Importance of Follow-Up and Early Detailed Evaluation in Early Onset Growth Restricted Fetuses

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ABSTRACT: Early onset fetal growth restriction (EO-FGR) is associated with significant feto-maternal complications, therefore efforts should be made to identify the causes and the potential outcome of the pregnancy. Some of the pitfalls in first-trimester imaging of the fetal anomalies are related to the inadequacy of the examination, because of the fetal position and limited clarity in relation to the size of the structures being examined. In this paper we present a case where careful ultrasound scan follow-up and the use of both approaches transabdominal and transvaginal were useful to complete a detailed structural evaluation as part of the diagnosis, management and prognosis of a fetuses diagnosed with EO-FGR in the first trimester and a tripodly with atypical ultrasound features.

KEYWORDS: Early onset fetal growth restriction, fetal complications, malformations, genetic anomalies, antenatal counseling

Introduction

EO-FGR is defined as insufficient fetal growth diagnosed below 32 weeks and differs from late onset FGR regarding its etiology, clinical manifestations, patterns of deterioration and severity of placental dysfunction [1,2,3].

Based on the pathophysiological mechanism, growth restriction may be placenta mediated or non-placental [4].

The latter group includes genetic and structural anomalies, congenital infections and inborn errors of metabolism and is strongly associated with early onset of the FGR.

Intrauterine growth restriction represents a frequent fetal morbidity with great variation in clinical practice, in terms of diagnosis, monitoring and counseling.

It is both a major cause and a potential effect of fetal morbidity, especially when considering EO-FGR. Prenatal recognition of fetal growth restriction (FGR) should represent one of the main targets at any gestational age.

There are no effective treatment modalities to reverse in utero the course of FGR and moreover, non-placental EO-FGR is frequently associated with major fetal anomalies that end up with pregnancy termination, as in the genetic pathology presented above.

Case presentation

A 25-year-old, gravida 2 nulliparous woman was referred to our center for fetal detailed evaluation at 12 weeks of gestation, following routine ultrasound screening because of progressive early grow restriction detected in the first trimester (Fig.1).

The patient and family history were negative for genetic syndromes or congenital malformations, and there was no history of medication use during pregnancy.
The combined test revealed low risk for Trisomies 21, 18 and 13 (1:440, 1:3500 and 1:1900, respectively), 0.22 multiples of median (MoMs) of human chorionic gonadotropin (hCGb) and 0.07 MoMs of pregnancy-associated plasma protein A (PAPP-A), normal nuchal translucency thickness, nasal bone present, normal tricuspid and ductus venosus flows (Fig.2) and increased fronto-maxillary angle (86°).

Fig.1. Progressive growth restriction at sequential evaluations during first and second trimester scans: dating scan at a menstrual age of 7 weeks+2 days with a discordance of one week (A,B); progressive discordance between amenorrhea and ultrasound measurements at 14 weeks+4 (C), 15 weeks+3 (D); 15 weeks+6 days (E-H)

Fig.2. Genetic markers: normal nuchal translucency and present nasal bone (A,B), increased frontomaxillary facial angle (B), positive „a“ wave at ductus venosus interrogation (C) and normal tricuspid flow (D)
Ultrasound transabdominal visualization of the fetus anatomy was severely impaired because of the oligohydramnios and vertical and hyperflexed position of the fetus (Fig.1.E).

Thus, the completion of the structural protocol was achieved only using transvaginal approach.

On detailed examination, it was noted asymmetrical severe growth restriction less the 3rd percentile, with increased ratio between the head parameters and abdominal circumference, ventriculomegaly, a posterior fossa cyst with abnormal posterior brain appearance, single umbilical artery and pyelectasis, short limbs with clenched fists and overlapping fingers, clubfoot, and cranio-facial dysmorphism with enlarged head, low-set ears, hypertelorism and micrognathia (Fig.3).

Choroid plexus cysts were not present.

Echocardiography showed normal segmental anatomy of the heart and great vessels, but reduced ventricular contractility and unusually large, irregular and multiple echogenic foci in both ventricles (Fig.4).

Doppler imaging demonstrated normal functional parameters (atrio-ventricular and ventriculo-arterial flows, tricuspid, mitral and ductus venosus flows and heart rate).

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**Fig.3. Fetal anomalies detected at the detailed transvaginal ultrasound scan. A: single umbilical artery; B-D: clenched hands; E: clubfoot; F: pyelectasis. G-H: craniofacial dysmorphism with normal thalamus (G), ventriculomegaly (H), posterior fossa cyst (I), hypertelorism (J,K), low-set ears (K)**

**Fig.4. Transvaginal sonographic evaluation of the heart and great vessels, duplex mode (grey-scale and high definition power Doppler). A, B: four-chamber plane, with unusually large and irregular echogenic foci in both ventricles; C: normal left ventricle outflow tract; D: normal right ventricle outflow tract; E: normal three vessel and trachea view; F,G: 4D STIC rendering with normal atrio-ventricular flows (F) and great arteries and innominate vein (G)**
Since the first trimester scan revealed anomalies, invasive genetic maneuver was proposed and accepted after counseling, although the combined test yield low genetic risks.

