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Prenatal karyotype results from 2169 invasive tests

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ABSTRACT

Objectives: Foetal karyotyping is a basic tool used to diagnose the most common genetic syndromes. Although new molecular methods such as FISH, MLPA or QF-PCR allow rapid prenatal testing, they are of limited value when diagnosing less frequent chromosomal abnormalities. Chromosomal microarray analysis offers higher test resolution than traditional karyotyping and has been recommended as first-line genetic testing in prenatal diagnosis.
The aim of the study was to confirm whether foetal karyotyping remains a valid approach to prenatal diagnosis by analysing its performance in a large population of pregnant women with a high risk of chromosomal aberration.

Material and methods: An analysis was performed of 2169 foetal karyotypes from two referral university centres for prenatal diagnostics in Lodz, Poland.

Results: Amniocentesis and foetal karyotyping were performed when screening methods had indicated a high risk of chromosomal aberration, or when prenatal ultrasound had proved foetal abnormality. The study group included 205 (9.4%) abnormal foetal karyotypes. Rare aberrations were observed in 34 cases (*e.g.*, translocations, inversions, deletions and duplication). A marker chromosome was present in five cases.

Conclusions: One third of the chromosomal abnormalities observed in the prenatal tests were rarer aberrations (i.e., not trisomy 21, 18 or 13). As many of these could not be detected by the new molecular methods, foetal karyotyping remains an important component of prenatal diagnosis.

Key words: amniocentesis; genetic testing; karyotype

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INTRODUCTION

Foetal karyotyping is a basic diagnostic tool used for identifying the most common genetic syndromes such as Down syndrome, Edwards syndrome or Patau syndrome. It can also detect other less frequent genetic abnormalities, such as balanced and unbalanced chromosomal rearrangements. Foetal karyotyping is available at most genetic centers, it often forms the basis for prenatal genetic counselling and may also be used in genetic testing among family members.

However, foetal karyotyping suffers from low resolution and requires a comparatively long time to perform. In contrast, rapid diagnostic methods like QF-PCR, MLPA or FISH are becoming cheaper and more available and are gaining popularity in genetic centres.

A chromosomal microarray analysis (CMA) offers higher test resolution than traditional G-band karyotyping and provides additional information in 6–7% of pregnancies with abnormal ultrasound findings. CMA has been recommended as first-line genetic testing in prenatal diagnosis [1]. CMA and rapid molecular methods cannot be used to examine the chromosomal structure and cannot differentiate between simple chromosomal trisomy and trisomy caused by chromosomal translocation. The newest genetic technics like whole exome sequencing (WES) improved the identification of genetic disorders in fetuses with structural abnormalities and showed an underlying genetic cause in 10% of fetuses that were negative in karyotype and CMA [2].

To determine whether foetal karyotyping still plays an important part in prenatal diagnosis, the present study examines its use in a large population of pregnant women with a high risk of chromosomal aberration.

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MATERIAL AND METHODS

The study was performed at the Department of Clinical Genetics and the Department of Foetal Medicine and Gynecology of the Medical University of Lodz. All amniocentesis results obtained through the operation of the clinic between 2005 and 2015 were analyzed. After 2015, the routine karyotype assessment was abandoned, and most tests were performed using chromosomal microarray analysis. Invasive diagnostics were performed in the case of advanced maternal age, positive screening test results, the presence of foetal defects indicated by foetal ultrasound, or chromosomal aberrations in at least one parent.

The amniotic fluid samples were cultured for conventional cytogenetic analysis according to standard protocols. The chromosomes obtained in the metaphase were subjected to Giemsa staining after trypsin treatment and analyzed on the Cytovision karyotyping platform. The results of chromosome analyses were grouped as normal or abnormal. In the case of structural abnormalities in the fetus, karyotyping was also performed in the parents.

RESULTS

Of 2169 analyzed cases, 205 (9.4%) abnormal foetal karyotypes were identified. The most common abnormality was Down syndrome, which was diagnosed in 93 cases. Among these, simple trisomy 21 was found in 90 cases and Robertsonian translocation in three cases. In addition, 32 cases of Edwards syndrome and 18 cases of Patau syndrome were identified. Two cases of Patau syndrome were caused by Robertsonian translocations. Abnormalities other than trisomy 21, 18 and 13 were found in 62 (30%) out of 205 positive cases. Turner syndrome was present in 17 cases, Klinefelter syndrome in three cases and triploidy in eight cases. Table 1 lists all cases of aneuploidy. Rare chromosomal aberrations were identified in 34 cases. Structural aberrations cases included 21 translocations, nine inversions, two deletions and one duplication. A marker chromosome was observed in five cases. In cases where structural aberrations were observed in the fetus, karyotyping was also performed in both parents (Tab. 2 and 3).

