Abstracts

Fetal Surgery Ural's Scientific School

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INTRODUCTION

Over the past three decades, great progress has been made in our ability to diagnose fetal abnormalities, predict their outcome, and to perform surgical interventions. The concept of the fetus as a patient has become a standard of care and the ethical framework for maternal fetal intervention is well developed.

This is a report on pilot study of 6 years experience in fetal surgery and fetoscopic manipulations performed in Maternity and Child Care Research Institute (Yekaterinburg, Russia). During this period a total of 286 intrauterine blood transfusions in rhesus hemolytic fetuses were successfully performed. Nephro-amniotic shunting was performed in 28 fetuses with severe urinary tract obstruction. All newborn infants, which are alive now, underwent postnatal surgical correction. The technique of fetoscopic laser vascular coagulation was used for the treatment of sacrococcygeal teratoma (six cases). The lethal diaphragmatic hernia was diagnosed in 12 fetuses and fetoscopic balloon tracheal occlusion was performed in six cases with effectiveness of 50%.

About 112 laser coagulations of the vascular placental anastomoses were performed for the treatment of twin–twin transfusion syndrome with effectiveness of 76%. The technical approaches to fetoscopic interventions and treatment of spina bifida were developed in six experiments on fetal lambs.

In its formative years, fetal surgery has been considered as experimental or innovative therapy. However, fetal surgery, as all medical and surgical therapy, needs to be validated by outcome-based research, which is an objective of future research development.

Fetal Breathing Movements as Indicator of Its Status in Physiological and Abnormal Pregnancy

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INTRODUCTION

Fetal breathing movements (FBM) have great physiological importance, stimulating lung growth and structural development during antenatal life. Fetal breathing movement promotes blood circulation's improvement, rising arterial tension, festinating pulse, and increasing umbilical blood flow's speed. Physiological meaning of FBM may be in respiratory system's preparation for future respiratory function's execution.

Ventilation in newborn's lungs starts being possibly after 26th gestation week. It is caused by formation of primitive acini, intense blood vessel development, and capillary ingrowth in pulmonary parenchyma, epithelial cell differentiation to 1st and 2nd pneumocystis' types, surfactant and fetal pulmonary liquid emergence, respiratory rate generation mechanism's start, and breathing formation patterns' formation on 26th week.

During 27 to 40 weeks' gestation period, 100% of gravidas with physiological pregnancy were registered with normal FBM. Normal FBM is characterized with 45 to 60 bpm frequency, 1.0 to 1.3 breathing cycle length, and amplitude less than 5 mm.

Hypertensive disorder during pregnancy is one of the main reasons of maternal and perinatal diseases and death. Long-term current and severe forms of hypertensive disorders during pregnancy adversely affect the fetoplacental complex and fetal status.

Gravidas with gestational (pregnancy-induced) hypertension without significant proteinuria (O13) had normal FBM in 85% of cases. Rapid FBM with normal and high amplitude (61–85 bpm rate; 5 mm and higher) were registered in 15% of cases.

Normal and pathological breathing types in moderate preeclampsia (O14.0) are equally frequent:

- Normal FBM (50%);
- Prolonged FBM with normal and low amplitude (15%), 26 to 40 bpm rate, breathing cycle duration 1.5 to 2.3 s, and amplitude <3 and 3 to 5 mm;
- Double-protracted (12%)—breathing double-inhale time dysrhythmia type, 35 to 43 bpm rate; breathing cycle duration 1.4 to 1.7 s, and normal amplitude 3 to 5 mm;
- Rapid FBM (8%);
- Gasping FBM (7%) with 4 to 8 bpm rate, breathing cycle duration 0.2 to 0.5 s, and amplitude <3 mm;
- Gasping with normal FBM (5%)—8 to 50 bpm rate, breathing cycle duration 1.5 to 2.4 s;
- Fetal respiratory activity absence (3%).

Only pathological FBM types diagnosed in severe preeclampsia (O14.1):

- Normal with gasping (40%);
- Prolonged with normal and high amplitude (30%);
- Gasping type FBM (20%);
- FBM absence (10%).

So, during antenatal period subsequent peculiarities were examined:

- Physiological pregnancy—normal FBM (100%);
- Gestational (pregnancy-induced) hypertension without significant proteinuria (O13)—normal FBM (85%).
- Moderate preeclampsia (O14.0)—normal FBM 50%;
- Severe preeclampsia (O14.1)—absence of normal FBM.

The study of FBM is a promising direction of assessing the condition of the fetus and its functions. Further research will be continued.

New Challenges and Controversies in Noninvasive Prenatal Testing/Screening in the United States

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INTRODUCTION

The past few years have been characterized by an influx of options for both screening and testing for genetic conditions of the fetus. Some of these options, such as microarray analysis after invasive testing, are designed to provide information about more conditions than were previously available. Other options, such as use of cell-free (cf) deoxyribonucleic acid (DNA), are designed to provide more accurate information than was available with earlier noninvasive screening tests. The terminology around the new noninvasive screening modalities frequently referred to as noninvasive prenatal testing and not noninvasive prenatal screening has led to confusion among both doctors and patients about what these tests offer. Screening tests for aneuploidy were designed to provide information for the common relevant autosomal trisomies: Specifically trisomy 21, 18, and 13. However, they are not diagnostic. Nonetheless, because of the high sensitivity and specificity of cfDNA screening, results have been interpreted as diagnostic, leading to pregnancy termination in the absence of confirmatory cytogenetic testing. Although cfDNA offers the most accurate results for common autosomal trisomies, it is also the test that identifies the narrowest range of disorders. The first trimester risk assessment with nuchal translucency and biomarkers has a lower sensitivity and specificity for trisomies; however, the ultrasound and biomarkers can identify fetuses at risk for other adverse outcomes, such as cardiac malformations. All options for noninvasive screening for aneuploidy are limited by the number of disorders for which they can provide information. Patients and doctors are reassured by negative results of screening tests. However, most clinically actionable genetic conditions can only be identified through invasive testing, not screening. Our ability to diagnose a wide variety of genetic conditions has advanced more rapidly than the strategies for counseling needed to ensure that our patients make decisions consistent with their values and goals.

Fetal Conditions associated with Maternal Diabetes

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INTRODUCTION

The global prevalence of diabetes mellitus (DM) is 6.4%, and varies regionally from 3.8% in Africa to 10.2% in the Western Pacific. The incidence of diabetes in pregnancy, however, varies with the geographical and ethnic background of women. About 3 to 5% of pregnancies are reported to be complicated by DM.

Despite steadily falling perinatal mortality rates fetal and neonatal mortality remains threefold or fourfold higher for mothers with type I or type II diabetes than for all normoglycemic population.

Diabetes during pregnancy has well-documented teratogenic effects and significantly increases the risk for major birth defects. The risk is increased threefold to eightfold compared with the 1 to 2% risk for the general population. Fetal congenital malformations are most common when maternal glucose control has been poor during the first trimester of pregnancy. Diabetic embryopathy can affect many organ systems but the most common malformations affect the heart or the neural tube. Congenital malformations of the heart or the neural tube are up to 10-fold more frequent with preexisting type I and type II DM. Fetal macrosomia, intrauterine growth restriction, risk for birth injury, neonatal hypertrophic and congestive cardiomyopathy, polycythemia, and hyperviscosity are very important conditions associated with DM in pregnancy. Holoprosencephaly and caudal regression syndrome are very rare conditions. Glycemic control during embryogenesis is the main factor in the genesis of diabetes-associated birth defects.

Exposure to this intrauterine diabetic environment has been shown to cause alterations in fetal growth patterns, which predispose these infants to developing overweight and obesity later in life.

Over the last two to three decades, the focus on this field of research has shifted from morphological and molecular characterization of the etiology of maternal diabetes-induced malformation to understanding the mechanisms behind how maternal diabetes alters fetal development. Finding suggests the possibility that maternal diabetes affects the epigenome of the developing embryo. While epigenetic mechanisms have been proposed to modify the expression of critical genes involved in development, the exact mechanism behind this still remains largely unidentified. The frequency of fetal malformations in diabetic pregnancy has been reported to be markedly reduced by dietary supplements of antioxidants, such as vitamin E, vitamin C, and butylated hydroxytoluene, suggesting that oxidative stress is involved in the etiology of fetal dysmorphogenesis. In the future, it will be interesting to elucidate how epigenetic mechanisms, such as deoxyribonucleic acid methylation, chromatin/histone modifications, and microribonucleic acids are activated in embryonic tissue by maternal diabetes.

Interhemispheric Supratentorial Cysts

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INTRODUCTION

Interhemispheric supratentorial cysts may be located from the anterior to the posterior aspect of the brain in three regions:

1. The area of the anterior complex: cavum septi pellucidi, frontal horns of the lateral ventricles, genu of the corpus callosum
2. The intermediate zone: thalami and third ventricle
3. The area of the posterior complex: arachnoidal space delimited by the parieto-occipital sulci and the splenium of the corpus callosum

AREA OF THE ANTERIOR COMPLEX

Dilatation of the cavum septi pellucidi and the posterior cavum vergae is a normal variant without any clinical consequence. In this case, the axial view of the brain shows a rectangular cystic structure located between the normally separated frontal horns. The sagittal view shows the C-shaped cystic structure located below a normal corpus callosum.

A midline cystic lesion may also be seen in case of agenesis of septum pellucidum (ASP). In this case the coronal section on the anterior complex shows the communication between the frontal horns secondary to the absence of the septum pellucidum. The midsagittal view shows a normal corpus callosum.

Isolated ASP is asymptomatic; however, 18% of the fetuses with ASP are affected by septo-optic dysplasia (SOD), complicated by visual impairment/blindness, hypothalamic-pituitary insufficiency (retarded growth, diabetes insipidum), seizures, and motorial handicap in case of SOD/plus schizencephaly.

The differential diagnosis between ASP and SOD may rely on growth hormone and adrenocorticotrophic hormone assays on the fetal blood or magnetic resonance imaging visualization of the optic chiasma in the third trimester; however, abnormal hormonal assays and chiasma hypoplasia may develop late in pregnancy or even after delivery.

