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*Original scientific paper*

# FETAL CHROMOSOMAL ANOMALIES IN SOUTHEAST SERBIA - SINGLE CENTER COHORT RETROSPECTIVE STUDY

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Congenital anomalies are the cause of prenatal death in 20-25% of the cases, while 3% of children are born with a malformation of varying size. Many of these anomalies can be detected before birth using different non-invasive and invasive prenatal diagnostic tests. This study was used to determine the distribution of genetic disorders in relation to the age of the mother, the frequency of aberrations and to study the effects and importance of prenatal diagnosis in South Serbia. Prenatal diagnostics was performed at the Pediatric Clinic within the Clinical Center of Niš. This retrospective study included a group of 8830 pregnant women, aged between 18 and 47 years during the period from 2004 to 2017. Amniocentesis was performed between the 16$^{th}$ and 18$^{th}$ week of pregnancy and involved the aspiration of 20 ml of amniotic fluid. Isolated cells were cultured in a medium that stimulates cell growth for 10 days. After cytogenetic processing, the obtained karyotype was analyzed using G-banding techniques. In 8830 samples of amniotic fluid cell cultures, 198 karyotypes with chromosomal aberrations were found - 179 with numerical aberrations and 19 with structural aberrations such as translocations, inversions and deletions. There were 85 karyotypes with autosomal numerical aberrations and 32 karyotypes with sex chromosome numerical aberrations. The most frequent one was trisomy 21 (106 cases). The highest number of autosomal numerical aberrations,

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84%, was found in pregnancies where maternal age was above 30 years. Preventive action, advice, education and availability of prenatal diagnosis can lead to a significant reduction in the number of children born with various malformations.

*Keywords*: Genetic disorder, prenatal diagnostics, amniocentesis, cytogenetics, chromosomal aberration.

## INTRODUCTION

Congenital anomalies are the cause of prenatal death in 20-25% of the cases, and 3% of children are born with malformations of varying degrees. The study has shown that 15% of children aged 1 year, with congenital anomalies, have chromosome aberrations (ZEITLIN *et al.*, 2009). Many of these anomalies can be detected before birth using different non-invasive and invasive prenatal diagnostic tests.

Non-invasive tests include determination of maternal serum markers, i.e. PAPP-A and beta HCG in the first trimester of pregnancy, and alpha-fetoprotein, chorionic gonadotropin and unconjugated estriol in the second trimester. A retrocervical subcutaneous collection of fluid at 11-14 weeks of gestation can be visualized by ultrasound as nuchal translucency (NT). Non-invasive tests combined with measurements of nuchal translucency allow assessment of the risks with a probability of 60 -70% for Down and Edwards syndromes, regardless of the maternal age (NIKOLAIDES, 2004).

Invasive tests, such as amniocentesis, chorionic villi sampling and cordocentesis are applied in cases of high-risk pregnancies with a risk assessment probability of 99%. The reasons for their application are most often the existence of personal or familial genetic predisposition. Indications have to be very strictly conformed to the expected benefits and the degree of risk.

Chromosome aberrations are present in 10% of all sperm cells and 25% of the mature oocytes (MUELLER and YOUNG, 1998). The frequency of numerical chromosome abnormalities in sperm of fertile men is 1–2% and the frequency of structural chromosome abnormalities in sperm varies from 7–14% (MARTIN, 2003). After the age of 35 years, the frequency of aneuploidies in oocytes increases sharply. Roughly 50-70% of mature oocytes from a 40-year-old woman have chromosomal abnormalities (YOLDEMIR, 2016). Over 50% of embryos are chromosomally abnormal and do not survive beyond the first few days or weeks after fertilization. Between 15-20% of all recognized pregnancies end in spontaneous miscarriage (FRAGOULI *et al.*, 2011).

