

Placental insufficiency markers to assess the risk of non-chromosomal genetic conditions in early-onset fetal growth restriction

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KEYWORDS: chromosomal microarray; fetal growth restriction; PlGF; sFlt-1; uterine artery Doppler; whole-exome sequencing

ABSTRACT

Objectives To assess the value of placental insufficiency markers for estimating the risk of genetic anomalies in fetuses with isolated early-onset fetal growth restriction (FGR), defined as an estimated fetal weight $\leq 3^{\text{rd}}$ percentile diagnosed $\leq 28 + 6$ weeks' gestation.

Methods We performed a retrospective analysis of data collected prospectively from cases that attended Vall d'Hebron University Hospital, Barcelona, Spain, between February 2016 and December 2022. Singleton pregnancies diagnosed with isolated early-onset FGR between $20 + 0$ and $28 + 6$ weeks' gestation were eligible for inclusion. Cases in which a pathogenic or likely pathogenic fetal genetic abnormality was detected by chromosomal microarray (CMA) or whole-exome sequencing (WES) were identified. Cases were stratified by soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio (< 38 vs ≥ 38), PlGF level (< 100 vs ≥ 100 pg/mL), mean uterine artery (UtA) pulsatility index (PI) ($< 95^{\text{th}}$ vs $\geq 95^{\text{th}}$ percentile) and fetal Doppler (normal vs abnormal) at the time of FGR diagnosis. Abnormal fetal Doppler was defined as a

PI $> 95^{\text{th}}$ percentile in the umbilical artery or ductus venosus, or a middle cerebral artery PI or cerebroplacental ratio $< 5^{\text{th}}$ percentile. The prevalence of genetic anomalies in each subgroup was compared with that of the overall cohort. Additionally, combinations of markers of placental insufficiency were investigated to determine whether specific combinations could improve the ability to identify cases at risk of genetic anomaly.

Results In the total cohort of 238 cases of isolated early-onset FGR, seven (2.9%) cases of genetic anomaly were detected. Of these, 2/7 (28.6%) were detected by prenatal or postnatal CMA and 5/7 (71.4%) by postnatal WES. Fetal Doppler alone and UtA-PI alone did not identify subgroups with a significantly different prevalence of genetic abnormality compared with the overall cohort. In contrast, a sFlt-1/PlGF ratio < 38 and PlGF level ≥ 100 pg/mL defined subgroups with a significantly higher prevalence of genetic abnormality, while no genetic anomalies were found in cases with a sFlt-1/PlGF ratio ≥ 38 or PlGF level < 45 pg/mL. Furthermore, smaller subgroups combining markers of placental insufficiency identified cases at significantly higher or lower risk of FGR-related genetic anomaly.

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Conclusions Placental insufficiency markers, particularly the sFlt-1/PIGF ratio and PIGF level, may enable refined risk stratification of genetic anomalies in cases of isolated early-onset FGR, which could be used to provide individualized prenatal counseling and to optimize the use of WES. Furthermore, combining markers of placental insufficiency, such as UtA-PI and fetal Doppler, may improve risk stratification, potentially defining smaller subgroups with a higher prevalence of genetic anomalies, for which WES may provide greater diagnostic yield. © 2026 The Author(s). *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Fetal growth restriction (FGR) is a condition in which the fetus fails to reach its growth potential due to underlying pathological processes¹. The most common cause of FGR is placental insufficiency, accounting for over 60% of cases², while other etiologies include fetal genetic disorders and intrauterine infections³. Prenatal diagnosis of genetic disorders requires amniocentesis, an invasive procedure that carries a small but non-negligible risk of amniotic membrane rupture. Moreover, genetic testing is costly and may detect conditions unrelated to fetal smallness or results of uncertain clinical significance⁴. Thus, accurately identifying cases of FGR that are more likely to have an underlying genetic disorder is essential to guide counseling on the need for invasive genetic testing.

The prevalence of genetic abnormalities in cases of FGR varies according to the clinical context, being highest in those diagnosed with FGR before 24 weeks' gestation with associated structural anomalies, and lowest in those diagnosed ≥ 32 weeks without major structural anomalies^{5,6}. In isolated FGR, an abnormal karyotype is identified in approximately 4.8% of cases⁷. Compared with conventional karyotyping, chromosomal microarray (CMA) provides an additional diagnostic yield of about 4.8%⁶. More recently, studies have shown that in isolated cases of FGR with a normal karyotype and normal CMA results, whole-exome sequencing (WES) can detect a further 1.6–12% of pathogenic variants^{8,9}. Despite this, there is no clear consensus regarding which cases of FGR warrant prenatal genetic testing^{10,11}. It has been suggested that when placental insufficiency is suspected, the likelihood of a genetic anomaly is low and is comparable to that of the general population^{4,12}. While plausible, this hypothesis lacks robust supporting evidence and the available reports do not provide a consistent definition of placental insufficiency in the context of FGR. In FGR, the most validated indicators of underlying placental insufficiency are an increased mean uterine artery (UtA) pulsatility index (PI)¹³, abnormal fetal Doppler findings^{14,15} and altered angiogenic factors, such as increased soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased placental growth factor (PIGF) levels^{16,17}. However, their utility in assessing the risk of genetic disorders

in early-onset FGR has not yet been evaluated. Therefore, this study aimed to determine whether mean UtA-PI, fetal Doppler and angiogenic factors can help stratify the risk of genetic anomalies in fetuses with isolated early-onset FGR.