Agenesis of septum pellucidum/SOD should be differentiated from lobar holoprosencephaly (HPE). In coronal section on the anterior complex ASP/SOD is characterized by the presence of the corpus callosum above the fused frontal horns and lobar HPE by the absence of the corpus callosum on the fused frontal horns, which have a typical squared shape.

INTERMEDIATE ZONE

A cystic structure in the intermediate zone may be due to dilatation of the third ventricle in case of aqueductal stenosis. In this case, both lateral ventricles are severely dilated and a normal corpus callosum may be seen.

In some cases of agenesis of the corpus callosum, the third ventricle may be dilated and protrudes upward as an interhemispheric cyst. The differential diagnosis with aqueductal stenosis is based on the absence of the corpus callosum above the dilated third ventricle and protrusion of the cyst between the two "bull's head"-shaped frontal horns in the coronal view of the anterior complex.

AREA OF THE POSTERIOR COMPLEX

Interhemispheric cysts located in the area of the posterior complex may originate from different regions, which can be recognized by the midsagittal section:

- Velum interpositum cyst is located below the splenium of the corpus callosum
- Quadrigeminal cyst is located posterior to the thalami in the area of the lamina quadrigemina
- Suprasellar cyst is located between the clivus and the brainstem

Arachnoid cysts have thin walls, do not communicate with the ventricular cavities, may cause compression but not disruption of the cerebral tissues, may cause ventriculomegaly independently from the cyst size.

In most cases neurological outcome is normal. Obstructed cerebrospinal fluid flow, visual impairment, endocrine disturbances in relation to location, and size of the cyst may occur. Surgery is rarely needed.

The Effect of Application of Effective Perinatal Care Program

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INTRODUCTION

"Parenthood bring with it the strong desire to see our children grow up happily and in good health. This is one of few constant points in life in all parts of the World"

(WHO General Director, Dr Lee Jong-Wook, April 2005)

However, in the world today, every minute one woman dies due to pregnancy-related complications.

Millions suffer from disabilities as the result of pregnancy-related complications.

Effective perinatal care (EPC) training package becomes an important issue in new strategies of education in perinatal care.

It is impossible to accept high number of maternal mortality because

- Evidence-based data demonstrate that 80% of all deaths happen due to four main obstetrical reasons and can be prevented with the help of simple, effective, and low-cost interventions. Also, It is impossible to accept high numbers of neonatal mortality because
- Many cases of infant and neonatal mortality can be prevented by known, available, and low-cost technologies if they are accessible to all.

Each woman has the right to receive proper perinatal care.

In health services for mother and baby's well-being EPC training package is focused on bringing fast new approach with low-cost technologies into clinical practice assuring mothers' and baby's safety.

Recommended evidence-based technologies:

- Companion delivery
- Early breastfeeding and rooming in
- Free visit in postpartum

Not recommended practices:

- Delivery in lithotomy position
- Routine episiotomy
- Prohibition of eating and drinking in delivery

Studies reported that women still have negative experiences of birth in public healthcare facilities in many countries of Eastern and Central Europe. Such healthcare facilities still widely use outdated nonevidence-based technologies in obstetrics and neonatology.

Care for pregnancy and childbirths calls for a holistic approach. Pregnancy and childbirth is an important personal, familial, and social experience. In pregnancy and childbirth, there should be a valid reason to interfere with the natural process. Care should be based on scientific evidence and be cost-effective. Perinatal care should be attended by well-trained health professionals. To make EPC training in healthcare professions a reality, education and training system should make a strong effort toward really open, flexible, and transparent education.

Comparative Prospective Observational Study of Ultrasound Diagnostic Efficacy in Neonates with Bronchopulmonary Dysplasia

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INTRODUCTION

Lung ultrasound (LUS) has become an important and highly effective method of diagnostic examination and monitoring of a range of pathologic pulmonary conditions recently (around 20 years). The main advantages of LUS are avoidance of radiation, bedside diagnosis, simplicity of interpretation, and cost-effectiveness. Multiple studies have shown LUS to be even more accurate than chest radiography in the diagnosis of pneumonia, atelectasis, pneumothorax (Ptx), interstitial lung diseases, pulmonary edema, and pulmonary effusion. In our study, we evaluate the accuracy of lung ultrasonography in the diagnosis of the most common neonatal respiratory diseases.

It was a prospective, single-center, observational study conducted at the Morozovskaya Children's Clinical Hospital (Moscow, Russia). About 76 neonates underwent LUS and chest radiography 2 to 11 times during their treatment in the neonatal intensive care unit. In 28 days of life they were divided into two groups: group I—infants with bronchopulmonary dysplasia (BPD) (n = 55) and group II—infants without BPD (n = 21). The mean gestation age of the patients was 27 (26–28) weeks in group I vs 35 (29–39) weeks in group II (p < 0.001), mean body weight 930 (780–1150) vs 1880 (1320–3550) gm, respectively (p < 0.001). Lung ultrasound was made by linear 6 to 15 MHz transducer via Loqic S8 ultrasound machine. Anterior, lateral, and posterior areas of the chest were scanned.

Subpleural lung consolidation of different volume is one of the main LUS symptoms of pulmonary pathology in neonates. Lung consolidation was registered in 68 patients: in 55 patients with BPD (100%) and in 13 patients (62%) without BPD. Lobar pneumonia with massive area of consolidation was registered in 36 (65%) patients with BPD *vs* 3 (14%) patients without BPD ($p < 0.001$), segmental pneumonia in 18 (33%) *vs* 2 (9.5%) patients, small focal areas of consolidation, which were interpreted as cortical pneumonia, in 9 (16%) *vs* 8 (38%) ($p = 0.04$). Several types of consolidation in one patient were registered only in patients with BPD—9 (16%) *vs* 0, respectively ($p = 0.048$).

Atelectasis was diagnosed in 24 patients, 6 of them had recurrent episodes of atelectasis. We detected static air bronchograms in 40% of patients with atelectasis, absence of air bronchograms in 60%. Lung ultrasound was more accurate in revealing atelectasis in comparison with chest X-ray. In 6 cases out of 24, the area of atelectasis was localized in lower lobe and was not determined on X-ray but was easily visualized by LUS.

Pulmonary interstitial emphysema has characteristic ultrasound pattern of small hyperechogenic foci and was detected in 15 patients with BPD, in 8 of them foci of emphysema were revealed also via computed tomography.

Seven patients had Ptx, two patients had tension Ptx, and three neonates had nontension Ptx. In all seven cases, the lung point was visualized. In nontension Ptx of minimal volume (three cases) lung point was located in anterior subdiaphragmatic area at the level of midclavicular line, in larger nontension Ptx (two cases) lung point was located at the level of anterior axillary line. In tension Ptx (two cases) lung point was located at the level of scapular line. A-lines and absence of B-lines and lung sliding were detected in all cases.

Thus, LUS is a feasible diagnostic tool in detection of pulmonary consolidation, atelectasis, interstitial pulmonary edema, and Ptx in neonates. Randomized controlled trials involving nonqualified operators (neonatologists) are required to implement LUS into routine clinical practice.

Uterine Fibroids, Ultrasound Diagnosis, and New Treatment Challenges

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INTRODUCTION

Uterine fibroids (UFs) are the most common benign gynecologic tumor in women of reproductive age. Uterine fibroids may cause bleeding, pain, distortion of uterine cavity, impairment of muscle contractility, and infertility. Whether fibroids cause symptoms or require treatment depends on their location, size, and number. It is difficult to determine the direct impact of UFs on fertility, since their incidence increases with age and fertility declines with age. Ultrasound (US) has been shown to be an important diagnostic tool for UFs. Within the last 10 years treatment of UFs has changed by new techniques, such as focused US, embolization, and more in addition to classical endoscopic and open surgery. For long time one tries to use various drugs for medical treatment, but with a lot of side effects and the problem of short time effect. Now since some years the innovative treatment with ulipristal acetate (UPA), a “selective progesterone receptor modulator” is available. The results of the studies PEARL (I–IV), and our modest experience shows a fast reduction of UFs volume and complains of the patients, and this without severe side effects. In opposite to the traditional medical treatment, the effect is sustained continuously.

MATERIALS AND METHODS

About 47 adult patients who presented at our clinic with symptomatic UFs were included in the trial. Ultrasound evaluation was done for each patient for evaluation of number, size, and location of fibroids. They were divided into two groups: the first group had 23 women in reproductive age, followed for bleeding, abdominal pain, or infertility and they all desired a pregnancy in the future. In the second group, we treated 24 perimenopausal women with symptomatic UFs. All patients, in both groups, were treated with UPA, 5 mg per day, for 3 months. We followed up patients for 6 to 12 months for size of UFs, hemorrhage, pain, hemoglobin levels, as well as the quality of life. For the first group, we also followed up pregnancy outcomes.

RESULTS

Ultrasound shows to be an adequate, rapid, safe, and cost-effective means of evaluating the size, number, and location of UFs. In patients treated with UPA, we found a quick time to control bleeding (6–7 days), and 93% of patients show amenorrhea or spotting. We found a volume reduction of UFs about 27 in 82% of patients and a sustained effect for more than 6 months. We found also a fast reduction of pain. There was a low rate of nonresponders (1% without control of bleeding or reduction of myoma). Ulipristal acetate does not induce menopausal symptoms. We found no decrease of estradiol serum levels. Side effects (headache, hot flashes) were very low (about 1.3% of patients). In the first group, 12 (52.2%) patients conceived within 6 to 12 months.

DISCUSSION

Progesterone receptors are located in high numbers in fibroids. Ulipristal acetate is a selective progesterone receptor modulator. Progesterone receptor ligands can possess activity ranging from pure antagonist activity through mixed antagonist/agonist activity to pure agonist activity. Progesterone and estrogen are key growth factors in the pathogenesis of fibroids. Fibroid cells express functional progesterone and estrogen receptor. Values of unbound estrogen receptor and progesterone receptor in fibroid are found to be higher than in myometrium. Estrogen receptor binding was twice and progesterone receptor binding

was three times higher in fibroids compared with myometrium. Ulipristal acetate induces selective apoptosis in myoma cells, but not in the myometrium.

