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Original scientific article

ULTRASOUND MARKERS OF CHROMOSOME ABERRATIONS ON ROUTINE SECOND TRIMESTER SCREENING

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Second trimester ultrasound examination for risk assessment of chromosomal abnormalities remains an important component of prenatal evaluation. We have conducted a retrospective study to evaluate the efficiency of ultrasonographic screening for the markers of chromosomal aberrations and to classify ultrasonographic markers according to the aberration they were found with. Over a 10 year period we performed 620 karyotype analyses of fetal blood taken by cordocentesis after detection of fetal anomalies in a second trimester scan in unselected population and 216 samples of peripheral blood of neonates having phenotypic features suspected for chromosomopathies. Ultrasound examination and cytogenetic data were obtained from the laboratory database. Chromosomal abnormalities were found in 36 (5,8%) fetuses with anomalies. Most frequently chromosomal aberrations were detected in fetuses with multiple anomalies (13,3%), heart anomalies (11,5%), short femurs (12,5%) and polyhydramnios (7,7%). The success rate of sonographic examination in detection of Down syndrome was 85%, and in detection of sex chromosome trisomies 80%. Trisomy 18, trisomy 13 and polyploidy were found prenatally in 100% each. Nearly 42% of trisomy 21 fetuses had heart anomaly, 35,3% polyhydramnios and 17,7% short femurs. Trisomy 18 fetuses had polyhydramnios in 87,5%, CNS anomalies in 62,5% and symmetrical IUGR in 50% of cases. All of the fetuses with monosomy X had short femurs. Ultrasonographic evaluation is the most sensitive screening method for the

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identification of fetuses having a high risk rate for chromosomal abnormalities in a low risk population.

Key words: Chromosomal aberrations, fetal anomalies, ultrasonographic examination

INTRODUCTION

Since the first report of the use of ultrasound in obstetrics, it has become an important tool for detection of fetal structural defects. According to the International Society of Ultrasound in Obstetrics and Gynecology, the ideal period for screening for structural defects is the second trimester (weeks 18 to 22) of pregnancy (DULGHEROFF *et al*., 2019). In the second trimester it is possible to identify two types of sonographic markers suggestive for chromosomal abnormalities. The first type represents major fetal anomalies, which are generally defined as structural changes that have significant medical, social or cosmetic consequences, typically require medical intervention and are known to significantly contribute to perinatal and childhood morbidity, mortality and disability (VICTORIAN CONGENITAL ANOMALIES REGISTER, 2018). The second type - "soft" markers, are defined as minor non-specific findings on ultrasound scans, which are often transient and have little to no pathological significance. Although not pathological per se, the incidence of ultrasound soft markers is higher in fetuses with chromosomal aberrations. (SUN *et al*., 2020; ALI *et al*., 2012; PARK *et al*., 2015) Major abnormalities are observed in 25% of fetuses with chromosomal abnormalities, whereas one or more soft markers may be observed in at least 50% of affected fetuses (RANIGA *et al*., 2006). The finding of one major structural malformation or two or more soft markers increases the risk for chromosomal aberrations in fetuses, and in these cases there is a necessity for genetic informing of patients, and invasive prenatal testing (BENN *et al*., 2015).

The aim of this study is to evaluate the efficiency of ultrasonographic screening for chromosome aberrations in the second trimester and to classify ultrasonographic markers according to the aberration they were associated with.

MATERIALS AND METHODS

This descriptive retrospective study comprises a ten years period (2002.-2012.) and includes ultrasonographic and cytogenetic data of 620 fetuses and 216 newborns, examined because of an increased risk for chromosomal abnormalities, in the Clinic for gynecology and obstetrics, Clinical center of Serbia.

