mL); p= 0.0006. Out of these 8 patients, 2 patients had no distant metastasis and slightly higher CA 15-3 values (mean 27.3 U/mL) compared to survivors.
DISCUSSION

The classic prognostic markers in breast cancer such as axillary lymph node status, tumor size, histological grade, and receptor expression require tissue sampling, are costly and cannot by themselves predict the risk of development of distant metastasis and outcome in patients with breast cancer. Tumor markers that can accurately predict overall survival, which can identify the group of patients needing close follow up and those who will benefit most from adjuvant therapy, are needed. Serum CA 15-3 has been the most frequently investigated tumor marker in breast cancer.

The most important application for CA 15-3 is in monitoring therapy in patients with advanced breast cancer [15]. CA 15-3 levels have also been demonstrated to predict outcome in breast cancer [9]. However, the potential role of CA 15-3 as a prognostic marker for breast cancer was investigated only in a few studies. Our results suggest that elevated pretreatment serum marker values were correlated with poor prognosis and death from the disease.

By comparing CA 15-3 levels in metastatic and non-metastatic disease, we found a statistically significant difference between the two categories. CA 15-3 can stratify patients into high and low risk groups. Patients in the high risk group have a poor prognosis, a higher risk of distant metastasis, of death from the disease and need close follow-up and most likely benefit from adjuvant therapy.

This study demonstrates a correlation between stage of breast cancer and CA 15-3 positivity rates. The higher the breast cancer stage, the more likely the CA 15-3 level will be elevated. Our results are comparable to results from other analyses with a similar study design [7,10]. Surprisingly, the 5 patients from our study with T4 non-metastatic tumors had a significantly lower CA 15-3 level in our analysis. A normal result does not prove absence of cancer [7,8].

The CA 15-3 level was also significantly related to death from disease. The higher the CA 15-3 levels, the poorer is the prognosis. In line with our findings, Duffy et al. evaluated the relationship between CA 15-3 levels and patient outcome and
has shown that high preoperative levels of CA 15-3 are associated with an adverse patient outcome [9]. Survival may be poorer in patients with an elevated serum marker level because of the statistically significant relationship between CA 15-3 and metastasis. Other authors have published similar observations. For example, Daniele et al., Berutti et al. and Horobin et al. reported that high preoperative levels of CA 15-3 can predict poor outcome in patients with breast cancer [11-13]. They confirmed our findings that patients with abnormal CA 15-3 levels have a shorter disease-free interval and overall survival rate compared to those with normal levels.

We found no correlation between CA 15-3 levels and recurrences of the disease. Daniele et al. and Iaffaioli et al., however, found that patients with abnormal preoperative CA 15-3 levels are significantly associated with early recurrence of the disease [11,14].

These results confirmed that elevated preoperative serum levels of CA 15-3 are significantly correlated with the presence of distant metastatic disease. However, CA 15-3 has not been shown to be a more useful prognostic tool than the routine traditional markers. Elevated CA 15-3 level is a useful parameter for predicting clinical outcomes and it may be used collectively with these markers in the management of breast cancer.

REFERENCES

IMPACT OF PRENATAL MAGNETIC RESONANCE IMAGING AT 3.0 TESLA IN THE OBSTETRICAL AND NEONATAL MANAGEMENT OF FETUSES WITH SUSPECTED CENTRAL NERVOUS SYSTEM ANOMALIES


*IMOGEN center – Radiology department, Cluj-Napoca, Romania
**IMOGEN center – Obstetrics department, Cluj-Napoca, Romania
*** UMF Iuliu Haţieganu

Abstract

The purpose of this study is to evaluate the impact of fetal magnetic resonance imaging (MRI) at 3 T, in the management of fetuses with cerebral anomalies detected or suspected by ultrasound.

Thirty-eight women with fetal cerebral anomalies suspected by prenatal ultrasonography (US) were referred to our department from January 2013 to August 2015 for fetal MRI.

In 12 cases, US and MRI findings were comparable. In 7 cases, MRI specified the diagnosis without changing management or counseling, while in 4 cases, additional findings led to a change in management and/or counseling. In 15 cases, the diagnosis was made based on MRI findings.

Fetal MRI has proven to have a significant impact in half the cases (19/38) by confirming, completing or correcting US diagnoses, enabling adequate management and counseling.

Rezumat: Rolul imagisticii prin rezonanta magnetica 3.0 Tesla in managementul sarcinii si planificarii terapeutice postnatale la fetii cu suspiciune de afectare a sistemului nervos central

Obiectivul acestui studiu este de a evalua impactul imagisticii prin rezonanta magnetica (IRM), in camp magnetic de 3 Tesla, asupra conduitei obstetrical si neonatale in cazurile de anomaliile cerebrale fetale, diagnosticate sau suspionate la ultrasonografie (US).

S-au efectuat 38 de investigatii IRM fetale, cu indicatia de suspiciune de afectare a sistemului nervos central, in perioada ianuarie 2013 – August 2015.