CONCLUSION

Ultrasound shows to be an adequate, rapid, safe, and cost-effective means of evaluating the size, number, and location of UFs. Treatment of fibroids should be individualized, and symptomatology may be a decisive factor in whether or not a fibroid needs to be treated or removed. Ulipristal acetate treatment of UFs resulted in clinically significant reduction of volume of myoma. Most patients had control of bleeding. We found also a continuous improvement of life quality, a rapid return of the regular cycle after the end of the treatment, and low rate of side effects. The treatment is short (3 months) and simple application form (1 tablet daily). Ulipristal acetate can be an alternative treatment of UFs, especially for women, who do prefer nonsurgical procedure. These are patients with bleeding problems, fertility problems, premenopausal women, patients who feel pain by pressure of large UFs, and others.

Fetoscopic Repair of Myelomeningocele

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INTRODUCTION

The publication of the Management of Myelomeningocele Study (MOMS) results in 2011 demonstrated that prenatal repair of spina bifida was superior to the classical postnatal surgery of this defect.

That article and its implications elicited a race toward the best surgical technique for the prenatal repair of spina bifida among several centers all over the world.

The MOMS had used an open approach (hysterotomy to expose the fetal myelomeningocele) for prenatal surgery; therefore, one of the main concerns since then has been to reduce the morbidity and the impact of this approach for the mother. That is why fetoscopy has been progressively implemented, although in a nonstandardized manner, in the hospital where this intervention is available.

Several studies and reviews have compared the outcomes of both open and fetoscopic approaches and the different techniques (patch, glue, skin closure, type of suture), namely in terms of perinatal mortality, operating time, preterm membrane rupture rate, gestational age at birth, postnatal reoperation and shunt rates, and uterine dehiscence.

There is lack of information regarding this topic, since no clinical trial comparing both approaches has yet been accomplished. Long-term functional data will also cast some light on this subject when available. Until then, the controversy is served.

Diagnosis and Management of Cesarean Scar Ectopic Pregnancy

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INTRODUCTION

Cesarean scar ectopic pregnancy is one of the rarest forms of ectopic pregnancy. The incidence has been estimated to be from 1:1800 to 1:2200. In the last decade, the number of reported cases has increased significantly. This could be explained by a better awareness of the condition and widespread use of ultrasound scanning in early pregnancy. With increasing numbers of cesarean sections it is also possible that there is a true rise in the prevalence of scar implantations. With transvaginal ultrasound, it is today possible to diagnose this condition early in the course of pregnancy and timely intervention can prevent serious late complications.

Several complications are related to cesarean scar ectopic pregnancy. The most serious for the women's health occurs as a consequence of abnormal placentation. The pregnancy usually implants in the myometrial defect at the site of the poorly healed cesarean section scar and this is often complicated by myometrial invasion of the placenta. Approximately 30% of clinically diagnosed pregnancies miscarry during the first or second trimester. If pregnancy progresses to third trimester, abnormally adherent placenta can lead to life-threatening hemorrhage, often requiring life-saving hysterectomy.

There is no universal consensus on the best approach to cesarean scar ectopic pregnancy management. Various approaches can be used, surgical or medical. Surgical evacuation of pregnancy can be performed transcervically or transabdominally. Transabdominal approach can be done by laparotomy or laparoscopy. Transcervical evacuation usually involves suction curettage or hysteroscopic resection. Medical treatment with methotrexate is also popular due to concerns about the risk of heavy bleeding during surgical treatment of ectopic pregnancy. Based on recent data, ultrasound-guided transcervical evacuation by suction curettage, combined with additional hemostatic measures if needed, is an effective method of treatment, associated with a low risk of blood transfusion and hysterectomy.

Ovarian Hyperstimulation Syndrome Complication from the Past

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INTRODUCTION

Efforts to minimize complications of medically assisted reproduction have become an increasingly important part of reproductive medicine in the last decade. Today, ovarian hyperstimulation syndrome (OHSS) is the main potentially life-threatening complication of ovarian stimulation. In recent years, gonadotropin-releasing hormone (GnRH) antagonist protocols have replaced GnRH agonist protocols as the most commonly used approach to controlled ovarian stimulation (COS). This is especially important when dealing with patients likely to experience a high response to COS as this approach has been associated with significant reduction in OHSS occurrence. But GnRH antagonist protocols also allow for implementation of additional measures, most notably the replacement of human chorionic gonadotropin with GnRH agonist to induce final oocyte maturation. Multiple studies have shown that the success of oocyte retrieval is comparable with using human chorionic gonadotropin in terms of oocyte number and maturation rate. However, significant luteolysis after agonist triggering is associated with luteal phase defect and elective embryo cryopreservation with embryo replacement in subsequent menstrual cycles can be used. The introduction of vitrification method for embryo cryopreservation has also significantly increased embryo post-thawing survival rates. We have performed a study evaluating this approach in 123 high-responding patients. Using the Kaplan–Meier survival analysis, a total of 65.9% (95% confidence interval (CI) 57.5–74.3) women achieved a live birth after a maximum of six embryo transfer cycles using the “conservative” approach. Applying the “optimistic” approach, presuming that women who still had cryopreserved embryos and did not return for embryo replacement had the same chance of achieving a live birth as those returning for replacement, the cumulative live birth rate estimated in six embryo transfer cycles was 76.6% (95% CI 69.1–84.1). There were no cases of severe OHSS recorded. Hence, high-responding patients can be reassured that a high proportion will achieve a live birth after only one cycle of ovarian stimulation if freeze-all policy is applied. This approach also virtually eliminates the risk of developing OHSS.

Ultrasound and Implantation

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INTRODUCTION

In recent years, the prediction and prevention, early detection, and treatment of health disorders of the fetus focus on the first trimester. Is this enough? If we analyze the period behind us, the progress has been made in the field of detection of multiple pregnancies, dating of pregnancy, and prenatal detection of chromosomal and structural fetal disorders, as well as a small progress in terms of prevention of preeclampsia. If these disorders are the consequence of the disturbed or dysfunctional placentation, then their roots go up to the time of implantation. This means that the changes that lead to the insufficient implantation should be sought in the preimplantation period, in relation between the embryo and endometrium. The diagnosis and interventions should be focused on the preconception and peri-implantation periods. The therapy should be on the subcellular and genetic levels by applying the latest biotechnological procedures. It is possible that the time is approaching when the listed disorders of pregnancy would be the indication for the application of a natural *in vitro* fertilization (without ovarian stimulation) with the use of new biotechnological achievements.

Hemolytic Disease of Fetus Management

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INTRODUCTION

Edema, anemia, and jaundice in a newborn were described as one disease for the first time in 1932 by Diamond LK. It was proved at the end of the twentieth century that moderate and severe fetal anemia lead to increased peak systolic velocity of blood flow in the fetal middle cerebral artery, which allowed monitoring of the fetal status by Doppler ultrasonography.

MATERIALS AND METHODS

The study included 477 examined pregnant women. All pregnant women were divided into groups according to the applied algorithm (before and after the introduction of measurement of peak systolic velocity of blood flow in the fetal middle cerebral artery) and the need for intrauterine transfusions. Four groups were formed: the first two groups of pregnant women who did

not undergo intrauterine transfusions and two more groups of pregnant women who had undergone intrauterine intravascular blood transfusions. We used nomograms established by G Mari. In the event that the peak systolic velocity of blood flow in the fetal middle cerebral artery was correlated to the median level, repeated measurements were made in a week, with an increase blood flow velocity up to 1.2 MoM—one examination in 7 to 10 days, at the level of blood flow velocity up to 1.2 to 1.4 MoM—one examination in 2 to 7 days. If the blood flow velocity was 1.5 MoM, cordocentesis was performed after 1 or 2 days of monitoring. Fetal hemoglobin 90 gm/L or less and a hematocrit 30% or less demand intrauterine transfusions. Decision about next transfusion was made based on the average rate of hematocrit falling by 1 to 2% per day and the blood flow velocity in the fetal middle cerebral artery. Transfusion ended when the hematocrit was increased near 48 to 55% and 40 to 45% in the case of fetal hydrops (or less depending on the fetal condition, heart rate). The last transfusion was made near to gestational age of 35 weeks.

RESULTS

The introduction of measurement of peak systolic velocity resulted in a significant reduction in the rate of invasive procedures associated with the diagnosis of fetal anemia (76 from 164 *vs* 15 from 252; Fisher's test <0.0001). There were 217 intrauterine transfusions to 61 pregnant women (fetal anemia 50, fetal hydrops 11). There were four fetal losses (two hydrops and two with anemia). Newborns who had got four or more intrauterine transfusions did not require an exchange blood transfusion. Obstetric management includes a delivery during from 2 to 3 weeks after last transfusion, so that the fetal hemoglobin remained on safe level. Transfusion up to 35 weeks allow to get term delivery without changing the standard obstetric care. We did not use plasmapheresis for the treatment of hemolytic disease.

CONCLUSION

- Measurement of the peak systolic velocity blood flow in the fetal middle cerebral artery is a noninvasive and well-reproducible test for the detection of fetal anemia.
 - The introduction of this method has reduced the rate of invasive procedures in pregnant women with alloimmunization and immune hemolytic anemia.
 - Fetal intravascular transfusion near to 35 weeks allows to get term delivery.
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Screening in Twins: How Far can We Go?

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INTRODUCTION

First or second trimester screening in twin pregnancies is feasible and still efficacious, either by using the combination of ultrasound and maternal serum biochemistry in the first trimester (80% detection rate) or maternal serum biochemistry in the second trimester (50–55% detection rate) or by noninvasive prenatal testing (NIPT).