METHODS

This was a retrospective observational cohort study performed using data collected prospectively from February 2016 to December 2022 at Vall d'Hebron University Hospital, Barcelona, Spain. Singleton pregnancies with early-onset FGR, defined as an estimated fetal weight (EFW) $\leq 3^{\text{rd}}$ percentile between 20 + 0 and 28 + 6 weeks' gestation, were eligible for inclusion. First-trimester combined screening was offered routinely to all participants, with additional non-invasive prenatal testing (NIPT) for cases with a risk of genetic anomaly between 1:251 and 1:1100. A routine second-trimester scan was performed for all participants as part of standard prenatal care, in accordance with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines for the performance of the routine mid-trimester fetal ultrasound scan¹⁸. In addition, at the time of FGR diagnosis, all participants underwent a further detailed fetal anatomical survey (including fetal echocardiography and neurosonography) to rule out structural anomalies, in accordance with our hospital protocol. Cases with major structural anomaly, intrauterine fetal death at diagnosis or missing sFlt-1/PIGF ratio results were excluded. Fetuses presenting with a single ultrasonographic soft marker (e.g. choroid plexus cyst, echogenic bowel, echogenic intracardiac focus, hypoplastic nasal bone, short femur, single umbilical artery, urinary tract dilatation)¹⁹ were not excluded. Gestational age was confirmed in all participants by fetal crown–rump length measurement during the first-trimester scan at 11 + 0 to 13 + 6 weeks' gestation¹². Serum levels of PIGF and sFlt-1 in maternal blood samples were measured using the fully automated Elecsys assay on an electrochemiluminescence immunoassay platform (Cobas e analyzer; Roche Diagnostics, Rotkreuz, Switzerland). EFW was calculated using biparietal diameter, head circumference, abdominal circumference and femur length²⁰. Additionally, mean UtA-PI was measured routinely using transabdominal Doppler velocimetry, following standard methodology²¹. EFW and UtA-PI percentiles were calculated based on local reference charts^{22,23}. Abnormal fetal Doppler was defined as a PI $> 95^{\text{th}}$ percentile in the umbilical artery²⁴ or ductus venosus²⁵, or a middle cerebral artery PI or cerebroplacental ratio $< 5^{\text{th}}$ percentile²⁶. The EFW, UtA-PI, fetal Doppler findings and PIGF and sFlt-1 values reported in this study were all assessed at the time of FGR diagnosis.

As per our local protocol, all women with early-onset FGR were offered amniocentesis to obtain samples for quantitative fluorescence polymerase chain reaction, TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus) screening and CMA. According to our protocol, WES is not performed prenatally in isolated early-onset FGR cases and is restricted

to those with major structural anomalies, multisystem malformations, polyhydramnios or discordant findings. Medical records of all included infants were reviewed at 2 years of age to identify neurodevelopmental impairment or results from postnatal genetic testing. The study protocol was approved by the Institutional Review Board (PR(AMI)356/2024) on 5 November 2024. Written informed consent was waived due to the retrospective nature of the study.

Chromosomal microarray

Prenatal DNA samples were analyzed by array-comparative genomic hybridization using a CytoSure® Constitutional v3 8x60K oligonucleotide array (Oxford Gene Technology, Kidlington, UK), following the manufacturer's protocol. The array features a backbone resolution of approximately 663 kb, enhanced to 189–375 kb within International Standard Cytogenomic Array (ISCA) Consortium-defined regions, with exon-level resolution in 354 genes and gene-level resolution in 288 genes curated in the ClinGen Dosage Sensitivity Map²⁷. Image acquisition was performed, followed by quantification and analysis using Agilent CytoGenomics software (Agilent Technologies, Santa Clara, CA, USA), utilizing the default Aberration Detection Method 2 (ADM-2) statistical algorithm with a sensitivity threshold set at 6.1. Detected copy-number variants were aligned to the GRCh37/hg19 human reference genome.

Whole-exome sequencing

Genomic DNA was captured using the Exome version 2 kit (Integrated DNA Technologies, Coralville, IA, USA), following the manufacturer's protocol. Paired-end libraries were sequenced on the NovaSeq 6000 sequencing platform (Illumina Inc., San Diego, CA, USA) with 2×100 -bp reads. Sequencing reads were aligned to the GRCh37/hg19 human reference genome using the Burrows–Wheeler aligner maximal exact matches (BWA-MEM) tool²⁸. Variant calling was performed using the Genome Analysis Toolkit (GATK)²⁹ and variant annotation was conducted using ANNOVAR³⁰. The analysis included identification and annotation of single nucleotide variants and small insertions and deletions. Variants were prioritized if supported by ≥ 10 reads, with an allelic balance $\geq 20\%$ and meeting established quality thresholds. Prioritized variants were compared with public and institutional databases (gnomAD, ClinVar, dbSNP, the Vall d'Hebron in-house database and Alamut® Visual) and evaluated using *in-silico* prediction algorithms (SIFT, PolyPhen, MutationTaster, CADD, REVEL and SpliceAI). Variants were described according to the Human Genome Variation Society recommendations (<http://www.hgvs.org>). As the genetic studies were performed on samples from singletons, targeted segregation analysis of candidate variants was carried out in the parents, when necessary, by Sanger sequencing.