In 12 cazuri rezultatele US si IRM au fost echivalente. In 7 cazuri IRM a adus un aport de informatii, insa fara sa modifice diagnosticul principal sau managementul obstetrical, in timp ce in 4 cazuri informatiile aditionale au fost relevante pentru managementul sarcinii. In 15 cazuri IRM a schimbat diagnosticul, cu efect asupra mangerului si/sau consilierii obstetricale.

IRM fetal a avut un impact relevant in jumata (19/38) din cazuri, prin confirmarea, completarea sau corectarea diagnosticului US, si a permis adaptarea consilierii parintilor si a conduit sitului obstetric si neonatala.

Cuvinte cheie: RMN fetal, ecografie fetală, malformații cerebrale, sistem nervos central, măsuri dintr-o postnatală, diagnostic prenatal

INTRODUCTION

A correct and complete diagnosis of fetal congenital disorders is crucial for the fetal and postnatal prognosis, for planning the delivery and treatment options, and for initiating early postnatal treatment by avoiding latency periods. It also plays a role in counseling parents about the current pregnancy status.
and possible future ones.

Currently fetal diagnosis is based on ultrasound (US), which is the main and so far irreplaceable imaging modality in obstetrics. Its advantages are wide availability, no known side effects, it is mobile, can be easily repeated and it has high acceptability among patients and clinicians. It is also the only appropriate imaging technique in the first trimester. In the hands of an experienced sonographer, ultrasound can readily detect most of the fetal intracranial abnormalities. However, in clinical practice, there are situations in which the ultrasound examination is either suboptimal, due to inherent limitations of the method or to pregnancy related imaging difficulties (1, 2).

Fetal magnetic resonance imaging (MRI) has been increasingly used for detailed visualization of the fetus in utero and has become an important and well-established diagnostic tool for suspected cerebral anomalies. Fetal MRI, as a second line diagnostic method, is generally indicated when fetal ultrasound is suspicious or the sonographic detection of fetal malformations requires further assessment. Because fetal MRI is rarely performed when there are no pathologic findings on ultrasound, it is difficult to assess the true predictive value.

Regarding the fetal safety at MRI there is no scientific evidence of any adverse effects on the human embryo/fetus from the use during pregnancy (3, 4, 5), and in the past few years this has been proved for higher magnetic fields (3 Tesla) as well (6, 7). Safety recommendations for in vivo scanning of fetuses at 3 Tesla include limiting the amount of imaging time and using alternative methods to decrease specific absorption rates (6, 7).

The objective of this study is to evaluate the impact of fetal MRI at 3 T, in the management of fetuses with cerebral anomalies detected or suspected by ultrasound.

**MATERIALS AND METHODS**

We conducted a retrospective study of all fetal MRI examinations performed for further evaluation of the sonographic suspicion or diagnosis of fetal cerebral anomalies, at IMOGEN center in Cluj-Napoa, Romania, for the period between January 2013 and August 2015.

After obtaining informed consent for fetal MRI, 37 pregnant women (age average of 29 years) were examined at a gestational age between 21 and 38 weeks (average of 29.8 weeks), with one patient being scanned twice at an interval of 10 weeks, for suspicion of complications. All cases were referred by the local prenatal ultrasound center, for sonographic suspicion of fetal cerebral anomalies.

**Imaging protocol**

The ultrasound examinations were performed by experienced obstetricians, in a tertiary reference center with modern equipment, using a combined transabdominal and transvaginal approach.

The MRI examinations were performed within a week of the ultrasonographic evaluation, on a GE Healthcare MR machine, in 3.0 Tesla (T) magnetic field, using a multichannel abdominal coil. The imaging protocol consisted of ultrafast T2 sequences (single shot fast spin-echo), acquired on all 3 planes, adapted to the position of the fetus, and T1 weighted 3D sequence (LAVA-Flex). In some cases, depending on the suspected pathology, additional diffusion or susceptibility sequences were also acquired. Six exams were realized using mild sedation (oral/i.v. Dormicum) due to maternal claustrophobia. The examinations were interpreted by a radiologist, experienced in pediatric and neonatal imaging, as part of doctoral studies. The fetus was assessed completely (head, thorax, abdomen and extremities), along with the placenta and umbilical cord and the quantity of amniotic fluid was estimated.

**The impact of MRI on obstetrical and postnatal management**

For this purpose we compared the results of the two imaging methods and we analyzed whether MRI contributed with additional information to the final diagnosis and thus changed the fetal prognosis.

We retrospectively analyzed the impact of the method on the obstetrical and postnatal management, based on the hospital charts and
discharge documents from the obstetrics and neonatology units. We looked at the recommendations regarding the delivery method, the moment of delivery and the changes in the perinatal therapeutic conduct, including parental counseling.

In order to reveal the impact of fetal MRI findings on the final diagnosis and obstetrical management, we adapted the classification proposed by Dill et al., and grouped the results into 4 categories: 1) MRI and US results were comparable, 2) Fetal MRI provided extra information in addition to US without changing diagnosis or affecting obstetric management and/or counseling, 3) Fetal MRI provided extra information in addition to US without changing diagnosis, but affecting obstetric management and/or counseling, 4) Fetal MRI changed the diagnosis, affecting obstetric management and/or counseling.

