INCIDENCE OF TRISOMY 18 PRENATALLY DIAGNOSED BY AMNIOCENTESIS - ONE CENTER EXPERIENCE

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Abstract: *The Trisomy 18 Syndrome (Edwards Syndrome) occurs due to the presence of an extra chromosome 18 (full or mosaic trisomy) or partial trisomy 18q and it is the second most common autosomal trisomy after trisomy 21. The aim of this study was to determine the incidence of the Edwards Syndrome in the population of fetuses whose mothers underwent diagnostic amniocentesis for fetal karyotyping and to display characteristics of individual cases. We performed a retrospective data analysis for 5421 pregnant women who underwent amniocentesis over 11 years. The incidence of fetuses with trisomy 18 is estimated to be 1:493 in pregnancies where amniocentesis was performed (0.2%). It has been noticed that there are significantly more (P<0.5) male fetuses with Edwards Syndrome than female (72.7% vs. 27.3%). These findings are inconsistent with the clinical reports that showed higher prevalence at birth in females.*

Keywords: *trisomy 18, Edwards Syndrome, amniocentesis*

1. INTRODUCTION

The Trisomy 18 Syndrome (Edwards Syndrome) occurs due to the presence of an extra chromosome 18 (full, or mosaic trisomy, or partial trisomy 18q). It is the second most common autosomal trisomy after trisomy 21. Prevalence is approximately 1 in 6000–8000 live births [1]. Edwards et al. and Smith et al. (1960) were the first to describe the trisomy18 syndrome [2, 3].
The most commonly present form is complete or full trisomy (in about 94% of the cases). Mosaicism can be found in less than 5% of cases, and partial trisomy 18 occurs in about 2% of the cases [1, 4].
Maternal origin of an extra chromosome 18 can be found in 90% of the cases, and it is caused by nondisjunction in meiosis II. Other human trisomies show a higher frequency of nondisjunction in maternal meiosis I. Cases with paternal origin of an extra chromosome 18 are in minority. The frequency of trisomy 18 increases with advanced maternal age [1,4]. In the mosaic form, individuals have two cell lines, one with full trisomy 18 and one normal cell line. Partial trisomy 18q is the result of a balanced translocation or inversion in the parent carrier [4].
Two critical extra regions, one proximal (18q12-q21.2) and one distal (18q22.3-qter), which work jointly, are necessary to produce trisomy 18 phenotype [1]. The syndrome phenotype consists of multiple minor and major congenital anomalies. The most common characteristics of trisomy 18 phenotype include mental and growth deficiencies, neonatal hypotonicity followed by hypertonicity, specific craniofacial dysmorphism (prominent occiput, narrow bifrontal diameter, short palpebral fissures, small mouth, narrow palate, malformed ears, micrognathia), hands with the 2nd finger overlapping the 3rd and the 5th finger overlapping the 4th, short dorsiflexed hallux, small hypoplastic nails, rocker bottom feet, short sternum, hernias, single umbilical artery, small pelvis, cryptorchidism, hirsutism, structural cardiac anomalies in more than 90% cases, and death within a few weeks from birth [5,6]. Crider et al. (2008) have published the study with the finding that prevalence of trisomy 18 at birth is higher in females in comparison to males, but among electively terminated fetuses occurance is similar in both sexes [7].
In this study we determined the incidence of fetuses with trisomy 18 in central Serbia among pregnant women who underwent amniocentesis over 11 years.

2. MATERIALS AND METHODS

This study included a group of 5421 pregnant women who underwent invasive prenatal diagnosis (amniocentesis) at the Department for Cytogenetic Diagnosis, Clinic of Obstetrics and Gynecology in the Clinical Centre of Kragujevac, Serbia.
Criteria for invasive prenatal diagnosis included: years of life (over 35 years at the time of conception), abnormal biochemical values of fetal markers in maternal serum, abnormal fetal ultrasound markers, present multiple congenital anomalies in fetuses or newborns in previous pregnancies, hereditary genetic diseases in the family, structural and numerical chromosomal aberrations in one of the parents.

Diagnostic amniocentesis was performed between 16 -18 NG. A sample of amniotic fluid was cultured in vitro for 10-15 days. Isolation, preparation, and staining of chromosomes with the G-band technique were carried out according to the standard procedure. Metaphase chromosomes were analyzed with magnification of 1000x under the light microscope (Leica DM 2500) and interpreted according to the international system for human cytogenetic nomenclature (ISCN) [8].
A retrospective analysis of all obtained karyotypes, as well as analysis of anamestic data for 11 karyotypes with trisomy 18 (Edwards Syndrome), was performed.

