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ORIGINAL RESEARCH ARTICLE

Small-for-gestational-age fetus diagnosed in the second trimester: Possible etiologies and short-term neonatal outcomes

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Abstract

Introduction: The aim of our study was to investigate the causes of fetal growth <10th centile diagnosed <26 weeks' gestation in singleton pregnancies and compare pregnancy outcomes in relation to the identified etiology.

Material and methods: Historical cohort study conducted in two Italian hospitals which included all small-for-gestational-age fetuses diagnosed between 18+0 and 26+0 weeks over a 10-year period. Fetuses were divided into three groups depending on the prenatally suspected etiology: chromosomal abnormalities (Group 1), malformations (Group 2) and isolated (Group 3). These groups were compared regarding pregnancy outcomes. Fetuses in Group 3 were divided into small-for-gestational-age and fetal growth restriction following the Delphi Consensus criteria and the outcomes were further compared. Fisher's Exact or Mann–Whitney test were used for comparison of groups.

Results: In all, 435 fetuses were included. Of these, 20 cases (4.6%) were associated with chromosomal abnormalities (Group 1), 98 (22.5%) with fetal malformations (Group 2) and 317 (72.9%) were isolated (Group 3). A higher percentage of live births was reported for Group 3 ($P < 0.001$). Termination of pregnancy was more common in Group 1 ($P < 0.001$). No differences in gestational age at delivery, birthweight, intrauterine death or neonatal death were detected within groups. Growth-restricted fetuses had lower gestational age at delivery, birthweight and number of live births ($P < 0.001$), higher rates of termination of pregnancy, intrauterine death ($P < 0.001$) and neonatal death <10 days ($P = 0.002$) compared to small-for-gestational-age. In 17 cases a chromosomal abnormality, genetic syndrome or adverse neurological outcome was diagnosed after birth: six from Group 2 (11.3% of live births in this group) and 11 from Group 3 (4.3%).

Abbreviations: EFW, estimated fetal weight; FGR, fetal growth restriction; SGA, small for gestational age.

Conclusions: We report that fetal growth <10th percentile diagnosed before 26 weeks is not isolated before birth in 27% of cases. Malformations and chromosomal abnormalities are common etiologies; therefore, detailed anomaly scans and invasive testing should be offered. In addition, there is a residual risk of neonatal death and postnatal diagnosis of a genetic syndrome or neurodevelopmental impairment despite normal prenatal tests. These results expand the small amount of information on the outcome of cases with very early diagnosis of impaired fetal growth currently available and highlight the importance of detailed counseling with couples.

KEYWORDS
aneuploidy, chromosomal abnormality, etiology, fetal growth restriction, fetal malformation, genetic syndrome, small for gestational age

1 | INTRODUCTION

The diagnosis of a small-for-gestational-age (SGA) fetus, generally defined as an abdominal circumference or estimated fetal weight (EFW) <10th centile,[1,2] is one of the most common in obstetric practice and it often creates anxiety in couples due to the uncertainty regarding the underlying cause of impaired growth and outcome of pregnancy, especially if the diagnosis comes at an early gestational age.

Randomized controlled trials have been conducted over the past decades to define the correct intrauterine management and timing of delivery of fetuses with this condition,[3,4] although with a specific interest in cases complicated by abdominal circumference <3rd centile, association with Doppler modifications or fall in growth velocity, which are the cases defined as fetal growh restriction (FGR) that the Delphi Consensus reached in 2016.[5] These studies, however, concentrated on the management of fetuses who reached viability, whereas limited data can be found for counseling couples with a very early diagnosis of this condition (<26 weeks of gestation) in relation to the etiology.[6,7]

In clinical practice, not only fetuses with FGR but also the larger category of the SGA fetuses require strict monitoring in pregnancy and labor for the increased risk of stillbirth compared with fetuses whose growth is at higher percentiles.[1–2,8] Moreover, the vast majority of SGA are considered constitutionally small, or eventually a consequence of placental insufficiency; however, chromosomal, genetic, structural or infective etiologies are also possible as well as cases due to maternal factors (maternal weight, smoking habit, abuse of alcohol or drugs, severe anemia) or comorbidities (maternal hypertension, preeclampsia, renal or autoimmune diseases, diabetes, thrombophilia).[2,9–10]

The aim of our study was to investigate the fetal causes underlying a diagnosis of SGA in singleton pregnancies diagnosed in the second trimester before 26 weeks and to compare pregnancy outcomes in relation to the identified etiology.