Chorionic villus sampling was performed at 13 weeks + 5 days.

The blood tests showed normal parameters, including a negative TORCH screen. The karyotype results revealed triploidy, and pregnancy was terminated at patients request following genetic counselling.

The pathology evaluation confirmed ultrasound findings (Fig. 5).

A written informed consent of the patient was obtained for publication of all the data.

Discussion

Trisomy 18, also called Edwards syndrome, is the second most common autosomal trisomy syndrome, with a reported incidence of 1.29/10,000 live births and a preponderance of female gender-61% [5].

The anomaly may imply a genetic male preponderance in the fetuses from maternal meiosis II errors pregnancies and a female preponderance in maternal meiosis I errors’ cases.

However, no significant difference was noted in maternal age or in associated major anomalies between the maternal and paternal cases [6].

This chromosomal condition is associated with FGR that was early diagnosed in our case and triggered furthermore evaluation.

Malformations are usually multiple, and, based on the presence of anatomical defects at the sonographic assessment, it was stated that proper ultrasound anomaly scan allows for a trisomy 18 syndrome detection with a sensitivity that may reach 100% [7].
Severe defects were reported in relation to fetal heart, with an incidence of 45-84%, central nervous system (87%) with ventriculomegaly, posterior fossa cysts, gastrointestinal (26%), and genitourinary (16%) [5,7].

A lot of minor abnormalities were also described: short ear length below the 10th percentile for gestational age (96%), short limbs and other skeletal malformations of upper extremities and hands (95%) with clenched fists and overlapping fingers, malformed lower extremities and feet, with clubfoot (63%), and craniofacial dysmorphism (small, strawberry shaped head with micrognathia and small mouth) (53%) [7].

Choroid plexus cysts were reported in half of the cases, but not as an isolated finding [7].

For all these reasons, the option for termination of pregnancy due to adverse outcome of fetuses should be offered to the parents. Even in the 5 to 10% of fetuses with this condition that survive through pregnancy and their first years, life-threatening medical problems and mental retardation are usually present.

Regarding the first trimester ultrasound findings, a large retrospective series of 53 cases of triploidy detected during a 12-year period, reported increased nuchal translucency thickness as the most common marker, found in 91% of cases [8], while absent or hypoplastic nasal bone was documented in 53% of the fetuses in which was specifically looked for.

Structural anomalies detected in the first trimester included omphalocele in 21%, abnormal posturing of the hands in 6%, megalacystis in 4%, bradycardia in 8% and abnormal heart appearance in 4%. EO-FGR was documented in 26% of the cases.

Many of these anomalies were diagnosed during the first trimester or before the 10th week of gestation, but sonographers should be aware that the characteristics of Trisomy 18 fetuses may differ from the classical pattern. The most frequent abnormal genetic markers-increased nuchal translucency, absent/hypoplastic nasal bone, choroid plexus cysts and bradycardia were not present in our case. Regarding the most common fetal malformation associated with Trisomy 18, we were not able to highlight cardiac malformations, but we noted a reduced ventricular contractility and unusually large, irregular and multiple echogenic foci in both ventricles. We do not exclude the possibility of a developing cardiac disease that was not visible at this early gestational age, when our investigation was conducted. It was acknowledged that cardiac lesions may be missed during the first trimester evaluation due to limited resolution, the small size of the lesion and low flow velocities, and that there can be cardiac lesions that evolve and become evident in utero as gestational age advances or even occur later in pregnancy: cardiomyopathy, endocardial fibroelastosis, hypoplastic cavities, aortic coarctation, aortic and pulmonary stenosis, tetralogy of Fallot, cardiac tumors [9,10].

Thus, the absence of a cardiac disease detected in the prenatal period does not entirely exclude the development of later cardiac anomalies, especially in cases as the one presented above, where the early scan raised some important functional issues, in terms of contractility [11].

Abnormal posterior brain morphometry in classic evaluation of facial profile has the potential to detect posterior fossa anomalies, as presented before by our reports [12].

Perhaps the most striking sonographic cardiac aspect in our case was related to the gross multiple echogenic intracardiac foci. Unusually appearing echogenic intracardiac foci were defined in literature as having an unusual large size, shape, structure or location/number (multiple). However, previous studies failed to find any correlation between unusually appearing echogenic foci and adverse perinatal outcome [13].

Due to the examination settings (fetal position, oligohydramnios), we were not able to conduct a detailed fetal evaluation transabdominally. Some factors have consistently been incriminated on the poor visualization during the first trimester anomaly scan, factors that cannot be altered by operators, such as high body mass index, anterior placentor or fibromiyomas, uterine retroversion, hypogastric surgical scars, unfavorable fetal position or reduced amniotic fluid. Our approach in such situations is to recommend re-evaluation or to use transvaginal technique to complete the structural assessment protocol, because a detailed diagnosis will lead to a better counseling for present and future pregnancies [14-16].