Chromosomopathies of autosomal and sex chromosomes are pathological states created as a result of numerical or structural chromosomal aberrations. Their prevalence in the general population is not high (0.6%) but in high-risk groups, they occur more often and require timely identification. A study of 3000 amniocenteses revealed a prevalence of chromosomal aberrations of 0.94% (ARTINI *et al.*, 2011). High-risk populations include women >35 years of age, women <20 years, men >50 years, the existence of chromosomal aberrations in the family history and a previous child born with aberration (STOJANOV *et al.*, 2006). The most reliable methods for aberration detection are amniocentesis with karyotyping of cultured amniocytes isolated between 16$^{th}$ and 18$^{th}$ week of gestation (period of the greatest viability of cells) and cordocentesis with karyotyping of cells from the fetal blood culture, isolated after the 20$^{th}$ week of gestation. Invasive methods of prenatal diagnostics enable the identification or exclusion of chromosome aberration by analysing a fetal tissue.

Prenatal diagnostics (amniocentesis and cordocentesis) were introduced into routine procedures at the Clinical Center of Niš in 2004.

The purpose of this study was to determine the type and frequency of genetic disorders/chromosome aberrations in relation to maternal age in South Serbia and to study the impact of the prenatal diagnosis.

## MATERIALS AND METHODS

Prenatal diagnostics was performed at the Pediatric Clinic, Clinical Center of Niš, between 2004 and 2017. This retrospective study included a group of 8830 pregnant women, aged between 18 and 47 years. The material used for the analysis was amniotic fluid obtained by amniocentesis done at the Department of Gynecology and Obstetrics, Clinical Center of Niš.

Amniocentesis was offered to the following risk groups: women older than 35 and younger than 20 years; families where a child had already been born with malformations; women with an increased risk observed by biochemical or ultrasound screening. Amniocentesis was performed between the $16^{th}$ and $18^{th}$ week of pregnancy. 20ml of amniotic fluid was aspirated. The cells in the amniotic fluid are stem, skin and epithelium cells of the urinary tract of the fetus. Isolated cells were cultured in a medium that stimulates cell growth for 10 days. After cytogenetic processing, the obtained karyotype was analyzed with G-banding techniques. Cell cultures of amniotic fluid were performed at the Pediatric Clinic at the Laboratory of Immunology and Genetics, Clinical Center of Niš. The number of failed cultures was less than 1%. Statistical analysis was performed by using percentages. The results are presented in tables and figures.

## RESULTS AND DISCUSSION

In a sample of 8830 amniotic fluid cell cultures, 198 aberrant karyotypes were found (2.24%). Of all the aberrant karyotypes, the most frequent were the ones with numerical aberrations, i.e. 90.4% (n = 179). Constitutive chromosome translocations are the most frequent structural chromosomal abnormalities in humans. Structural aberrations - translocations, inversions (pericentric inversion of chromosome 9 and Robertsonian translocations not included) and deletions were found in 9.6% (n = 19) of karyotypes with chromosomal aberrations (Figure 1).

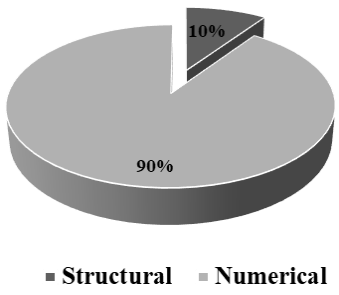


Figure 1. The incidence of structural and numerical chromosomal aberrations

We detected 15 cases of autosomal translocations, two marker chromosomes, one inversion chromosome 1 and one $18q^{+}$. There were Robertsonian translocations involving

acrocentric chromosomes, reciprocal translocation between autosome chromosomes or sex chromosome translocations. An overall frequency of all Robertsonian translocations was 0.11% as shown in Table 1. Of all observed aberrated karyotypes, the highest number of structural aberrations (70.2%) was found in pregnant women whose indication for amniocentesis was age (maternal age >35). Pericentric inversion of chromosome 9 alone was found in 91 of the karyotypes (45.9 % of aberrated ones).

