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CASE REPORT

EDWARDS' SYNDROME DIAGNOSIS BETWEEN FIRST TRIMESTER SCREENING AND ULTRASOUND MINOR MARKERS

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Summary

Edwards' syndrome, also known as trisomy 18, is a genetic disease caused by an extra copy of chromosome 18 in some or in all of the body cells [1,2]. It is the second most common autosomal trisomy after trisomy 21(with an incidence of 1 in 8000 births) [3] but it is also more serious. Almost half of trisomy 18 infants die within the first week of life, and the majority of the remaining ones die in the next 12 months because of central apnea, upper airway obstruction, respiratory insufficiency, aspiration, cardiac failure, or a combination of these and other factors [1,4]. Currently most cases of trisomy 18 are prenatally diagnosed, based on screening by maternal age, maternal serum marker screening, or detection of sonographic abnormalities e.g increased nuchal translucency thickness, growth retardation, choroid plexus cyst, overlapping of fingers, and congenital heart defects [3].Ultrasound scan for fetal anomalies is the most effective screening test for trisomy 18. A policy of conservative management for women with positive second-trimester biochemical screening or first-trimester combined screening for trisomy 18 is reasonable in the absence of ultrasound fetal abnormalities according to some authors. Unnecessary invasive tests can be avoided [5]. However, when can we decide on a conservative management and when do we need to check by amniocentesis and fetal DNA analyzing? It is a question without a clear answer despite numerous studies and articles on the subject. In our case the diagnosis was suggested by an ultrasound marker considered minor (choroid plexus cyst) and it would have been missed or found much later if we ignore this marker and we rely on

Résumé

Le diagnostic du syndrome d'Edwards entre l'échographie du premier trimestre et celle des marqueurs mineurs

Le syndrome d'Edwards, également connu sous le nom de la trisomie 18 est une maladie génétique provoquée par une copie supplémentaire du chromosome 18 dans certaines ou dans toutes les cellules du corps [1,2]. C'est la deuxième, la plus fréquente trisomie autosomique après la trisomie 21 (à une incidence de 1 à 8000 naissances) [3], mais, aussi, plus grave. Presque la moitié des enfants atteints de la trisomie 18 meurent dans leur première semaine de vie et la plupart de ceux qui restant meurent dans les 12 prochains mois en raison de l'apnée centrale, l'obstruction des voies aériennes supérieures, l'insuffisance respiratoire, l'aspiration, l'insuffisance cardiaque ou une combinaison entre ceux-ci ou d'autres facteurs [4]. Actuellement, la plupart des cas de trisomie 18 sont diagnostiqués avant la naissance, le dépistage se leasant sur l'âge maternel, les marqueurs sériques maternels, l'échographie de détection d'anomalies, par exemple la croissance de l'épaisseur de la clarté nucale, le retard de croissance, le kyste choroïde, le chevauchement des orteils ou les malformations cardiaques congénitales [3]. L'échographie pour les anomalies foetales est le test de dépistage le plus efficace pour la trisomie 18. Une politique d'approche conservatoire pour les femmes avec dépistage biochimique positive au deuxième trimestre ou pour le dépistage combiné du premier trimestre pour la trisomie 18 est raisonnable en l'absence d'anomalies fœtales détectées par les ultrasons après certains auteurs. Les tests invasifs inutiles peuvent être évités [5]. Néanmoins, quand est-ce qu'on peut décider sur une gestion conservatrice et quand est-ce qu'on do't vérifier par amniocentèse et

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the normal result of first-trimester screening with the nuchal translucency and biochemical markers in normal range.
Key words: Edwards' syndrome, trisomy 18, choroid plexus cyst, ultrasound markers, minor marker, amniocentesis

l'analyse de l'ADN foetal? C'est une question sans une réponse nette, malgré les nombreux études et articles sur ce sujet. Dans notre cas le diagnostic a été suggéré par une échographie du marqueur considéré mineur (le kyste du plexus choroïde) et il aurait été manqué ou trouvé beaucoup plus tard si nous ignorions ce marqueur et avions compté sur le résultat normal de dépistage du premier trimestre aves la clarté nuchale et les marqueurs biochimiques dans la plage normale.
Mots clés: syndrome d'Edwards, trisomie 18, kyste du plexus choroïde, marqueurs ultrasono-graphiques, marqueur mineur, amniocentèse

