Review

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Genetics Etiologies Associated with Fetal Growth Restriction

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Abstract

Fetal growth restriction (FGR) is associated with multiple adverse perinatal outcomes, such as increased risk of intrauterine death, neonatal morbidity and mortality, and long-term adverse outcomes. Genetic etiological factors are critical in fetuses with intrauterine growth restriction, including chromosomal abnormalities, copy number variants, single gene disorders, uniparental disomy, epigenetic changes, and confined placental mosaicism. This paper aims to provide an overview of genetic defects related to FGR and to highlight the importance of prenatal genetic counseling and testing for precise diagnosis and management of FGR.

Keywords: Genetics; Fetal growth restriction; Etiology

Introduction

Fetal growth restriction (FGR), also known as intrauterine growth restriction (IUGR), is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for the gestational age[1,2] and a condition in which fetal growth has not yet reached its intrinsic growth potential. It has been a challenge in clinical practice to distinguish constitutionally small but healthy fetuses from those unable to reach their growth potential due to various causes.[3] The etiology of FGR is multifactorial and includes maternal complications, fetal diseases, and placental abnormalities. FGR related to maternal and placental diseases can have relatively good outcomes through appropriate intrauterine surveillance and treatments.[4,5] However, there has been no effective prenatal intervention for FGR caused by genetic abnormalities.

This overview aims to summarize the fetal and placental genetic defects associated with FGR and help prenatal genetic counselling with appropriate genetic testing for FGR.

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Fetal genetic etiologies of FGR

Fetal chromosomal abnormalities

Fetal chromosomal abnormalities include numerical and structural anomalies and accounted for 19.4% (89/458) of the etiologies of FGR (defined as AC < 5th percentile for gestational age (GA)) at 17 to 39 weeks of gestation by conventional karyotyping, of which 92.13% (82/89) were numerical and 7.87% (7/89) were structural abnormalities on traditional karyotyping.[6] The most common chromosomal numerical abnormalities associated with FGR were triploid (69,XXX and 69,XXY) and trisomy 18, 21, and 13.[6,7] Trisomy 18 was identified in over 50% of chromosomal numerical abnormalities in severe FGR, defined as AC ≤ 3rd percentile for GA.[8] For FGR associated with fetal structural abnormalities (FGR defined as AC < 5th percentile for GA), the detection rate of fetal aneuploidy was 21% (4/19), while for isolated FGR diagnosed before 24 weeks of gestational age, the detection rate of fetal aneuploidy was 20% (3/15).[9]

Despite the heterogeneity in definitions for FGR, the studies above all indicated that amniocentesis with karyotyping should be offered to rule out chromosomal abnormalities for FGR with fetal structural anomalies, severe FGR defined as AC ≤ 3rd percentile for GA or early-onset FGR diagnosed before 24 weeks gestational age even if isolated.[1,10,11]

Fetal copy number variants (CNVs)

CNVs mainly include microscopic and submicroscopic structural abnormalities, such as chromosomal deletions and duplications, with a minimum range of a few kilobases, which cannot be routinely detected by conventional karyotyping. The pathogenic role of CNVs in fetal diseases has been widely examined, and prenatal testing of microscopic structural chromosomal abnormalities can be accomplished through chromosomal microarray analysis (CMA), which includes array comparative genomic hybridization (array-CGH) and single nucleotide polymorphism array (SNP-array), and copy number

variation sequencing (CNV-seq).[12] One systematic review summarized the results from ten studies, including 376 fetuses with growth restrictions, and found that the incremental detection rate of pathogenic CNVs related to FGR was 10% for the fetal structural anomalies group and 4% for the isolated FGR group. Furthermore, the most common pathogenic CNVs related to FGR were duplication in 22q11.2, and deletions in 7q11.23 and Xp22.3.[13]

In a study of 149 pregnant women with FGR (defined as EFW < 10^{th} percentile for GA), the detection rate of chromosomal abnormalities and CNVs was 13.42% (20/149) by CMA, with a 6.71% (10/149) increased yield of CMA over karyotype analysis within 0.25–8.7Mb duplication and deletion. The detection rate of diagnostic CNVs was significantly different among three FGR groups; 33.33% for the FGR with fetal structural anomalies group; 8.77% FGR with soft markers and without structural anomalies group; and 8.06% isolated FGR group.[7] A recent retrospective study from 13 fetal medicine centers including 146 fetuses diagnosed with isolated FGR (defined as EFW < 10^{th} percentile for GA), demonstrated that the total genetic anomalies identified by CMA were 7.5% (11/146); furthermore, CMA provided an incremental diagnostic rate of 3.4% (5/146) compared with karyotype analysis, with the detection of duplication at 16p12.2 and deletions at 19q12q13.12, 12q13.13, and 19p13.2p13.11.[14] Another study analyzed 133 fetuses with FGR (defined as EFW < 3^{th} percentile for GA) before 32 weeks of gestation and showed that the incremented yield of the diagnostic CNVs by CMA compared with karyotyping was 10.5% for FGR with fetal structural abnormalities, 10.0% for FGR with soft markers and without structural anomalies, and 4.8% for isolated FGR.[15]

