

Value of prenatal chromosomal microarray analysis (CMA) in isolated foetal growth restriction diagnosed before 26 weeks of gestation

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ABSTRACT

Aim. To evaluate the diagnostic yield of amniocentesis with quantitative fluorescent polymerase chain reaction (QF-PCR) and chromosomal microarray analysis (CMA) in pregnancies with apparently isolated at the time of pre-amniocentesis assessment early-onset foetal growth restriction (FGR) diagnosed before 26 weeks of gestation and to explore associations with perinatal outcomes.

Material and methods. This retrospective cohort study was conducted at a tertiary perinatal centre in Poland. From 1655 amniocenteses performed between 2018 and 2023, we identified 31 singleton pregnancies with isolated FGR (EFW/AC <3rd percentile) before 26 weeks, excluding all cases with structural anomalies or major maternal confounders. All cases underwent QF-PCR and CMA. Descriptive statistics and group comparisons were performed.

Results. Abnormal genetic results were found in 9/31 cases (yield 29.0%; 95% CI 14.2–48.0%), including 3 triploidies and 6 pathogenic/likely pathogenic CNVs. CMA provided an incremental yield of 19.4% over QF-PCR alone. Mean gestational age at delivery was 32.4 weeks, and adverse perinatal outcomes occurred in 29% of cases.

Conclusions. In isolated early-onset FGR before 26 weeks, QF-PCR combined with CMA achieved a high diagnostic yield of 29%. These findings support routine use of CMA in this high-risk subgroup and highlight the prognostic importance of genetic testing.

Introduction

Foetal growth restriction (FGR), defined as an estimated foetal weight below the 3rd percentile for gestational age, is a major obstetric complication associated with increased perinatal morbidity, mortality, and long-term neurodevelopmental risks [1,2]. Isolated early-onset FGR, diagnosed before 26 weeks of gestation without accompanying structural anomalies, poses particular diagnostic challenges due to its heterogeneous aetiology, including placental insufficiency, maternal factors, and genetic abnormalities [3,4]. Genetic causes account for 15–20% of FGR cases, with chromosomal aneuploidies (e.g., triploidy, trisomy 18) and submicroscopic copy number variants (CNVs) being prominent contributors, especially in symmetric and severe forms [5,6].

Traditional karyotyping detects aneuploidies and large structural variants in approximately 2–6% of isolated FGR cases, but its resolution limits detection of smaller pathogenic alterations [7–9]. Chromosomal microarray analysis (CMA) offers superior detection of CNVs and uniparental disomy (UPD), providing an incremental yield of 3–10% over karyotyping in isolated FGR. Systematic reviews and meta-analyses report overall CMA yields of 6–13% in isolated FGR, with higher rates (up to 19%) in early-onset or severe cases [9,10].

For CMA-negative cases, whole-exome sequencing (WES) further enhances diagnostic utility, revealing pathogenic/likely pathogenic variants in 11–24% of isolated FGR cohorts, particularly those with short long bones or additional subtle features [11]. Recent studies emphasise that WES is particularly valuable in early-onset isolated FGR, where monogenic disorders may contribute significantly beyond chromosomal abnormalities [12].

Despite these advances, the genetic aetiology of very early-onset isolated FGR (<26 weeks) remains incompletely characterised, with limited data from Central European populations [13,14]. Guidelines from the American College of Obstetricians and Gynaecologists (ACOG) and the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) recommend invasive prenatal testing, including CMA, for early-onset FGR, but the role of quantitative fluorescent polymerase chain reaction (QF-PCR) for rapid aneuploidy detection and sequential WES in unre-

solved cases requires further validation [1,15]. Abnormal genetic findings are associated with earlier delivery and higher adverse perinatal outcomes, underscoring the prognostic importance of comprehensive testing.

This study evaluates the diagnostic yield of amniocentesis using QF-PCR and CMA in a Polish cohort of 31 pregnancies with isolated early-onset FGR <26 weeks, to inform genetic counselling and management strategies for this underrepresented population.

Materials and methods

This was a retrospective cohort study conducted at a tertiary-referral perinatal centre in Poland, which serves as a national reference unit for complex foetal medicine and prenatal genetics. Patients are referred from a wide geographic area across the country, making the cohort representative of high-risk pregnancies managed in a specialised Polish setting.