RESULTS

1. US indications for fetal MRI

The analysis of the lesions detected by US, which required further assessment with MRI (Table 1), revealed that ventriculomegaly was the predominant finding (27/38 cases, 71%). According to US reports, ventriculomegaly was isolated in 7 cases (uni- or bilateral), while in the rest of 19 cases associated lesions were identified or suspected, mostly corpus callosum agenesis. The rest of the ultrasonographic indications were midline anomalies (5/38 cases), encephalocoeles (2/38), cerebral parenchyma lesions (2/38), one posterior fossa anomaly and one suspicion of fetal infection following maternal CMV seroconversion during pregnancy.

The indication for fetal MRI was to confirm the ultrasound suspicion, adding diagnostic confidence, and to search for additional pathologic findings, or to clarify the etiology of pathological sonographic findings.

2. Fetal MRI results compared to US findings and impact on pregnancy management

Both methods had similar results, with no added diagnostic value from MRI, in 12/38 (31%) cases. Fetal MRI contributed to the final diagnosis by detecting additional lesions in 26/38 cases (68.42%). The additional information provided by MRI had no prognostic value in 7 (18%) cases, was relevant for the fetal prognostic and obstetric management, without changing the main diagnosis, in 4 (11%) cases, and changed the final diagnosis in 15 (39%) cases. Thus the additional information provided by MRI changed the prognosis, affecting counseling, obstetric management and neonatal treatment planning in 19/38 cases (50%). All 38 MRI examinations were of diagnostic quality and all MRI findings were confirmed postnatal by ultrasound and/or MRI, or by fetal autopsy.

Table 1. US indications for fetal MRI

<table>
<thead>
<tr>
<th>Fetal cerebral ultrasound findings, which required further assessment by MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated ventriculomegaly (7)</td>
</tr>
<tr>
<td>Agenesis of the corpus callosum</td>
</tr>
<tr>
<td>Septo-optic dysplasia</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
</tr>
<tr>
<td>Mass lesion</td>
</tr>
<tr>
<td>Vermian hypoplasia</td>
</tr>
<tr>
<td>Total 38</td>
</tr>
</tbody>
</table>

Roxana Popa-Stânilã
2.1. **Category 1: Similar results reported by US and MRI**

In 12/38 cases US and MRI findings were comparable, with no added information by MRI (Table 2). There were three cases in this group with some differences in reported details between the two methods: in a case of choroid plexus cyst with unilateral ventricular enlargement, the cyst wall was more conspicuous with US. In a case of corpus callosum agenesis, the pericallosal artery as seen by Doppler US suggested the presence of an anterior callosal remnant, which was confirmed postnatal. In the third case MRI depicted more maternal uterine fibroids, than reported by US. In this category, the decisions regarding the obstetrical management were based on the clinical and ultrasound evolution of the pregnancy. In one case the postnatal MRI differed from the fetal mild symmetric lateral ventricle enlargement, as seen at 22 weeks of gestation, progressed until birth to asymmetrical ventricular dilatation, due to congenital obstruction of both foramen of Monro.

**Table 2. Category 1: Similar results reported by US and MRI**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Ultrasound (US) diagnosis</th>
<th>MRI diagnosis</th>
<th>Gestational age in weeks at birth</th>
<th>Delivery mode</th>
<th>Neonatal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Choroid plexus cyst, unilateral ventriculomegaly</td>
<td>unilateral ventriculomegaly</td>
<td>39</td>
<td>Vaginal delivery</td>
<td>US follow-up, disappearance until the age of one month</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>Asymmetrical ventriculomegaly</td>
<td>Asymmetrical ventriculomegaly</td>
<td>40</td>
<td>Vaginal delivery</td>
<td>US follow-up, spontaneous resolution</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Asymmetrical ventriculomegaly</td>
<td>Mild asymmetrical ventriculomegaly</td>
<td>40</td>
<td>Vaginal delivery</td>
<td>US follow-up, spontaneous resolution</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Ventriculomegaly</td>
<td>Mild enlargement of occipital horns</td>
<td>37</td>
<td>Vaginal delivery</td>
<td>US follow-up, decreasing mild ventricular asymmetry</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>Borderline ventriculomegaly, suspicion of fingers malformation</td>
<td>Borderline symmetrical ventriculomegaly, normal 3rd and 4th ventricle</td>
<td>40</td>
<td>Vaginal delivery</td>
<td>Progression to asymmetrical lateral ventriculomegaly secondary to bilateral malformation of the 3rd ventricle. Endoscopic intervention.</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>Ventriculomegaly, Chiari II, spina bifida</td>
<td>Ventriculomegaly, Chiari II, lumbar myelomeningocele</td>
<td>39</td>
<td>Caesarean section</td>
<td>Surgical repair in the first day, ventriculoperitoneal shunt at 26 days</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>Ventriculomegaly, Chiari II, spina bifida, 2. maternal uterine fibroids</td>
<td>Ventriculomegaly, Chiari II, sacral myelomeningocele; 6 uterine fibroids</td>
<td>57</td>
<td>Caesarean section</td>
<td>Surgical repair, ventriculoperitoneal shunt. Mild cerebral atrophy.</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>Corpus callosum agenesis</td>
<td>Corpus callosum agenesis</td>
<td>28</td>
<td>Termination of pregnancy</td>
<td>Postmertem confirmation</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>Partial agenesis of corpus callosum, fetal hypotrophy</td>
<td>Corpus callosum agenesis, fetal hypotrophy</td>
<td>37</td>
<td>Vaginal delivery</td>
<td>US follow-up, confirmation of partial agenesis of corpus callosum</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>Alobar holoprosencephaly, cyclopia, left heart hypoplasia</td>
<td>Alobar holoprosencephaly, cyclopia</td>
<td>22</td>
<td>Termination of pregnancy</td>
<td>Postmertem confirmation</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>Ventriculomegaly, vermian agenesis</td>
<td>Dandy Walker malformation (vermian hypoplasia), ventriculomegaly</td>
<td>38</td>
<td>Vaginal delivery</td>
<td>Perinatal asphyxia, confirmation of prenatal diagnosis</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>Maternal CMV seroconversion, normal fetal US</td>
<td>Normal fetal cerebral development</td>
<td>89</td>
<td>Caesarean section</td>
<td>CMV negative</td>
</tr>
</tbody>
</table>