INTRODUCTION

The trisomy 18 syndrome, also known as Edwards' syndrome was first recognized as a specific entity in 1960 by Edwards et al. and Smith et al. [1,2] and it is the second most common autosomal trisomy after trisomy 21 [1,3]. It is characterized by the presence of an extra copy of chromosome 18, as full, mosaic (less than 5% of cases)or partial trisomy 18q. The live-born prevalence is about 0.15/1000 and the general prevalence is believed to be higher 0.4/1000 due to the high rate of fetal loss and pregnancy termination after prenatal diagnosis [1,2]. The prevalence of this syndrome increases with maternal age. The recurrence risk for a family of a child with Edwards' syndrome is about 1% [1,3]. White ethnicity, female gender and being a singleton seem to increase the risk for trisomy 18 [1,6].

In pregnancies with Edwards' syndrome there is a high risk of fetal loss and stillbirth [3,7] but nowadays most cases are prenatal diagnosed based on first-trimester combined screening and amniocentesis followed by pregnancy termination in a significant percentage of cases [3,8].

In our case first trimester screening was within normal limits, diagnosis suspicion of Edwards' syndrome was raised starting from a ultrasound minor marker detected at 18 weeks of gestation, namely unilateral choroid plexus cyst and later confirmed by amniocentesis and analysis of fetal karyotype. Sonography can show abnormalities in many fetuses with chromosomal aberration [9,10] and the sensitivity of sonography for detecting these abnormalities varies with a number of factors, including the type of chromosome abnormality, gestational age at the time of sonography, reasons for referral, criteria for positive sonographic findings and the quality of the sonography [9,11]. These abnormalities may include both major or structural defects and nonstructural findings, also known as minor sonographic markers. Unlike structural anomalies, minor sonographic markers of fetal aneuploidy are insignificant by them selves and nonspecific with regard to outcome, most frequently seen in normal fetuses.The most common minor sonographic markers of fetal aneuploidy in the second trimester are nuchal thickening, hyperechoic bowel, shortened extremities, renal pyelectasis, echogenic intra-cardiac foci, choroid plexus cysts and skeletal abnormalities which include clenched hands [12,13], club feet, and radial aplasia or limb shortening. In the third trimester, some fetuses with trisomy 18 may primarily have intrauterine growth restriction, which is often associated with polyhydramnios [9].

CASE REPORT

A 35 years old woman, 20 weeks pregnant, which was detected for the first time by ultrasound screening at 18 weeks whith unilateral, 10 mm, choroid plexus cysts,are admitted to our clinic in order to establish therapeutic specialist conduct. In the patient's personal history we noted that she has a normal birth with a perfect normal child 11 years ago and 1 miscarriage, is nonsmoker, without teratogenic potential disease, exposure to radiation or toxic substances in the first trimester. Also there was no personal family history of congenital malformations. The screening for chromosomal abnormalities in the first trimester and TORCH serology were in normal range. The double test with a normal nuchal translucency (TN=1,3 mm!) performed at 12 weeks and 6 days, found a very low risk of trisomy 13 or 18 appreciated as 1 / 10.000. After completing the clinical and laboratory exams with blood tests within normal limits, a detailed ultrasound examination was performed with biometrics appropriate gestational age of 20 weeks. Besides 10 mm choroid plexus cyst there were observed dilated pulmonary artery and ductus arteriosus (DA) with a value Pulmonary / Aorta= 2,15. After we explained that we do not detect by ultrasound a major anomaly, only a marker considered minor, rather poorly associated with trisomy 18 according to some authors (choroid plexus cyst) but still there is a suspicion of chromosomal abnormality, we decided together with the patient, after informed consent, to perform a diagnostic amniocentesis.