Outcome definition

Interpretation and classification of variants followed the American College of Medical Genetics (ACMG), ClinGen and Association for Molecular Pathology (AMP) guidelines^{31–33}, with variants categorized as pathogenic, likely pathogenic, benign, likely benign or a variant of unknown significance (VUS). Clinical interpretation was based on the most current and comprehensive evidence available at the time of analysis. In the analysis, we included only pathogenic or likely pathogenic variants identified by CMA or WES in genes that were associated with the corresponding Human Phenotype Ontology (HPO) terms 'small for gestational age' (HP:0001518) or 'intrauterine growth restriction' (HP:0001511)³⁴. 'Hot' VUS (high risk) found in genes considered relevant to the fetal phenotype were also considered in the analysis³⁵. All such variants were included irrespective of whether they were detected prenatally or postnatally, as they could potentially have been diagnosed before delivery. Cases with low-risk VUS or genetic anomalies not related to the selected HPO terms and cases without genetic testing but with normal neurodevelopment at 2 years of age (as assessed by a pediatrician) were considered to have normal genetic findings. Pregnancy outcome data were extracted from patient and infant medical records. The accuracy of predicting a genetic condition was evaluated by calculating the screen-positive rate, detection rate and prevalence, with the respective 95% CI, for the various subgroups, including: normal or abnormal fetal Doppler findings; mean UtA-PI ($< 95^{\text{th}}$ or $\geq 95^{\text{th}}$ percentile); PlGF level (< 100 or ≥ 100 pg/mL); and sFlt-1/PlGF ratio (< 38 or ≥ 38). Additionally, we investigated whether combining markers of placental insufficiency could improve the ability to identify or to exclude those at high risk of genetic anomaly. However, we anticipated that such analyses may result in several small subgroups and these were therefore conducted as exploratory, hypothesis-generating analyses only; thus, no adjustment for multiple testing was applied.

Statistical analysis

Descriptive data are presented as median (interquartile range) for continuous variables and as n (%) for categorical variables. Group comparisons were conducted using the chi-square test or Fisher's exact test, as appropriate. To investigate the ability of biomarkers and Doppler indices to assess the risk of genetic anomalies, the prevalence of genetic conditions in the overall cohort was compared with that observed in each subgroup. Statistical analyses were performed using JAMOV version 2.3 (The Jamovi Project (2022); www.jamovi.org) with the Rj Editor module version 2.6.0 (Rj Editor module (2022); [www.github.com/jamovi/rj](https://github.com/jamovi/rj)). $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, 238 cases of isolated early-onset FGR with available sFlt-1/PlGF ratio results were

identified. Baseline characteristics are summarized in Table 1. Amniocentesis for CMA was offered to all patients and 118 (49.6%) pregnant individuals underwent the procedure. Two pathogenic findings were identified on prenatal CMA, of which one (1/118 (0.85%)) genetic anomaly was associated with FGR, while the other represented an incidental finding. According to our

Table 1 Baseline characteristics and pregnancy outcomes of 238 cases of isolated early-onset fetal growth restriction (FGR) diagnosed $\leq 28 + 6$ weeks' gestation with estimated fetal weight $\leq 3^{\text{rd}}$ percentile

Characteristic	Value
Maternal age (years)	34.0 (29.0–37.0)
BMI (kg/m^2)	24.5 (21.5–28.5)
Ethnicity	
White/Latin American	201 (84.5)
Southeast Asian	17 (7.1)
Black	15 (6.3)
East Asian	3 (1.3)
Mixed	2 (0.8)
Nulliparous	147 (61.8)
Previous FGR or SGA	32 (13.4)
Medical history	
Chronic hypertension	24 (10.1)
Pregestational diabetes	8 (3.4)
Antiphospholipid syndrome	10 (4.2)
Systemic lupus erythematosus	5 (2.1)
Smoking during pregnancy	33 (13.9)
Mode of conception	
Spontaneous	196 (82.4)
IVF	39 (16.4)
Artificial insemination	3 (1.3)
Gestational age at diagnosis (weeks)	25.0 (23.1–26.8)
sFlt-1/PlGF ratio ≥ 38 at diagnosis	157 (66.0)
sFlt-1/PlGF ratio ≥ 85 at diagnosis	117 (49.2)
PlGF < 100 pg/mL at diagnosis	155 (65.1)
Abnormal fetal Doppler at diagnosis*	113 (47.5)
Mean UtA-PI $\geq 95^{\text{th}}$ percentile at diagnosis	163 (68.5)
Pre-eclampsia at diagnosis	44 (18.5)
Pre-eclampsia after diagnosis	49 (20.6)
Termination of pregnancy	15 (6.3)
Gestational age at delivery (weeks)	32.0 (28.3–37.0)
Time from FGR diagnosis to delivery (weeks)	7.3 (3.3–11.5)
Birth weight (g)	1243 (743–2100)
Adverse perinatal outcome	131 (55.0)
5-min Apgar score < 7	51 (21.4)
Umbilical cord arterial pH < 7.0	4 (1.7)
NICU admission for > 48 h	127 (53.4)
Stillbirth†	19 (8.0)
Neonatal death	12 (5.0)
Respiratory distress syndrome	81 (34.0)
Bronchopulmonary dysplasia	41 (17.2)
Necrotizing enterocolitis	12 (5.0)
Retinopathy Grade III–IV	12 (5.0)
IVH Grade III–IV	6 (2.5)
Periventricular leukomalacia	3 (1.3)

Data are given as median (interquartile range) or n (%).