**Table 3. Category2: Fetal MRI provided extra information in addition to US without changing diagnosis or affecting obstetric management and/or counseling**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Gestational age in weeks at MRI exam</th>
<th>Ultrasound (US) diagnosis</th>
<th>MRI diagnosis</th>
<th>Gestational age in weeks at birth</th>
<th>Delivery mode</th>
<th>Neonatal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>31</td>
<td>Mild asymmetrical ventriculomegaly, shortend long bones, suboptimal</td>
<td>Normal ventricular size, shortend long bones</td>
<td>38</td>
<td>Vaginal delivery</td>
<td>Congenital cardiac malformation, decreased at 8 days</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>27</td>
<td>Severe ventriculomegaly</td>
<td>Hydrocephalus, bilateral obstruction of the foramen Monro</td>
<td>28</td>
<td>Vaginal delivery</td>
<td>Stillborn, no autopsy</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>38</td>
<td>Ventriculomegaly, spina bifida, suspected corpus callosum agenesis</td>
<td>Ventriculomegaly, Chiari II, lumbar myelomeningocele, compressed corpus callosum</td>
<td>40</td>
<td>Vaginal delivery</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>22</td>
<td>Lumbo-sacral spina bifida, Chiari II, suspected semilobar holoprosencephaly, clubfoot.</td>
<td>Lumbo-sacral spina bifida, Chiari II, suspected semilobar holoprosencephaly, Bilateral clubfoot.</td>
<td>22</td>
<td>Termination of pregnancy</td>
<td>Postmertem confirmation</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>34</td>
<td>Moderate ventriculomegaly, suspected corpus callosum agenesis, colpocephaly</td>
<td>Isolated corpus callosum agenesis, colpocephaly</td>
<td>40</td>
<td>Vaginal delivery</td>
<td>US confirmation of isolated corpus callosum agenesis</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>26</td>
<td>Semilobar holoprosencephaly</td>
<td>Alobar holoprosencephaly</td>
<td>25</td>
<td>Termination of pregnancy</td>
<td>Postmertem confirmation</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>24</td>
<td>Semilobar holoprosencephaly</td>
<td>Alobar holoprosencephaly</td>
<td>24</td>
<td>Termination of pregnancy</td>
<td>Postmertem confirmation</td>
</tr>
</tbody>
</table>
2.2. Fetal MRI provided extra information in addition to US without changing diagnosis or affecting obstetric management and/or counseling

In 7/38 cases, the additional findings detected by fetal MRI did not change the main diagnosis or affected the decision regarding termination of pregnancy (Table 3). Fetal MRI rather raised diagnostic confidence by either invalidating a weak suspicion of associated lesions (case 1, 3 and 4), or confirming a strong sonographic suspicion (case 2 and 5), or by specifying the exact type of holoprosencephaly (case 6 and 7).

2.3. Fetal MRI provided extra information in addition to US without changing diagnosis, but affecting obstetric management and/or counseling

In 4/38 cases fetal MRI confirmed the main US diagnosis and detected additional findings which altered the overall prognosis (Table 4).

In two fetuses with corpus callosum dysgenesis, MRI revealed a delay in gyration, an arachnoid cyst of the posterior fossa, respectively periventricular cysts and white matter diffuse lesions. In these cases, the postnatal prognosis was more accurately predicted after fetal MRI, but there were no chromosomal syndrome or congenital infection detected postnatal, as suggested.