The study protocol was approved by the local ethics committee with a waiver of informed consent due to the retrospective nature of the analysis and the use of anonymised clinical data.

Study Population

The study population and procedural details have been previously described in detail [16]. Briefly, we reviewed the medical records of all 1655 singleton pregnancies that underwent amniocentesis at our institution between January 2018 and December 2023. From this population, we selected cases in which the primary indication for invasive prenatal testing was foetal growth restriction diagnosed before 26 weeks of gestation. FGR was defined according to ISUOG and SMFM criteria as an estimated foetal weight (EFW) or abdominal circumference (AC) below the 3rd percentile for gestational age, confirmed by serial ultrasound examinations and, when available, Doppler assessment. Foetal weight was estimated using the Hadlock formula, and centiles were assigned according to the INTERGROWTH-21st international foetal growth standards, adjusted for gestational age.

Exclusion criteria were applied to ensure a homogeneous cohort of apparently isolated at the time of pre-amniocentesis assessment, FGR:

- Presence of any structural anomaly detected on prenatal ultrasound (e.g., cardiac defects, central nervous system malformations, renal anomalies, or evident skeletal dysplasias).
- Multiple gestation.
- Known maternal conditions strongly associated with secondary FGR (e.g., severe preeclampsia diagnosed prior to amniocentesis, uncontrolled diabetes, or systemic disorders with documented placental insufficiency).
- Incomplete genetic testing results or missing key clinical outcome data.

After application of these criteria, 31 pregnancies with isolated early-onset FGR remained eligible for analysis. All included cases had amniocentesis performed due to isolated FGR before 26 weeks, with no ultrasonographically detectable structural malformations at the time of the procedure. In this retrospective study, 'isolated FGR' therefore referred to the absence of documented major structural anomalies at the time of invasive testing; complete first-trimester data and detailed retrospective information on placental morphology, amniotic-fluid volume and Doppler studies were not available for all cases.

Genetic Testing Protocol

Amniocentesis was performed under continuous ultrasound guidance using a 22-gauge spinal needle. Amniotic fluid samples were processed according to standard laboratory protocols at our institution's prenatal genetic laboratory.

- **Rapid aneuploidy detection:** Quantitative fluorescent polymerase chain reaction (QF-PCR) was performed for chromosomes 13, 18, 21, X, and Y in all cases to provide rapid results (typically within 24–48 hours). QF-PCR enabled the diagnosis of whole-genome triploidy in three cases. Conventional array-CGH was used primarily for CNV detection; its results were interpreted in light of the method's known limited ability to detect balanced whole-genome ploidy abnormalities.
- **Chromosomal microarray analysis (CMA):** Array comparative genomic hybridisation (aCGH) was performed using commercially available platforms at a resolution of 50–100 kb. Pathogenic or likely pathogenic copy number variants (CNVs) and regions of homozygosity suggestive of uniparental disomy were reported in accordance with ACMG guidelines.

All genetic results were interpreted by a clinical geneticist and discussed in multidisciplinary prenatal counselling sessions. Parental origin of the additional haploid set in triploid pregnancies was not assessed.

Data Collection and Variables

Clinical data were retrospectively extracted from electronic medical records and ultrasound reports. Collected variables included:

- Maternal age, gravidity, parity, and relevant medical history.
- Gestational age at diagnosis of FGR and at amniocentesis.
- Ultrasound findings at the time of amniocentesis.
- Genetic testing results (QF-PCR, CMA).
- Pregnancy outcomes: gestational age at delivery or termination, route of delivery, indication for delivery, perinatal complications (e.g., intrauterine foetal demise, neonatal death).
- Neonatal data (when available): birth weight, Apgar scores, neonatal intensive care admission, and final diagnosis.

Adverse perinatal outcomes were defined as intrauterine foetal demise, termination of pregnancy for medical reasons, neonatal death, or extreme preterm delivery (<28 weeks). Results of first- and second-trimester prenatal screening, including the combined (double) test, triple test, and serum marker screening, were not systematically available in the records and were therefore not included in the analysis.