DISCUSSION

Foetal karyotyping revealed the presence of chromosomal abnormalities in 9.4% of the 2169 tested pregnant women with a high risk of such abnormalities. Similar frequencies have been recorded by other studies [3]. Small differences were observed among the study groups, and these may be attributed to variations in selection criteria. Our present findings confirm that trisomies 21, 18 and 13 were the most common aberrations, accounting for 70% (143/205) of all positive results. In most cases, these were simple trisomies. Robertsonian translocations were observed in 3.2% of fetuses with trisomy 21 and 11% of fetuses with trisomy 13. The remaining 30% of aberrations comprised sex chromosome abnormalities, triploidies, monosomy 13, marker chromosomes and structural changes. Previous studies have found chromosomal aberrations other than trisomies 21,18 and 13 to be present in about 50% of positive cases [4, 5].

Our results confirm that many of the chromosomal abnormalities present in the sample could not be detected by the new rapid molecular methods, like FISH, MLPA or QF-PCR. The most frequent structural aberrations observed in our study were chromosomal translocations, most of which were balanced (76%). While such balanced translocations may not cause any abnormalities in a fetus, this finding may be used in genetic testing among other family members. Balanced chromosomal translocations accounted for 0.7% (16/2169) of the study group. Karyotyping remains the most sensitive method for detecting balanced transloca-

Table 1. Aneuploidy

Karyotype	No	
Trisomy 21	93	Three cases with Robertsonian translocations and one case with mosaicism
Trisomy 18	32	One case with karyotype 48,XYY,+18
Trisomy 13	18	Two cases with Robertsonian translocations
Triploidy	8	
Turner syndrome	17	Two cases with mosaicism
47,XXY	3	
Mos 46,XY,-13,+mar[9]/46,XY[13]	1	Normal parental karyotypes
Mos 47,XY,+mar[81]/46,XY[5]	1	Normal parental karyotypes
Mos 46,XX[18]/47,XX,+mar[4]	1	Normal parental karyotypes
47,XY,+mar	1	The same marker in maternal karyotype
47,XX,+mar	1	Normal parental karyotypes

Table 2. Translocations (n = 21)

Fetal karyotype	Maternal karyotype	Paternal karyotype
45,XX,der(13;14)(q10:q10)		
45,XY,der(13;14)(q10;q10)pat	46,XX	45,XY,der(13;14)(q10;q10)
45,XY,der(13;14)(q10;q10)		
46,XY,t(7;20)(q32;p11.2)		
46,XX,t(15;18)(q21.3;q22~q23)mat	46,XX,t(15;18)(q21.3;q22~q23)	46,XY
46,XX,t(2;9)(q33;p23)mat	46,XX,t(2;9)(q33;p23)	46,XY
46,XX,t(5;16)(q33.1;p11.2)pat	46,XX	46,XX,t(5;16)(q33.1;p11.2)
46,XX,t(6;8)(p12;p12)pat	46,XX	46,XX,t(6;8)(p12;p12)
46,XY,?der(21)t(6;21)		
46,XY,t(3;10)(p21.1;q26.1)mat	46,XY,t(3;10)(p21.1;q26.1)	46,XY
46,XY,t(3;6)(q21;q11)mat	46,XY,t(3;6)(q21;q11)	46,XY
46,XY,t(3;9)(q21;p13)pat	46,XX	46,XY,t(3;9)(q21;p13)
46,XY.ish der(15)t(3;15)pat	46,XX	46,XY.ish der(15)t(3;15)
46,XY,t(11,12)(p11.12;q24.33)		
46,XX,t(4;20)(q21:p13)		
46,XX,t(14:16)(q23:q23)		
46,XY,+21,der(21;22)(q22;q11)		
46,XY,+21,der(21;21)(q10:q10)	46,XX	46,XY
46,XX,+21,der(14;21)(q10;q10),		
46,XX,+13,der(13;14)(q10:q10)		
46,XY,+13,der(13;22)(q10;q10)		

Table 3. Other structural aberrations (n = 18)