Key message

Women with fetuses <10th centile should be offered detailed anomaly scan, genetic counseling and invasive testing. So far, these recommendations have not been universally recognized as useful in the case of fetuses with growth <10th, only in those with growth <3rd centile.

2 | MATERIAL AND METHODS

This was a historical cohort study conducted in two tertiary referral centers, Azienda Ospedaliero-Universitaria Careggi, in Florence, and Spedali Civili, in Brescia, both in Italy. Fetuses with a diagnosis of SGA with or without uterine and umbilical artery Doppler abnormalities were identified from the electronic ultrasound databases routinely used in clinical practice (Florence: Astraia-Astraia Software GmbH, Munich, Germany, from 2010 to June 2015; View point-GE Healthcare, Frankfurt, Germany, from July 2015; Brescia: View point-GE Healthcare, Frankfurt, Germany). We included all SGA fetuses between 18+0 and 26+0 weeks of gestation followed at our hospitals from 2007 to 2017. Criteria for defining SGA fetus were the presence of abdominal circumference and/or EFW <10th centile.[11] EFW was derived from the Hadlock formula, which combines biparietal diameter, head circumference, abdominal circumference and femur length.[12] Only fetuses from singleton pregnancies and with complete follow-up were included. Follow-up was obtained from hospital medical records and patient interviews.

Gestational age was derived from the routine ultrasound scan performed in the first trimester of pregnancy (between 11+0 and 13+6 weeks) following the Guidelines of the Italian society of Ultrasound in Obstetrics and Gynecology for pregnancy dating.[13]

Data on fetal anatomy, invasive testing and infection screening were analyzed and the population was divided into groups depending on the prenatally suspected etiology underlying the fetal condition: association with chromosomal abnormalities confirmed with prenatal testing (Group 1), association with malformations (Group 2) and isolated (Group 3). We did not report the presence of short long bones, echogenic bowel or cardiomegaly, as they are not considered structural malformations in the presence of isolated SGA or FGR. We also did not report cases of four-chamber disproportion without

an underlying cardiac malformation and isolated soft markers such as golf ball and choroid plexus cysts.

With regard to other possible etiologies, no cases of SGA associated with a genetic syndrome or fetal infection documented before birth were detected.

The three groups were compared for maternal demographic and fetal characteristics (maternal age, maternal body mass index, smoking status, presence of maternal comorbidities, gestational age at diagnosis, percentile of abdominal circumference, percentage of abdominal circumference <3rd percentile). The comorbidities recorded were chronic hypertension, diabetes and autoimmune diseases.

Based on umbilical and uterine artery Doppler status and fetal growth, a subgroup of FGR fetuses was identified for Group 3 following the Delphi Consensus criteria.[5]

Pregnancy outcomes (live birth, gestational age at delivery and birthweight, termination of pregnancy, intrauterine fetal death, neonatal death before 10 days or 1 month) were evaluated and compared depending on the underlying etiology. For each group we also reported the cases where an adverse outcome was diagnosed after birth, namely, all cases of postnatal diagnosis of a chromosomal abnormality, a genetic or hormonal disorder or adverse neurological outcome (neurological impairment, motor impairment or both and neurodevelopmental disorders.

2.1 | Statistical analyses

Statistical analysis was performed with IBM SPSS Statistics v. 21.0 (IBM). Frequencies were compared with Fisher's Exact test and continuous variables with the Mann–Whitney test. A *P*-value <0.05 was considered statistically significant.

2.2 | Ethics statement

The study protocol was approved by the local Ethics Committees (CEAVC n.13740_oss) on October 3, 2018.

