

# Fetal karyotype: can we always trust its result?

## Cariótipo fetal: podemos confiar sempre no seu resultado?

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### ABSTRACT

We retrospectively investigated six cases of discrepancy between prenatal fetal karyotype and postnatal findings. In five cases, the chromosomal abnormalities initially found by CVS or amniocentesis were not confirmed by later analyses and postnatal examination. In one case, the fetal karyotype found to be normal by CVS had to be checked due to sonographic features and clinical anomalies found after birth. In most cases, the normal development on sonographic examination raised the doubt about the abnormal fetal karyotype. Discrepant findings between fetal karyotype results and sonographic findings require great caution in their interpretation and counseling of parents. Placental confined mosaicism seems to be the most frequent cause of such discrepant results. The interpretation of fetal karyotype results should always be correlated with sonographic and clinical findings.

**Keywords:** Prenatal diagnosis; Karyotyping; Mosaicism; Chorionic villus sampling; Amniocentesis; Uniparental disomy; Case reports

### RESUMO

Estudo retrospectivo de seis casos em que houve discrepância entre cariótipo pré-natal e achados pós-natais. Em cinco deles as anomalias cromossômicas que foram encontradas inicialmente pela biópsia de vilosidades coriônicas ou amniocentese não foram compatíveis com resultados posteriores. Já em um caso, o cariótipo inicial normal pela biópsia de vilosidades coriônicas necessitou de novo controle devido ao aparecimento de sinais ultra-sonográficos pré-natais e sinais clínicos pós-natais. Na maioria dos casos a evolução favorável ultra-sonográfica foi o que levantou a dúvida sobre o cariótipo inicial anormal. Quando os achados ultra-sonográficos são discordantes do cariótipo encontrado inicialmente, muita cautela é necessária na interpretação dos resultados e no aconselhamento genético desses casais. O mosaicismismo confinado à placenta é uma das principais

causas de resultados discordantes. Desta forma, a interpretação do cariótipo fetal depende da correlação com os achados clínicos/ultra-sonográficos pré-natais.

**Descritores:** Diagnóstico pré-natal; Cariotipagem; Mosaicismismo; Biópsia da vilosidade coriônica; Amniocentese; Dissomia uniparental; Relatos de casos

### INTRODUCTION

With the advances in prenatal diagnosis and screening of chromosome anomalies, fetal karyotype analysis by chorionic villus sampling (CVS) has been increasingly used. Since it is performed between the 11<sup>th</sup> and the 14<sup>th</sup> weeks, CVS allows an earlier diagnosis compared to amniocentesis, which is usually performed only after 15 weeks.

The main indications for its performance are: advanced maternal age, a history of chromosome disorder, malformations detected by fetal ultrasound and, more recently, an indication of elevated risk by first trimester screening, when nuchal translucency (NT) measurements and other sonographic and maternal markers are evaluated (serum biochemistry: PAPP-A and free beta HCG).

The most commonly used techniques for karyotype analysis by CVS are: direct preparation and culture. In the direct preparation, the evaluation is done on the cytotrophoblast, in which the chromosomes are analyzed in spontaneous mitoses of cells, with a quick result (three to five days) and without the risk of contamination by maternal cells. Cell culture allows a

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more refined analysis of chromosomal structures, but the result can take ten to 20 days. The association of both methods allows reducing the risks of false-positive and false-negative results of each technique, besides allowing elucidation of some structural anomalies and the presence of mosaicism<sup>(1)</sup>.

It is expected that the karyotype result found in the trophoblast tissue represents the fetal karyotype, once they both develop from the same zygote. However, in approximately 2% of cases, the karyotype obtained from the chorionic villus may reveal a cytogenetic anomaly characterized by the finding of two different cell lines, determining the presence of a placental mosaic.

In most cases this alteration is present only in the placenta, not being identified in the fetus<sup>(2-5)</sup>. This situation is named confined placental mosaicism (CPM) and can be associated by the end of pregnancy with growth restriction without an apparent cause (idiopathic)<sup>(6)</sup>. However, in ten to 23% of cases, this may represent a true mosaicism, in which the chromosomal alteration is present both in the placental tissue and in the fetus.