*Table 1. The incidence and type of chromosomal translocations from prenatal diagnosis of 8830 cases*

| Chromosomal translocations | Breakpoint | Number of cases | Balanced/Unbalanced |
|---|---|---|---|
| 45, XY, rob (13;13) | (q10;q10) | 1 | balanced |
| 45, XY, rob (13;14) | (q10;q10) | 5 | balanced |
| 45, XY, rob (15;14) | (q10;q10) | 1 | balanced |
| 45, XY, rob (14;21) | (q10;q10) | 2 | balanced |
| 45, XY, rob (21;21) | (q10;q10) | 1 | balanced |
| 46, XX, t (4;6) | (q13;q31) | 2 | balanced |
| 46, XY, t (4;6) | (q31;q21) | 1 | balanced |
| 46, XX, t (5;8) | (q32;q13) | 1 | balanced |
| 46, XY, t (5;4) | (q21;q34) | 1 | balanced |
| 69, XXY, t (5;22) | (p13;q12) | 1 | unbalanced |
| 46, XY, t (6;13) | (p22;q33) | 1 | balanced |
| 46, XX, t (3;21) | (q13;p12) | 1 | balanced |
| 46, XY, t (4;13) | (q34;q22) | 1 | balanced |
| 46, XY, t (2;4) | (p23;q31.3) | 1 | balanced |
| 46, XX, t (8;20) | (p21.3;13,3) | 1 | balanced |
| 46, XX, /46,XX, t(1;9) | (p31;q23) | 1 | unbalanced |
| 46, XX, t (11;15) | (p15;q10) | 1 | balanced |
| 46, XY, t (14;17) | (q12;q23) | 1 | balanced |

Numerical aberration of autosomal chromosomes was found in 139 pregnant women (77.6%) and the remaining 22.34% (n = 40) were aberrations of the sex chromosomes (Figure 2).

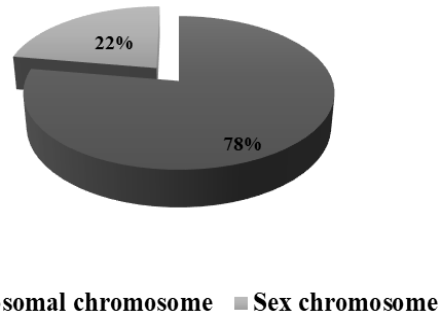


Figure 2. The incidence and type of numerical chromosomal aberrations

The most common autosomal numerical aberration was trisomy 21 (76.3%), the type and frequency of other aberrations are given in Table 2.

*Table 2. The incidence and type of autosomal numerical aberrations*

| Autosomal numerical aberrations | Number of cases (%) |
|---|---|
| Sy Down | 106 (76.3%) |
| Sy Edwards | 27 (19.4%) |
| Sy Patau | 4 (2.9%) |
| 47, XX+M | 1(0.7%) |
| 47, XY+M | 1(0.7%) |
| Total | 139 (100%) |

The highest number of numerical aberrations (75.4%) was found in pregnant women older than 30 years.

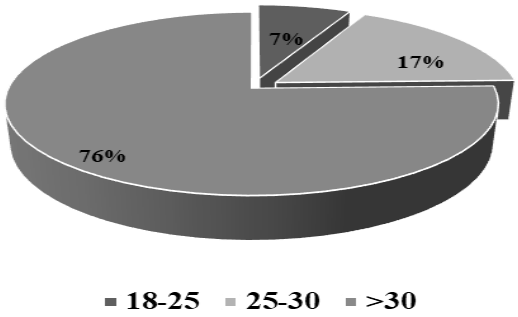


Figure 3. The incidence of numerical aberrations correlated with maternal age

Aberrations of sex chromosomes were determined in 40 cases, where the most frequent one was monosomy of X chromosome, i.e. Turner syndrome, with 52.5% (n = 21). Klinefelter syndrome was present in 15% of cases (n = 6), with all the mothers being older than 35 years. Triploidy – 69, XXX, mainly found during the analysis of spontaneously aborted fetuses, was detected in 5 pregnant women. Other numerical aberrations of sex chromosomes are shown in Table 3.