Chorionicity should always be taken into account for the calculation of risks. Until more data are available from larger studies on the distribution of markers in concordant or discordant twins, nuchal translucency (NT), nasal bones, and ductus venosus blood flow evaluation estimated for each fetuses should be the predominant factor by which women presenting with increased risk should be counseled regarding invasive testing. In dizygotic pregnancies, pregnancy-specific risk should be calculated by summing the individual risk estimates for each fetus. In monozygotic twins, the risk should be calculated based on the geometric mean of both NT measurements, not forgetting that the false-positive rate of NT screening is expectantly higher than in singletons. Nevertheless, the calculated detection rates modeled using this method are still 10% lower than in singleton pregnancies.

More recently, the introduction of NIPT in clinical practice demonstrated the possibility of detection of fetal trisomies and the Y chromosome in twin pregnancies. The detection rate for trisomy 21 in twins appears to be in line with that of singletons. The limited number of affected cases for other trisomies precluded the conclusive determination of those detection rates. In summary, massively parallel next-generation whole-genome sequencing of cell-free deoxyribonucleic acid from maternal plasma performs well in twin pregnancies, with overall very low false-positive frequencies.

Advantages of Noninvasive Prenatal Screening

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INTRODUCTION

During the past few years, an increasing tendency to favor noninvasive tests for the detection of chromosomal defects in the first trimester could be observed. A qualified first-trimester screening (nuchal translucency, pregnancy-associated plasma protein-A,

free beta-human chorionic gonadotropin, and the additional markers nasal bone, ductus venosus, and tricuspid flow pattern) allows the detection of the most frequent chromosomal anomalies (trisomy 21, 18, and 13) in more than 90% of the examined cases. Furthermore, first-trimester screening with a detailed ultrasound examination not only allows an early detection of the most frequent chromosomal anomalies but also provides evidence of fetal cardiac anomalies or other structural defects or genetic syndromes.

The introduction of noninvasive prenatal testing, i.e., the analysis of cell-free fetal deoxyribonucleic acid from the maternal blood to diagnose fetal chromosomal abnormalities, has resulted in a further rapid change in prenatal screening around the world and in a further significant reduction in invasive procedures with a high detection rate for the most common chromosomal abnormalities: trisomy 21: 99.3 to 99.4%, trisomy 18: 97.4 to 97.7%, trisomy 13: 90.6 to 97.4%, monosomy X: 90.3 to 92.9%, other anomalies of the sex chromosomes (without monosomy X): 93.0% and also some individual deletions, such as DiGeorge or Prader-Willi syndrome.

Noninvasive screening tests have the advantage that also younger pregnant women <35 years of age and women who have undergone successful *in vitro* fertilization may have a risk calculation and may decide against invasive diagnostic procedures in the case of a low risk profile, in order to keep the risk of an abortion as low as possible.

Nevertheless, it should be stressed that chromosomal abnormalities account for only approximately 8.5% of the total spectrum of all fetal anomalies. The large majority of abnormalities are structural defects, which can only be detected by a qualified ultrasound examination in the first trimester.¹ This includes severe cerebrospinal fluid and facial malformations, spinal defects, thoracic, cardiac, and abdominal defects, severe urogenital defects, extremity defects, and twin deformities. Therefore, ultrasound plays the most important role in any early noninvasive fetal screening program.

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Late Selective Reduction and Single Fetal Death in Multiple Pregnancies

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INTRODUCTION

The rate of single fetal death (sFD) in multiple pregnancies varies between 3.7 and 6.8%. The prognosis for the cotwin is highly associated with type of chorionicity. There is no intertwin blood circulation in dichorionic twins. So sFD has not provided any direct influence on cotwin development. In monochorionic pregnancies around 98% of placentas have intertwin vascular anastomoses that connect fetal blood circulations. In monochorionic sFD alive cotwin subsequently could suffer from hypotension, hypoperfusion, and anemia, which cause tissue hypoxia, acidosis, and end organ, especially central nervous system, damage.

The risk for the cotwin at early dichorionic pregnancy sFD was not established. In monochorionic pregnancies, the prognosis for sFD nowadays is not clear. Due to the early formation of the placental vascular anastomoses, sFD could increase the potential risk of negative impact on the subsequent development of the alive fetus. The specific complications of monochorionic pregnancy, such as twin-to-twin transfusion syndrome, selective intrauterine growth restriction, or twin reverse arterial perfusion could provoke sFD. The prognosis for the surviving cotwin is pure because of the high rate of sequential antenatal mortality or severe brain damage. In the case of sFD the surviving cotwin middle cerebral artery maximal systolic blood speed as a marker of fetal anemia should be evaluated by Doppler ultrasound (US). Intrauterine intravenous transfusion of donor red blood cells to the surviving anemic cotwin could be performed. Magnetic resonance imaging and precise fetal brain US examinations are very important for assessment of the prognosis for subsequent development of the surviving cotwin. However, reliable data of the effectiveness of such treatment are currently not available due to the limited number of cases that existed in the literature.

The possibility of late selective feticide is determined by the legislation of the specific country depending on pregnancy age. The methods of selective feticide in congenital abnormalities and inborn defects depend on chorionicity type of multiple pregnancies. If it is legal, the selective feticide in dichorionic multiple pregnancies could be performed at any gestational age by intracardial or intravenous KCl or lidocaine injection. This procedure is not possible in monochorionic twins. The umbilical cord clamping or laser ablation connects with the relatively high rate of pregnancy lost or very preterm birth. Intranatal feticide by lidocaine intravenous injection with combination with fetal pain relief after cesarean delivery of unaffected cotwin could be suggested as alternative care if there are no legal limitations.

Multidisciplinary approach and wide medical and psychological support of the family are essential to provide beneficial outcomes both for mother and for unaffected twin.

Invasive vs Noninvasive Prenatal Diagnosis and Screening

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INTRODUCTION

In the last three decades, prenatal screening programs have developed different analysis, such as maternal age, specific analytes in maternal serum, ultrasound markers, and ultrasonic findings in the first and second trimester with detection rate for aneuploidies between 85 and 95%.

In the meantime, the fetal loss rate due to invasive procedures by chorionic villous sampling (CVS) and amniocentesis has decreased significantly from 1 to 100 to 1 in 600 to 800 and this lower risk of fetal loss, together with the first trimester noninvasive ultrasound and biochemistry screening, has significantly decreased the request for invasive prenatal diagnosis by CVS and amniocentesis for fetal chromosomal anomalies.

Recently, noninvasive prenatal screening (NIPS) using cell-free fetal deoxyribonucleic acid (DNA) in peripheral maternal blood has increased the detection rate for aneuploidies to 90 to 99% with fewer false positives.

The effect of the recent introduction of prenatal screening by cell-free fetal DNA has further decreased the requests for amniocentesis of 60% and of an important 30% increase of CVS, with a significant rise of chromosomopathies diagnosed in the first trimester.

The cell-free fetal DNA or NIPS, although not being a test but a "super screening," is raising more issues regarding prenatal counseling of chromosomopathies with new possibilities for well-off couples and apprehension for those who cannot afford it, seeing the elevated cost of NIPS.

Furthermore, the possibilities for young fellows to be trained in CVS and amniocentesis in prenatal diagnosis centers are getting drastically slimmer and this is why the invasive procedures must be performed and centralized in few specialized centers in order to guarantee an annual minimum of procedures, better manual skills, and less risks of fetal loss.

During the nondirective pretest counseling, the patient should always be informed in detail about the risks of CVS and amnio, about the false positives and negatives and misdiagnosis, about the diagnostic results, and the detection rate of NIPS (99% for trisomy 21, 97% for trisomies 18 and 13, 90% for monosomy X). The pregnant woman should also be informed of the fact that about 10 to 30% of the other chromosomal anomalies are not individualized.

Also, it is advisable to perform NIPS following first-trimester risk assessment by nuchal translucency and biochemical screening, which are fundamental and of paramount importance also because numerous fetal anatomic defects can be identified by ultrasound in the early period of pregnancy.

Patients with abnormal NIPS should receive complete genetic counseling and be given the possibility to have an invasive diagnostic test by CVS or amniocentesis.

Invasive prenatal procedures remain, however, essential, together with the microarray analysis technique, not only for the detection of chromosomopathies but also for the indispensable diagnosis of other genetic, metabolic, and infective congenital pathologies.

In this article, we discuss the advantages and the limits, the success and the failure, and the women's choice of all screening tests and invasive prenatal procedures.

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Ultrasound Evaluation of Lungs in Critically Ill Neonates

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INTRODUCTION

Preterm neonates are the major category of neonatal intensive care unit (NICU) patients. Respiratory disorders are one of the leading causes of neonatal morbidity and mortality among preterm infants. One study revealed that during their stay in the NICU, neonates with extremely low birth weight were subjected to a significant number of X-ray procedures, 32 on average (1–159), and the average ionizing radiation exposure was 1467 μ Gy (28–7790). Patients included in our study were subjected to 21 X-ray procedures on average (1–100). In 2008 Lichtenstein created the BLUE protocol for diagnosing respiratory disorders among adults. We have attempted to use statements of the protocol in diagnosing neonatal lung condition, and ultrasonic detector of 9 to 11 MHz was used in our study. Also five of seven profiles described in BLUE protocol were evaluated in our study: “normal lung,” “pneumothorax,” “interstitial syndrome (pulmonary edema),” “alveolar consolidation,” and “pleural effusion.” Ultrasound (US) investigation was performed in 30 preterm neonates in different days of life. The average birth weight in our group of patients was 1,161 gm (550–3,440 gm), average gestational age (GA) was 28^{5/7} weeks (23^{5/7}–35^{4/7}). Ultrasound scanning was performed in anterior, lateral, and posterior areas of chest if possible.

Normal lung profile (Fig. 1) shows a well-aerated lung, the prevalence of A-lines (parallel to pleural line, pointed with narrow arrows), and pleural sliding sign in real time (wide arrow). This profile was mostly found in neonates with mild or without any respiratory problems. Disappearing of A-lines was associated with respiratory deterioration in 100% of cases and counterclockwise clinical improvements were associated with appearing A-lines on US. Pleural sliding symptom means absence of pneumothorax. Figure 1 was obtained from 1-hour-aged neonate born at 34^{1/7} GA with mild respiratory disorder during the first hour of life.