*Abnormal fetal Doppler was defined as a pulsatility index (PI) $> 95^{\text{th}}$ percentile in the umbilical artery or ductus venosus, or a middle cerebral artery PI or cerebroplacental ratio $< 5^{\text{th}}$ percentile.

†Fetal death > 20 weeks' gestation. BMI, body mass index;

IVF, *in-vitro* fertilization; IVH, intraventricular hemorrhage;

NICU, neonatal intensive care unit; PlGF, placental growth factor;

sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small-for-

gestational age; UtA, uterine artery.

local protocol, prenatal WES was not performed, as all cases had isolated FGR. Postnatally, 27 (11.3%) infants underwent genetic testing due to neurodevelopmental impairment or a phenotype suggestive of a genetic disorder; 13 of these infants had previously undergone prenatal CMA and had received a normal genetic result. Overall, 106 (44.5%) cases did not undergo prenatal or postnatal genetic testing; postnatal testing was not performed due to normal postnatal neurodevelopment. Among the postnatally tested cases, six genetic disorders associated with FGR were diagnosed: one by CMA and five by WES (including three pathogenic variants, one likely pathogenic variant and one hot VUS). An additional postnatally detected case with a pathogenic variant detectable by WES but a normal prenatal CMA result was identified; this variant was not associated with FGR and was excluded from the FGR-related genetic anomaly group. CMA was performed in all cases that underwent postnatal genetic testing, followed by WES when CMA was normal; therefore, WES was performed in 26 infants.

Overall, 231 (97.1%) cases either had a normal genetic test result (including two low-risk VUS detected postnatally and two genetic anomalies unrelated to FGR) or demonstrated normal postnatal neurodevelopment, whereas seven (2.9%) cases had a genetic abnormality diagnosed prenatally or postnatally (two diagnosed by CMA and five diagnosed by WES) (Figure 1, Tables 2, S1 and S2).

When stratifying the prevalence of genetic conditions by biophysical and biochemical markers, cases with a sFlt-1/PlGF ratio < 38 represented 34.0% of the overall cohort, yet accounted for 100% (7/7) of cases of genetic anomaly, corresponding to a prevalence of 8.6% ($P < 0.001$). A PlGF level ≥ 100 pg/mL was observed in 34.9% of the cohort and in 71.4% (5/7) of cases with a genetic anomaly, corresponding to a prevalence of 6.0% ($P = 0.039$) (Table 3). Moreover, all cases with a genetic anomaly had PlGF ≥ 45 pg/mL (Figure 2, Table 2). In contrast, 66.0% of all cases had a sFlt-1/PlGF ratio ≥ 38 , among whom no genetic anomalies were detected ($P < 0.001$).

When analyzed individually, subgroups defined by UtA-PI ($< 95^{\text{th}}$ or $\geq 95^{\text{th}}$ percentile) or fetal Doppler findings (normal or abnormal) did not show a significant difference in the prevalence of genetic anomalies compared with the entire cohort (Table 3). However, smaller subgroups combining UtA-PI with angiogenic factors, UtA-PI with fetal Doppler, and abnormal fetal Doppler with angiogenic factors, identified cases with significantly higher or lower risk of FGR-related genetic anomaly (Table S3).

DISCUSSION

In a cohort of singleton pregnancies with isolated early-onset FGR diagnosed between $20 + 0$ and $28 + 6$ weeks' gestation with an EFW $\leq 3^{\text{rd}}$ percentile, markers of placental insufficiency (particularly the sFlt-1/PlGF ratio and PlGF level) may help stratify the risk of