3 | RESULTS

A total of 435 fetuses fulfilled the inclusion criteria. Of these, 20 cases (4.6% of the total population) were associated with chromosomal abnormalities (Group 1), 98 (22.5% of cases) with fetal malformations (Group 2) and 317 (72.9% of cases) were isolated (Group 3). Figure 1 shows the subdivision of the total population in the three groups. The demographic characteristics of the total population and the three groups separately are reported in Table 1. Median maternal age in the total population was 32 (28–36) years. The percentage of women with maternal age >35 years was higher in Group 1 than in the other groups; the difference was significant when compared with Group 2 ($P=0.043$). Median body mass index was 22.6 (20.4–26.4), 7.1% of women were smokers and 13.8% of women had maternal comorbidities. No differences within groups were noted for body mass index, percentage of smoking women and presence of comorbidities. Gestational age at diagnosis of the fetal condition in the total population was 21.6 weeks (20.3–24); this was lower in Group 1 than in the other two groups ($P<0.001$). Fetuses in Group 2 showed a lower abdominal circumference percentile compared with Group 3 ($P<0.001$). The percentage of fetuses with abdominal circumference <3rd percentile was higher in Groups 1 and 2 than in Group 3 ($P=0.027$ and $P<0.001$, respectively).

Table 2 lists in detail the chromosomal abnormalities detected in Group 1. As previously stated, no cases of genetic syndromes were detected prenatally. With regard to fetal malformations, in 58 (59.2%) cases fetuses showed an isolated anomaly, and the presence of multiple malformations was detected in 40 (40.8%) cases: in 22 cases there were two fetal malformations, and in 18 there were three or more malformations. The most frequent malformations detected were the presence of single umbilical artery ($n=25$), ventricular septal defect ($n=18$), ventriculomegaly ($n=10$), clubfoot ($n=9$) and omphalocele ($n=8$). When grouped by organ system, the most common anomalies were cardiac defects (48 cases) and central nervous system anomalies (35 cases). Table S1 shows in detail all fetal malformations prenatally detected in Group 2. Among the fetuses with two or more structural malformations, only three cases underwent an invasive

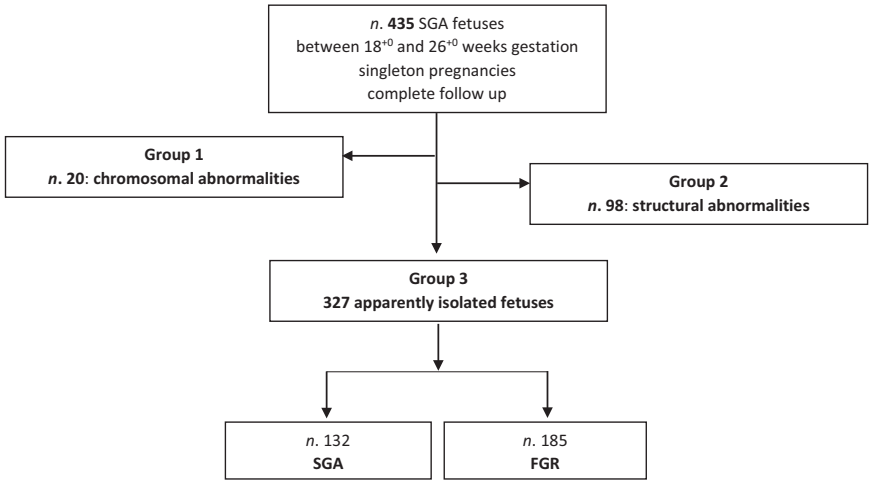

FIGURE 1 The diagram shows the subdivision of the cohort in groups depending on the prenatally suspected etiology.

TABLE 1 Demographic characteristics of the total population and divided by possible etiology (Group 1: association with chromosomal abnormality; Group 2: association with fetal malformation; Group 3: isolated).