In our case, the effort to complete an early anomaly scan allowed for an earlier diagnosis, as the indication for invasive genetics was established based on the anatomical abnormal features and at the time of the sonographic assessment.
Conclusions

In general perception, EO-FGR is a major cause of fetal morbidity, but we should keep in mind that this entity may represent a manifestation or an effect of a serious genetic fetal condition. Thus, this finding should trigger careful structural and genetic fetal investigations. Concomitantly, a proper dating exam of the pregnancy may prove crucial for the detection of major fetal syndromes.

Transvaginal approach is an alternative useful technique to complete the structural assessment protocol, that should be used in unfavorable settings in order to achieve a detailed diagnosis that may lead to a better counseling and a more rapid diagnosis.

Sonographers should be aware that the characteristics of Trisomy 18 fetuses may differ from the classical pattern. Also, early in pregnancy, cardiac disease may show only discrete features, as reduced contractility.

Solitary presence of unusual features of echogenic intracardiac foci (large, irregular or multiple) was previously considered benign, but future studies should investigate if the association of these aspects is predictive for congenital heart disease or for genetic syndromes.

References

1. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzivoort W, Hecher K, Martinelli P, Ostermayer E, Papageorgiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcanomico A, Visser GH, Wolf H. TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE) Ultrasound Obstet Gynecol, 2013, 42:400-408.
2. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet, 1992, 339:283-287.
3. Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health, 2014, 128:698-702.
4. Villar J, Atman DG, Purwar M, Noble JA, Knight HE, Ruyan P, Chelik Ismail L, Barros FC, Lambert A, Papageorgiou AT, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Bhutta SH K, the International Fetal and Newborn Growth Consortium for the 21st century (INTERGROWTH-21ST). The objectives, design and implementation of the INTERGROWTH-21ST Project. BJOG, 2013, 120(Suppl 2):9-26.
5. Pont SJ, Robbins JM, Bird TM, Gibson JB, Cleves MA, Tifford JM, Aitken ME. Congenital malformations among liveborn infants with trisomies 18 and 13. Am J Med Genet A, 2006, 15, 140(16):1749-1756.
6. Chen CP, Chem SR, Tsai FJ, Lin CY, Lin YH, Wang W. A comparison of maternal age, sex ratio and associated major anomalies among fetal trisomy 18 cases with different cell division of error. Prenat Diagn, 2005, 25(4):327-330.
7. Yeo L, Guzman ER, Day-Salvatore D, Walters C, Chavez D, Vintzileos AM. Prenatal detection of fetal trisomy 18 through abnormal sonographic features. J Ultrasound Med, 2003, 22(6):581-90.
8. Sepulveda W, Wong AE, Dezerega V. First-trimester sonographic findings in trisomy 18: a review of 53 cases. Prenat Diagn, 2010, 30(3):256-259.
9. Smrcke JM, Berg C, Geipel A, Fimmers R, Axtil-Fliedner R, Diedrich K. et al. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. J Ultrasound Med, 2006, 25(2):187-196.
10. Carvalho JS, Moscoso G, Tekay A, Campbell S, Thilaganathan B, Shinebourne EA. Clinical impact of first and early second trimester fetal echocardiography on high risk pregnancies. Heart, 2004, 90(8):921-926.
11. Haak MC, van Vugt JM. Echocardiography in early pregnancy: review of literature. J Ultrasound Med, 2003, 22(3):271-280.
12. Iliescu D, Comănescu A, Antsaklis P, Tudorache S, Ghiliuş M, Comănescu V, Paulescu D, Ceauşu I, Antsaklis A, Novac L, Cernea N. Neuroimaging parameters in early open spina bifida detection. Further benefit in first trimester screening? Rom J Morphol Embryol, 2011, 52(3):809-817.
13. Petrikovsky BA, Challenger M, Gross B. Unusual appearances of echogenic foci within the fetal heart: are they benign? Ultrasound Obstet Gynecol, 1996, 8(4):229-231.
14. Iliescu D, Tudorache S, Comănescu A, Antsaklis P, Cotarace S, Novac L, Cernea N, Antsaklis A. Improved detection rate of structural abnormalities in the first trimester using an extended examination protocol. Ultrasound Obstet Gynecol, 2013, 42(3):300-309.
15. Şorop-Florea M, Ciurea RN, Ioana M, Stepan AE, Stoica GA, Tanase F, Comănescu MC, Novac MB, Drăgan I, Pătru CL, Drăguşin RC, Zoril GL, Cărbunaru OM, Oprescu ND, Ceauşu I, Vălcăreanu S, Tudorache Ş, Iliescu DG. The importance of perinatal autopsy. Review of the literature and series of cases. Rom J Morphol Embryol, 2017, 58(2):323-337.
16. Dragusin R, Florea M, Iliescu D, Cotarace S, Tudorache S, Novac L, Cernea N. The contribution and the importance of modern ultrasound techniques in the diagnosis of major structural abnormalities in the first trimester-case reports. Curr Health Sci J, 2012, 38(1):20-24.