Therefore, several guidelines recommend CMA as the first choice for prenatal genetic testing of fetuses with complicated with structural anomalies and soft markers, as well as for isolated FGR defined as EFW < 3^{rd} percentile for GA diagnosed before 32 weeks of gestation.[10,11,16]

Fetal single-gene disorders

FGR, especially severe FGR (EFW < 3^{rd} percentile), may be one of the phenotypes caused by single-gene mutation syndromes,[17] but the total incidence is not yet known. There are 378 entries in the Online Mendelian Inheritance in Man (OMIM) database including the FGR phenotype associated with a wide range of genetic syndromes with autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, or multifactorial inheritance patterns. The most commonly reported syndromes related to FGR include Silver-Russell syndrome (*CDKN1C*), Noonan syndrome (*PTPN11* and *SOS1*), achondroplasia (*FGFR3*), Meier-Gorlin syndrome (*ORCs* and *CDC*), and 3 M syndrome (*CUL7*, *OBSL1*, and *CCDC8*).[18–22]

With the application of next-generation sequencing (NGS) in prenatal diagnosis, it is possible to identify underlying single-gene disorders in fetuses with FGR. There are few studies focused on the incidence of monogenic disease or the incremental yield of the exome sequencing (ES) in FGR cases. A prospective cohort study showed that ES improved the 10% (3/29) diagnostic rate for monogenic disease in FGR cases with structural anomalies; the most common mutant genes included *RAC1*, *KDMT2D*, and *FGFR3*.[23]

There is no compelling evidence on what type and severity of FGR would benefit from prenatal whole-exome sequencing (WES) genetic testing. When FGR is associated with structural abnormalities, genetic testing, such as targeted gene panels, clinical ES, or WES, should be offered during prenatal genetic counseling. For isolated FGR with non-diagnostic CMA results, whether additional genetic testing should be offered is still controversial due to the lower diagnostic yield found in limited studies.

Fetal uniparental disomy (UPD) and epigenetic changes

UPD occurs when two copies of a chromosome originate from the same parent, in contrast to the normal situation where each parent contributes one copy of the chromosome. Moreover, UPD may result from the trisomy rescue mechanism. FGR probably presents as a phenotypic manifestation of the disruption of normal genetic imprinting due to UPD. The underlying mechanism of FGR may involve genomic imprinting and the unmasking of autosomal recessive genes.

In a recent meta-analysis, FGR was reported in 60% (21/35) of UPD cases. However, UPD cases ($n=35$) did not significantly increase the risk of FGR compared with non-UPD ($n=83$) cases ($P=0.151$).[24] UPD can be implicated in multiple diseases, the most familiar disease being Prader Willi Syndrome caused by UPD 15.[25] Furthermore, using the SNP-array analysis, a study identified an IUGR fetus carrying a segmental maternal UPD 16.[26] The imprinted genes on chromosome 16 had two maternal imprinted genes, *ZNF597* and *NAA60*. In the UPD database, 33% (4/12) of FGR cases were identified in all maternal chromosome 16 UPD, which suggested that maternal chromosome 16 UPD is correlated with IUGR. Moreover, the OMIM database also showed syndromes characterized by FGR in chromosome 16, such as Meier-Gorlin syndrome, a congenital disorder of glycosylation, and chromosome 16p12.2-p11.2 deletion syndrome. Paternal and maternal UPD 6 has also been verified to correlate with FGR, and FGR was documented in 60% (9/15) of maternal UPD 6 cases.[27]

Methylation changes have been considered as one of the epigenetic alterations leading to IUGR. Silver-Russell syndrome (SRS) is a rare imprinting syndrome associated with prenatal and postnatal growth restriction. In addition to maternal UPD 7, autosomal dominant and autosomal recessive inheritance, the etiology of SRS can also be related to the loss of methylation that modifies the expression of genes in the imprinted region of chromosome 11p15, which is observed in 40% to 60% of patients. Moreover, a retrospective analysis of 58 cases diagnosed with SRS identified 37 cases (63.8%) with partial loss of methylation in chromosome 11p15.[28] SRS is controlled by the paternally methylated imprinting region H19/IGF2 intergenic differentially methylated region.[29] Hypomethylation of the H19/IGF2 region reduced the expression level of paternal IGF2 and increased the level of maternal H19, leading to FGR.[30]