Statistical Analysis

Descriptive statistics were used to summarise continuous variables (mean $\pm$ standard deviation, median, range) and categorical variables (frequencies and percentages). The diagnostic yield of genetic testing was calculated as the proportion of cases with pathogenic or likely pathogenic findings. Comparisons between groups with normal vs abnormal genetic results were performed using Welch's t-test or Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. All analyses were conducted using PQStat software (version 1.8.6). P-values <0.05 were considered statistically significant; however, given the small sample size, results are presented primarily as descriptive trends.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and local regulations. For this retrospective analysis of anonymised clinical data, the institutional ethics committee waived the requirement for formal informed consent. Patient confidentiality was maintained throughout the study.

This section follows standard reporting guidelines for retrospective cohort studies in prenatal genetics and is structured similarly to comparable publications in the field (e.g., Luo et al., 2026; Shi et al., 2025).

Results

In this retrospective study, 31 patients were identified who underwent amniocentesis due to isolated early-onset foetal growth restriction (FGR) before 26 weeks of gestation. All cases met the criteria for isolated FGR (absence of coexisting structural anomalies of the central nervous system, heart defects, chromosomal abnormalities in family history, or other anomalies visible on ultrasound prior to amniocentesis). Baseline characteristics of the entire cohort are presented in **Table 1**.

Table 1. Baseline characteristics of the entire cohort (n = 31)

Parameter	Value
Maternal age (mean; IQR / median / range)	29.7 / 30; 25.0–33.8 / 19–42
Gestational age at amniocentesis (mean / median; IQR / range)	23.1 / 24; 22.0–25.0 / 18–26
Gravidity (median / range)	2 / 1–4
Parity (median / range)	0 / 0–3
Multiparous (parity ≥1) (n / %)	15 / 48.4%
Gestational age at delivery/termination (mean / median; IQR / range)	32.4 / 34; 27.0–37.0 / 19–40
Adverse perinatal outcomes (intrauterine demise, termination, neonatal death) (n / %)	9 / 29.0%

Table 2. Characteristics of cases with abnormal amniocentesis results

Case	Maternal age	GA at amniocentesis (weeks)	Amniocentesis result	Indication for delivery / neonatal outcome
2	32	26	CMA – microduplication 1q21.1–q21.2	GA at delivery: 30 weeks; indication: impending eclampsia; BW: 1100 g; Apgar: 6/8; no neonatal death.
4	19	25	QF-PCR – triploidy	GA at delivery: 31 weeks; indication: placental abruption; BW: 1200 g; Apgar: 5/7; neonatal death on day 4.
5	24	22	CMA – microdeletion 1q21.1	GA at delivery: 37 weeks; indication: signs of fetal compromise; BW: 2300 g; Apgar: 8/9; no neonatal death.
9	27	24	CMA – heterozygous deletion Xp22.33 and Xp22.33–p22.32	GA at delivery: 40 weeks; indication: high risk of shoulder dystocia; BW: 2800 g; Apgar: 9/10; no neonatal death.
16	29	18	QF-PCR – triploidy	GA at termination: 19 weeks; indication: medical termination; BW: N/A; Apgar: N/A; no neonatal death (TOP).
22	36	20	CMA – microduplication 15q13.3 and 20p12.3–p11.23	GA at delivery: 27 weeks; indication: severe preeclampsia superimposed on chronic hypertension + HELLP syndrome; BW: 850 g; Apgar: 4/6; no neonatal death.
23	36	23	CMA – deletion 21q22.2–q22.3	GA at IUFD: 27 weeks; indication: intrauterine fetal demise; BW: N/A; Apgar: N/A; fetal death.
25	25	22	CMA – deletion 1p13.3–p12	GA at delivery: 35 weeks; indication: signs of fetal compromise; BW: 1900 g; Apgar: 7/8; no neonatal death (placental edema, ventriculomegaly, hyperechoic bowel noted).
31	32	20	QF-PCR – triploidy	GA at termination: 20 weeks; indication: medical termination; BW: N/A; Apgar: N/A; no neonatal death (TOP).

Note: In all three triploid pregnancies, triploidy was diagnosed by QF-PCR. Conventional CMA did not independently identify the whole-genome ploidy abnormality, and the parental origin of the additional haploid set was not assessed. BW: birth weight; GA: gestational age; IUFD: intrauterine fetal demise; TOP: termination of pregnancy; N/A: not applicable.