In two cases of encephaloceles, the ischemic lesions of the herniated cerebral and cerebellar parenchyma were only conspicuous at MRI and prompted early delivery by Caesarean section. No additional postnatal imaging exams were required prior to the surgical interventions.

2.4. Fetal MRI changed the diagnosis, with impact on obstetric management and/or counseling

This category is comprised of 15/38 cases, in which fetal MRI disagreed with the US diagnosis or was able to determine the etiology of US findings (Table 5). MRI revealed the cause of ventriculomegaly to be aqueductal stenosis in 3 cases (two with additional findings of occipital infarcts), corpus callosum agenesis in 4 cases (two isolated and two others associated with interhemispheric cysts or with other cerebral lesions suggestive of fetal CMV infection), septo-optic dysplasia in one fetus and secondary to cerebral atrophy in 2 fetuses with large arachnoid cysts, seen at US as asymmetrical ventricular enlargement. In one fetus who was scanned twice, the US diagnosis of midline abnormalities was disproved. In two cases an intracranial mass lesion was suspected on US, but MRI showed normal cerebral morphology. And finally, the posterior fossa was better assessed with MRI in one case.

DISCUSSION

Comparison to literature

Our data demonstrates an impact of fetal MRI, as a second line diagnostic tool, in the diagnosis and obstetric management of cases with fetal nervous system anomalies. Fetal MRI confirmed the US diagnosis in 23/38 cases (60%), and provided additional informations in 11/38 cases (29%). In 15/38 (39%) MRI was decisive for the final diagnosis, and overall was relevant for obstetrical decisions and counseling in 19/38 cases (50%).

We compared our data to literature reviews concerning the value of fetal MRI in the prenatal diagnosis of cerebral anomalies, published in the past years (2012-2015) ([10,11]). We found an agreement between our results and those reported in the literature. Rossi et al. ([1]) showed that there is an average of approximately 65% agreement between ultrasound and MRI in detecting CNS anomalies and that MRI provided additional information in 22% of cases. In 30% of cases, the ultrasound diagnosis was so revised by MRI that management and parental counseling changed completely. As opposed to the review data that reported 2.5 false positive MRI findings, we had none.

The studies on which these reviews are based, report variable results regarding the clinical significance of fetal MRI for the prenatal diagnosis,
### Table 4. Category 3: Fetal MRI provided extra information in addition to US without changing diagnosis, but affecting obstetric management and/or counseling

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Ultrasound (US) diagnosis</th>
<th>MRI diagnosis</th>
<th>Gestational age in weeks at birth</th>
<th>Delivery mode</th>
<th>Neonatal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Corpus callosum agenesis</td>
<td>Corpus callosum agenesis, posterior fossa arachnoid cyst, delayed cerebral gyration, low set ears, hypertelorism</td>
<td>Caesarean section</td>
<td>No chromosomal abnormality</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Corpus callosum agenesis, fetal hypotrophy</td>
<td>Partial agenesis of corpus callosum, periventricular cysts, diffuse white matter injury, fetal hypotrophy</td>
<td>Vaginal delivery</td>
<td>Neurological follow-up: marked hypotonia</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>Occipital meningocele</td>
<td>Occipital encephalocele with small cerebellar engagement, ventricular enlargement and diffuse white matter injury</td>
<td>Caesarean section</td>
<td>Surgical repair: At 3 months: mild cerebral atrophy and cerebellar hypotrophy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Interventricular proruding mass</td>
<td>Frontal encephalocele, ischemic lesion of the herniated cerebral parenchyma</td>
<td>Caesarean section</td>
<td>Scheduled for surgical repair</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Fetal MRI changed the diagnosis, with impact on obstetric management and/or counseling