Detection of mosaicism by CVS or of a discrepancy between the cytogenetic and the sonographic findings, for example if CVS shows a karyotype that is incompatible with life and a living fetus is seen on the ultrasound, makes it necessary to extend the investigation by means of amniocentesis and/or fetal blood collection.

Another genetic abnormality that can lead to discrepancy between the karyotypes obtained by CVS and by amniocentesis is the presence of uniparental disomy (UPD). UPD can occur in one third of cases of mosaicism and can be explained by the trisomy rescue mechanism, when the chromosomes that remain in the diploid fetus are both inherited from one of the

parents. UPD can manifest itself clinically as a result of the imprinting phenomenon or by originating recessive diseases and, consequently, fetal anomalies or mental retardation<sup>(7-8)</sup>.

Thus, the interpretation of the fetal karyotype (as of any other laboratory test) depends on a correlation with the prenatal clinical/sonographic findings<sup>(9-10)</sup>.

## OBJECTIVE

The objective of this report is to alert the specialists in ultrasound, obstetrics and fetal medicine about the aspects which should raise suspicions in the interpretation of a fetal karyotype result.

## METHODS

Six cases of discrepant results between cytogenetics and clinical and sonographic findings were evaluated. The six cases are described below and a comparison between them is presented in Table 1. It is worth pointing out that the karyotypes were performed in different laboratories, except one of the control karyotypes, performed at the laboratory of Hospital Israelita Albert Einstein (HIAE).

## RESULTS

### Case 1

Female patient, aged 36 years, G IV, P I, A II. The patient was referred due to a diagnosis of symmetrical fetal intrauterine growth restriction (IUGR) at 31 weeks, observed since the 18<sup>th</sup> week. The nuchal translucency measure at 13 weeks was 1.5 mm. At 31 weeks, the amount of amniotic fluid was normal,

**Tabela 1.** Resultados e evoluções dos casos estudados

Case	MA	Diag GA (weeks)	NT(mm)	Indication	Karyotype/sample	Complemental karyotype	Weight/GA at birth in weeks (kg/weeks)	Outcome	Present age (years/months/days)
1	36	18	1.5	IUGR	47,XX+16/ CVS	46, XX/AF	1,530/35	UPD, NNPD	4 to 6 months
2	32	11	3	INT	48,XX+15+20/ CVS	46, XX/AF	3,025/41	NNPD	4 months
3	38	12	6.2	INT	46,XX/ CVS	46XX,+18, der(18) t(18;21)(p?11)(?q11)/FB	2,500/39	Syndromic facies CRA and RP	6 months
4	30	12	1.8	ANB	46XY,del (3)(q21→q25), t (5;18)(q12;p11.2?)/AF	46, XY/AF	3,125/38	NNPD	1 year
5	37	12	1.9	OMP	92,XXXX/ CVS	46, XX/AF	NFU	NFU	NFU
6	30	13	2.7	INT	45, X/ CVS	Mosaic46XX45X/FB	2,600/38		15 days

MA = maternal age, GA = gestational age, NT = nuchal translucency, AF = amniotic fluid, UPD = uniparental disomy, NNPD = normal neuropsychomotor development, IUGR = intrauterine growth restriction, INT = increased nuchal translucency, CRA = cardiorespiratory arrest, RP = recurrent pneumonias, FB = fetal blood, ANB = absent nasal bone, OMP = omphalocele, NFU = no follow-up, CVS = chorionic villus sampling

but the placenta was rather atypical, thickened and containing multiple “anechoic images”. A fetal echocardiogram revealed the presence of cardiac interatrial communication (IAC) and a Doppler velocimetry of the umbilical arteries showed zero diastole flow in one vessel, and increased resistance in the other. A transplacental amniocentesis was performed and, upon needle withdrawal, chorionic villus was collected. In the placenta, 15 cells were analyzed presenting a 47,XX,+16 karyotype as a result, and another 15 cells were analyzed in the amniotic fluid, showing 46,XX as a result. A molecular study of the amniocytes revealed that the fetus was a carrier of maternal uniparental disomy (UPD) for chromosome 16 (both chromosomes 16 of the fetus were of maternal origin), and this diagnosis was confirmed in peripheral blood collected after delivery. The mother developed severe pre-eclampsia from the 32<sup>nd</sup> week on (presence of maternal ascites), which indicated a premature delivery at 35 weeks. The newborn, a female, weighed 1,530 g, and the IAC was confirmed and was under follow-up (without clinical repercussions) until the present age of four years and six months. Longitudinal growth and neuropsychomotor development are normal, according to the assisting pediatrician.