The evolution after amniocentesis was favorable with normal uterine tone, without uterine contractions, without blood or amniotic fluid loss.

Karyotype analysis of the amniotic fluid puts the final-cytogenetic diagnosis of homogeneous trisomy 18.All metaphases examined had an extra chromosome 18; Cytogenetics formula was: 47,XX+18; female gender.

After genetic counseling of couple we have decided together drug induction of abortion. Under antibiotic prophylaxis and monitoring in the delivery room, patient aborted a product of conception with no signs of viability,

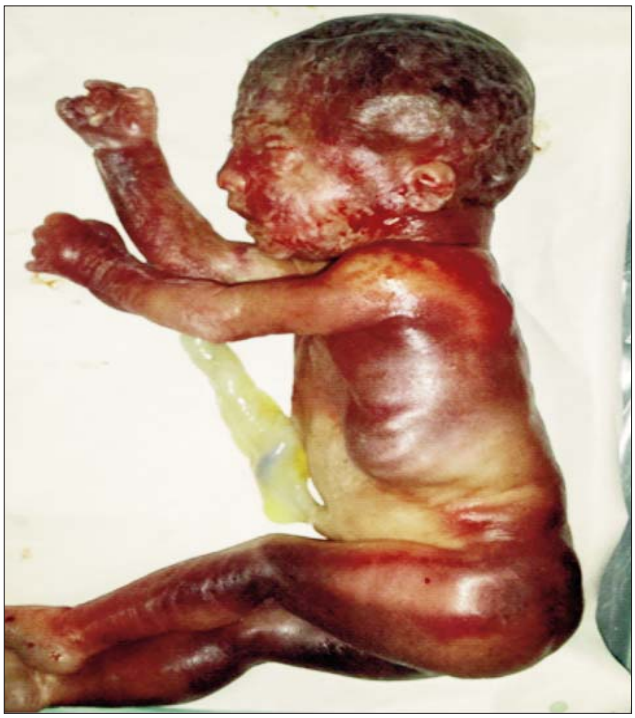

Figure 1 - Fetus phenotype

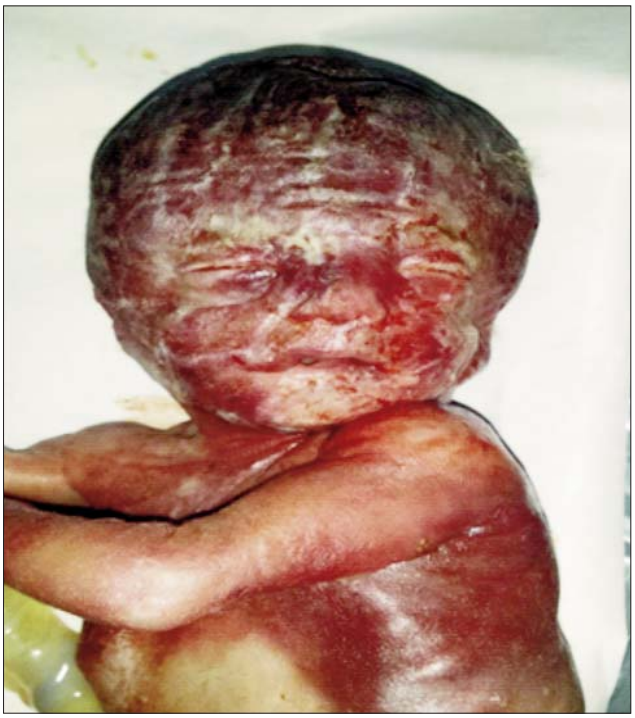

Figure 2 - Fetal face