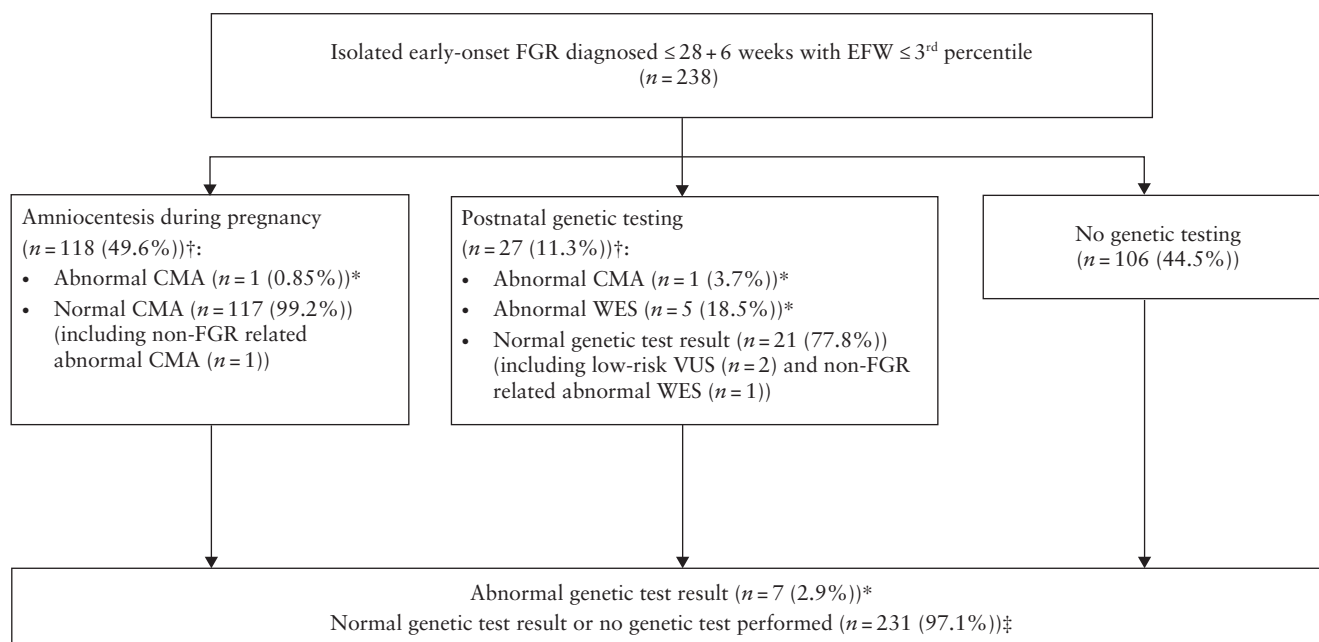


Figure 1 Flowchart summarizing results of prenatal and postnatal genetic testing in cohort of fetuses with isolated early-onset fetal growth restriction (FGR). *Abnormal genetic test result refers to genetic findings associated with FGR. †Thirteen cases underwent prenatal and postnatal genetic testing and had a normal result for both. ‡Includes 104 (46.8%) cases with normal genetic test result on prenatal-only testing, 13 (5.6%) cases with a normal result on both pre- and postnatal testing, eight cases with a normal result on postnatal-only testing, and 106 (45.9%) with no genetic testing performed; of those with normal genetic test result, one case had non-FGR related abnormal chromosomal microarray (CMA) result, two had low-risk variants of unknown significance (VUS) and one had non-FGR related abnormal whole-exome sequencing (WES) result. EFW, estimated fetal weight.

Table 2 Clinical characteristics and ultrasound findings in cases of isolated early-onset fetal growth restriction (FGR) with genetic anomalies identified by chromosomal microarray (CMA) or whole-exome sequencing (WES)

Case	GA (weeks)	Mean UtA-PI (percentile)	Fetal Doppler*	sFlt-1/PIGF ratio	PIGF (pg/mL)	Prenatal invasive test	Genetic anomaly	Detectable with CMA	Detectable with WES	Diagnosis	Ultrasound findings
1	27 + 0	≥ 95 th	Normal	24.3	75.9	No	Diamond–Blackfan anemia	No	Yes	Postnatal	Isolated
2	27 + 6	Normal	Abnormal	6.4	191.2	Yes	Cornelia de Lange syndrome	No	Yes	Postnatal	Isolated
3	28 + 3	≥ 95 th	Abnormal	28.4	46.8	Yes	Pseudohypoparathyroidism type 1a	No	Yes	Postnatal	Isolated
4	28 + 0	Normal	Abnormal	1.9	684.5	Yes	Wiedemann–Steiner syndrome	No	Yes	Postnatal	CPC‡
5	24 + 1	Normal	Abnormal	4.7	353.7	Yes	Acrodisostosis	No	Yes	Postnatal	Isolated
6	23 + 0	Normal	Abnormal	9.5	172.1	Yes	Temple syndrome	Yes†	Yes	Prenatal	Isolated
7	24 + 2	≥ 95 th	Normal	11.2	174.3	No	arr(9) × 2 ~ 3 (chromosomal mosaicism/aneuploidy)	Yes	No	Postnatal	Isolated

*Abnormal fetal Doppler was defined as a pulsatility index (PI) > 95th percentile in the umbilical artery or ductus venosus, or a middle cerebral artery PI or cerebroplacental ratio < 5th percentile. †Additional testing with methylation-specific multiplex ligation-dependent probe amplification was performed, as required, for definitive diagnosis of Temple syndrome. ‡Fetuses presenting a single ultrasonographic soft marker, including choroid plexus cyst (CPC), were not excluded from consideration as isolated early-onset FGR. GA, gestational age; PIGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA, uterine artery.

genetic abnormalities. In this study, we identified several subgroups in which the risk of abnormal genetic findings differed significantly from the overall cohort. Notably, no genetic anomalies were diagnosed in the subgroups with more evident signs of placental insufficiency, such as those with sFlt-1/PIGF ≥ 38 and PIGF < 45 pg/mL.

The use of placental insufficiency markers for stratifying the risk of genetic abnormalities among fetuses with isolated early-onset FGR has not been evaluated previously. Earlier studies have focused mainly on the prevalence of genetic abnormalities across different clinical presentations and on the performance of diagnostic variables. These studies have shown that the

risk of chromosomal anomalies in apparently isolated FGR depends on both gestational age at diagnosis and the severity of growth restriction⁵. The degree of fetal smallness also influences risk, rising from 7.8% in cases with an EFW < 10th percentile to 18% in those with an EFW < 3rd percentile³⁶. Regarding diagnostic tools, CMA provides an incremental yield of approximately 4% over karyotyping^{6,37}, while WES identifies pathogenic variants in up to 12% of cases^{8,9}. In this study, 71.4% (5/7) of anomalies were detectable only by WES, including one hot VUS (c.1111 + 1del) in *HDAC8*, a previously unreported variant predicted to result in a canonical splice site loss-of-function mutation, which is a well-established

Table 3 Screen-positive rate (SPR), detection rate (DR) and prevalence of genetic anomalies stratified by placental insufficiency markers