### Case 2

Female patient, aged 32 years, G I. On the 11<sup>th</sup> week (CRL=41 mm), the nuchal translucency measurement was 3 mm, the nasal bone was visualized, and the Doppler result of the venous duct was normal. Chorionic villus sampling was indicated and the resulting karyotype was 48,XX,+15,+20, in 20 analyzed cells. At 16 weeks, the fetus was still alive and apparently normal, when amniocentesis was performed and revealed a normal 46,XX karyotype. On ultrasound follow-up, a major hydrops fetalis was observed at 19 weeks of gestation, with edema of the subcutaneous tissues, ascites and pleural effusion. A fetal echocardiogram was normal, and Doppler velocimetry of the medium cerebral artery did not show any signs of fetal anemia. Ultrasound follow-up was performed every two weeks, and spontaneous resolution of the hydrops fetalis was observed at 24 weeks. The fetal echocardiogram was normal. Delivery by C-section was indicated at 41 weeks, and the newborn, a female, weighed 3,025 g. No apparent malformations were observed. Placental histopathology was normal. The child follow-up to the age of four months showed normal neuropsychomotor development, according to information from the pediatrician.

### Case 3

Female patient, aged 38 years, G II, P I. Ultrasound at 12 weeks revealed nuchal translucency of 6.2 mm, pointing to a risk of chromosomal anomaly (calculated by means of the Fetal Medicine Foundation program) that went from 1/117, based on the patient's age, to a corrected risk of 1/2. A chorionic villus biopsy was performed and revealed a normal karyotype (46, XX). On ultrasound follow-up, polycystic kidneys were suspected and IUGR was diagnosed, along with a normal volume of amniotic fluid and a Doppler flow measurement without alterations. Delivery by C-section was performed at 39 weeks and six days, because of a previous C-section and no uterine conditions for labor induction. The newborn, a female, weighed 2,500 g and presented a syndromic facies, but the parents chose not to perform any additional tests. At two months of age, the child suffered cardiorespiratory arrest at home and recovered. Upon complementary investigation, a peripheral blood karyotype was performed, and the result was 46,XX,+18,der(18)t(18;21)(?p11)(?q11). The child is developing with recurrent pneumonias (a total of three) and is currently alive and aged six months. Karyotype analysis of the parents showed normal results in both.

### Case 4

Female primiparous patient, aged 30 years, A first-trimester morphological ultrasound was performed at 12 weeks and six days, in which the nasal bone was not visualized and the nuchal translucency measurement was 1.8 mm. The risk of chromosomal anomaly calculated by the Fetal Medicine Foundation program went from 1/667, based on the patient's age, to 1/69 based on translucency and nasal bone, presenting a final risk, corrected by a biochemical study of 1/486. Amniocentesis was performed at 14 weeks and six days, and the following structural alterations were detected: 46,XY,del(3)(q21→q25),t(5;18)(q12;p11.2?), suggesting interstitial deletion of a segment of the long arm of chromosome 3 and an apparently balanced translocation between the long arm of a chromosome 5 and the short arm of a chromosome 18, in 15 analyzed cells. The parents' karyotypes were normal. On ultrasound follow-up, the fetus presented normal development and the patient was submitted to a new amniocentesis, which resulted in a 46,XY karyotype. The pregnancy progressed uneventfully and the newborn, a male, was born at 38 weeks and five days of gestation, weighing 3,125 g, measuring 48 cm, with an Apgar score of five and eight, and without any

apparent anomalies. Several fragments of the placenta and peripheral blood were sent for karyotyping, and the results were also normal.

### Case 5

Female patient, aged 37 years, G II, P I, referred at 12 weeks and two days for suspected fetal omphalocele (containing liver), which was confirmed. The nuchal translucency measurement was 1.9 mm, and the nasal bone was visualized. The maternal age-related risk for trisomies 13 and 18 was 1/274 and increased to 1/4. A chorionic villus biopsy was performed and showed tetraploidy (92,XXXX). The fetus remained alive and with good activity up to the 15<sup>th</sup> week, when the patient underwent amniocentesis showing a normal 46,XX karyotype. Follow-up of this pregnancy was lost thereafter.