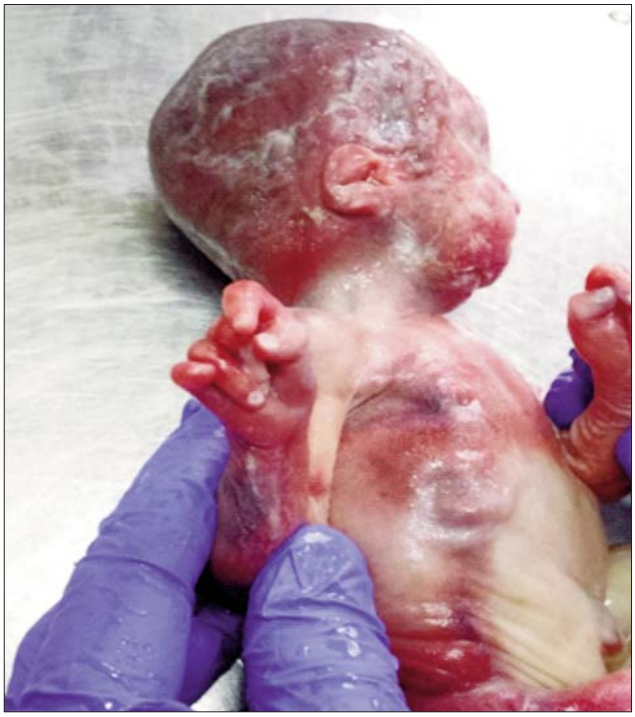

Figure 3 - Clenched hand and overlapping fingers: index finger overlaps third finger and fifth finger overlaps fourth finger

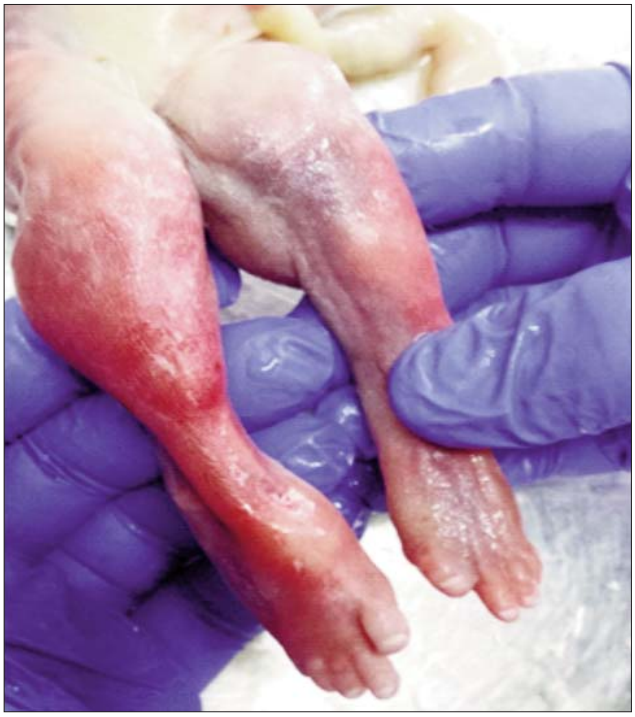

Figure 4 - Short hallux with single phalanx

female gender, weighing 540 g, which is sent along with the placenta (160 g) at histopathological examination.

Phenotypically fetus has short neck, low set and small ears, small and retruded chin (fig. 1 and 2) and clenched hand and overlapping fingers: index finger overlaps third finger and fifth finger overlaps fourth finger, characteristics frequently seen trisomy 18 (fig. 3). Also one single phalanx at the hallux level it was found (fig. 4).