	Total population	Group 1	Group 2	Group 3	1 vs 2, *P*-value	1 vs 3, *P*-value	2 vs 3, *P*-value
n (%)	435	20 (4.6%)	98 (22.5%)	317 (72.9%)			
Maternal age, median (IQR)	32 (28–36)	35 (29.8–39.3)	32 (28–35)	32 (28–36)	0.05	0.107	0.258
Maternal age ≥35 years, *n* (%)	153 (35%)	11 (55%)	30 (30.6%)	112 (35.3%)	**0.043**	0.094	0.463
BMI, median (IQR)	22.6 (20.4–26.4)	21.6 (20.3–25)	22.3 (19.9–25.4)	22.9 (20.6–26.6)	0.957	0.401	0.19
Smokers, *n* (%)	31 (7.1%)	0	7 (7.1%)	24 (7.6%)	0.601	0.38	1.0
Comorbidities (chronic hypertension, diabetes mellitus, autoimmune disease), *n* (%)	60 (13.8%)	1 (5%)	11 (11.2%)	48 (15.1%)	0.688	0.33	0.409
Gestational age at diagnosis, weeks, median (IQR)	21.6 (20.3–24)	19.4 (18.3–20.8)	21.4 (20.6–23.1)	21.9 (20.3–24.4)	**<0.001**	**<0.001**	0.292
Abdominal circumference percentile, median (IQR)	4 (1–6.8)	2.9 (0.5–5.1)	2.3 (0–5)	4.9 (1.9–7.7)	0.477	0.061	**<0.001**
Abdominal circumference < 3 percentile, *n* (%)	173 (39.8%)	12 (60%)	56 (57%)	105 (33.1%)	1.0	**0.027**	**<0.001**

Abbreviations: BMI, body mass index; IQR, interquartile range; ns, not significant.

TABLE 2 Details of chromosomal abnormalities prenatally identified in Group 1.

n	Type of chromosomal abnormality
4	Trisomy 21
4	Trisomy 18
2	Trisomy 13
2	Triploidy
2	47,XXX
1	47,XXY
1	Trisomy 2
1	47,XXY/48,XXY + 18 mosaicism
1	45,X [11]/46,XY[39]
1	*t*(8,10)
1	Chromosome 9 anomaly

procedure and were diagnosed with a normal karyotype; the other 37 cases were not tested. Of this latter group, 13 fetuses were born alive and two were postnatally diagnosed with a chromosomal abnormality, while 24 cases had intrauterine fetal death or termination of pregnancy and post-mortem karyotyping was not performed.

With regard to pregnancy outcomes in relation to the three groups (Table 3), a higher percentage of live births was reported for isolated SGA fetuses (Group 3) compared with the other groups ($P < 0.001$), while there was a higher proportion of termination of pregnancy in the groups affected by prenatally detected fetal chromosomal abnormalities or malformations ($P < 0.001$ compared with Group 3). No differences in gestational age at delivery, birthweight, intrauterine death and neonatal death were detected within groups.

When dividing Group 3 into SGA and FGR fetuses (Table 4), lower gestational age at delivery, birthweight and number of live births were recorded for FGR fetuses ($P < 0.001$), while the were higher rates of termination of pregnancy, intrauterine death ($P < 0.001$) and neonatal death <10 days ($P = 0.002$) compared with the SGA subgroup.

In 17 cases a severe postnatal condition was diagnosed after birth (which included a chromosomal abnormality, a genetic syndrome, a hormonal disorder or an adverse neurological outcome – Table 3); six from Group 2 (11.3% of all livebirths in this group) and 11 from Group 3 (4.3% of livebirths in this group). Details of such cases are provided in Table 5.

4 | DISCUSSION

In this study we report the etiologies of a large cohort of SGA fetuses and show that one-quarter of all cases were not isolated before birth. In fact, diagnosis of chromosomal abnormality was possible prenatally in 4.6% of cases, whereas 22.5% of cases showed an association with one or more fetal malformations. Impaired fetal growth without an underlying prenatally identifiable chromosomal abnormality, genetic syndrome or fetal malformation was seen in 72.9% of cases. No cases of genetic syndromes or fetal infections were detected before birth, whereas four fetuses (1.3% of live-born children) had a chromosomal abnormality, five (1.7%) a genetic syndrome and seven cases (2.2%) a neurological/endocrine adverse outcome identified after birth.

Counseling couples who receive a diagnosis of SGA fetus at an early stage of pregnancy, when the fetus has not reached the gestational age or weight to be considered viable, represents a challenge for fetal medicine specialists. The possible association of this finding with chromosomal, genetic, structural anomalies or fetal infections is well known;[10] however, only a few studies have systematically

TABLE 3 Pregnancy outcome in relation to the study group (Group 1: association with chromosomal abnormality; Group 2: association with fetal malformation; Group 3: isolated).