B+-lines and/or “white lung” (Fig. 2) is a profile of interstitial syndrome (pulmonary edema). In 94% of these findings, neonates were dependent on any kind of respiratory support and in 73.5% of all cases they needed mechanical ventilation. In 53% of all cases when B+-lines or white lung was found on US scans neonates needed additional oxygen supplementation. Figure 2 was obtained from 1-day-old preterm neonate, 26^{4/7} GA. In 17 hours after surfactant administration US scanning revealed A-lines appearing. During scanning pneumothorax is also presented with A-lines pattern but in contrast, the pleural sliding in real time will not be found. Additional diagnostic signs can be found in M-mode: seashore (Fig. 3) symptom due to pleural sliding and bar-code (Fig. 4) symptom in pneumothorax. The alveolar consolidation (Fig. 5) was found in 19 US scans. In 94.7% cases when this profile was found neonates needed respiratory support and in 73.7% cases they needed mechanical ventilation. In 47.4% of all cases, this profile was found when neonates had ongoing pneumonia and in 36.8% of neonates with severe respiratory distress syndrome (100% were treated with surfactant). Figure 5 was obtained from a preterm neonate with left lower lobe atelectasis, aerated bronchioles are pointed with arrows. The last profile is pleural effusion. Due to specific features of NICU patients (mostly supine position) US scanning for pleural effusion should be performed in the back chest area above diaphragm. Measurement of pleural leaf separation may be used for calculation of the fluid amount. Figure 6 demonstrates pleural effusion in preterm neonate with severe heart insufficiency due to severe pulmonary hypertension caused by bronchopulmonary dysplasia (arrows are pointing to pleural leaf separation).

Despite small number of patients included in our study, US scan analysis revealed that five out of seven BLUE protocol profiles can be easily found in preterm neonates. Further studies are necessary to estimate the diagnostic value of each profile, but it is obvious that ultrasonography is a helpful tool in NICU, which can be used as bedside diagnostics of respiratory disorders in preterm neonates and will help to decrease ionizing radiation exposure. All NICU doctors can be taught to perform lung US scanning and evaluate the efficacy of treatment, regardless of skill of an X-ray lab. Besides, according to our calculation US picture can be obtained in 2 minutes 2 seconds from turning US machine on.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Ultrasound of Fetal Abnormalities in Pregnant Women with Cytomegalovirus

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INTRODUCTION

Congenital cytomegalovirus (CMV) infection is the most common cause of congenital viral infection in Georgia and can lead to severe sequelae. The CMV infection is caused by herpes virus family. Infecting primarily the human body, the "sleeping" CMV virus stays for lifetime without any known damage. Nevertheless, activation of CMV is possible under the special conditions. Activation is extremely dangerous, since only when activated, the virus becomes aggressive and has significant damaging capabilities. It is reliably established that CMV is activated with a decrease in immunity caused by unfavorable environmental conditions. Activation of virus is possible also in case of pathological pregnancy or with a decrease in the adaptive and compensatory mechanisms of a pregnant woman in normal pregnancy. Only in the active stage, CMV infects the fetus and the newborn and causes damages. The frequency of infection varies among different population groups and, according to data published over the past 10 years, ranges from 25 to 100%. Identification of intrauterine viral infection, including CMV, is possible in immunological and molecular biology techniques. However, only ultrasound (US) examination is capable to detect most of the structural alteration typical of intrauterine viral infection.

OBJECTIVE

Evaluation of fetal US accuracy for determination of the sequelae in CMV-infected fetuses after maternal primary CMV infection and to identify the possibility of following prenatal therapy.

MATERIALS AND METHODS

Screening US was performed in 1,115 of 2,540 pregnant women in the 2nd and 3rd trimester. Also US was performed in 30 of 73 pregnant patients with CMV identified primarily using biochemical markers.

RESULTS

In 17 of 35 pregnant women (group I) screening US determined the following specific changes in the fetus and placenta: hydrocephaly 1, intrauterine growth restriction (IUGR) 7, calcification of fetal liver, brain, and intestine 4, placenta calcification 3, placental intervillous gap dilatation 7, placental circulation abnormalities 3. Next biochemical verification confirmed persistence of CMV infection in 9 of 21 women. Thirty of 73 pregnant women had biochemically identified CMV (group II); of these, 11 women had mildly inappropriate calcification of fetal organs, placenta, cord, and membranes. In six cases CNS structural damage and in two cases IUGR was determined. Also in two cases different fetal malformation was found out. Doppler investigation detected the fetal-placental circulation abnormalities in 16 cases. The features of screening US examination to detect CMV intrauterine infection were the following:

- Sensitivity: 36.1%
- Specificity: 75.4%
- Prevalence: 51%
- Negative predictive value: 46%
- Positive predictive value: 64%
- Negative likelihood ratio: 0.84
- Positive likelihood ratio: 0.50

CONCLUSION

Ultrasound scanning is capable to detect most of the grave alterations typical of fetal CMV infection. Doppler studies can be used to evaluate the alterations in vascular flow that result from congenital CMV infection. The use of routine US examination as a screening test to detect intrauterine CMV infection has certain limitations and can be applied in combination with further biochemical tests. Combined study increases the specificity and sensitivity of CMV detection and thereby the possibility of prognosis of the disease and the possibility of effective therapy.

Intrauterine Blood Transfusions in Severely Anemic Fetuses: Indications, Complications, and Outcomes

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INTRODUCTION

Unfortunately up to now Rh-alloimmunization is an urgent problem in Russia owing to the absence of the state immunoprophylactic programs. So, in big hospitals some specialized departments were organized to provide medical assistance in this field.

It is known that severe fetal anemia caused by alloimmunization, viral infections, growth restriction, twin-to-twin transfusion syndrome, or twin anemia polycythemia sequence is the most frequent indication for intrauterine blood transfusions. In case of alloimmunization clinically significant forms of the fetal disease can be related not only by anti-D but also by other erythrocyte antigens, e.g., anti-K that causes erythropoiesis depression.

Analysis of indications, complications, and outcomes of 168 intrauterine intravascular transfusions in 61 women with 1:16–1:32768 titer of antierythrocytic antibodies titer in 19 to 35th week of pregnancy was done. In 98.4% of this, patients' immunohematological study revealed anti-D antibodies. Among them, 57.4% had only anti-D and 41% had combined sensitization by another Rhesus antigens (D, C, E) or in four cases, Kell system anti-K. Patients with Kell sensitization had extremely severe fetal anemia, and in three of them hydrops fetalis was observed. Immunoglobulin (Ig)G3 and/or IgG1 was revealed in all women's blood serum. In 92% IgG3 and/or IgG1 antibodies were present in 1:100 high concentration.

In 21% of patients, the first transfusion was carried out for hydrops fetalis; in the rest it was for fetal hyperdynamic type of cerebral blood flow (Mari et al). A method of combined transfusion of donor's washed and filtered 0(I) Rh(–) erythrocytes with 20% albumin solution was used. To immobilize the fetus immediately before the transfusion nondepolarizing neuromuscular blocker pipecuronium bromide (0.1 mg/kg electromagnetic flow meter) was infused into the umbilical vein. About 36% of fetuses before treatment had moderate anemia [hemoglobin (Hb) 0.55–0.64 MoM], the rest had severe anemia (Hb <0.55 MoM). Volume of transfused blood was calculated according to nomogram (Mandelbrot et al).

In our study, the survival rate of fetuses with moderate anemia made up 95.5%, with severe anemia 84.6%. Fetuses with hydrops fetalis have survived in 84.6%. The overall survival rate of fetuses and neonates receiving prenatal treatment made up 88.5%.

Fetal bradycardia was the most frequent complication of the transfusions. In 6% of cases it was connected with transient spasm of umbilical artery, in 27% with the formation of umbilical cord hematoma. It was not possible to reveal the objective cause of bradycardia in the rest of the cases. In 79% bradycardia was of transient character. In 21% bradycardia had persistent character and became the reason for urgent delivery.

In six cases (9.8%) there was antenatal fetal death. Only three of them was directly connected with transfusion and occurred during the nearest 12 hours after its termination: one at 18 weeks with Ht 5% and presence of hydrops fetalis and three have died outside a medical institution in connection with the patients's decision to interrupt severe fetal anemia treatment. Among 55 patients whose pregnancies have ended with live birth, 85.5% had preterm labor.

CONCLUSION

Timely intrauterine intravascular transfusions ensure high survival rate of severe anemic fetuses including hydrops. Close ultrasonomic control allows to decrease the number of transfusion therapy complications, most rare of which is bradycardia.

The Management of Abnormally Invasive Placenta: One Center Experience

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INTRODUCTION

Abnormally invasive placenta (AIP) increases the risk of massive maternal blood loss. Risk factors for AIP have been well researched. Modern diagnostic imaging methods (ultrasound and magnetic) enabled timely diagnosis of AIP and appropriate treatment with the implementation of organ-preserving techniques. The aim of the study is to present retrospective experience with the treatment of the women with AIP in our center.

MATERIALS AND METHODS

Patients with AIP at the Perinatal Center (PC) of the Second Regional Clinical Hospital in Krasnodar (Russia) were retrospectively analyzed for a period of 32 months (January 2014 to August 2016). The rate of women with blood loss more than 1000 mL was 0.94% (n = 227) from 24,078, out of which 17.6% women (n = 40) were diagnosed with AIP. The average age was 31.5 ± 0.8 (20 to 41) years. The number of pregnancies, not including present, was 2.8 ± 2.3 (0–9). Only 1 out of 40 women was primigravida, 10 were with one, 7 with two, 12 with three, 6 with four, 2 with five, and 2 with more than five pregnancies. History of cesarean section (CS) was present in 34 out of 40 women (85%) with the following distribution: one previous CS present in 14, two CS in 12, and three CS in 8 patients. Previous history of artificial abortion was present in 15 out of 40 patients with the range from one to six.