At autopsy most of the internal organs appeared normal on gross examination and congested on microscopy. The genitalia were feminin with a normal uterus. The kidneys, liver and spine were normal. Placenta was normal. At the

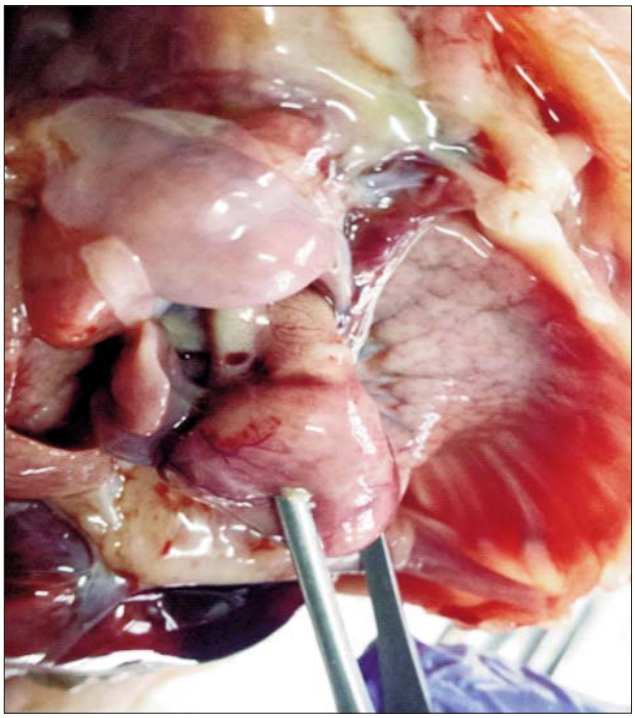

Figure 5 - Great arteries with parallel route

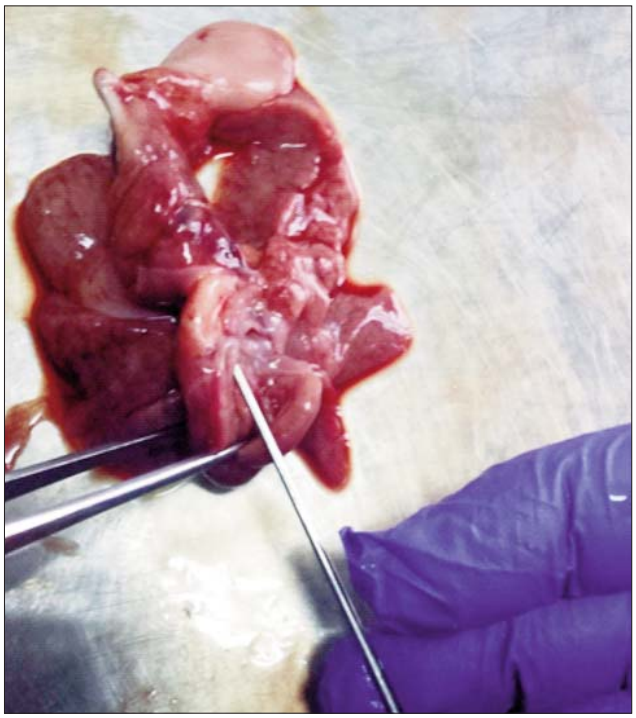

Figure 6 - Pulmonary artery emerging from the left ventricle

heart level was diagnosed complete transposition of great arteries (fig. 5) with pulmonary artery emerging from the left ventricle (fig. 6) and aortic origin at the right ventricle level. A cyst was found in the lateral ventricle of the brain (fig. 7).