*Table 3. The incidence and type of sex chromosome numerical aberrations*

| Sex chromosome numerical aberrations | Number of cases (%) |
|---|---|
| Sy Turner | 21 (52.5%) |
| Sy Klinefelter | 6 (15%) |
| Triploidy, 69, XXX | 5 (12.5%) |
| Triple X, 47, XXX | 5 (12.5%) |
| 47, XYY | 2 (5%) |
| 46, XX/XY | 1 (2.5%) |
| Total | 40 (100%) |

The area covered by the Clinical Center of Niš as a reference health center includes territories of Southern and Eastern Serbia with a total population of about two million inhabitants. Since 2004, prenatal diagnostic has been applied in the detection of chromosomal abnormalities. Amniocentesis is performed if pregnant women are older than 35 years or if younger women exhibit certain risk factors. Over a period of 14 years, we carried out 8830 amniocenteses to determine the existence of aberrations in the karyotype of the fetus. The frequency of aberrations was 22/1000, i.e. 2.24%.

The frequency of numerical aberrations was 22/1000, or 2.03%, of which 139 (1.6%) were autosomal and 40 (0.45%) were found on the sex chromosomes. The frequency of structural chromosome aberrations was 2/1000 (0.21%). These results are similar to the ones observed in the study of VASILEVSKA *et al*. (2013), where the overall frequency of all translocation in Macedonia was 0,42%. Pericentric inversion of chromosome 9 was found in 91 karyotypes (1.03%). It represents a balanced structural change considered as a chromosome variant, not an aberration. It is found in 0.85% - 1.65% of the general population, and it does not have any harmful phenotypic effect (YAMADA, 1992).

The most common indication for prenatal diagnostics was the age of pregnant women and the most frequent aberration found within this group was trisomy of chromosomes. Although it is considered that maternal age >35 years represents a risk factor, our study shows a trend of progressive lowering of this limit. Down syndrome (DS) is the most common aberration and it is estimated that in the world it occurs in approximately 1:800 of newborns (SCALA *et al.*, 2006), in the USA 1:732 (SHERMAN *et al.*, 2007). In Serbia, the incidence is 1:733, and in the area of west Serbia 1:721 (DIMITRIJEVIĆ *et al.*, 2013). Significant differences exist when considering maternal age. In pregnant women aged 20 years DS occurs in 0.6:1000, and at the age of 40 years 1:1000 (MORRIS *et al.*, 2003). In most cases, DS is the result of an additional chromosome 21 (SHERMAN *et al.*, 2005).

In our study, 106 (1.2%) fetal karyotypes with trisomy 21 were found, in 71.7% of those, pregnant women were over 30, and in the age range from 18 to 30 years, 28.3% of cases were detected. Similar results were found in the area of north Serbia –Vojvodina (KRSTIĆ, 2006). In the case of subjects aged 30 to 35, in 10 (15%) pregnant women, this trisomy was found (KRSTIĆ, 2006). In a study in the UK in 2000, the overall incidence of Down's syndrome was 2.1% per 1000, or 50% higher than in national reports (WELLESLEY *et al*., 2002). This result suggests that a large number of pregnant women younger than 35 years should be included in additional routine screening programs aiming to detect fetuses with chromosomal aberrations.

Trisomy of chromosome 18, i.e. Edwards syndrome, was found in 27 cases (0.3%). 77.8% of them were found in pregnant women aged older than 30, and 22.2% of them were in the group of women aged 25 to 30 years. These results are similar to the ones from the study of ŠOŠIĆ *et al.* (2017) where the incidence of Edwards syndrome was connected with maternal age.

In 18 identified structural chromosomal aberrations (100%) all pregnant women were older than 30 years, and 22.2% of them were aged between 30 and 35 years. These results were expected because there is strong evidence of the impact of maternal age on the development of these disorders. In our work, in addition to confirming the impact of age on the occurrence of chromosomal abnormalities, we observed the trend of lowering the age limit, which may be below 35 years of age, i.e. 30 years of age, as can be seen from our results. The rate of detected mutations in a group of pregnant women aged 18-30 years was 26 (23.2%).