RESULTS

As risk factors for AIP besides previous CS were curettage after artificial abortion in two women due to postabortion inflammatory complications and in two patients after CS and one after spontaneous labor, there was a history of curettage in puerperium due to the subinvolution of the uterus. Uterine scar was present in two women due to surgery other than CS. The interval between previous instrumental delivery and actual pregnancy was between 23 and 60 months. All pregnancies in women diagnosed with AIP were in natural menstrual cycle and natural fertilization. The AIP was first diagnosed in pregnancy at 35.1 ± 0.8 (11–39) weeks of gestation, mostly in the third trimester of pregnancy (in 36 out of 40 women). The diagnosis of AIP based on ultrasound and magnetic resonance imaging (MRI) findings has been confirmed intraoperatively and histologically in 26 (65%) out of 40 patients. Discrepancy between ultrasound and MRI finding was found in 8 (5%) out of 40 patients in whom diagnosis of AIP was made by ultrasound not confirmed by MRI. In 5 (12.5%) patients with positive ultrasound and/or MRI diagnosis of AIP, it was not confirmed either intraoperatively or histologically. So, for ultrasound imaging sensitivity = 100% [95% confidence interval (CI) 89.7–100], specificity = 16.7% (95% CI 0.42–64.1), positive predictive value = 87.2% (95% CI 82.6–90.7), negative predictive value = 100. For MRI sensitivity = 76.5% (95% CI 58.8–89.3), specificity = 16.7% (95% CI 0.42–64.1), positive predictive value = 83.9% (95% CI 77.7–88.6), negative predictive value = 11.1% (95% CI 1.9–45.3). Most of the patients were delivered by CS (34 out of 40–85%) at the gestational age of 37 weeks. Placenta previa was present in 3 (7.5%) out of 40 patients. In 27 (72.9%) women, placenta was located at the uterine scar after CS, in 6 (15%) on the uterine front wall, in 2 (5%) on the left side, and in 3 (7.5%) on the back side of the uterus. Localization of placenta dictated the CS operative approach and localization of hysterotomy. Bottom CS was made in 33 while lower uterine segment horizontal section was performed in 7 patients. The length of abnormally attached placenta measured ultrasonographically was between 20 and 110 mm with average value and standard deviation of 73.8 ± 21.2 mm, while the thickness of myometrium at the site of placental attachment was from 0.3 to 2.0 mm (average 1.2 ± 0.10 mm). In all patients, intervention radiology methods of treatment for local pelvic devascularization were performed. The balloon dilatation of iliac arteries was performed in 34 (85%) patients, while 6 (15%) patients underwent uterine artery embolization. In 29 (72.5%) women reconstruction of uterine wall after resection of the site of the placental attachment was successful. In six (15%) of the women hysterectomy was indicated due to the failure of other treatment options. Blood loss was dependent on the localization of placenta. The most severe blood loss occurred in patients with placenta previa and when placenta was located at the scar after previous CS. In all patients with localization of the placenta, hysterectomy was indicated as the only option of treatment. Blood loss was as follows: in 4 (10%) patients, blood loss was estimated to be less than 500 mL, in 21 (53%) patients it was from 500 to 1000 mL, in 9 (23%) patients from 1000 to 1500 mL, while in 2 patients it was 2000 mL and more. On average, blood loss was 1153 ± 108 mL (400–3500 gm) which was also counted as the blood loss on the body weight of patients from 5.0 to 58.3 mL/kg (average 15.5 ± 1.7 mL/kg). The average level of hemoglobin before delivery in all women was 11.1 ± 0.2 (8.9–13.8) gm/dL, while in 15 out of 40 women, anemia was detected prenatally. After delivery the average level of hemoglobin was 10.0 ± 0.2 (6.3–13.2) gm/dL.

CONCLUSION

Early diagnosis of placental abnormalities, with regionalized approach in perinatal health, makes it possible not only to preserve the women's reproductive health and fertility but also to minimize postpartum hemorrhage.

Fetal Facial Structure and Fetal Brain by Three-Dimensional/Four-Dimensional HDlive Technology and Silhouette

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INTRODUCTION

New fields of neuro-sonoembryology and fetal neurology have been established by remarkable contribution of three-dimensional/four-dimensional (3D/4D) ultrasound technology. Recent evolution in prenatal imaging is HDlive silhouette/flow technology. By HDlive silhouette mode, an inner cystic structure with fluid collection can be depicted through the outer surface structure of the body and it can be appropriately named as "see-through fashion." HDlive flow mode adds more spatial resolution to conventional 3D ultrasound angiogram. We have utilized this technology in neuroimaging and investigated its clinical significance. The equipment used in this study was Voluson® E10 with 6 to 12 MHz/256 element 3D/4D transvaginal transducer (GE Healthcare, Milwaukee, USA).

HDlive silhouette imaging demonstrated clear images of ventricular system with outer fetal surface structure in early pregnancy as well as in the middle gestation. HDlive flow imaging can demonstrate cerebral vascular structure of fine arteries and veins in whole gestation. By HDlive silhouette and flow, inner cystic as well as noncystic structure can be demonstrated with outer surface. HDlive flow imaging can demonstrate fine peripheral brain vasculature. Furthermore, the recent application of studio live imaging, lightning/shadowing by three different light sources is available. By combination of silhouette and studio live, inner structure is clearly demonstrated.

By use of 3D silhouette ultrasound and flow imaging, fetal facial structure, including eye lens and vitreous body as well as brain structure, is well demonstrated in detail.

Ultrasound Evaluation of Tubal Patency

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PURPOSE

The aim of the article is to present technical details and our experience with a new two-dimensional(2D)/three-dimensional(3D) ultrasound (US) technique with contrast media that is used for the evaluation of tubal patency—HyCoSy.

MATERIALS AND METHODS

The evaluation of a tubal status in female infertility is one of the first steps in diagnostic procedures. Before carrying out the procedure, it is essential to exclude acute inflammation of pelvis and male factor infertility. The HyCoSy is performed in the proliferative phase of the menstrual cycle. A 5Fr or 7Fr two-canal balloon catheter is used. The balloon is inflated in the cervical canal. ExEm foam (ExEm gel mixed with purified water)—positive contrast media is used. This is a very viscous media with stable characteristics. The transvaginal 2D/3D 5 to 9 Hz probe is inserted into the vagina. The contrast media is slowly injected into the uterus. A transverse 3D swipe (180st) is performed for both tubes including the uterus. Three-dimensional coded contrast imaging with reduced power is performed, and it enables us to see a positive contrast. The volume is analyzed to reconstruct the uterine cavity and tubal courses on both sides and to reconstruct the spill around both ovaries. B-flow can be added to the contrast media, which enables us to see more clearly the distal parts of the tubes and spilling of the contrast around the ovaries, and this is much better than using the contrast alone.

RESULTS

A report on 245 HyCoSy performed in Medical center Dravlje is presented. In 90% of cases we could evaluate tubal patency with the combination of 2D and 3D US. In 10% we were not sure about the result. In 0.4% of the patients we could not perform the test due to cervical stenosis. In 38 cases we performed laparoscopy with chromohidroperturbation, which is a golden standard for tubal patency. The accuracy of HyCoSy with laparoscopy was 83%; the laparoscopy was performed in unclear situation. About 10% of the women got pregnant 1 year after the procedure. Some side effects were detected in 4.9%; in 0.6% nausea and/or vomiting was detected; in 0.2% vasovagal syncope was discovered, and in 4.1% suspicious of inflammation, antibiotic was given preventively. The average pain score for the whole procedure was 3.4 after visual analog scale. The most painful part of the procedure was the flow of the contrast media throughout the uterus and tubes.

CONCLUSION

Two-dimensional/three-dimensional US HyCoSy screening technique has high feasibility. It is quick, reproducible, and can be easily performed in outpatient settings without any exposure to radiation or laparoscopy. The accuracy of HyCoSy with laparoscopy calculated in our case was low, because laparoscopy was mainly performed in the cases where HyCoSy was not clearly defined.

Obstetrical Management for Fetal Abnormalities: Timing and Mode of Delivery

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INTRODUCTION

A significant improvement in obstetric management of fetal abnormalities results from early prenatal diagnosis. Prenatal identification of congenital anomalies allows providers to organize the delivery mode and the timing of delivery. Obstetrical management depends on the type of congenital malformation, the postnatal surgical intervention options, and the parents' choice.

Several cases of fetal abnormalities from our center are presented and discussed mainly from the viewpoint of timing and mode of delivery. Case presentation includes pathological ultrasound and IRM findings, differential diagnosis, case evolution, the timing, the mode of delivery, and the postnatal evolution.

For most anomalies, there is no benefit to preterm delivery but there are some abnormalities that present a risk to the fetus—increased risk of fetal death, bleeding, or organic damage. The advantages of premature delivery may include avoiding an ongoing risk of fetal death associated with an abnormality and allowing delivery in a controlled setting with availability of subspecialists. Most fetal anomalies carry no maternal risks other than maternal anxiety. In some selected circumstances, there are specific risks for the mother of continuing pregnancy near term (uterine rupture, "mirror syndrome").

There are few fetal abnormalities requiring a cesarean section but for most anomalies, the mode of delivery is unchanged. For most pregnancies complicated by anomalies, there is no change to obstetrical management regarding timing of delivery.

Ultrasound and Magnetic Resonance Imaging of Neonatal Brain: Are They Complementary or Alternatives?

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INTRODUCTION

Ultrasound (US) has become the most widely used technique for evaluation of morphology of lesions of neonatal brain. It can identify not only the presence of lesions but also their type and extent. Magnetic resonance imaging (MRI) is a rapidly developing imaging technique, becoming unavoidable diagnostic tool before initiation of treatment or determination of prognosis in neonates. "The two greatest obstacles we face in imaging infants and children are the proper preparation of the subject and the selection of the right combination of imaging parameters to achieve the desired result" (Ball WS Jr, 1997). Magnetic resonance imaging equipment is designated to accommodate adult patients and needs special adaptation for diagnostics of infants and small children.