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Ultrasound (US) diagnosis</th>
<th>MRI diagnosis</th>
<th>Gestational age in weeks at birth</th>
<th>Delivery mode</th>
<th>Neonatal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Ventriculomegaly, absent septum pellucidum, septo optic dysplasia</td>
<td>Ventriculomegaly with secondary distortion of septal leaflets, no SOD</td>
<td>Caesarean section</td>
<td>US follow-up</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Ventriculomegaly, absent septum pellucidum, absent corpus callosum</td>
<td>Ventriculomegaly with secondary distortion of septal leaflets, normal corpus callosum</td>
<td>Caesarean section</td>
<td>US follow-up, normal development at 1.4 years</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>Unilateral ventriculomegaly</td>
<td>Aqueductal stenosis, hydrocephalus, bilateral occipital leukomalacia</td>
<td>Caesarean section</td>
<td>Endoscopic third ventriculostomy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Hydrocephalus, corpus callosum agenesis</td>
<td>Aqueductal stenosis, hydrocephalus, bilateral occipital and temporal leukomalacia</td>
<td>Caesarean section</td>
<td>Endoscopic third ventriculostomy</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>Ventriculomegaly, corpus callosum agenesis</td>
<td>Aqueductal stenosis, hydrocephalus</td>
<td>Caesarean section</td>
<td>Decreasing triventricular enlargement; normal neurological exam</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>Asymmetrical lateral ventricles</td>
<td>Absent septum pellucidum, septo-optic dysplasia</td>
<td>Vaginal delivery</td>
<td>US follow-up, normal ophthalmologic and neurological exam at 3.5 months</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>Ventriculomegaly</td>
<td>Partial agenesis of corpus callosum</td>
<td>Termination of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>Ventriculomegaly</td>
<td>Agenesis of corpus callosum</td>
<td>Caesarean section</td>
<td>US follow-up: agenesis of corpus callosum, decreasing ventriculomegaly</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>Interhemispheric cyst</td>
<td>Agenesis of corpus callosum, large bilateral parieto-occipital parasagittal arachnoid cysts</td>
<td>Caesarean section</td>
<td>Enlargement of arachnoid cysts, temoporization of surgical intervention</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>Ventriculomegaly, corpus callosum agenesis</td>
<td>Partial agenesis of corpus callosum, subependymal calcifications, polymicrogyria, ventriculomegaly</td>
<td>Vaginal delivery</td>
<td>Congenital CMV infection confirmed</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>Ventriculomegaly, absent septum pellucidum, agenesis of corpus callosum</td>
<td>Large parieto-occipital arachnoid cyst, paraventriculomegaly, cerebral atrophy, thinned corpus callosum, bilateral genu recurvatum</td>
<td>Caesarean section</td>
<td>Ventricular and cystic shunt without reduction</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>Porencephaly, polyhydranmosis</td>
<td>Large occipital arachnoid cyst, occipital and temporal lobe atrophy</td>
<td>Termination of pregnancy</td>
<td>Postmortem confirmation</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>Cerebellar vermis agenesis</td>
<td>Normal vermis, arachnoid cyst of the posterior fossa</td>
<td>Vaginal delivery</td>
<td>Posterior fossa cyst decreased in size</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>Interhemispheric lipoma</td>
<td>Normal fetal MRI</td>
<td>Caesarean section</td>
<td>Normal cerebral morphology and normal neurological development</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>Cerebral tumor, fetal hypotrophy</td>
<td>Normal cerebral morphology, fetal hypotrophy</td>
<td>Caesarean section</td>
<td>Normal cerebral morphology and normal neurological development</td>
<td></td>
</tr>
</tbody>
</table>
with added information ranging between 6% and 53% (\(^{10}\)). One of the explanations under debate for this variability is that some studies compared a referral routine transabdominal US examination with an MRI performed at a neuroradiological unit at a third-level facility. Malinger et al (\(^{12}\)) argued that MRI is not superior to the US investigation when performed by a dedicated neurosonographer and the interpretation of the findings is made by a multidisciplinary team.

In clinical practice the radiologists are usually informed about the patients’ history and US findings, whereas ultrasound is performed on unselected populations as a screening test. This might influence the high accuracy of MRI.

In our study both US and MRI were performed in the same tertiary care center and were scheduled under a week from each other, usually with a follow-up sonographic examination just hours before MRI. The sonographers were experienced in obstetric ultrasound, used modern equipment to acquire 2D and 3D fetal images, using a combined transabdominal and transvaginal approach. The radiologist who interpreted the MRI findings was experienced in pediatric and neonatal radiology, but had a limited experience with fetal MRI, these being the first results reported by our center, since introducing this method, in 2012. The radiologist was informed in advance about the ultrasound suspicion and the patient history. The MRI results were discussed with the obstetric team and other specialists as required by the pathology in question (neonatologist, neurosurgeon, pediatric neurologist and geneticist).

The main imaging protocol difference between our study and those reviewed is the use of a 3 Tesla MRI clinical system as opposed to the more widespread 1.5 Tesla machines. This might be the reason for the approximately 7% difference of our results, in favor for MRI. The current tendency is to switch to 3.0 T, with a rise in the installation rate of these systems already reported in 2011 (\(^{13}\)). Fetal MRI at 3.0 T poses advantages, as well as challenges: the gain of signal-to-noise ratio provided at 3.0 T can be used to enhance the image resolution and/or to shorten the scanning time, while certain artifacts increase and measures must be taken to counter them (\(^{13,14}\)).

**Characterisation of additional fetal cerebral findings detected by MRI**

In our study, fetal MRI provided additional information regarding the etiology of ventriculomegaly, detected cerebral parenchymal abnormalities, described better the posterior fossa changes and the large intracranial cystic lesions.

The overall appearance of the fetal ventricular system provided by MRI was useful in finding the etiology of ventriculomegaly, the most frequent US finding that prompted further investigation. Ventriculomegaly was either isolated (n=5), secondary to obstruction (n=5) or part of a syndrome/malformative complex: Chiari II malformation (n=4), dysgenesis of the corpus callosum (n=9), Dandy-Walker malformation (n=1), septo-optic dysplasia (1) and alobar holoprosencephaly (2).