Table 3. Detailed pathogenic and likely pathogenic copy number variants detected by chromosomal microarray analysis in pregnancies with isolated early-onset fetal growth restriction

Case	Array result GRCh37	CNV type	Cytogenetic region	Genomic interval GRCh37	Size	Selected clinically relevant genes	Classification
2	arr[GRCh37] 15q13.3(31972646_33064391)x3	Interstitial duplication	15q13.3	chr15:31,972,646- 33,064,391	1.09 Mb	CHRNA7	Pathogenic or likely pathogenic (laboratory/ clinical-genetics interpretation)
5	arr[GRCh37] 1q21.1q21.2(146507518_147824207)x1	Interstitial deletion	1q21.1-q21.2	chr1:146,507,518- 147,824,207	1.32 Mb	Not specified in the supplied clinical-genetics interpretation	Pathogenic (laboratory/ clinical-genetics interpretation)
9	arr[GRCh37] Xp22.33(305449_2772032)x1, Xp22.33p22.32(2772032_4764155)x0	Two adjacent Xp deletions with different copy-number states	Xp22.33 and Xp22.33-p22.32	chrX:305,449- 2,772,032 (x1); chrX:2,772,032- 4,764,155 (x0)	2.47 Mb and 1.99 Mb, respectively	SHOX; ARSE	Pathogenic (laboratory/ clinical-genetics interpretation)
22	arr[GRCh37] 15q13.3(32065000_32509926)x3, 20p12.3p11.23(8256690_18278919)x3	Two interstitial duplications	15q13.3 and 20p12.3-p11.23	chr15:32,065,000- 32,509,926 (x3); chr20:8,256,690- 18,278,919 (x3)	0.445 Mb and 10.02 Mb, respectively	CHRNA7 within the 15q13.3 duplication; no additional key gene specified in the supplied interpretation	Pathogenic or likely pathogenic (laboratory/ clinical-genetics interpretation)
23	arr[GRCh37] 21q22.2q22.3(39992487_48084156)x1	Distal/terminal deletion	21q22.2-q22.3	chr21:39,992,487- 48,084,156	8.09 Mb	Not specified in the supplied clinical-genetics interpretation	Pathogenic or likely pathogenic (laboratory/ clinical-genetics interpretation)
25	arr[GRCh37] 1p13.3p12(109619643_120516701)x1	Interstitial deletion	1p13.3-p12	chr1:109,619,643- 120,516,701	10.90 Mb	Not specified in the supplied clinical-genetics interpretation	Pathogenic or likely pathogenic (laboratory/ clinical-genetics interpretation)

Cohort Characteristics

The mean maternal age was 29.7 ± 6.4 years (median 30 years, range 19–42 years). The median gravidity was 2 (range 1–4), and the median parity was 0 (range 0–3). Nearly half of the patients (15/31, 48.4%) were multiparous (parity ≥ 1).

The mean gestational age (GA) at the time of amniocentesis was 23.1 ± 2.4 weeks (median 24 weeks, range 18–26 weeks).

Genetic Testing Results

Amniocentesis yielded an abnormal result in 9 out of 31 cases, corresponding to a diagnostic performance of 29.0% (95% CI: 14.2–48.0%).

QF-PCR identified whole-genome triploidy in 3 cases (9.7%). In these pregnancies, CMA did not independently detect triploidy and did not identify an additional pathogenic or likely pathogenic CNV. However, CMA detected additional pathogenic or likely pathogenic CNVs in 6 further cases (19.4%), resulting in an overall diagnostic value of 29.0% (9/31; 95% CI 14.2–48.0%). The incremental yield of CMA over QF-PCR alone was therefore 19.4% (6/31).

Limiting diagnostic testing to QF-PCR alone would have reduced the detection rate of genetic abnormalities from 29.0% to only 9.7%, missing two-thirds of the identified pathogenic findings (mainly CNVs).

The abnormal findings included:

- triploidy – 3 cases (33.3% of abnormal results),
- microdeletions / deletions – 4 cases (44.4%),
- microduplications / duplications – 2 cases (22.2%).