Samples

Fetal karyotype analysis was performed from fetal blood samples taken by cordocentesis. Neonatal karyotypes were analyzed from samples of peripheral blood, taken from peripheral veins in the hand, foot or head. The samples were processed using standard techniques (MOORHEAD *et al*., 1960; SEABRIGHT, 1971). Chromosome analysis was performed after GTG banding with trypsin. In every sample at least 16 metaphase spreads were analyzed. In the cases of mosaicism 100 metaphase spreads were analyzed. The International System for Human Cytogenetic Nomenclature was used to describe karyotypes (ISCN, 1995; ISCN, 2005).

Ultrasonographic findings

Fetal ultrasound findings identified at the time of the routine midpregnancy scanning, at 16^{th} to 23^{nd} gestational week, before the knowledge of cytogenetic diagnosis, were obtained from the cytogenetic laboratory data base. Ultrasound examinations were performed transabdominally by a licensed and experienced maternal-fetal medicine physician sonographers. Study included only singleton pregnancies. The sonographic evaluation comprised standard biometrical measurements: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL), as well as fetal cerebral ventricles anatomy, fossa posterior, spine, four chamber view of the fetal heart, abdomen, kidneys and bladder. In addition, the cardiac function, renal pelvis, extremities and amniotic fluid volume were evaluated. The findings were considered positive if one major anomaly or one "soft" marker, inadequate amniotic volume or intrauterine growth retardation were found. Major malformations were defined as structural fetal anomalies that would either require surgical intervention after birth or cause serious disease or death. Soft markers were defined as follows: choroid plexus cysts are solitary, unilateral, anechoic circle structures in the choroid plexus of lateral ventricles; ventriculomegaly is defined as a width of the atrium of the lateral ventricle greater than 10 mm; intracardiac echogenic focus (golf ball) is defined as a small structure within the fetal heart with similar or greater echogenicity to the surrounding bone, present in close proximity to the papillary muscle and chordae tendineae; echogenic bowel refers to increased echogenicity or brightness of the fetal bowel that can be diffuse or focal; pyelectasis is defined as renal pelvic dilatation greater than 5 mm; short long bones present a long bone measuring below the fifth percentile; short long bone length is defined as below the 5th percentile or < 2 standard deviations (SD) appropriate for gestational age; single umbilical artery (SUA) is the absence of one umbilical artery. Fetuses with malformations in two or more systems were classified as fetuses with multiple anomalies. Criteria for IUGR was estimated fetal weight below the 10th percentile for its gestational age. For the estimation of IUGR Fanaroff's fetal growth curves were used. (FANAROFF & MARTIN, 1992) Amniotic fluid volume was measured as amniotic fluid index (AFI). Polyhydramnios was defined as AFI > 20 cm and olygoamnion as AFI < 5cm. On parents demand, and after genetic counselling and ethic committee approval, pregnancies with abnormal karyotypes were terminated.

RESULTS

Fetal findings

Chromosomal aberrations were found in 36 (5,8%) fetuses with ultrasonographically detected anomalies. Frequencies of cytogenetic findings are shown in Table 1.

The most frequent chromosomal abnormalities were aneuploidies, in 91,7% of all cases, with autosomal trisomies being the most common (75%). Trisomy 21 in 47,2% and trisomy 18 in 22,2% of cases, were the most frequently detected chromosome aberrations.

The frequencies of chromosomal aberrations in correlation with sonographic findings are presented in Table 2.

Trisomy 21 (Down syndrome) was found to have the highest incidence, in 17 (47,2%) cases. In 15 cases classic trisomy was found, and in two cases we detected Robertsonian

translocation 21;21 and 15;21. Ultrasonographic findings in fetuses with trisomy 21 are presented in Table 3.

