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THE FREQUENCY OF CHROMOSOMAL ABNORMALITIES DIAGNOSED PRENATALLY IN A ROMANIAN POPULATION

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ABSTRACT

Introduction: Chromosomal abnormalities are an important cause of congenital anomalies and pregnancy loss, occurring in approximately 1 of every 150-200 live births. The aim of this study was to evaluate the incidence and type of chromosomal abnormalities in high risk pregnancies using standard cytogenetic technique. **Methods**: A total of 465 amniotic fluid samples were analyzed by conventional karyotyping at Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Romania. **Results**: The indications for prenatal cytogenetic testing were as follows: abnormal results of combined or triple test (43%), fetal anomalies detected using ultrasound examination (32%), advanced maternal age (21%) and positive family history (4%). Abnormal karyotypes were detected in 27 of 465 cases (5.8%). Numerical abnormalities were observed in 4.3% of cases, trisomy 21 being the most common (2.7%), followed by trisomy 18 (0.6%). Structural rearrangements such as robertsonian translocation or duplications were detected in 1.5% of cases. **Conclusion:** This study confirms the importance of conventional cytogenetic analysis in the prenatal diagnosis for detection of large chromosomal abnormalities.

KEYWORDS: Prenatal diagnosis, amniotic fluid, karyotype, chromosomal abnormalities.

INTRODUCTION

Chromosomal abnormalities are a leading known cause of congenital abnormalities and pregnancy loss,[1,2] occurring with a frequency between 1:150 and 1:200 live-born babies.[3]

Conventional cytogenetic analysis remains one of the most used genetic methods for prenatal diagnosis in many genetic laboratories, despite the widespread application of molecular genetic testing. The karyotype is highly reliable for detection of numerical chromosome abnormalities (aneuploidies and polyploidies) and large structural rearrangements higher than 5-10 megabases. The major limits include the requirement of fresh tissue, delay in obtaining results (usually at least 2 weeks) and failure to detect structural chromosomal abnormalities smaller than the achievable optical resolution.[4] For prenatal diagnosis, the samples are obtained by invasive procedures, either chorionic villus sampling in the first trimester or amniocentesis in the second trimester of pregnancy.[5] The ultrasound findings suggestive for a genetic disease, abnormal biochemical screening, positive results of cell-free DNA screening, increased maternal age, presence of a balanced structural abnormality in a parent or a chromosomal abnormality in a previous child are the main reasons for invasive prenatal cytogenetic diagnosis.[6-8]

The aim of our study was to evaluate the frequency and type of chromosomal abnormalities in high risk pregnancies using karyotype analysis of amniotic fluid cells in Oltenia region, Romania.

METHODS

This retrospective study was carried out in Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Romania. A total of 465 prenatal amniotic fluid samples were included in the study, between 2013 and 2017. Genetic counseling has been provided to all patients and signed informed consent was obtained from all pregnant women to use data and sample for research studies. The study was approved by the Ethics Committee of University of Medicine and Pharmacy of Craiova, Romania.

Conventional cytogenetic analysis was performed using flasks method. Long-term cultures from amniotic fluid were established using complete cell culture medium

(Amniomax, Life Technologies, Thermo Fisher Scientific) in 2 or 3 separate flasks in a humid environment at 37 ºC with 5% CO2. After 10-11 days, the cells were arrested by colcemid in metaphase. After chromosome harvesting, standard cytogenetic methods were applied to obtain spread chromosomes on the slides. G-bands were induced by trypsin treatment and a resolution of at least 400 bands was obtained. Minimum 20 metaphases were analyzed for each case and the karyotypes were described in accordance with the International System for Human Cytogenetic Nomenclature (ISCN) 2013.[9]