Prenatal methylation analysis, mainly including methylation-specific multiplex-ligation probe amplification

(MS-MLPA) and methylation-specific polymerase chain reaction (MS-PCR), should be considered to determine whether a fetus with normal karyotype is affected by uniparental disomy.[31]

Placental genetic etiologies for FGR

Confined placental mosaicism (CPM)

CPM is defined as the presence of cell lines with chromosomal abnormalities in the placenta of a fetus with normal chromosomes. CPM may occur due to a mitotic error of non-disjunction in a diploid zygote, or trisomic rescue,[32] can be categorized into three subtypes according to the distribution of chromosomal abnormalities in the placenta. Chromosomal abnormalities are restricted to the cytotrophoblast in CPM type 1; in CPM type 2, they are restricted to the mesenchymal core of the chorionic villi, and in CPM type 3, they occur in both the cytotrophoblast and mesenchymal core.

Previous literature reviews have shown that CPM can be associated with FGR by affecting placental function.[33] The CPM rate ranges from 9% to 16% among FGR cases.[17] Over tenfold aneuploidy was identified on karyotype analysis in placentas from 70 FGR cases compared to those from 70 controls (15.7% versus 1.4%, respectively; $P=0.008$).[34] A recently published meta-analysis revealed that higher levels of mosaicism in chorionic villus sampling (CVS) were significantly associated with higher rates of FGR ($P=0.003$). In addition, pregnancies complicated by CPM showed growth restriction in 71.7% of the cohort ($n=138$).[24] It has been reported that CPM can lead to FGR, especially in cases of trisomy 2, 3, 7, 13, 15, 16, and 22.[24] A study involving 181 pregnancies with CPM revealed that CPM of trisomy 16 was associated with an increased incidence of birthweight below the third percentile ($P=0.007$).[35] Another study of 50 FGR cases (<2.0 *SD*) showed that 16% (8/50) had CPM, including chromosomes 2, 7, 13, and 22.[36] Furthermore, some studies showed that the placentas of FGR cases had a higher incidence of tetraploidy, whereas the underlying mechanism of tetraploid dominance remains to be established.[34]

Mosaicism with CNVs could also disrupt the placental function and cause IUGR. A case report discovered that a newborn (birth weight $<1^{st}$ percentile for GA) was affected by placental mosaicism involving eight de novo duplications of 2.4–3.9 Mb in length of chromosomes 1, 5, 6, 7, 8, and 11.[37]

UPD may occur in the placenta as a condition of CPM. If the CMA analysis following amniocentesis for FGR cases were normal, UPD should be considered when the maternal cell-free DNA (cfDNA) sequencing finds a trisomy involving a chromosome of imprinted genes 6, 7, 11, 14, 15, and 20.[17]

Given the evidence above, placental mosaicism may have diagnostic and prognostic implications for FGR as a marker of placental function. However, it is controversial whether non-invasive prenatal testing (NIPT) is superior to CVS, for detecting placental mosaicism. On the one hand, NIPT can detect CPM because cfDNA in maternal circulation is from placental trophoblast DNA and was suggested to offered with amniocentesis to screen placental abnormalities as a non-invasive technique in growth-restricted fetuses.[38] However, NIPT is just a screening strategy and can only analyze the placental cytotrophoblast, which includes CPM type I and type III, but can not determine CPM type II because it is derived from the mesenchymal core of the chorionic villi.[24] In contrast, some researchers have concurred that it would be reasonable to recommend CVS directly for pregnancies with early-onset severe symmetrical FGR < 24 weeks.[39] The disadvantage of this method is that the anomaly and level of mosaicism detected by CVS do not represent the entire condition of the placenta. Meanwhile, when mosaicism is detected in CVS, amniocentesis should also be performed for fetal karyotyping to differentiate CPM from fetal mosaicism concurrently, which may increase the risk of procedure-related pregnancy loss.

In summary, prenatal genetic evaluation of the placenta by traditional karyotyping or CMA may be helpful in identifying FGR related to placental insufficiency secondary to genetic etiologies, further guiding appropriate intrauterine counseling and management.

Conclusion

The use of CMA and NGS could increase the prenatal diagnosis of genetic diseases associated with FGR. Prenatal evaluation of the genetic etiology of FGR is crucial, especially for early-onset and severe FGR or FGR accompanied by structural abnormalities. In those cases, amniocentesis with CMA and WES should be recommended to rule out underlying chromosomal abnormalities and single-gene variations. Further well-designed and prospective clinical studies are needed to fill the knowledge gaps concerning the need for prenatal diagnosis in cases of isolated, late-onset, or mild and moderate FGR, and which genetic tests would be most appropriate.

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Conflicts of Interest

None.

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