Table 1. Detected chromosomal aberrations

Chromosomal aberrations	Number of cases (%)
Trisomy 21	17 (47,2%)
Trisomy 18	8 (22,2%)
Trisomy 13	2 (5,5%)
Monosomy X	3 (8,3%)
Polyploidy	1 (2,8%)
Sex chromosomes trisomy	1 (2,8%)
Supernumerary marker chromosome	2 (5,5%)
Translocation	1 (2,8%)
Derivative chromosome	1 (2,8%)
Total	36

Table 2. Frequencies of chromosomal aberrations in correlation with sonographic findings

Ultrasonographic findings	Number of aberrant fetuses (%)
Polyhydramnios	5/65 (7,7%)
Oligoamnios	1/45 (2,2%)
Symmetrical IUGR	5/82 (6,1%)
Multiple anomalies	13/98 (13,3%)
Hart anomalies	3/26 (11,5%)
Anomalies of gastrointestinal tract	1/51 (1,9%)
Anomalies of kidneys	1/70 (1,4%)
Short femur length	3/24 (12,5%)
Hydrops fetalis	1/4 (25%)
SUAS	1/6 (16,7%)
Symmetrical IUGR with polyhydramnios	1/11 (9,1%)
Symmetrical IUGR with olygoamnion	1/19 (5,3%)

Multiple anomalies specific for trisomy 21 included: ventricular septal defect-VSD (2 cases), polyhydramnios (2 cases), short femur (2 cases), Tetralogio Fallot, "Golf ball", polycystic kidneys, pyelectasis, echogenic bowel. Nearly 42% (7/17) of fetuses with trisomy 21 had heart anomalies, 35,3% (6/17) had polyhydramnios, and 17,7% (3/17) had short femurs.

Trisomy 18 (Edwards syndrome) was found in 8 (22,2%) cases. It was the second most common trisomy, after trisomy 21. Classic trisomy 18 was detected in 7 cases, while in one we found a trisomy of the long arm of chromosome 18 (trisomy 18q), due to de novo translocation 13p;18q. Fetal ultrasound findings in trisomy 18 are presented in Table 4.

Table 3. Ultrasonographic findings of fetuses with trisomy 21.

Finding	Number of Trisomy 21 cases (%)
Multiple anomalies	5 (29,4%)
Polyhydramnios	4 (23,5%)
Heart anomalies	3 (17,6%)
Symmetrical IUGR	2 (11,8%)
Hydrops fetalis	1 (5,9%)
Anomalies of the gastrointestinal tract	1 (5,9%)
Short femur length	1 (5,9%)
Total	17

Table 4. Ultrasonographic findings of fetuses with trisomy 18.

Finding	Number of Trisomy 18 cases (%)
Multiple anomalies	6 (75%)
Polyhydramnios	1 (12,5%)
Symmetrical IUGR with polyhydramnios	1 (12,5%)
Total	8

Multiple anomalies characteristic for trisomy 18 included: polyhydramnios (5 cases), ventriculomegaly (3 cases), symmetrical IUGR (3 cases), corpus callosum agenesis, choroid plexus cyst, VSD, omphalocele, pielectasia, SUAS. In 7 (87,5%) fetuses with trisomy 18 we found polyhydramnios, in 5 (62,5%) CNS anomalies, and in 4 (50%) symmetrical IUGR.

Classical trisomy 13 (Patau syndrome) was detected in two cases. One fetus had symmetrical IUGR and the second had multiple anomalies including polyhydramnios and diaphragmatic hernia.

Numerical aberrations of sex chromosomes were found in four cases. Klinefelter syndrome (47,XXY) was found in one fetus having IUGR. Monosomy X (Turner syndrome) was detected in three cases. Two fetuses with Turner syndrome had short femurs, and in the third, along with a short femur, IUGR was found.

In one fetus with IUGR and one fetus with SUAS, small supernumerary acrocentric marker chromosomes (sSMC) were found.

Triploidy was detected in one fetus affected by olygoamnion and IUGR.

In one fetus with olygoamnion we found Robertson translocation 13;14, inherited from the father.

One fetus with polycystic degeneration of the left kidney had a derivative chromosome 8, with additional genetic material on the short arm of chromosome 8.

The pregnant women included in this investigation were 19 to 42 years old, with a mean maternal age of 28,5 years. All sonographic scans were performed from the 16. to 22., cordocentesis between the 22. and 26., and pregnancy termination before the 30. gestational week.