Among the three pregnancies with triploidy, severe FGR was diagnosed at 18, 19 and 25 weeks' gestation. No major foetal structural

anomaly was documented before amniocentesis. The pregnancies diagnosed at 18 and 19 weeks were terminated within one week after the QF-PCR result; hence, the subsequent evolution of the foetal phenotype could not be assessed. In the pregnancy diagnosed at 25 weeks, delivery by caesarean section was performed at 31 weeks because of non-reassuring foetal status, and the neonate died on day 4 of life.

Detailed abnormal genetic results are presented in **Table 2**. The summary of abnormal CMA results is presented in **Table 3**.

Obstetric and Neonatal Outcomes

Delivery data were available for all pregnancies. The mean gestational age at delivery or termination was 32.4 ± 5.4 weeks (median 34 weeks, range 19–40 weeks). Preterm delivery or termination before 32 weeks occurred in 12 cases (40.0%). Adverse perinatal outcomes, defined as intrauterine foetal demise, termination of pregnancy for medical reasons, or neonatal death, were observed in 9 cases (29.0% of the cohort).

Birth weight was available in all live-born cases, with a mean of 1780 ± 820 g. Apgar scores at 1 and 5 minutes were also documented, with median values of 7 (range 3–9) and 8 (range 5–10), respectively.

Neonatal death occurred in 4 cases (19.0% of live births).

Comparison of Groups with Normal vs Abnormal Amniocentesis Results

Selected parameters comparing the normal and abnormal amniocentesis groups are presented in **Table 4**.

Table 4. Comparison of key parameters between groups with normal and abnormal amniocentesis results

Parameter	Abnormal result (n = 9)	Normal result (n = 22)	p-value*
Maternal age (mean / median; IQR / range)	28.9 / 29; 25.0–32.0 / 19–36	30.0 / 30; 25.0–34.0 / 19–42	0.65
GA at amniocentesis (mean / median; IQR / range)	22.2 / 22; 20.0–24.0 / 18–26	24.0 / 24; 22.0–24.0 / 18–26	0.21
GA at delivery (mean / median; IQR / range)	29.6 / 30; 27.0–35.0 / 19–40	33.4 / 34; 30.5–37.0 / 25–38	0.17
Adverse perinatal outcomes (n / %)	4 / 44.4%	5 / 22.7%	0.38
Gravidity (median / range)	1 / 1–3	1 / 1–4	0.12
Parity (median / range)	0 / 0–1	0 / 0–2	0.22

* Continuous variables are presented as median (interquartile range, IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as percentages (%) and are compared using Fisher's exact test. All tests were two-sided. P-values should be interpreted as exploratory owing to the small sample size.

Discussion

The present retrospective study of 31 pregnancies complicated by isolated early-onset foetal growth restriction (FGR) diagnosed before 26 weeks of gestation and subjected to amniocentesis demonstrates a diagnostic yield of 29.0% for clinically significant genetic abnormalities using quantitative fluorescent polymerase chain reaction (QF-PCR) and chromosomal microarray analysis (CMA). This yield is notably higher than many previously reported figures for isolated FGR, particularly when considering the very early gestational age at diagnosis in our cohort (mean 23.1 weeks).

Literature reviews and meta-analyses consistently report lower average yields for chromosomal microarray in isolated foetal growth restriction diagnosed in the second trimester (typically 20–32 weeks). For instance, a systematic review and meta-analysis estimated the mean rate of chromosomal aberrations in apparently isolated FGR at approximately 6.4% (range 0–26.3%), with an incremental yield of CMA over karyotyping around 4–6% in unselected cases. More recent data from larger cohorts and meta-analyses indicate incremental yields of CMA over karyotyping in isolated FGR ranging from 3–6%, with overall pathogenic findings by CMA in early-onset cases often between 6–8%. In contrast, our observed 29% yield (including triploidies, deletions, and duplications) aligns more closely with reports focusing on very early-onset (<26 weeks) or severe isolated FGR, where yields can reach 15–30% due to a higher prevalence of chromosomal aneuploidies (e.g., triploidy) and submicroscopic copy number variants (CNVs) that impair early placental and foetal development. Our cohort, restricted to apparently isolated early-onset FGR before 26 weeks at the time of pre-amniocentesis assessment, demonstrates a yield of 29.0%, which aligns with the upper range observed in this specific subgroup and exceeds the average reported for broader isolated FGR populations.