Regarding the fetal cerebral parenchymal lesions, MRI was able to detect cortical folding anomalies (polymicrogyria and delayed cortical folding) and white matter lesions (focal ischemic lesions, periventricular cysts and diffuse injury like edema and transependymal resorption of spinal fluid), missed by US.

The posterior fossa modifications that were better depicted by MRI regarded the herniation of cerebellar structures in Chiari II malformation and occipital encephalocele. The cerebellar vermis was described as hypoplastic in a Dandy Walker malformation and normal in a case with an arachnoid cyst at the level of cisterna magna, as opposed to the US diagnosis of vermian agenesis.

Large arachnoid cysts were misinterpreted with US as part of a dilated ventricle or as porencephalic lesions. These lesions were better defined by MRI with regard to location, origin and parenchymal compression.

**CONCLUSIONS**

Fetal MRI is a non-invasive imaging method that supplements the information provided by ultrasound. It is a useful diagnostic tool in problem solving the cases of fetal cerebral anomalies, by
allowing precise visualization and determination of the extent and severity of fetal anomalies.

Based on the findings of fetal MRI, the parents’ counseling was influenced in about half of the cases in our study. Our data shows a slightly better performance compared with previous observations regarding the value of fetal MRI in the prenatal diagnosis of central nervous system anomalies, most likely due to imaging at higher magnetic field.

Because this additional information may change radically management of the pregnancy, MRIs should be considered in selected fetuses with CNS anomalies suspected on ultrasound.

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RARE RENAL ANOMALIES DESCRIBED IN SECOND TRIMESTER FOETUSES USING POST MORTEM MRI CASE SERIES


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Abstract

The current study describes the renal anomalies of three second trimester fetuses using post-mortem Magnetic Resonance Imaging (pm-MRI). The results were compared with the conventional autopsy. This study demonstrates that without altering the integrity of the human body the pm-MRI using a 7 Tesla machine is a reliable option in describing congenital renal anomalies. Also it reinforces the idea that post mortem imagistic procedures may provide an important adjuvant to conventional autopsy in small gestational age fetuses.

INTRODUCTION

Urinary tract abnormalities are accountable for approximately half of the structural abnormalities detected in utero (1). Early recognising of this pathology plays an important role in establishing the proper therapeutic management, and can influence the long term prognosis of these patients. Prenatal findings are commonly confirmed by conventional post mortem examination but, in the last decades an increasing interest has been noted
for the non invasive approach using post mortem MRI (pm-MRI) (2), especially as an alternative offered for the parents who do not agree to standard procedure.

While foetal nervous and cardiac pathology is extensively study using pm-MRI, there is less information about how well intra-abdominal abnormalities can be detected and characterised at early gestational ages using non invasive imagistic methods (3).

In the present study, we explore whether pm-MRI using a magnetic resonance imaging machine of 7T magnetic field may provide reliable information for the diagnostic of renal anomalies in second trimester foetuses comparing with conventional autopsy.

**MATERIALS AND METHODS**

We examined using pm-MRI two foetuses age 16 respectively 17 weeks of gestation and one pair of kidneys from an 18 weeks of gestation foetus. The foetuses were referred to termination of pregnancy for chromosomal or severe abnormalities diagnosed by detailed prenatal imaging in our prenatal diagnosis department. The therapeutic abortion was induced using prostaglandin, after the committee decision that the foetus is over the therapeutic resources.

The examinations were performed on a 7 Tesla machine (Bruker Biospec), belonging to the National Centre for Magnetic Resonance of Cluj – Napoca.

Each embryo was placed in dorsal position, head first and scanned after a 24-hour setting in formaldehyde solution.

First foetus was scanned using a 35 slice 2D TurboRare-High Res sequence with a field of view of 4.33 cm, in coronal orientation, 0.75 mm slice thickness and a 384 x 384 matrix that offer a resolution of 0.0146 cm/pixel, the repetition time of 6883.6 ms and the echo time to 12 ms.

In the third case, we analyzed the kidneys ex vivo acquiring 59 axial slices using a 2D TurboRare-high Res sequence, with a field of view of 4.33 cm, with 0.75 mm slice thickness and a 384 x 384 matrix, offering a resolution of 0.0113 cm / pixel, repetition time of 7002.3 ms and the echo time to 12 ms.

The images obtained were interpreted by a radiologist and the autopsy was conducted by a paediatric pathologist, after being informed about the radiological report.

The results were compared with the conventional autopsy. The study protocol was approved by the local Ethics Committee and written informed consent was obtained before the procedures.

**RESULTS**

First case analysed was a foetus diagnosed at 16 weeks of gestations with Trisomy 18.

The pm-MRI examination of the foetal abdomen revealed a complex renal malformation with a bilateral duplex collecting system and a fusion anomaly of the inferior renal poles – horseshoe kidney. All four collecting systems were dilated, probably secondary to uretero-pelvic junction obstruction, as a common complication of horseshoe kidney. There were no dilated urethers and no bladder distension. The renal parenchyma showed polycystic dysplasia and no cortico-medullary differentiation.