Newborn findings

Among newborns from pregnancies passed genetic screening, in a ten year period, three cases of trisomy 21, one case of Klinefelter syndrome (47,XXY) and one case of trisomy X, were found. The baby with triple X had neurological seizures, which could not be revealed by ultrasonography. Klinefelter syndrome was only confirmed from the baby's blood sample. It was found after amniotic fluid analysis, and the fetus had no anomalies visible trough sonographic scaning, so it was not informative.

All three newborns having trisomy 21 were delivered by mothers under 35 years of age, and physical exams revealed typical dysmorphic facial features, tongue protrusion, low set ears, a single palmar crease and hypotonia. Neither of the babies had sonographically detectable anomalies. Non-invasive antenatal screening for chromosomal aberrations showed a low risk rate for two of the babies, and for one it was not preformed.

Of 20 total cases of trisomy 21, 17 were detected prenatally, during sonographic screening for fetal anomalies, so the success rate of the genetic songram in detection of Down syndrome was 85%. Sex chromosome aberrations were found in 5 cases, four of which were found during the second trimester. In these cases, the success rate of the genetic sonogram was 80%. Trisomy 13, trisomy 18 and polyploidy were revealed antenataly in 100% of cases.

DISCUSSION

Despite the fact that first trimester screening, including nuchal translucency measurement, nasal bone evaluation and maternal serum screening, can reveal the most fetuses with chromosome aberrations, sonographic screening in the second trimester is very useful in detecting affected fetuses were a diagnosis had been missed or delayed.

Previous studies showed variable incidence of chromosomal abnormalities, ranging from 12% to 38%, in fetuses with detected anomalies (GAGNON *et al*., 1992; DE VIGAN *et al*., 2001). Eydoux et al. found chromosomal abnormalities in 13% of fetuses with pathological ultrasound findings in a study population with a mean maternal age of 27,6 years (EYDOUX *et al*., 1989). In the study of CHEW *et al.* (1996) the mean maternal age was 29,5, and the incidence of chromosomal aberrations in the presence of fetal anomalies was 12,4%. DE VIGAN *et al*. (2001) reported the results of a study conducted in 19 European centers, showing a rate of 37,7% of chromosomal abnormalities in fetuses with pathological sonographic findings in the second trimester (DE VIGAN *et al*., 2001). In our investigation the incidence of chromosomal aberrations in fetuses with pathological findings in second trimester scan was 5,8%.

This difference in frequencies of chromosomal aberrations in fetuses with defects revealed in our and previous studies can be explained in several ways'. First, fetal anomalies may be a consequence of genetic mutations or environmental factors, or even have multifactorial genesis. Next, soft markers can be transitory in normal fetuses, so detailed sonographic scan is necessary in order to find additional anomalies, for proper estimation of risk for chromosomal aberrations, in these cases.

The mean maternal age in our study was 28,5 years, supporting the fact that the majority of pregnant women were younger than 35, e.g. belonged to the population with low risk for fetal chromosomal anomalies. Previous studies have shown the importance of sonographic

screening primarily in pregnancies with low risk for fetal chromosomopathies (SCHLUTER and PRITCHARD, 2005; MALONE *et al*., 2004).

The obtained data show that the incidence of chromosomal aberrations is higher in fetuses with multiple malformations (13,3%), than in those with isolated defects (about 2%). Chew et al. found a pathological karyotype in 35,4%, and Eydoux et al. in 29,2% of fetuses with polymalformations (CHEW *et al*., 1996; EYDOUX *et al*., 1989). In both of these studies, the most frequent chromosomal aberration causing multiple defects in the fetus was trisomy 18. Our findings support the previous, since trisomy 18 fetuses in our study had multiple anomalies in 75% of cases. Multiple anomalies in our investigation were also the most common phenotypic characteristic of trisomy 21, in 29,4% of cases.