Parameter	SPR	DR	Prevalence	P*
All cases (reference)	238	7	7/238 (2.9 (1.3–6.2))	—
sFlt-1/PlGF ratio				
< 38	81 (34.0 (28.1–40.5))	7 (100.0 (56.1–100))	7/81 (8.6 (3.8–17.5))	< 0.001
≥ 38	157 (66.0 (59.5–71.9))	0 (0 (0–43.9))	0/157 (0 (0–3.0))	< 0.001
PlGF				
≥ 100 pg/mL	83 (34.9 (28.9–41.3))	5 (71.4 (30.3–94.9))	5/83 (6.0 (2.2–14.1))	0.039
< 100 pg/mL	155 (65.1 (58.7–71.1))	2 (28.6 (5.1–69.7))	2/155 (1.3 (0.2–5.1))	0.039
Mean UtA-PI				
< 95 th percentile	75 (31.5 (25.8–37.9))	4 (57.1 (20.2–88.2))	4/75 (5.3 (1.7–13.8))	0.138
≥ 95 th percentile	163 (68.5 (62.1–74.3))	3 (42.9 (11.8–79.8))	3/163 (1.8 (0.5–5.7))	0.138
Fetal Doppler				
Normal	125 (52.5 (46.0–59.0))	2 (28.6 (5.1–69.7))	2/125 (1.6 (0.3–6.2))	0.198
Abnormal†	113 (47.5 (41.0–54.0))	5 (71.4 (30.3–94.9))	5/113 (4.4 (1.6–10.5))	0.198

Data are given as *n*, *n* (%) (95% CI) or *n/N* (%) (95% CI). *Comparison between genetic anomaly prevalence for each parameter with that of the reference group. †Abnormal fetal Doppler was defined as a pulsatility index (PI) > 95th percentile in the umbilical artery or ductus venosus, or a middle cerebral artery PI or cerebroplacental ratio < 5th percentile. PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA, uterine artery.

	High risk	Low risk
sFlt-1/PlGF ratio	sFlt-1/PlGF ratio < 38 (81/238 (34.0%)) DR = 100% (7/7)	sFlt-1/PlGF ratio ≥ 38 (157/238 (66.0%)) DR = 0% (0/7)
PlGF	PlGF ≥ 45 pg/mL (136/238 (57.1%)) DR = 100% (7/7)	PlGF < 45 pg/mL (102/238 (42.9%)) DR = 0% (0/7)
Fetal Doppler and mean UtA-PI	Mean UtA-PI < 95 th percentile* (<i>n</i> = 75) + Mean UtA-PI ≥ 95 th percentile + normal fetal Doppler (<i>n</i> = 74) (149/238 (62.6%)) DR = 85.7% (6/7)	Mean UtA-PI ≥ 95 th percentile + abnormal fetal Doppler† (89/238 (37.4%)) DR = 14.3% (1/7)

Figure 2 Risk stratification of genetic abnormalities in 238 pregnancies with isolated early-onset fetal growth restriction (FGR), based on soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio, PlGF level and different combinations of fetal Doppler findings and mean uterine artery (UtA) pulsatility index (PI). Following prenatal and/or postnatal genetic testing, genetic abnormalities related to FGR were identified in seven cases. *Combination of abnormal and normal fetal Doppler with UtA-PI included to avoid excessive subgrouping that could compromise the external validity of the findings. †Abnormal fetal Doppler was defined as a PI > 95th percentile in the umbilical artery or ductus venosus, or a middle cerebral artery PI or cerebroplacental ratio < 5th percentile. DR, detection rate.

disease mechanism in Cornelia de Lange syndrome³⁸. Despite its clinical utility in the assessment of FGR, WES is not used routinely in most prenatal settings due to its cost, limited availability and the absence of consensus regarding optimal indications in current guidelines. This limited use reflects both the scarcity of data and the modest diagnostic yield of prenatal genetic studies on isolated FGR³⁹. Indeed, some authors have suggested that evidence of placental insufficiency may identify fetuses with early-onset FGR at lower risk of genetic anomalies, potentially further explaining the modest diagnostic

yield⁸. Our findings support this hypothesis; however, the small number of genetic anomalies detected in this study could affect the precision of prevalence estimates, and the results should be interpreted with caution.

In our cohort, a higher prevalence of genetic disorders was observed in cases with normal angiogenic factors (sFlt-1/PlGF ratio < 38 and PlGF ≥ 100 pg/mL) or in cases with discordant Doppler findings, such as normal UtA-PI (< 95th percentile) with abnormal fetal Doppler. Taken together, these observations suggest that in genetically mediated FGR, growth impairment may result from intrinsic fetal or placental defects rather than defective placentation. Such mechanisms may not compromise trophoblast invasion or uterine vascular resistance, but could influence angiogenic factor production or fetal hemodynamics, thereby altering fetal Doppler indices. This hypothesis is supported by studies demonstrating that genetically abnormal placentae function less efficiently⁴⁰, thus increasing the risk of low birth weight⁴¹. Furthermore, fetal trisomies can affect angiogenic factors and fetal Doppler parameters^{42–44}, although no cases of trisomy were identified in our cohort, likely because such cases were either excluded due to structural anomalies or detected earlier through routine first-trimester combined screening, followed by cell-free DNA testing in intermediate-risk pregnancies.