### Case 6

Female patient, aged 30 years, G II, P I, referred at 13 weeks and five days for increase in nuchal translucency, which measured 2.7 mm (CRL 71 mm); the nasal bone was visualized. The maternal age-related risk of trisomy 21 (FMF-London) was 1/667, but considering the NT measurement it increased to 1/399. A chorionic villus biopsy was performed and the karyotype found was 45,X in all 15 cells analyzed. A fetal echocardiogram and further control sonograms were normal. Delivery by C-section was performed at 38 weeks (at the mother's choice), and the newborn, a female, weighed 2,600 g. A peripheral blood karyotype was obtained revealing a mosaic (46,XX and 45,X) in 15 out of the 30 cells analyzed, but there were no apparent malformations or Turner Syndrome signs. Abdominal ultrasound and echocardiogram were normal. The child is currently 15 days old.

## DISCUSSION

Divergent results between the fetal karyotype obtained from chorionic villus and/or amniotic fluid and the karyotype and/or phenotype at birth, although infrequent, may occur in clinical practice. Therefore, great caution is required in the interpretation of results and genetic counseling of these couples.

Despite these possible divergences, CVS is considered a safe and effective method that detects numerical and/or structural chromosome anomalies with an accuracy of 99%<sup>(11)</sup>. In a large study (EUCROMIC) which analyzed the results of 62,865 chorionic villus biopsies, 94.8% of true negative, 3.7% of true positive, 0.15% of true mosaicism, and 1% of confined placental mosaicism results were found<sup>(12)</sup>.

From the experience of a renowned laboratory in the United States, the authors reported 62 cases of discrepancy between the fetal sex chromosome complement and the phenotypic sex among 500 thousand cases of prenatal diagnosis performed over a seven-year period. Of these 62 cases, 18 were true biological discrepancies, 14 due to failure in sex identification on the ultrasound, eight involved multiple gestations, 12 were typing errors, and six due to a change of samples<sup>(13)</sup>.

In our present series, maternal age varied from 30 to 37 years (mean age: 33.5 years), and the main indication for the invasive procedure was the presence of a marker/anomaly found on first-trimester ultrasound, such as increased nuchal translucency in cases 2, 3 and 6; absence of a bone in case 4, and a suspicion of omphalocele in case 5. Increase in nuchal translucency is mainly associated to chromosome disorders, gene diseases and fetal cardiac malformations. When none of these alterations is present in the fetus, it is difficult to find an etiology to explain such an increase. It is known that fluid accumulation in the nuchal region, which occurs in a transient manner during this phase, is associated with the development of lymph drainage; consequently, a delay or an alteration in this drainage system could *per se* lead to an alteration of this measurement.

There is a study in which the association between increased nuchal translucency and mosaicism was found in two out of a total of 151 newborns with nuchal translucency higher than 3 mm and with a normal prenatal karyotype<sup>(14)</sup>. However, the possible causes of this association are not clear yet. In case 2, we found an anomaly on CVS (48,XX,+15,+20) associated with a live fetus whose amniocentesis showed a normal karyotype, and no malformations were found either before or after birth, but which presented transient fetal hydrops. This association could, therefore, be explained by the placental alteration, but the mechanism justifying it remains to be established. Mosaic trisomy of chromosome 20 is a relatively common finding (approximately 16%) in amniocenteses and in 90% of cases it has no phenotypic implication. Its occurrence in other fetal tissues or placenta, however, is the rarest<sup>(15)</sup>.

Fetal growth and structural anomalies are also indications for a fetal chromosome analysis, as in case 1, in which the finding of fetal growth restriction on ultrasound follow-up associated to a normal quantity of amniotic fluid raised the suspicion of a chromosomal alteration, leading to performing the procedure. In the presence of IUGR without an apparent cause, confined placental mosaicism is one of the possible etiologies, observed in up to 20% of cases of idiopathic growth restriction<sup>(16-17)</sup>.

When confined placental mosaicism is associated with uniparental disomy, there seems to be an even more negative effect on fetal growth<sup>(18)</sup>. This theory could explain the severe progression of case 1, with fetal growth restriction associated to maternal pre-eclampsia and low birth weight.