3. RESULTS

In our work 5421 amniocentesis were performed. In the examined time period, among all preformed amniocentesis, a sample of 11 trizomies 18 (Sy Edwards) was detected (0.2%). In the given sample, there were 10 (90.9%) full trisomies 18, and one (0.1%) male karyotype with present balanced Robertsonian translocation of chromosomes 13 and 14 with trisomy of chromosomes 18 (46,XY,t(13;14)(p11;p11)+18).
Mean age of mothers whose fetuses had trisomy 18 was 33.27 ± 6.65 (ranging from 21 to 41). Five of them were younger than 35 years old and six were aged 35 years and over.
None of the pregnant women with fetal trisomy 18 had previous spontaneous abortions, IUFD, fetal anomalies, or children with multiple congenital anomalies. These pregnant women were healthy, without the presence of chronic diseases, genetic diseases or chromosomal aberration, or carriers of balanced chromosomal aberrations in their families.
Indications for prenatal diagnostic procedure (amniocentesis) in the group of pregnant women with fetal trisomy 18 were, in most cases, the mother's years of life and the abnormal value of the biochemical markers screening of the first trimester - Double Test (81.8%), followed by 9.1% of abnormal findings of ultrasound markers (one fetus with NT>5.8 mm), and 9.1% abnormal findings of Double test and congenital anomaly (cystic formations on the neck size 5.7 mm in one fetus) (Table1).
For most women with fetal trisomy 18, this was the second pregnancy (63.6%), without previous spontaneous abortions and with one healthy child previously born, followed by 4th pregnancy in two pregnant women with three healthy children previously born. In the observed group of pregnant women, the highest cumulative presence of trisomy 18 occurred in the first three pregnancies (81.8%) (Table 2).
Biochemical markers screening of the first trimester - Double Test in pregnant women with established presence of fetuses with trisomy 18 by amnicentesis showed a risk of 1:48 to 1: 343 for Tr 21 and from 1: 5 to 1:14 for Tr 13/18. The NT values ranged from 1.9 mm to 5. 8 mm with an average value of 3.3 ± 1.82 mm.
In our sample of mothers of fetuses with trisomy 18 we haven't found any statistically significant differences in the number of pregnancies, the number of patients who are <35 years versus ≥35 years, and in the indications for amniocentesis.
The fetal karyotypes showed the presence of 8 (72.7%) fetuses of the male sex (47, XY + 18) and 3 (27.3%) fetuses of the female sex (47, XX + 18). The incidence of Edwards Syndrome in male fetuses was found significantly higher than that in female fetuses ($P< 0.05$) (Figures 1)

3.1. Tables

Table 1: Indications for amniocentesis in the group of pregnant women with fetal trisomy 18

Indications for amniocentesis	Frequency (N°)	Valid percentage (%)	Cumulative percentage (%)
Age	5	45.5	45.5
Double test	4	36.4	81.8
Ultrasound markers	1	9.1	90.9
Double test and congenital anomaly	1	9.1	100.0
Total	11	100.0	

Table 2: Distribution of consecutive pregnancies in pregnant women with established presence of fetuses with trisomy 18

Pregnancy in order	Frequency (N°)	Valid percentage (%)	Cumulative percentage (%)
1st	1	9,1	9,1
2nd	7	63,6	72,7
3rd	1	9,1	81,8
4th	2	18,2	100,0