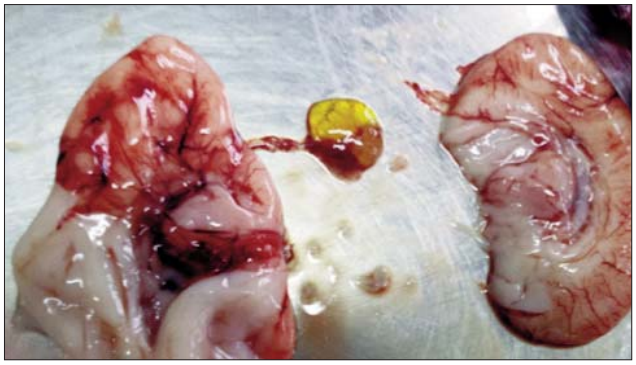

Figure 7 - Choroid plexus cyst

Discussion

Trisomy 18 is the second most common autosomal trisomy and at 10–14 weeks of gestation the relative proportion of trisomy 21 to trisomy 18 is about three to one [14, 15]. Almost half of trisomy 18 infants die within the first week of life, and the majority of the remaining ones die in the next 12 months, only 5% to 10% of these infants survive the first year. The death usually is due to central apnea, upper air way obstruction, respiratory insufficiency, aspiration, cardiac failure, or a combination of these and other factors (including decisions for palliative care)[1,4]. Currently most cases of Edwards' syndrome are prenatally diagnosed, based on several methods: maternal serum screening in the first trimester (βHCG dosing and PAPP-A), ultrasound in the first trimester that can detect increased nuchal translucency, maternal serum screening in the second trimester (AFP dosing, βHCG and uE3), morphological ultrasound in the second trimester that can detect neural tube defects, growth retardation, choroid plexus cyst, overlapping of fingers, and congenital heart defects. Final diagnosis is performed by amniocentesis or chorionic villus biopsy, followed by analysis of fetal karyotype [3]. Several reports of biochemical markers have suggested that trisomy 18 is associated with a decrease in maternal serum free βHCGand PAPP-A [14,18,19,20,21, 22,23,24]. First-trimester screening for trisomy 21 by a combination of maternal age, fetal nuchal translucency thickness (NT) and serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A(PAPP-A) can detect about 90% of affected pregnancies at a false-positive rate (FPR) of about 5% [25,26]. However, with the use of specific algorithms for each trisomy, which incorporate not only their similarities but also their differences in biomarker pattern, including high serum free β-hCG in trisomy 21 and low levels in trisomies 18, it is possible to increase the detection rate (DR) of trisomies 18 to about 95% with a small increase in the overall FPR from 5 to 5.2% [25,27]. Ultrasonographic features of trisomy 18 in the first trimester include increased nuchal translucency, reported in about 75 per cent of cases [14,28], early onset intra-uterine growth retardation and exomphalos, found in about 30 per cent of fetuses [14,29]. Edwards' syndrome markers detected at ultrasound in the second trimester are classified as minor and major. Typical minor anomalies include characteristic craniofacial features, clenched fist with overriding fingers, small fingernails, underdeveloped thumbs, and short sternum. The

presence of major malformations is common, and the most frequent are heart and kidney anomalies [9,11]. The most common abnormalities noted were persistent abnormal position of fetal fingers (89%); choroid plexus cysts (43%); abnormally shaped fetal head (strawberry or lemon) (43%); two-vessel umbilical cord (40%); cardiac defects (37%); intrauterine growth restriction (29%); omphalocele (20%); neural tube defects (9%); and cystic hygroma or lymphangiectasia (14%). Abnormalities of amniotic fluid volume (12%) and renal defects (9%) were seen less frequently. These data suggest that in the early second trimester, the time of most routine screening ultrasonographic examinations, most but not all fetuses with trisomy 18 have sonographically detectable anatomic abnormalities. The fetal hand appears to be abnormal in most fetuses with trisomy 18, early in the second trimester, but the anomaly can be subtle and /or unilateral [30]. Of these, choroid plexus cysts have been the most controversial and the subject of considerable interest [9,31] because unlike some of the other potential markers choroid plexus cysts have noknown association with other adverse outcomes when the karyotype is normal [9].

However, when we can decide a conservative management and when we need to check by amniocentesis and fetal DNA analyzing? It is a question without a clear answer despite numerous studies and articles on the subject. In our case the diagnosis it was suggested by an ultrasound marker considered minor (choroid plexus cyst) and it would have been missed or found much later if we ignore this marker and we rely on the normal result of first-trimester screening whit the nuchal translucency and biochemical markers in normal range.