The predominance of triploidy (3/9 abnormal cases, 33%) and CNVs involving deletions/duplications (e.g., 1q21.1, 15q13.3, 21q22) in our series is consistent with established patterns in early-onset FGR. Triploidy and trisomies (particularly 18 and 21) are well-recognised causes of severe,

symmetric early growth impairment, often leading to early foetal demise or termination.

The three triploid pregnancies were classified as isolated FGR because no major structural anomaly was documented before amniocentesis. This operational definition should not be interpreted as evidence that all recognised triploidy-associated features were absent. In particular, detailed first-trimester and placental data were unavailable, and two pregnancies were terminated shortly after genetic diagnosis, precluding assessment of later phenotypic evolution.

The pathogenic or likely pathogenic classification of the CNVs in our cohort establishes their clinical relevance but does not, by itself, demonstrate that each CNV was the sole cause of FGR. This distinction is important because several of the detected CNVs have variable expressivity, incomplete penetrance, and phenotypes that are recognised mainly after birth. The 15q13.3 duplications in Cases 2 and 22 include *CHRNA7*. Although affected cohorts have shown developmental delay, autism spectrum disorder and attention-deficit/hyperactivity disorder, *CHRNA7* duplications have also been identified in apparently unaffected parents and control individuals; therefore, their penetrance and prenatal phenotypic predictability are limited [17].

In contrast, the 1q21.1-q21.2 deletion in Case 5 has more direct prenatal support [18]. In a recent prenatal series of recurrent 1q21.1 deletions, FGR was reported among the common ultrasound indications, although the deletion was inherited in a proportion of tested families, and the authors emphasised the need for further genotype-phenotype data [19]. Thus, this CNV may have contributed to the growth phenotype, but a direct influence cannot be determined from our single case.

The complex Xp22.33/Xp22.32 loss in Case 9 includes *SHOX* and *ARSE* genes. *SHOX* loss is biologically relevant to linear growth and skeletal development, but prenatal phenotypes of *SHOX*-containing Xp22.33 deletions are heterogeneous: reported fetuses have ranged from skeletal abnormalities to isolated soft markers or no ultrasound abnormality [20]. Accordingly, this result provides a possible genetic explanation for impaired growth. However, the absence of documented structural anomalies before amniocentesis prevents drawing more specific prenatal genotype-phenotype conclusions.

Case 22 carried both a 20p12.3-p11.23 duplication and a 15q13.3 duplication involving *CHRNA7*. Isolated partial trisomy 20p is rare, and its phenotype remains poorly defined because most published cases also carry other chromosomal imbalances. It is therefore not possible to determine whether the 20p duplication contributed to foetal growth restriction in this pregnancy [21]. The 15q13.3 duplication has limited and variable penetrance, with reported neurodevelopmental and behavioural phenotypes, but it also occurs in apparently unaffected individuals; it likewise does not allow direct attribution of FGR [17]. Similarly, the distal 21q22.2-q22.3 deletion in Case 23 was classified as pathogenic or likely pathogenic due to its well-established broad phenotypic consequences. Prenatal reports of terminal 21q22 deletion remain limited, and the phenotype may lack multiple or severe malformations; this limits prenatal genotype-phenotype prediction [22].

The large 1p13.3-p12 deletion found in Case 25 was classified as pathogenic or likely pathogenic. Published data on partially overlapping 1p deletions remain limited. One reported de novo case showed postnatal growth deceleration and mild developmental delay, but birth size was normal. These findings therefore do not establish a link between this CNV and prenatal foetal growth restriction [23]. In our case, the clinical-genetics interpretation noted that deletions of similar extent have been reported with intrauterine growth restriction and short stature; this should be considered a possible, rather than proven, explanation for FGR (**Table 3**).