RESULTS

A total of 465 amniotic samples were analyzed by conventional cytogenetic analysis. In our study, the amniocentesis indications were as follows: altered maternal serum screening results (43%), abnormal ultrasound findings (32%), advanced maternal age (21%) and previous child with congenital anomaly or family history of chromosome aberration (4%). The mean age of included women was 32.7 years (range: 18 to 44 years). According to ISCN (2013), heterocromatic variants, pericentric inversion of chromosome 9 and double satellites or marked satellites on acrocentric chromosomes were considered normal variants. Abnormal karyotypes were detected in 27 of 465 cases (5.8%). Among these cases, 14 (52%) had abnormal ultrasound findings, 11 (41%) had altered biochemical marker screen test and in 2 cases (13.6%) advanced maternal age was recorded. The spectrum of detected chromosomal abnormalities is shown in Table 1.

Table 1: The frequency and type of chromosomal findings.

Karyotype	Cases (%)
Normal	438 (94.2%)
Abnormal	27 (5.8%)
Numerical abnormalities	
- trisomy 21	14 (3.00%)
- trisomy 18	4 (0.87%)
- mosaic trisomy 20	1 (0.22%)
- monosomy X	1 (0.22%)
Structural rearrangements	
- robertsonian translocation	2 (0.44%)
- duplication	2 (0.44%)
- inversion	1 (0.22%)
- deletion	1 (0.22%)
- small chromosome marker	1 (0.22%)

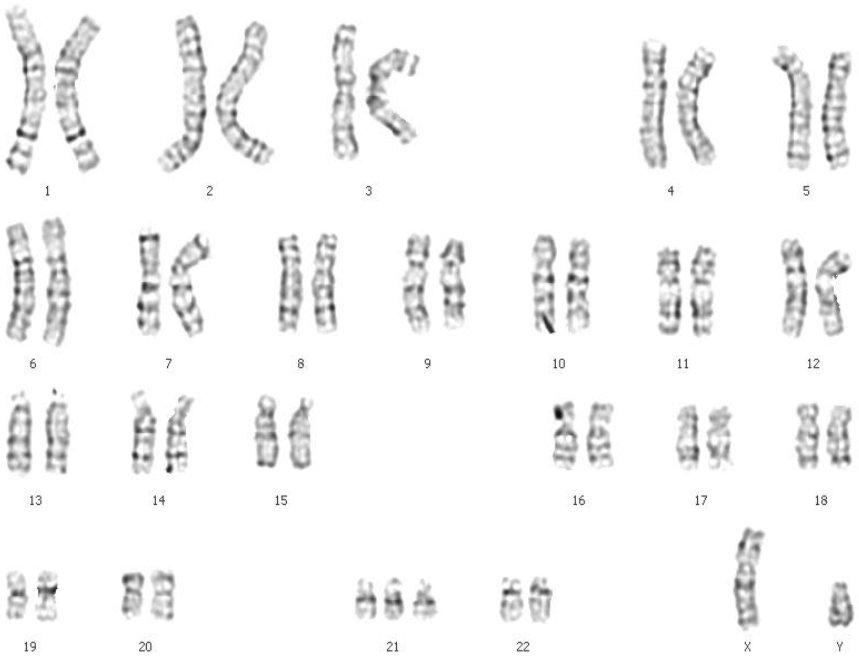

Figure 1: 47,XY,+21 karyotye – trisomy 21.

Numerical abnormalities were detected in 20 cases (4.3%), trisomy 21 being the most common (14 cases - 2.7%) (Fig. 1), followed by trisomy 18 (4 cases - 0.6%). The mosaic trisomy 20 and the monosomy X were each detected in one case (0.2%).