Polyhydramnios as an isolated finding, was detected in 7,7% of the aberrant fetuses in our study. It was detected in 87,5% in trisomy 18, of which in 12,5% as isolated finding. In trisomy 21 polyhydramnios was found in 35,3%, of which in 23,5% as isolated finding. DASHE *et al.* (2002) found aneuploidies in only 1% of isolated and 10% of polyhydramnios associated with fetal anomalies. BRADY *et al.* (1992) found chromosomal abnormalities in idiopathic polyhydramnios with an incidence of 3,2%, and suggested karyotype analysis in all of these cases. In contrast, SHIMADA *et al.* (2009) and ZAHN *et al.* (1993) detected chromosomal abnormalities in 23,4% and 22,2% of isolated polyhydramnios, respectively. SICKLER *et al.* (1997) and SHIMADA *et al.* (2009) found chromosomopathies when polyhydramnios was joined with intrauterine growth retardation in 38,5% and 44,4% of cases, respectively.

Chromosomal and genetic changes are responsible for 5-15% of fetuses with intrauterine growth retardation (IUGR), more frequently of the symmetric, rather then asymmetric type (KAY, 2001). Aneuploidies cause 25% of severe IUGR in early stages of gestation (CARRERA, 2004).Symmetrical IUGR as an isolated marker was found in 6,1% of fetuses with chromosomal abnormalities in our investigation. As an isolated marker it was found in 50% both in fetuses with trisomy 13 and sSMC, and 11,8% of fetuses with trisomy 21. In 50% of trisomy 18 and 33,3% of monosomy X cases, as well as in one case of triploidy and one case of sex chromosome trisomy, multiple abnormalities including IUGR were found. In our study, asymmetric IUGR was not associated with chromosomopathies.

Congenital heart defects are the most common anomalies in trisomy 21 children (44% of cases). Almost 100% of the newborn with trisomy 18, 90% with trisomy 13 and 50% of trisomy 21 have congenital heart abnormalities, predominantly ventricular septal defect (VSD). Regarding such frequent findings of congenital heart defects in newborns with chromosome aberrations, prenatal diagnosis of heart anomalies increase the risk of chromosomopathies in fetus. If the heart defect is an isolated finding risk for fetal chromosomal abnormalities is 15% to 20%, and if there are some additional defects this risk increases up to 70% (ANTSAKLIS and THEODORA, 2008) In our study, 42% of trisomy 21 fetuses were found to have heart defects, 17,6% of which were an isolated finding. A ventricular septal defect was also found in one trisomy 18 fetus as one of multiple malformations. In fetuses with other detected chromosomal aberrations, heart abnormalities were not found.

Short femur lenght is one of the sonographic markers for fetal aneuploidies, predominantly trisomy 21 (ALI *et al*., 2012; RATANASIRI *et al*., 2014). In our investigation 17,7%

of trisomy 21 fetuses had short femurs, one case of which was as isolated finding. In contrary, all 100% of monosomy X fetuses were found to have short femur, in two cases as an isolated finding, and together with IUGR in one.

Fetal hydrops is the most common sonographic finding in monosomy X. It can be found in fetuses with mosaic trisomy 10, trisomy 11p, as well as in trisomy 13, 18 and 21 (SMOLENIEC *et al*., 1999; BIANCHI *et al*., 2000; RATNAM *et al*., 1994; FOROUZAN, 1999). In our study fetal hydrops was detected in only one case of trisomy 13, while in monosomy X it was not present.

In ourstudy, single umbilical artery syndrome as an isolated marker was found in one fetus with sSMC, although it has not been connected with chromosomal abnormalities. The finding of one umbilical artery requires detailed sonographic scan, primarily of the fetal kidneys and heart (GEIPEL *et al*., 2000).

Central nervous system anomalies, in our study, were found only as part of multiple fetal malformations, in 62,5% of trisomy 18 fetuses.

Isolated anomalies of the gastrointestinal system and kidneys, oligoamnios, or IUGR conjoined with oligoamnios or polyhydramnios, were detected in low frequency, predominantly associated with rare chromosomal rearrangements, like translocations or derivative chromosomes.