AIM

To compare two imaging methods in diagnosis of brain lesions in preterm and term neonates.

MATERIALS AND METHODS

Neonatal two- and three-dimensional US was compared with conventional MRI in the diagnosis and follow-up of brain lesions in newborns.

RESULTS

Ultrasound has important role in the detection and follow-up of intracranial hemorrhage, periventricular leukomalacia, brain infections, hydrocephalus and ventriculomegaly, congenital malformations, neonatal stroke, and vascular lesions. A good correlation was found between US findings and signs of neurological impairment in the neonatal period and later in childhood. Cranial US can be a good predictor of disabling and nondisabling cerebral palsy (CP) at the age of 2 years in low birth weight infants and it can be in relation with impaired motor function in 5-year-old children. Brain lesions of the white matter diagnosed by US were found to be a powerful predictor of disabling CP. While US is powerful for the detection of the gray matter lesions, almost one-third of the brain white matter lesions cannot be diagnosed by US compared with MRI.

CONCLUSION

In the comparison with other neuroimaging methods like MRI, US has potential as a suitable and easy to perform screening method in the neonatal intensive care unit, without necessity of transportation of very sick neonates to specially designed rooms. Magnetic resonance imaging is burdened with many safety issues. For diagnostic purposes, especially of the white matter assessment and functional tests of the brain, MRI remains the method of choice. Ultrasound and MRI are the complementary methods for the assessment of neonatal brain.

Preeclampsia and Placental Dysfunction: Cause or Effect?

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INTRODUCTION

Placentation is uniquely associated with physiological remodeling of the spiral arteries by the invading trophoblast to produce a low-resistance uterine circulation. Defective placentation is associated with persistence of a high-resistance uterine circulation, impaired placental perfusion, and an antiangiogenic stress response leading to preeclampsia (PE). However, a critical literature review does not demonstrate a higher prevalence of placental villous and vascular histological lesions in term PE. These apparently characteristic placental lesions appear neither specific nor sensitive for PE (Ultrasound Obstet Gynecol 2017;49:7-9). Impaired fetal growth is an expected consequence of poor placental development in PE, as evidenced by abnormal second trimester uterine Doppler indices and low first trimester placental growth factor (PlGF) in these women. However, over 80% of PE cases occur at term, where there is preponderance of large for gestational age birth and poor screening effectiveness of both uterine artery Doppler indices and PlGF. These inconsistencies with the placental origin hypothesis have been attributed to disease heterogeneity or the maternal form of PE—which are neither adequate nor actual explanations (TEDx talk: <http://bit.ly/2i1SqDk>).

The concept that placental dysfunction is secondary to a maternal disorder is not new when one considers the clinical similarities between PE and gestational diabetes—both conditions only develop in pregnancy and are cured by birth. It is well accepted that gestational diabetes develops when the maternal pancreas is unable to manage the increasing glucose load of pregnancy. Similarly, pregnancy is known to present a substantial cardiovascular load on the maternal heart—which is an order of magnitude greater than observed in elite athletes and predisposes to cardiac dysfunction toward term (Hypertension 2016;67:754-762). Furthermore, PE is associated with substantial cardiac dysfunction—mild-to-moderate left ventricular diastolic dysfunction is seen in 50% of early-onset PE, with 20% of women having biventricular systolic dysfunction (Circulation 2014;130:703-714). There is a 50% risk of developing diabetes in the subsequent decade after gestational diabetes, and women whose pregnancies were complicated with PE are also predisposed to increased postpartum cardiovascular morbidity and mortality (Brehens I et al BMJ 2017, in press).

To date, the placenta has been considered in isolation without regard to the fact that its functioning is dependent on adequate perfusion by the maternal circulation. We must not disregard the emerging evidence that failure of the maternal cardiovascular system to adapt to pregnancy may well be the primary mechanism leading to secondary placental dysfunction in PE.

Use and Abuse of Cell-free Deoxyribonucleic Acid Screening in Clinical Practice

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INTRODUCTION

Women should be able to access noninvasive prenatal testing (NIPT) to enable them to find out at an early stage of pregnancy, if they wish, whether their fetus has a significant medical condition or impairment that manifests after birth. This information can be clinically useful and enable women and couples to have meaningful reproductive choice. However, such testing should only be available within an environment that enables women to make informed choices, and where steps are taken to minimize potential harms.

Noninvasive prenatal testing should only be offered if it provides an accurate prediction of whether a fetus has the condition or impairment that is being tested for. Private providers should stop offering NIPT for conditions where test performance is poor or unknown, such as NIPT for some microdeletions. Most governments and institutional bodies support the introduction of NIPT for trisomies in women who have been found to have a high risk on a primary screening test, albeit at various thresholds of risk as determined by local resources.

Providers of NIPT for significant medical conditions have a responsibility to provide high-quality information and support. Noninvasive prenatal testing should only be offered by healthcare professionals with the knowledge and skills needed to support women to make informed choices. Education and training must be compulsory for all health and social care professionals involved

in prenatal screening. Accurate, balanced, and nondirective information should be readily available to women and couples in accessible written and multimedia formats. This information and training should be developed with the support of those with genetic conditions or their families. Some providers of NIPT do not meet their obligations to offer good quality information and support to pregnant women. Certification from recognized information quality assurance schemes may be needed to minimize this practice.

Regulatory bodies should pay close attention to the advertising practices of NIPT manufacturers and providers to ensure that they are not misleading, harmful, or offensive. Hospitals and clinics should only offer NIPT as part of a package of care that should include, at a minimum, counseling before and after testing and follow-up diagnostic testing where this is required. Noninvasive prenatal testing should not be available on a direct-to-consumer basis unless it is offered as part of this package.

Biochemical Screening: Suspicion on Chromosomal Aberrations

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INTRODUCTION

Chromosomal aberrations contribute significantly to perinatal morbidity and mortality. According to this fact, screening programs of chromosomal aberrations became an essential task in perinatal care. Screening tests assess the degree of risk, or chance, that the fetus may potentially have certain common birth defects. The most common reason for prenatal diagnosis of chromosome abnormalities is to look for evidence of trisomies, Turner syndrome, and triploidy. Trisomy 13, 18, and 21 are the most common, with trisomy 21 comprising about half of all the trisomies identified.

There are a variety of screening programs on chromosomal aberrations including:

- Single analysis of various combinations of maternal serum analytes
- Combined biochemical and sonographic markers
- Integrated first and second trimester markers into single test

The methods of screening to identify the high-risk group are maternal age, ultrasound findings at 11 to 14 weeks, and/or in the second trimester, and maternal serum biochemical testing at 11 to 14 weeks and/or in the second trimester. Maternal serum biochemistry combined with ultrasound became a very efficient noninvasive technique for detecting risks of chromosomal aberrations. Various biochemical analytes in maternal serum showed as eligible for the prenatal screening of chromosomal aberrations during the first and second trimester of pregnancy.

Maternal serum analytes include pregnancy-associated plasma protein A (PAPP-A), maternal serum alfa-fetoprotein (MSAFP), free beta human chorionic gonadotropin (hCG), total hCG, unconjugated estriol (uE3), inhibin-A.

Pregnancy-associated plasma protein A When the fetus is affected with trisomy 21, PAPP-A levels are decreased by more than half. Low PAPP-A is also associated with trisomy 18 and 13. Using PAPP-A alone, detection rate of Down's syndrome is about 40%. The PAPP-A combined with maternal age, the increases detection rate to 50% with a 5% screen-positive rate. Decreased production of PAPP-A may cause intrauterine growth restriction.

Maternal serum alfa-fetoprotein High MSAFP levels may occur in underestimated gestational age, multiple gestation, neural tube defects, and Turner's syndrome without hygroma. The MSAFP less than the median may indicate an increased risk of chromosomal abnormalities, such as trisomy 21 and 18. The level of MSAFP in Down's syndrome pregnancies is about 72% of the normal values for weeks 14 to 21. Using maternal age and MSAFP level, the detection rate of Down's syndrome pregnancies is about 25 to 33%, at a false positive rate of 5%.

Beta hCG In trisomy 21 pregnancies, second-trimester hCG levels are elevated varying from 2.04 to 2.5 MoM or greater while in trisomy 18 and 13, hCG levels are lower than normal. Using maternal age and hCG levels, Down's syndrome detection rate is about 60% at a false positive rate of 6.7%. Each β -hCG and PAPP-A level represents a likelihood ratio that is multiplied by the a priori risk to calculate the new risk. The higher the level of β -hCG and the lower the level of PAPP-A, the higher the risk for trisomy 21.

Unconjugated estriol uE3 tends to be lower when trisomy 21 or 18 is present and when there is adrenal hypoplasia with anencephaly. Second-trimester maternal serum uE3 levels in Down's syndrome pregnancies are approximated 75% of the values expected in normal pregnancies.

Inhibin-A Maternal serum levels of inhibin-A are twice as high in pregnancies affected by Down's syndrome as in unaffected pregnancies while in trisomy 18, inhibin-A levels are lower than normal. Inhibin-A is used with three other analytes (MSAFP, hCG, uE3) and maternal age to characterize more accurately Down's syndrome risk, and a reduction of the false positive rate was detected.

In the first trimester of pregnancy (11–13 weeks of gestation), a biochemical screening called "Double test" is taken. It implies determining serum values of two markers (β -hCG and PAPP-A). Combined with ultrasound examination data, the following is recalculated: risk for trisomy 21, a combined risk for trisomy 21, risk for trisomy 13/18 + nuchal translucency (NT). Screening of trisomy and presence of neural tube defect performed in the second trimester implies determination of three markers in the serum of the mother (triple), or four markers (quadruple) test (14–20 weeks of gestation). Free β -hCG showed as the only marker that is effective in both the first- and second-trimester pregnancies.