Our findings indicate that angiogenic factors and Doppler studies may be valuable tools for stratifying the risk of genetic conditions in isolated early-onset FGR. In our cohort, pregnancies with an elevated sFlt-1/PlGF ratio or reduced PlGF level had no genetic abnormalities, suggesting a lower prevalence of genetic anomalies in these subgroups. In contrast, most genetic anomalies were detected in cases with normal angiogenic factors or discordant fetal Doppler findings. Specifically, cases with a sFlt-1/PlGF ratio < 38 (34.0% of the total cohort) accounted for all detected genetic anomalies (7/7). Similar results were obtained using a PlGF threshold of ≥ 45 pg/mL, which captured all genetic anomalies in

57.1% of the total cohort. In settings without access to angiogenic factor levels, our results suggest that risk stratification could still be performed using a combination of UtA-PI and fetal Doppler, which identified 85.7% (6/7) of genetic anomalies in a subgroup representing 62.6% of the cohort (Figure 2).

The main strength of this study was the inclusion of a relatively large, homogeneous cohort of isolated early-onset FGR cases, with postnatal follow-up extending to 2 years after delivery. This design allowed identification of both prenatal and postnatal genetic diagnoses, minimizing underestimation of true genetic disorder prevalence. Additionally, we evaluated well-validated markers of placental insufficiency, some of which are accessible in routine clinical practice, and our findings have direct clinical applicability to enhance prenatal counseling. Importantly, although it is biologically plausible that cases with more severe placental insufficiency have a lower prevalence of genetic anomalies, this study is the first to our knowledge to formally provide quantitative evidence supporting a hypothesis long suggested by experts in the field. Finally, the rate of genetic anomalies detected in our cohort was lower than that in previous studies; however, this likely reflects the absence of chromosomal defects, consistent with contemporary clinical practice, in which most cases of fetal trisomy are identified during first-trimester combined screening or via detection of structural anomalies on ultrasound, rather than presenting as isolated early-onset FGR.

Nonetheless, several limitations should be acknowledged. First, although all predictive markers were systematically collected prospectively, the retrospective design of the study carries inherent bias. Second, no cases of trisomy were included due to routine first-trimester combined screening, NIPT and comprehensive ultrasound scans; thus, findings may not apply to settings lacking such detailed screening or to chromosomally affected cases. Third, genetic testing was not performed in 44.5% of cases, introducing some uncertainty regarding undetected conditions; however, all infants who did not undergo testing exhibited normal neurodevelopment at 2 years of age, which, from both a clinical and parental perspective, may be a more meaningful outcome than confirmation of a normal genetic test result. Fourth, the consistently higher risk of genetic anomalies in subgroups without markers of placental insufficiency supports this relationship; however, the small number of cases limits the precision of the prevalence estimates. Finally, subgroup analyses based on combinations of markers of placental insufficiency resulted in an even smaller number of cases in specific categories, further limiting statistical power and external validity. For these reasons, future studies should validate our findings in larger cohorts. In the meantime, our findings should not be used to discourage offering invasive testing when clinically indicated, but rather to provide updated and more individualized risk scores to support prenatal counseling.

In conclusion, markers of placental insufficiency at the time of FGR diagnosis, particularly the sFlt-1/PIGF

ratio, PlGF level and the combination of UtA-PI and fetal Doppler, may help to identify subgroups of isolated early-onset FGR in which the risk of genetic anomalies differs significantly from that of the overall cohort. Such risk stratification may improve the precision of prenatal counseling, support shared decision-making regarding invasive testing and help optimize the selective use of WES in isolated early-onset FGR.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Details of genetic anomalies diagnosed in study cohort.

Table S2 Details of variants of unknown significance (VUS) and genetic anomalies unrelated to fetal growth restriction diagnosed in study cohort.

Table S3 Screen-positive rate (SPR), detection rate and prevalence of genetic anomalies across various combinations of Doppler indices and placental insufficiency biomarkers.



Marcadores de insuficiencia placentaria para evaluar el riesgo de condiciones genéticas no cromosómicas en fetos con restricción del crecimiento de aparición temprana

RESUMEN

Objetivos. Evaluar el valor de los marcadores de insuficiencia placentaria para estimar el riesgo de anomalías genéticas en fetos con restricción del crecimiento fetal (RCF) aislada de aparición temprana, definida como un peso fetal estimado $\leq 3^{\text{er}}$ percentil diagnosticado a $\leq 28+6$ semanas de gestación.

Métodos. Se realizó un análisis retrospectivo de los datos recogidos prospectivamente de los casos que acudieron al Hospital Universitario Vall d'Hebron de Barcelona en España, entre febrero de 2016 y diciembre de 2022. Se consideraron elegibles para la inclusión en el estudio los embarazos con feto único diagnosticados con RCF aislada de aparición temprana entre las 20+0 y las 28+6 semanas de gestación. Se identificaron los casos en los que se detectó una anomalía genética fetal patogénica, o probablemente patogénica, mediante análisis de microarrays cromosómicos (AMC) o secuenciación del exoma completo (WES, por sus siglas en inglés). Los casos se estratificaron en función de la relación tirosina quinasa-1 soluble tipo fms (sFlt-1)/factor de crecimiento placentario sérico (FCPI) (<38 frente a ≥ 38), el nivel de FCPI (<100 frente a ≥ 100 pg/mL), el índice de pulsatilidad (PI) medio de la arteria uterina (UtA) (UtA-PI, por sus siglas en inglés) (<95 frente a ≥ 95 percentil) y el Doppler fetal (normal frente a anómalo) en el momento del diagnóstico de la RCF. El Doppler fetal anómalo se definió como un PI $>95^{\circ}$ percentil en la arteria umbilical o el ductus venoso, o un PI de la arteria cerebral media o una relación cerebroplacentaria $<5^{\circ}$ percentil. La prevalencia de anomalías genéticas en cada subgrupo se comparó con la de la cohorte global. Además, se investigaron combinaciones de marcadores de insuficiencia placentaria para determinar si ciertas combinaciones específicas podían mejorar la capacidad de identificar casos con riesgo de anomalía genética.