Snijders et al reported that among 107 fetuses with isolated choroid plexus cysts who had karyotyping, 2 had chromosome defects (1 each oftrisomy 18 and 21), whereas no chromosome abnormality was found among the 174 fetuses with choroid plexus cysts who did not have amniocentesis and found that isolated choroid plexus cysts carried only a marginally increased risk for trisomy 18, but the presence of another abnormality increased the risk approximately 20 times [9,32]. Similar opinions have been reached by a number of other authors, including Chitty et al who evaluated 658 fetuses with choroid plexus cysts [9,33]. Ghidini and colleagues observed that isolated choroid plexus cysts were detected in 6.7% (13 of194) of fetuses with trisomy and 0.9% (752 of79,583) of control fetuses, yielding a likelihood ratio of 7.1 [9,34]. In another report, Yoder et al evaluated 13 prospective studies comprising 246,545 second-trimester scans and found a likelihood ratio of 13.8 for trisomy 18 [9,35]. Despite this relatively high likelihood ratio, the authors concluded that fetal karyotyping should be offered only when maternal age at delivery is 36 years or older orwhen the risk for trisomy 18 detected by serum multiple-marker screening is more than 1 per 3000 [9]. Among other variables, there is good evidence to suggest that larger choroid plexus cysts further increase the risk of trisomy 18 compared with smaller cysts [9,36,37]. A choroid plexus cyst can be presumed to be isolated only after a detailed fetal survey fails to show structural abnormalities or other sonographic markers of fetal aneuploidy. As an isolated finding after high-quality sonography, and assuming the patient is otherwise considered at low risk for fetal aneuploidy, we think that detection of choroid plexus cysts should notalter obstetric management. Additional reassurance can be obtained by correlating sonographic findings with serum biochemical markers [9,38,39].

Ultrasound scan for fetal anomalies is the most effective screening test for trisomy 18. A policy of conservative management for women with positive second-trimester biochemical screening or first-trimester combined screening for trisomy 18 is reasonable in the absence of ultrasound fetal abnormalities [5].

Conclusions

The risk of recurrence of trisomy 18 is very low and is estimated to be around 0.5-1%, however, genetic testing for the partners is recommended.

Evolution and prognosis

Edwards' Syndrome is a very serious genetic diseases, only 5% of children survive to age 1 year. Long-term survival is exceptional, there is a risk of hepatoblastoma and Wilms' tumor and severe mental retardation. Trisomy 18 has no cure, patients need special treatment in a hospital with intensive care. Those who survive frequently need long term support: surgical correction of congenital abnormalities, physiotherapy, psychological counseling, genetic evaluation.

In our case the genetic diagnosis was in a major contradiction with the first-trimester screening result. Actually this was the reason for we wanted to report this case. Considered a minor marker by many authors, very common in trisomy 18 - after other studies, choroid plexus cyst - was the thing that prompted us to perform amniocentesis and fetal karyotype. Basically it was the decisive factor that helped early genetic diagnosis – before the fetal morphological 3D/4D ultrasound screening clearly identified transposition of the great vessels or suggestive aspects of the fetal face and hands.

The genetic result was somehow surprising because fetal phenotypic aspects are sometimes difficult to view and detailed examination of the heart is also very dependent on fetal position. Sometimes a clear diagnosis of cardiac malformations is done by serial ultrasound scans in second or third trimester of pregnancy which certainly unwanted delay the fetal DNA analysis and final genetic diagnosis. Initially we too have tended to minimize the importance of choroid plexus cyst. Maternal age under 35, the risk appreciated as very low - less than 1 / 10,000 at first trimester screening, normal nuchal translucency of 1.3 mm are generally considered very important elements but in our case it would have led us to missing a very severe diagnosis. But we finally decided invasive testing both draw us more on the mother's desire rather than on the existence of clear medical criteria as we would like in a evidence-based medicine. So choroid plexus cyst, a minor marker, sometimes actually signals a chromosomal abnormality and should not be ignored but

followed by repeated ultrasound exams and further investigated. Of course we want clearer criteria, internationally accepted management guidelines, and fetal DNA non-invasive tests accessible for our patients, until then, we try to judge each case - as same as always - based on our experience and quite often on personal intuition.

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