3.2 Figure

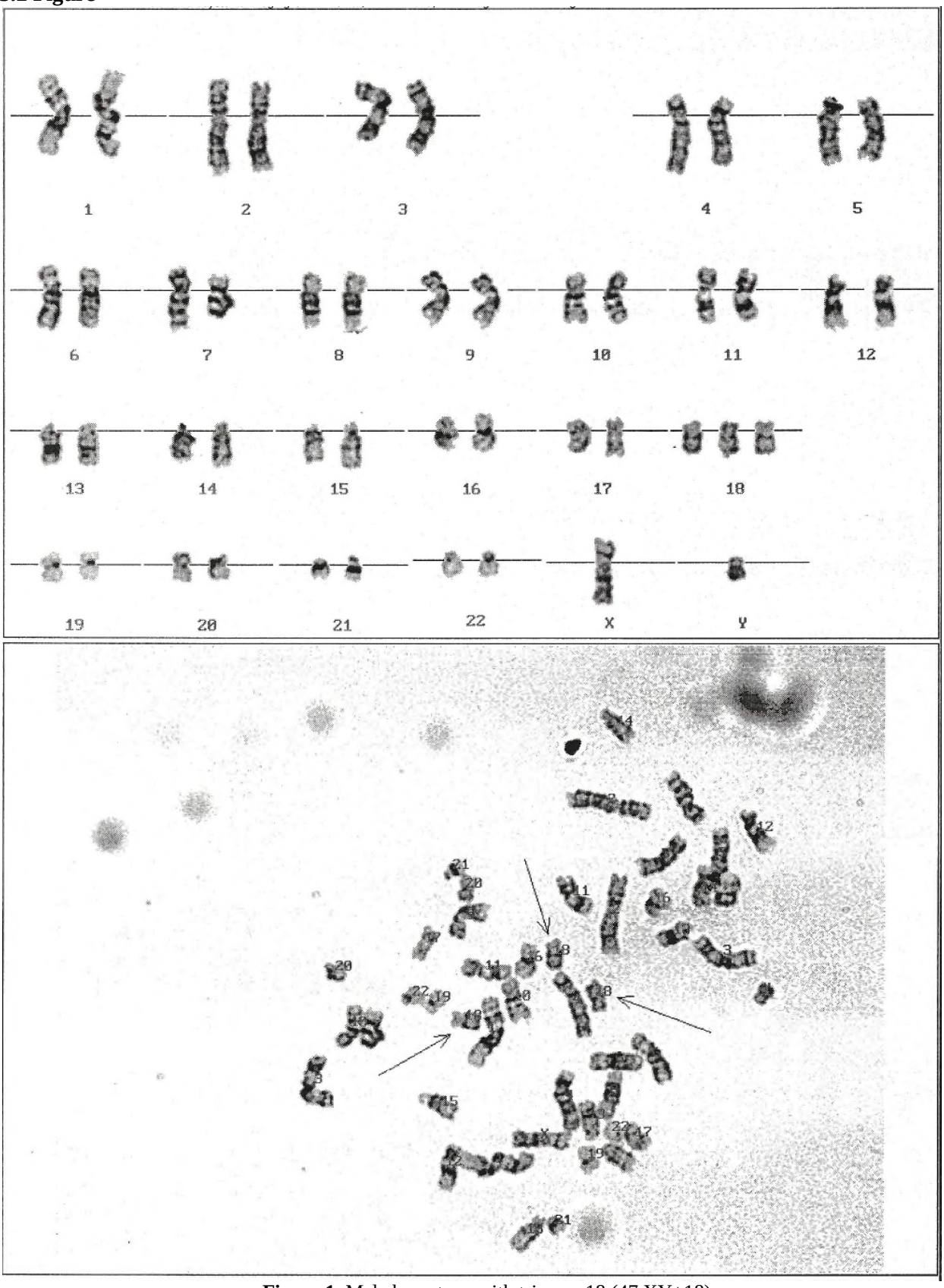

Figure 1. Male karyotype with trisomy 18 (47,XY+18)

4. DISCUSSION

The prevalence of trisomy 18 in liveborns is 1: 6000/1:8000, but the overall prevalence is higher (1/2500-1/2600) due to the high frequency of fetal death and pregnancy termination after prenatal diagnosis [4]. In our work, the prevalence of trisomy 18 among pregnancies which underwent amniocentesis was 0.2%, which coincided with the results of previous studies.
The noninvasive screening in the first trimester is based on a combination of maternal age-related risk, ultrasonografic "soft marker" (nuchal translucency and nasal bone) and two maternal serum biochemical markers, free beta human chorionic gonadotropin (FbhCG) and pregnancy associated plasma protein A (PAPP-A) are now being applied routinely and have high sensitivity for the diagnosis of trisomy 18 [4].
Maternal serum markers are significantly lower in pregnancies with trisomy 18. The most present ultrasonographic markers are increased nuchal translucency (NT) and the absence or hypoplasia of the nasal bone [4]. Previous works have shown an increased tendency for fetal trisomies with advancing maternal age. Savva et al. has shown that the prevalence of trisomy 18 is constant until age 30, then increases exponentially before beginning to become constant again at age 45 [9].
In this study we have identified one case of fetal trisomy 18 based on sonographic findings, one case on the combination of Double test and sonographic findings, four based on maternal serum biochemical markers, and five were in relation with advancing maternal age. There weren't any statistical differences between indications for amniocentesis in mothers of fetuses with trisomy 18. In this sample the number of mothers under the age of 35 did not differ from the number of mothers over 35 years of age.
The recurrence risk, for a family with a child with complete trisomy 18 is about 1%. The recurrence risk in families with partial trisomy 18 could be higher than in those with full trisomy 18 [4]. In our study, we identified pregnancies with complete trisomy 18. From previous pregnancies all of the mothers had normal healthy children.
Most fetuses with Edwards syndrome die during the embryonic and fetal life. Neonatal and infant mortality is high. The median of survival among live births has usually varied between 2.5 and 14.5 days [10]. There is 50% chance of survival beyond one week [11]. 5-8% of infants with trisomy 18 live until their first birthday without special care [4].
The prevalence at birth is higher in females compared to males (F: M %, 60.4), but this difference is not present among electively terminated fetuses (F:M % 48:51.) [4] The studies have shown that the fetal death is higher for males compared to females [12, 13].
In ours results we have found discordance in sex ratio for trisomy 18 fetuses and difference in sex ratio with more male fetuses. (M:F % 72.7:27.8) (P <0.05).

5. CONCLUSION

In this study, we presented the results of detected trisomies 18 after amniocentesis in a period of 11 years in the female population of central Serbia.
We have shown that in prenatal screening for fetal aneuploidy an equal risk is indicated by advanced years of mother's life, maternal serum screaning and ultrasonographic markers. After amniocentesis, the obtained karyotypes in our study showed the presence of a larger number of male fetuses with trisomy 18, which is inconsistent with the clinical reports that showed higher prevalence at birth of trisomy 18 in female neonates.
These findings can be explained by the higher rate of elimination of male fetuses with trisomy 18 in comparison with female fetuses.

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