The pathological exam confirmed the fusion of the kidneys at the lower poles, the existing bilateral duplex collecting system and undifferentiated tubular structures surrounded by primitive mesenchyme consistent with multicystic dysplasia (Figure 1).

The second foetus was detected at 17 weeks of gestation with hydrocephaly.

The pm-MRI examination revealed a complex cerebral anomaly with marked enlargement of the lateral ventricles and 3rd ventricle with floor displaced downward into the interpeduncular cistern, secondary to aqueduct stenosis.

At the level of the foetal abdomen, both ureters presented in the proximal portion a tortuous,
corkscrew-like course. Furthermore was noted bilateral slightly dilated renal pelvis (Figure 2).

The findings were confirmed by the foetal necropsy.

The third patient was referred to in vivo MRI for severe oligoamnios and diagnosed with renal malformations at the prenatal ultrasound at 18 weeks of gestation.

The in vivo foetal MRI identified a plurimalformed foetus with enlarged micropolycystic kidneys, with cysts up to 3.8 mm diameter. The investigation of the foetal abdomen revealed liver fibrosis and dilatation of the intrahepatic biliary ducts, splenic fibrosis and pancreatic cysts and ascites.

Also the foetus presented hypoplastic lungs, curved short and long bones and associated cervical occult spina bifida and occipital cervical oedema.

The post mortem examination of the kidneys completed the in vivo MRI investigation, depicting a micropolycystic sponge-like parenchyma and collapsed renal sinus and collecting system.

The pathological examination confirmed all the imaging findings (Figure 3).

The information obtained from both examinations was consistent with a Potter type 1 sequence. Therefore genetic testing was offered to the patient, in order to detect a mutation in the PKHD1 gene.

DISCUSSIONS

The constant development of ultrasonography and magnetic resonance imaging has consequently determined an increased incidence of...
prenatally detected congenital anomalies of the kidney and the urinary tract.

This vast category of anomalies includes: kidney abnormalities such as kidney aplasia, multicystic dysplastic kidney, hypoplastic kidney, ureteropelvic abnormalities such as ureteropelvic junction obstruction, or megaureter, duplex collecting system, ectopic ureteral orifice, ureterovesical junction obstruction or incompetence and anomalies of the bladder and urethra (4).

Up to present the description of these abnormalities was the prerogative of the pathological examination.

Still, considering the small sizes of second trimester foetuses, the manipulation and dissection is extremely difficult thus requiring high experienced pathologists and appropriate equipment.

Using high-resolution post-mortem MRI we were able to identify important details regarding the existing renal abnormalities and also provide a guide for the fetal autopsy.

Although the horseshoe kidney identified in the first case, is a common renal fusion anomaly and may be encountered in two-thirds of the patients with Trisomy 18 (5), the association with multicystic dysplasia diseases and a bilateral duplex collecting system is rare and may pose diagnostic challenges, thus requiring autopsy for final confirmation (6).

The excessive spiral twisting of the ureters observed in the second case analyzed is considered normal for the second trimester foetuses, being the consequence of a differential growth rate between the urinary tract and the spine (7).

Although it may have limited clinical importance, in some cases, the tortuous course of the proximal portion of the ureters may explain the dilated aspect of the renal pelvis and can be the cause of obstructive hydrenephrosis (8).

For the third foetus analysed, the imagistic details discovered using in vivo and pm-MRI oriented towards a targeted genetic analysis, thus improving the patient counseling.

Figure 3. A) 3T in vivo MRI, T2, WI depicting micropolycystic kidneys. B) 7T post mortem MRI T2, proving similar appearance and collapsed renal sinus and collecting system (arrow). C) Cut section of the kidneys with a sponge-like renal parenchyma composed of fusiform cysts in the cortex.
In the present study, the images obtained using 7T pm-MRI was comparable with the microscopic panoramic view and additional information was revealed only at magnifications higher than 10 X, using special stains.

Our case series was examined using an experimental 7T MRI machine, and it could be argued that there are limited applications in the clinical setting. However, there are several current clinical studies being performed using ultra-high field MRI on human subjects (9).

Higher magnetic field strengths in MRI are becoming a new strong trend because of a superior signal-to-noise ratio, stronger spectral resolution and susceptibility effects, compared with lower magnetic fields (10).

In our study of foetal renal pathology, using pm-MRI of higher magnetic field we were able to overcome some of the weaknesses of conventional autopsy.

The present research shows an important concordance between conventional autopsy and 7T pm-MRI. The non-invasive technique is a valid method to detect and describe small renal lesions in second trimester foetuses, this aspect being entirely confirmed by the microscopic pathological examination.

The images obtained offered a permanent three-dimensional record and may be useful in future studies or in clinical practice as an important reference for the in vivo MR appearance of the pathology.

Advanced imaging studies may help improve the pathology analysis and prenatal diagnosis facilitating further patient counseling and fetal care.

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ERATĂ

Transabdominal Approach for Chorionic Villus Sampling

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