Fetal karyotype	Maternal karyotype	Paternal karyotype
46,XY,ins(16)(p13.1q13q23.2)	46,XX,inv(9)(q21.1~q21.2q33~q34.1)	46,XY,ins(16)(p13.1q13q23.2)
46,XX,inv(9)(q21.1~q21.2q33~q34.1), ins(16)(p13.q13q23.2)	46,XX,inv(9)(q21.1~q21.2q33~q34.1)	46,XY,ins(16)(p13.1q13q23.2)
46,XX,?inv(11)(p15?q14).ish		
46,XX,inv(10)(p11.2;q21.2)	46,XX,inv(10)(p11.2;q21.2)	46,XX
46,XX,inv(10)(p11.2q21)pat	46,XX	46,XX,inv(10)(p11.2q21)
46,XY,inv(9)(p11q13)		
46,XY,inv(9)(p11q13)		
46,XX,inv(9)(p11q13)		
46,XX,inv(9)(p11q13)		
46,XY,inv(9)(p11q13)		
46,XX,del(18)(p11.1)	46,XX	46,XY
46,XY,del(7)(p?15),7ps,add(22)		
46,XY,dup(3)(p21p26)		

tions, and the presence of abnormalities in fetal karyotype may indicate the presence of chromosomal aberrations in parents and other family members. Therefore, the karyotypes both parents were also examined in ten out of the 21 cases displaying translocation. In nine of these cases, the translocation was found to be inherited from one of the parents. In a similar study of 3800 karyotypes, Zhang et al. [6] found balanced translocation to be present in 0.4% of cases and that balanced translocations were more frequently inherited from fathers than mothers. In contrast, balanced translocations were found to be transmitted almost equally from mothers and fathers in the present group.

Eight of the 21 (38%) translocations identified in the present study were Robertsonian translocations, and five of these were unbalanced. Balanced Robertsonian translocations are the most commonly observed chromosome rearrangements in humans, with a frequency of 1 in 1,000 in newborn surveys [7]. Robertsonian translocations of chromosomes 13 and 14 constitute nearly three quarters of all Robertsonian translocations [8]. In our group, Robertsonian translocations were observed in chromosomes 21, 22, 13 and 14 with similar frequencies. Unbalanced Robertsonian translocations can occur *de novo* in the fetus or can be inherited from a parent who is a carrier of a balanced Robertsonian translocation. Carriers of Robertsonian translocations are at greater risk of having another child with the same trisomy. Both balanced and unbalanced Robertsonian translocations can be best diagnosed though karyotyping, as the results allow a simple trisomy to be to distinguish from one derived by translocation. Therefore, in all cases with trisomy 21 or trisomy 13 detected by molecular techniques, further karyotype assessment should be performed in foetus or both parents. It will allow us to exclude them as Robertsonian translocation carriers and to provide genetic counseling for the family.

Nine inversions were identified in our study. Five of them were pericentric inversions in the heterochromatic regions of chromosome 9, what is a common (1–3%) heteromorphism in the general population. However, many reports suggest that this inversion may be associated with subfertility, recurrent abortions and some abnormal clinical conditions [9–11].

The diagnosis and interpretation of results is always complicated by the presence of mosaicism and marker chromosomes. Six cases of mosaicism were identified in the present study: two with Turner syndrome, one with trisomy 21, one with monosomy 13 and two with a marker chromosome. Although mosaicism is not a very common finding, it can make genetic counseling more complicated because the prognosis is difficult to estimate. Marker chromosomes are structurally abnormal chromosomes that have a broad spectrum of clinical consequences ranging from normal phenotype to severe disorders. Marker chromosomes are often seen in patients with developmental disorders. Five cases were observed in the present study (0.23%), three of which were mosaic, and only one case was inherited from a mother. Previous studies have found marker chromosomes to be present in 0.075% of unselected prenatal cases [12]. The higher incidence identified in the present analysis might be due to the different selection criteria. A molecular method like CMA or FISH is usually required to assess the genotype-phenotype correlation in cases with marker chromosomes. Only two deletions and one duplication were diagnosed. Interestingly, the frequency of deletions of 0,09% was the same as that reported in a previous study (0.09%) [13]. This low detection rate of deletions and duplications may be caused by the low resolution of karyotyping. The diagnosis of chromosomal deletions and duplications has improved significantly since the use of chromosomal microarray analysis (CMA) [1]. The karyotype is not a good diagnostic tool for detecting deletions and duplications.

CONCLUSIONS

Trisomy 21, 18, and 13 accounted for two-thirds of the identified chromosomal abnormalities, the remaining third were rarer aberrations, including balanced aberrations. Rapid molecular methods and CMA will not detect balanced aberrations and do not distinguish between simple trisomy and Robertsonian translocation. Therefore, foetal karyotyping remains an important component of prenatal diagnosis.

Conflict of interest

All authors declare no conflict of interest.

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