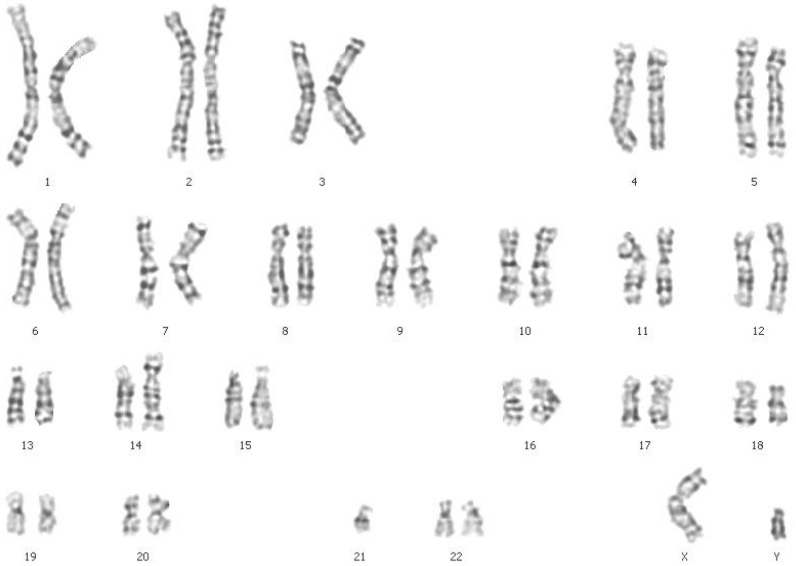

Figure 2: 45,XY,rob(14;21)(q10;q10) karyotype – robertsonian translocation.

Structural abnormalities were found in 7 samples: robertsonian translocations in 2 cases (Fig. 2), duplications in 2 cases, inversion in 1 case, deletion in 1 case and small supernumerary chromosome marker in 1 case.

DISCUSSION

In this study, we evaluated the incidence and type of chromosomal abnormalities in amniotic fluid samples using conventional cytogenetic analysis. In the prenatal testing, the diagnosis accuracy of chromosome analysis in cultured amniotic fluid cells seems to be slightly increased compared to chorionic villus sampling.[10] In our study, the invasive procedure was performed between 15 and 25 weeks of gestation, in the most cases between 17-19 weeks. Similar to other studies the most frequent indications for amniocentesis were positive maternal serum screening, abnormal ultrasound findings and advanced maternal age. We found numerical abnormalities in 4.3% and structural in 1.5% of cases. So far, the most frequent single abnormality was trisomy 21 (3%). The reported incidence of prenatal chromosomal abnormalities is variable, while some studies indicated similar results with our finding, others found different values. Interestingly, another study conducted in a Romanian cohort showed a higher incidence of chromosomal abnormalities (7.09%) than our findings, mainly due to an increased incidence of structural rearrangements (4.50%). This marked difference can be attributed to the inclusion of heteromorphic variants such as pericentric inversion of chromosome 9.[11] Pergament et al. found an incidence of 4.58% chromosomal alterations in a cohort consisting of 3969 American women. In a large Korean study, including 31615 cases, chromosomal abnormalities were detected in 973 cases (3.1%). Numerical abnormalities were seen in 595 cases (1.9%), trisomy 21 being the most common and among of the 378 cases (1.2%) with structural abnormalities, most were reciprocal translocations between two autosomes.[12] Different values were reported in another Korean cohort with a lower number of samples, the incidence of numerical and structural abnormalities being 3.85% and 0.7% respectively.[13] Another Asian study conducted in Taiwan found an incidence of 2.90% chromosomal abnormalities (2% were numerical and 0.9% structural abnormalities).[14] Also, in a Turkish collaborative study, Karagouz et al. showed an incidence of abnormal karyotypes of 3.0% (2.1% numerical and 0.9% structural aberrations).[15] Furthermore, a higher incidence of chromosomal abnormalities was reported in Brazilian and Western Indian populations, where chromosomal frequencies of 8.4% and 7.2%, respectively were reported.[16,17]

A potential explanation for our results and different published findings on various populations can include the bias associated with selection and screening of patients or the inclusion of normal variants such as pericentric inversion of chromosome 9.

In conclusion, conventional cytogenetic analysis maintains an important role as a prenatal diagnostic tool in detecting numerical and large structural chromosomal abnormalities.

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