Studies showed that combined biochemical and sonographic markers estimate risk results in higher rate combined either than alone. Combination of a multiple marker test (PAPP-A and free β -hCG) and an ultrasound at 11 to 14 weeks which is targeted to look NT, and maternal age gives high detectable rate of aneuploidy. Combination of serum and ultrasound markers of chromosomal aberrations, the detection efficiency ranges from 85 to 90%, and detection of nasal bone and flow into the ductus venosus increase performance by up to 95%.

Various factors affect the accuracy of biochemical tests, such as gestational age, maternal weight, multiple pregnancies, smoking, and other maternal diseases so screening tests should represent proper choice among pregnancies with no previous risk factors. These combined screening test should identify a group of women in high-risk groups of chromosomal aberrations and choose further diagnostic tests.

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Role of Three-dimensional Ultrasound in Adnexal Masses

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INTRODUCTION

This presentation will look at the evolution of three-dimensional (3D) scanning in gynecological ultrasound. We will present the applicability, feasibility, and practicalities of 3D ultrasound. We will discuss the advantages and disadvantages of using a 3D scan. This presentation will discuss the difference and use of two-dimensional and 3D ultrasound for the evaluation of adnexal masses, including the risk of malignancy. Using International Ovarian Tumor Analysis (IOTA) terminology, we will discuss how to describe an adnexal mass and how to calculate the various risks of malignancy indicators, namely Risk of Malignancy Index, Simple Rules, Logistic Regression model 2, and ADNEX.

Counseling before Invasive Prenatal Diagnosis and Noninvasive Prenatal Testing/Screening

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INTRODUCTION

Pregnant women considered to be at high risk have been offered prenatal diagnosis to detect chromosomal disorders since the late 1960s. Chorionic villus sampling and amniocentesis are the most common methods available for diagnostic testing; both of these are invasive procedures and are associated with an increased risk (almost 1%) of iatrogenic pregnancy loss.

Due to these risks, common practice is that health care providers recommend the option of diagnostic testing only to women at high risk of having a chromosomally abnormal fetus.

Since the 1970s the decision to offer pregnant women prenatal diagnosis for genetic diseases has had an age-based trigger, according to the fact that the risk of major chromosomal abnormalities increases with age. Maternal age alone is a poor minimum standard for prenatal screening for aneuploidy, and it should not be used as a basis for recommending invasive testing when noninvasive prenatal screening for aneuploidy is available in order to avoid unintended fetal loss resulting from miscarriage following invasive diagnostic testing.

Various screening tests to determine risk for fetal trisomy 21 are currently available including measurement of: nuchal translucency (NT) only, serum-only (in the first and/or second trimester), or the combination of NT and serum markers. Using these methods, detection rates vary from 70 to 94% with false positive rates of 1 to 5% depending on the screen performed, the gestational age at the time it is performed, and maternal age. The combined test is an effective test, especially for women who want to complete their prenatal pathway within the first trimester, while the integrated test is a better instrument for women with a normal ultrasound examination at 11 to 13⁺⁶ weeks. Most laboratories also provide screening results for trisomy 18 and, less often, trisomy 13.

Noninvasive prenatal testing (NIPT) of cell-free fetal deoxyribonucleic acid with its very low false positive rate (about 0.1%) has been entering and transforming prenatal care rapidly during the last few years, while invasive diagnostic procedures have shown a decreasing trend all over the world.

This has led to a number of position statements in relation to practical standards for NIPT services from professional organizations. In 2010 the Italian Ministry of Health in its guidelines for Healthy Pregnancy has recommended to inform all pregnant women about prenatal screening and diagnosis of Down syndrome at the first contact with a health care practitioner.

Each pregnant woman should be counseled about:

- The main clinic features of Down syndrome;
- The pathway for screening test and prenatal diagnosis of Down syndrome (risk evaluation for each pregnant woman to have an affected child, the possibility to perform a screening test, the adjunctive risk of abortion related to invasive procedures, the possibility to perform diagnostic procedure if the risk is higher than a specified risk cut-off);
- The different types of screening test (the NT measurement at 11–13 weeks is recommended, associated with biochemical markers of first trimester or of first and second trimesters);
- The diagnostic invasive procedures;
- The possibility to terminate an affected pregnancy, according to the 194/1978 Italian law.

Prenatal counseling is an essential part of the obstetrical care and must be provided as soon as possible.

The most rational approach for counseling any woman is to allow her to choose the prenatal path that best meets her particular needs (the highest detection rate *vs* the earliest results *vs* the lowest false positive rate) in order to let her decide whether and how to proceed. With this approach, in a prenatal diagnostic universe of rapidly expanding potential and complexity, the core obstetrical ethic of respect for patient autonomy will continue to be honored.

In conclusion, effective screening tests for fetal aneuploidies are now available so as to carry out invasive diagnostic procedures only in pregnancies considered to be at high risk for fetal chromosomal abnormalities. Health care providers should discuss the screening tests with all pregnant women and must be satisfied when patients understand the screening available and that they are making an informed decision about whether to have testing.

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How to understand Holoprosencephaly?

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INTRODUCTION

Holoprosencephaly is a group of complex structural malformations of the forebrain that results from complete or incomplete nonseparation of the prosencephalon that yields an incomplete division of the cerebral hemispheres and of the telencephalon from the diencephalon. According to the severity of the malformation, holoprosencephaly is categorized into four subtypes: lobar holoprosencephaly, semilobar holoprosencephaly, lobar holoprosencephaly, and a middle interhemispheric fusion variant (syntelencephaly). The incidence of holoprosencephaly is 1 in 10,000 to 15,000 births. According to a study by Michalski et al, the male-to-female ratio for holoprosencephaly is 1:1.56. The etiology of holoprosencephaly is very heterogeneous, the identified causes until now are: chromosomal (most commonly trisomy 13), monogenic, and teratogenic. Maternal diabetes mellitus is a known risk factor; maternal use of alcohol, retinoic acid, diphenylhydantoin, aspirin, misoprostol, methotrexate, and cholesterol-lowering agents have been implicated but not proven to be causative. Lobar holoprosencephaly is the most severe form with no separation of the cerebral hemispheres usually characterized by a single ventricle; corpus callosum and interhemispheric fissure are absent, and the thalami is unseparated. In semilobar holoprosencephaly, the cerebral hemispheres separate posteriorly but not anteriorly. Lobar holoprosencephaly is characterized by almost complete separation of the cerebral hemispheres except at the frontal lobes. Holoprosencephaly represents a continuous spectrum of malformations based on the severity of lack of cleavage and this leads to the attempt of some researchers to incorporate degrees of nonseparation of subcortical structures into

the classification system, and therefore, the term septopreoptic holoprosencephaly has been used to describe a mild subtype of lobar holoprosencephaly with nonseparation restricted to the septal or preoptic region. Most cases of holoprosencephaly are characterized by various craniofacial malformations, the most severe craniofacial deformity remaining cyclopia with a single or partially divided eye in a single orbit with a proboscis above the eye and absent nose. Other malformations may include: a single central maxillary incisor, midline cleft lip and palate, bilateral cleft lip and palate with intermaxillary rudiment, flat nose, absent nasal bridge, microphthalmia, absence of lateral philtral ridges, and absence of the superior lingual frenulum. The first step of the diagnostics is based on the ultrasound visualization of cerebral ventricular abnormalities, on axial plane of the fetal brain, and on the facial anomalies. The most frequently associated anomalies include the central nervous system, the heart, the skeleton, and the gastrointestinal tract, association that increases the risk of chromosomal and genetic anomalies that is why karyotyping should always be performed. The empiric recurrence risk is 5 to 6%. If holoprosencephaly occurs in the context of a syndrome, the recurrence risk is that of the syndrome. Mortality and morbidity associated with holoprosencephaly depend on the severity of the malformations and most affected pregnancies result in miscarriage. Among live births, those with the severe type often die within days of birth; meanwhile most persons with milder malformations survive beyond infancy. Life expectancy is poorest among those with syndromal and alobar holoprosencephaly.

Ultrasound Imaging in Neonatal Hypoxic-ischemic Injuries

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INTRODUCTION

The aim of this article is to evaluate the role of ultrasonography in neonates with hypoxic-ischemic encephalopathy and perinatal asphyxia regarding brain lesions and multisystem involvement (kidney, heart, intestines, liver) in the acute setting in order to guide therapeutic management and to predict a long-term prognosis.

MATERIALS AND METHODS

Analysis of PubMed and Cochrane databases retrieved data on the impact of ultrasonography regarding the acute management and long-term prognosis of both term and preterm neonates with hypoxic-ischemic encephalopathy and perinatal asphyxia.

RESULTS

Exposure of the fetus to acute episodes of hypoxia determines a different lesion pattern in the term neonate and the premature neonate. Areas of the brain that contain the highest concentration of glutamate and other amino acid receptors are more susceptible to excitotoxic injury. The different lesion pattern is also attributed to the presence of compensatory blood flow at the expense of other organs (kidney, lung, heart, intestines). Ultrasonography is useful in the evaluation of the resistive index in anterior and middle cerebral artery, renal artery, and superior mesenteric artery. A low resistance index is associated with a poor long-term prognosis. The presence of multiorgan dysfunction appears to predict worse outcome.

CONCLUSION

Ultrasonography plays an important role in the acute clinical setting due to the fact that evaluation of blood flow velocities of the neonate can give information about the brain as well as multiple system organ failure in the context of asphyxia. A low resistance index and an increase of the end-diastolic flow Doppler in the anterior cerebral artery are associated with perinatal asphyxia. The initial ultrasonography assessment is affected by the duration and severity of the asphyxiating injury, the affected brain region, and the maturity of the affected territory. The optimal time to perform ultrasound Doppler is the interval of 12 ± 2 hours of life. Ultrasound must be repeated to assess the full extent of the lesions. Cerebral ultrasound can be used to assess the stage of the intraventricular hemorrhage. Ultrasonography can bring useful information about the gastrointestinal tract regarding intestinal appearance, blood flow velocities and mural perfusion.