	Group 1	Group 2	Group 3	1 vs 2, *P*-value	1 vs 3, *P*-value	2 vs 3, *P*-value
n (%)	20 (4.6%)	98 (22.5%)	317 (72.9%)			
Live born, *n* (%)	8/20 (40%)	53/98 (54.1%)	259/317 (81.7%)	0.328	**<0.001**	**<0.001**
Gestational age at delivery, weeks, median (IQR)	38.7 (37.9–40.4)	36.7 (34.1–39)	37.6 (32.3–39.4)	0.578	0.581	0.931
Birthweight, g, median (IQR)	2715 (2377.5–3216.25)	2220 (1370–2680)	2270 (1120–2822.5)	0.609	0.584	0.861
Termination of pregnancy, *n* (%)	10/20 (50%)	32/98 (32.7%)	17/317 (5.4%)	0.199	**<0.001**	**<0.001**
Intrauterine death, *n* (%)	2/10 (20%)	13/66 (19.7%)	41/300 (13.7%)	1.0	0.634	0.249
Neonatal death <10 days, *n* (%)	–	–	10[a]/259 (3.9%)			
Neonatal death <1 month, *n* (%)	–	1[b]/53 (1.9%)	5[c]/259 (1.9%)			1.0
Adverse neonatal outcome,[d] *n* (%)	–	6/53 (11.3%)	11/259 (4.3%)			**0.05**

Abbreviation: IQR, interquartile range.

[a]Median gestational age at birth 27.85 weeks (25.74–29.28).

[b]Newborn affected by omphalocele.

[c]One newborn affected by neonatal hemochromatosis. Median gestational age at birth 27.84 weeks (27.14–28).

[d]Presence of chromosomal abnormality, genetic syndrome or other adverse neonatal outcomes detected after birth.

TABLE 4 Comparison between small-for-gestational-age (SGA) and fetal growth restriction FGR fetuses in Group 3.

	SGA	FGR	*P*-value
n (%)	132 (46.6%)	185 (58.4%)	
Gestational age at diagnosis, weeks, median (IQR)	20.86 (20–23.61)	23 (20.71–24.57)	**<0.001**
Abdominal circumference percentile, median (IQR)	7.26 (5.33–8.96)	2 (0.4–5)	**<0.001**
Live born, *n* (%)	128/132 (97%)	131/185 (70.8%)	**<0.001**
Gestational age at delivery, weeks, median (IQR)	39 (37.84–40.18)	33.21 (28.56–37.89)	**<0.001**
Birthweight, g, median (IQR)	2770 (2288–2981.5)	1120 (632–2140)	**<0.001**
Termination of pregnancy, *n* (%)	0/132 (0%)	17/185 (9.2%)	**<0.001**
Intrauterine death, *n* (%)	4/132 (3%)	37/168 (22%)	**<0.001**
Neonatal death <10 days, *n* (%)	0/128	10/131 (7.6%)	**0.002**
Neonatal death <1 month, *n* (%)	1/128 (0.8%)	4/131 (3.1%)	0.37
Adverse neonatal outcome,[a] *n* (%)	3/128 (2.3%)	8/131 (6.1%)	0.217

Abbreviations: FGR, fetal growth restriction; IQR, interquartile range; SGA, small-for-gestational-age.

[a]Presence of chromosomal abnormality, genetic syndrome or other adverse neonatal outcomes detected after birth.

described the incidence of these associations, and the outcomes of these pregnancies.

In a cohort of 239 fetuses with abdominal circumference <5th centile diagnosed between 14 and 27 weeks, Vanlieferinghen et al.[6] report that 15% of cases were associated with a chromosomal or genetic etiology, of which the most frequent was trisomy 18. Older studies reported an association with aneuploidies of between 7% and 19% and an increased incidence of triploidy in FGR fetuses <26 weeks.[10,14] In our group, diagnosis of a karyotype abnormality was less frequent (4.6%), with the most commonly diagnosed syndromes being trisomy 18 and trisomy 21 (4 cases each). These cases are normally associated with advanced maternal age; in fact, there was a significant difference between the percentage of women >35 years old in this group compared with the other groups (P = 0.043). Possibly, the reduced incidence of aneuploidy in our cohort reflects the high rate of adherence of women to first trimester

TABLE 5 Postnatally detected adverse outcomes in Groups 2 (malformations) and 3 (isolated).