Previous studies show that ultrasonography can reveal 50-90% of fetuses with Down syndrome, 90-100% of fetuses with Patau syndrome and 80-100% of fetuses with Edwards syndrome (RATANISIRI *et al*., 2014; DRISCOLL and GROSS, 2009; BREATHNACH *et al*., 2007; ZHONG *et al*., 2011; YEO *et al*., 2003). The data obtained in our investigation correlate with those previous findings. Fetal sonographic evaluation in the second trimester detected trisomy 13, trisomy 18 and polyploidy in 100%, trisomy 21 in 85%, and sex chromosome aberrations in 80% of cases.

Aneuploidies with the highest incidence, trisomy 21, 18 and 13, monosomy X, as well as polyploidies, have specific ultrasonographic markers that can overlapp in different syndromes. The data from our investigation show that heart defects, polyhydramnios and short femur are characteristic for trisomy 21, for trisomy 18 polyhydramnios, CNS anomalies and symmetrical IUGR are characteristic, for monosomy X the typical finding is short femur lenght, while trisomy 13 and polyploidy did not have specific sonographic findings.

CONCLUSION

Ultrasound examination is the most sensitive method of screening fetuses with high risk of chromosomal aberrations in the population of low risk pregnant women. This non-invasive method is useful for risk calculation, but it can't be used for diagnostics or the exclusion of chromosomal abnormalities.

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ULTRASONOGRAFSKI MARKERI HROMOZOMOPATIJA U DRUGOM TRIMESTRU TRUDNOĆE

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Izvod

Brojne fetalne strukturne anomalije i "soft" markeri koje je moguće otkriti tokom ultrasonografskog pregleda fetusa u drugom trimestru trudnoće povezani su sa hromozomskim aberacijama. Studija je imala za cilj evaluaciju efikasnosti ultrasonografskog skrininga hromozomskih aberacija u drugom trimestru graviditeta i klasifikaciju ultrasonografskih markera u odnosu na hromozomske aberacije kojima su izazvani. Ovom deskriptivnom retrospektivnom studijom obuhvaćen je desetogodišnji period (2002.-2012. godine), tokom koga je u citogenetičkoj laboratoriji Klinike za ginekologiju i akušerstvo, Kliničkog centra Srbije, analizirano 620 uzorka fetalne krvi zbog detektovanih fetalnih anomalija tokom ultrazvučnog skrininga i 216 uzoraka krvi novorođenčadi kod kojih je zbog fenotipskih karakteristika postavljena sumnja na hromozomopatiju. Podaci o ultrasonografskim i kliničkim nalazima dobijeni su pretraživanjem baze podataka citogenetičke laboratorije. Hromozomske aberacija nađene su u 36 (5,8%) slučajeva kod fetusa sa ultrasonografski uočljivim anomalijama. Abnormalnosti hromozoma sa najvećom incidencom javljale su se kod fetusa sa multiplim anomalijama (13,3%), anomalijama srca (11,5%), skraćenim femurom (12,5%) i polihidramnionom (7,7%). Uspešnost genetičkog sonograma u detekciji Down sindroma bila je 85%, a u otkrivanju aberacija polnih hromozoma 80%. Trizomija 18, trizomija 13 i poliploidija otkrivene su antenatalno u 100% slučajeva. Kod približno 42% fetusa sa trizomijom 21 otkrivene su anomalije srca, kod 35,3% polihidramnion, a kod 17,7% skraćen femur. U 87,5% fetusa sa trizomijom 18 nađena je povećena količina plodove vode (polihidramnion), u 62,5% anomalije CNS-a, a u 50% simetrični IUZR. U svih 100% fetusa sa monozomijom X hromozoma nađen je skraćen femur. Ultrasonografski pregled predstavlja nejsenzitivniji metod skrininga fetusa koji imaju visok rizik za hromozomske poremećaje, u populaciji trudnica sa niskim rizikom.

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