Bearing in mind that in this age group a large number of numerical aberrations of sex chromosomes was detected (Turner syndrome represented 73%), we believe that a better selection can be achieved by using a combination of ultrasound diagnostics and biochemical markers in the serum of pregnant women in the first trimester. Triploidy – 69, XXX in human genetics is found mainly in cytogenetic analysis of spontaneously aborted fetuses. In 80% of triploidy the additional haploid set of chromosomes is inherited from the father, leading to the development of partial hydatidiform mole, type of pathological pregnancy in which certain placental villi are cystically transformed (ŠOŠIĆ *et al*., 2013.). In our tests, this triploidy was found in 5 pregnant women, accounting for 3.7% of aberrant karyotypes. In the cases where the disorders were found in a fetus, prenatal diagnosis allowed parents to decide on the further course of pregnancy.

Chromosomal translocations are represented in our study with an overall frequency of 0,27%. The frequency of translocations in a balanced state was 0,25% and of translocations in an unbalanced state was 0,02%. There were ten detected Robertsonian translocations in a balanced state (0,11%).

Based on the results of this study, the incidence of chromosome inversion 9 with breakpoints p11q13 was about 1.5%, which is similar to the results previously described in the literature, where this incidence is 1% to 3% in the general population (AMIEL *et al.*, 2001). Chromosome 9 inversion (inv p11q13) has no phenotypic expression because it involves the heterochromatic region of the secondary constriction. In all cases, the karyotype of both parents was analyzed, which showed that inversion was not, in any case, deformed more deeply by one parent.

## CONCLUSION

Application of modern technologies and the increasing knowledge in the field of hereditary and non-hereditary chromosomal aberrations provides access to their diagnosis and prevention. The ideal is striving to identify the couples at risk and performing the assessment before pregnancy. An alternative is to identify those couples in early pregnancy and then allowing them to consider all prenatal diagnostic possibilities. From an individual point of view, chromosomal defects are unfortunate events for parents and represent a public health problem, bearing in mind the continuing decline of the population growth in Serbia. Preventive action, advice, education and the availability of prenatal diagnostics can lead to a significant reduction in the birth of children with various malformations. The desire for healthy offspring is imperative for the family and the whole community, therefore, prenatal diagnosis is the place to achieve this objective.

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# FETALNE HROMOZOMSKE ANOMALIE U JUGOISTOČNOJ SRBIJI - RETROSPEKTIVNA STUDIJA JEDNOG CENTRA

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Izvod

Kongenitalne anomalije uzrok su prenatalne smrti u 20-25% slučajeva, dok se 3% dece rodi sa nekom malformacijom. Mnoge od njih mogu biti otkrivene pre rođenja primenom neivazivnih i invazivnih metoda prenatalne dijagnostike. Cilj ovog rada je utvrđivanje distribucije genopatija u odnosu na godine starosti trudnica, učestalost aberacija i ispitivanje važnosti prenatalne dijagostike na području Južne Srbije. Prenatalna dijagostika rađena je na Klinici za dečje interne bolesti, Kliničkog centra Niš. Ovom retrospektivnom studijom obuhvaćeno je 8830 trudnica, starosti od 18 do 47 godina u periodu od 2004. do 2017. godine. Amniocenteza je rađena između 16. i 18. nedelje trudnoće i uključivala je aspiraciju 20 ml amnionske tečnosti. Izdvojene ćelije kultivisane su u medijumu koji stimuliše rast ćelija u trajanju od 10 dana. Nakon citogenetske obrade dobijeni kariotip analiziran je primenom tehnike G-traka. U uzorku od 8830 plodovih voda utvrđeno je prisustvo 198 aberantih kariotipova – 179 sa numeričkim i 19 sa strukturnim aberacijama, kao što su translokacije, inverzije i delecije. Autozomalne numeričke aberacije bile su prisutne u 85 kariotipova, dok su numeričke aberacije polih hromozoma uočene u 32 uzorka. Najčešća anomalija bila je trizomija 21 (106 slučaja). Najveći broj autozomalnih numeričkih aberacija (84%) uočen je u trudnoćama u kojima su majke starije od 30 godina. Preventivno delovanje i mogućnost da se prenatalna dijagnostika učini dostupnom svakom pojedincu može dovesti do značajnog smanjenja rađanja dece sa različitim malformacijama.

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