Apparently, the higher the level of aneuploidy found in the placental tissue, the greater the risk of fetal repercussion. As a rule, the aspect most commonly affected in these cases is fetal growth, which may occur in 35% of cases<sup>(6)</sup>.

In a study which analyzed the placentas of fetuses with IUGR, the incidence of mosaicism was higher, mainly related to triploidy<sup>(19)</sup>.

Another fact that should draw our attention is the finding of a chromosome disorder, which is unusual in CVS and is incompatible with the ultrasound findings. In these cases, a confined placental mosaicism should be suspected, once placental mosaicism can be found in 1 to 2% of chorionic villus biopsy results<sup>(20)</sup>.

In cases 2 and 5 of this study, the doubt about the fetal karyotype resulted from the finding of an infrequent chromosome anomaly on CVS analysis, which would normally be incompatible with normal fetal development. Especially in such cases, ultrasound follow-up and complementary analyses of the fetal karyotype in amniotic fluid along with UPD investigation seem to be essential for the elucidation of the fetal diagnosis, since in both cases the postnatal findings were compatible with normal newborns. In case 6, the favorable development of the newborn also led to performing a postnatal control karyotype, showing a discrepancy between CVS and fetal blood.

Considering the mosaicism found in the analysis of chorionic villus, it is prudent to keep the fetus under ultrasound follow-up and to extend the investigation<sup>(2)</sup>. It is, however, important to remind that, even if the amniotic fluid karyotype result is normal, there is a risk of uniparental disomy, as seen in case 1.

Detection of uniparental disomy requires molecular DNA analysis for diagnosis<sup>(21-22)</sup>. Even though this alteration was detected in case 1, there has been so far a favorable progression, with good neuropsychomotor development. Trisomy of chromosome 16 occurs in about 1% of all clinically recognized pregnancies. When it is complete, it usually results in a spontaneous first-trimester abortion. Thus, when it is detected in a fetus with normal development, it raises the suspicion of mosaicism. In most of the cases the development is favorable, although there is a higher risk of premature delivery<sup>(23)</sup>.

Mosaicism may persist in the placenta during the whole gestation and can then be confirmed, after birth, by placental analysis<sup>(6)</sup> or disappear and not be

found on placental analysis at term<sup>(24)</sup>. Apparently, the earlier the gestational age, in which placental analysis is performed, the greater the chance of finding a chromosomal anomaly. False-negative CVS results have an incidence of 0.1% and seem to be more frequent in direct preparations than in cultures<sup>(20,25)</sup>. In a review of 10,741 chorionic villus biopsies, three cases were found with a normal result in the direct study, corrected by the culture result. Even more rarely, a false-negative result can be found in culture too<sup>(26)</sup>. In this case, only an ultrasound follow-up can alert about the false-negative result of CVS, as in case 3, indicating that, when there are alterations in the ultrasound findings after CVS, a false-negative result should be suspected and, in our opinion, there is an indication for a control amniocentesis.

The incidence of true mosaicism detected by amniocentesis is much lower than that found by chorionic villus biopsy<sup>(27-28)</sup>. Usually, amniocentesis is the method of choice to elucidate the cases of placental mosaicism, because it represents the fetal karyotype. However, in about 12 to 14% of the cultured amniotic fluid samples, more than one cell type is detected<sup>(29-30)</sup>. In general, this kind of mosaicism, called pseudomosaicism, does not reflect a true fetal mosaicism. In these cases, the chromosomal alteration can have occurred during cell division *in vitro*, i.e., in the culture itself. The discrepancy found in case 4, in which the fetal karyotype was abnormal in the first amniocentesis and normal in the second, can be explained by a smaller number of cells analyzed or by failure to detect the mosaicism, due to the difference in growth speed between the abnormal and the normal cells. In this case, the possibility of mosaicism in the fetus is impossible to rule out completely<sup>(9)</sup>.

## CONCLUSIONS

Our objective in reporting these cases, in which there were discrepancies between karyotype alteration and ultrasound findings, was to alert mainly those who are beginning to work in Fetal Medicine about the concrete possibility of a karyotype not reflecting with 100% accuracy the chromosomal normality or abnormality of the fetus. This complexity of prenatal diagnosis makes genetic counseling essential, before performing any invasive procedures. Whenever there are discrepancies between the clinical picture and the laboratory result, further diagnostic work-up and ultrasound follow-up seem to be essential for a correct management.

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