Clinically relevant trends emerged when comparing pregnancies with abnormal versus normal genetic results. Although no statistically significant differences were found (likely due to the small sample size), abnormal findings were associated with earlier gestational age at amniocentesis (22.2 vs 23.5 weeks), earlier delivery (29.6 vs 33.4 weeks), and a higher rate of adverse perinatal outcomes (44.4% vs 22.7%). These observations support the concept that genetically driven early-onset FGR tends to manifest more severely and earlier, often resulting in intrauterine foetal demise, termination, or extreme preterm delivery. Similar associations between early diagnosis, genetic aetiology, and poor prognosis have been reported in cohorts with early-onset isolated FGR.

The high proportion of multiparous women (45.2%) and relatively low mean parity (0.39) in our cohort may reflect referral patterns in a specialised perinatal centre, but the trend toward lower gravidity and parity in the abnormal genetic group suggests that nulliparity or low parity could be a subtle risk marker for genetic aetiology in very early FGR—possibly due to fewer confounding maternal-placental factors accumulated in multiparous pregnancies.

Several limitations must be acknowledged. The retrospective design and modest sample size ($n = 31$) limit statistical power and generalizability; post hoc p-values should be interpreted cautiously as exploratory. Neonatal follow-up was partial, and long-term neurodevelopmental outcomes were not assessed. Nevertheless, the focus on a homogeneous group of very early-onset isolated FGR in a single Polish centre provides valuable local data in a region underrepresented in the international literature. In addition, incomplete retrospective availability of first-trimester ultrasound findings and of detailed placental, amniotic-fluid and Doppler assessments limited phenotypic characterisation of the triploid pregnancies. The early termination of two triploid pregnancies also precluded evaluation of abnormalities that might have become apparent later in gestation.

Also, first- and second-trimester prenatal screening results were not systematically available because many patients were referred after screening was performed outside of our centre. We were therefore unable to assess the relation between screening results, referral patterns and the decision to undergo invasive testing.

Finally, the parental origin of the additional haploid set was not assessed in the triploid pregnancies; consequently, their classification as digynic or diandric could not be determined.

In conclusion, our findings support offering invasive prenatal genetic testing (QF-PCR + CMA) in pregnancies with isolated FGR diagnosed before 26 weeks, given the substantial diagnostic yield and prognostic implications. In our series, QF-PCR was essential for identifying whole-genome triploidy, while CMA enabled the detection of additional pathogenic CNVs. Larger, prospective multicentre studies are needed to refine risk stratification, optimise testing algorithms, and improve genetic counselling for this challenging subgroup of pregnancies.

Conclusions

In this retrospective study of 31 pregnancies with apparently isolated at the time of pre-amniocentesis assessment early-onset foetal growth restriction diagnosed before 26 weeks of gestation, amniocentesis with QF-PCR and chromosomal microarray analysis achieved a diagnostic yield of 29.0% for clinically significant genetic abnormalities. This rate exceeds the 6–13% overall CMA yields and 3–10% incremental yields over karyotyping reported in most meta-analyses and large cohorts of isolated FGR. Triploidy and pathogenic CNVs predominated among abnormal results, consistent with patterns in very early and severe FGR.

Although limited by the small sample size, pregnancies with abnormal genetic results showed numerically earlier gestational age at amniocentesis (22.2 vs 23.5 weeks), earlier delivery or termination (29.6 vs 33.4 weeks), and a higher proportion of adverse perinatal outcomes (44.4% vs 22.7%). However, none of these differences reached statistical significance (all $p > 0.05$), and no clinically meaningful prognostic value of earlier amniocentesis was demonstrated in this analysis.

These results support routine invasive genetic testing (QF-PCR + CMA) in isolated early-onset FGR <26 weeks, even in the absence of structural anomalies, and highlight the prognostic value of positive findings. Larger prospective studies are required to confirm these observations, refine testing algorithms, and strengthen evidence-based counselling in this high-risk subgroup.

Statements

Author Contributions

All authors contributed equally to this work. They all participated in the conception and design of the study, data collection, analysis and interpretation of results, drafting and critical revision of the manuscript, and approved the final version for submission.

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Ethical Approval

Ethics approval statement is not applicable.

Patient Consent

Due to the retrospective nature of the study and the use of anonymised data, the requirement for informed consent was waived by the Bioethics Committee of Poznan University of Medical Sciences.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of interest statement

The authors declare no conflict of interest.

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