Resultados. En la cohorte total de 238 casos de RCF aislada de aparición temprana, se detectaron siete (2,9%) casos con anomalía genética. De ellos, 2/7 (28,6%) fueron detectados por AMC prenatal o postnatal y 5/7 (71,4%) por WES postnatal. El Doppler fetal por sí solo y el UtA-PI por sí solo no identificaron subgrupos con una prevalencia de anomalías genéticas significativamente diferente en comparación con la cohorte global. Por el contrario, un cociente sFlt-1/FCPI <38 y un nivel de FCPI ≥ 100 pg/mL definieron subgrupos con una prevalencia significativamente mayor de anomalía genética, mientras que no se encontraron anomalías genéticas en los casos con un cociente sFlt-1/FCPI ≥ 38 o un nivel de FCPI <45 pg/mL. Además, en subgrupos más pequeños que combinaban marcadores de insuficiencia placentaria se identificaron casos con un riesgo significativamente mayor o menor de anomalía genética relacionada con la RCF.

Conclusiones. Los marcadores de insuficiencia placentaria, en particular la relación sFlt-1/FCPI y el nivel de FCPI, pueden permitir una estratificación más afinada del riesgo de anomalías genéticas en casos de RCF aislado de aparición temprana, lo que podría utilizarse para proporcionar un asesoramiento prenatal a medida y optimizar el uso de la WES. Además, la combinación de marcadores de insuficiencia placentaria, como la UtA-PI y el Doppler fetal, puede mejorar la estratificación del riesgo, con la que definir potencialmente subgrupos más pequeños con una mayor prevalencia de anomalías genéticas, para los que la WES puede proporcionar un mayor rendimiento del diagnóstico.

胎盘功能不全标志物在早发型胎儿生长受限中评估非染色体遗传病风险的价值

摘要

目的 评估胎盘功能不全标志物在估算孤立性早发型胎儿生长受限 (FGR) 胎儿遗传异常风险中的价值。孤立性早发型 FGR 定义为 $\leq 28+6$ 周诊断且估测胎儿体重 $\leq$ 第 3 百分位数。

方法 我们对 2016 年 2 月至 2022 年 12 月期间在西班牙巴塞罗那 Vall d'Hebron 大学医院就诊的病例中前瞻性收集的数据进行了回顾性分析。纳入标准为孕 20+0 至 28+6 周诊断为孤立性早发型 FGR 的单胎妊娠。通过染色体微阵列分析 (CMA) 或全外显子组测序 (WES) 检出致病性或可能致病性胎儿遗传异常的病例被识别。根据 FGR 诊断时的可溶性 fms 酪氨酸激酶-1 (sFlt-1)/胎盘生长因子 (PlGF) 比值 (<38 vs ≥ 38)、PlGF 水平 (<100 vs ≥ 100 pg/mL)、平均子宫动脉 (UtA) 搏动指数 (PI) ($<$ 第 95 百分位数 vs $\geq$ 第 95 百分位数) 以及胎儿多普勒 (正常 vs 异常) 对病例进行分层。异常胎儿多普勒定义为脐动脉或静脉导管 PI $>$ 第 95 百分位数, 或大脑中动脉 PI 或脑胎盘比值 $<$ 第 5 百分位数。比较各亚组中遗传异常的发生率与总队列的发生率。此外, 探讨胎盘功能不全标志物的组合, 以确定特定组合是否能提高识别遗传异常风险病例的能力。

结果 在总共 238 例孤立性早发型 FGR 病例中, 检出 7 例 (2.9%) 遗传异常。其中, 2/7 (28.6%) 通过产前或产后 CMA 检出, 5/7 (71.4%) 通过产后 WES 检出。单独胎儿多普勒和单独 UtA-PI 未能识别出遗传异常发生率与总队列有显著差异的亚组。相反, sFlt-1/PlGF 比值 <38 和 PlGF 水平 ≥ 100 pg/mL 定义了遗传异常发生率显著较高的亚组, 而在 sFlt-1/PlGF 比值 ≥ 38 或 PlGF 水平 <45 pg/mL 的病例中未发现遗传异常。此外, 结合胎盘功能不全标志物的较小亚组识别出了 FGR 相关遗传异常风险显著较高或较低的病例。

结论 胎盘功能不全标志物, 尤其是 sFlt-1/PlGF 比值和 PlGF 水平, 可能有助于对孤立性早发型 FGR 病例的遗传异常进行精细化风险分层, 从而可用于提供个体化产前咨询并优化 WES 的应用。此外, 结合胎盘功能不全标志物 (如 UtA-PI 和胎儿多普勒) 可能改善风险分层, 或可界定出遗传异常发生率更高的较小亚组, 对这些亚组行 WES 可能具有更高的诊断效能。