	Group 2	Group 3
n (%)	6	11
Chromosomal abnormality	3/6 • Chromosome 2 deletion • 47,XX+m/46,XX) • Trisomy 13	1/10 • Turner Syndrome (45,X)
Genetic syndrome	2/6 • Polycystic kidney disease • Russell–Silver syndrome	3/6 • Russell–Silver syndrome • Prader–Willy syndrome • Neonatal hemochromatosis
Others	1/6 • Psychomotor delay	7/10 • Psychomotor delay (2) • Growth hormone deficiency (2) • Neurocognitive impairment • Hemiparesis • Attention deficit disorder

screening, allowing the majority of these cases to be diagnosed at an earlier gestational age.

The association with fetal structural defects and growth restriction is known and the risk of impaired fetal growth increases with the number of multiple malformations which affect a fetus.[15] In the same study from Vanlieferinghen et al.,[6] 28% of fetuses were affected by a morphological abnormality; this figure was slightly lower in our cohort (22.5%). In our study, this group showed a smaller average abdominal circumference compared with cases with other etiologies, possibly due to a high percentage of abdominal wall defects (omphalocele and gastroschisis, 11/98 cases), although the most common malformations identified were in the heart and the central nervous system.

Groups 1 and 2 showed the lowest percentage of live births (40% and 54.1%, respectively, compared with 81.7% in Group 3), mainly due to the high incidence of termination of pregnancy. This figure was expected considering the high proportion of fetuses with severe chromosomal abnormalities and multiple malformations. While there was no difference in terms of gestational age at delivery and birthweight among Groups A, B and C in the ongoing pregnancies, a difference in these two outcomes was noticed when SGA and FGR fetuses in Group 3 were compared: FGR fetuses were delivered on average 6 weeks before SGA fetuses and the birthweight in this group was the lowest. This was also the group with the highest number of neonatal deaths (10.7% of live births), mainly associated with complications of premature birth (median gestational age at birth 27.8 weeks).

A recent retrospective study by Dall'Asta et al.[7] of 188 fetuses, compared a group of 52 anomalous growth-restricted fetuses ($n=17$, 9% of cases, with genetic abnormalities and $n=35$, 18.6%, with structural abnormalities) with 136 (72%) non-anomalous growth-restricted fetuses. In that study, a higher proportion of pregnancies with both anomalous and non-anomalous growth-restricted fetuses ended with intrauterine death (25% and 32.4%, respectively); neonatal death occurred more frequently than in our cohort of anomalous fetuses (15.4%) and the same percentage (11% vs 10.7%) was noted in the non-anomalous fetuses compared with our isolated FGR group. Gestational age at delivery (34+0 weeks in anomalous FGR and 28+3 weeks in non-anomalous FGR) and birthweight (1280 and 610 g, respectively) were also lower in both groups than in our cohort. Some of these differences could be explained by more restrictive selection criteria (only fetuses with abdominal circumference ≤3rd centile between 22+0 and 25+6 weeks were included in their study).

When interpreting these results and their use in clinical counseling, we have to take into account that not all cases were prenatally tested for karyotype or genetic abnormalities. In particular, Group 2 included 24 fetuses (5.5%) with two or more anatomical defects who had intrauterine death or termination of pregnancy without performing an invasive procedure before birth and for whom postmortem karyotype was not available. This could have led to an underestimation of cases that should be included in Group 1 rather than Group 2. With regard to the five cases in Groups 2 and 3 with postnatally detected genetic syndromes (Table 5), these are not necessarily identifiable from fetal karyotyping and CGH-array and therefore the routine invasive testing would not increase the detection rate of these pathologies and couples cannot completely be reassured even though all prenatal tests are normal.

Other limitations of this study are its retrospective nature and the possible role played by referral bias (mitigated, however, by the inclusion of all consecutive cases followed at our tertiary referral center). The strengths of the study are its multicentric design, the high number of fetuses with an early diagnosis of impaired fetal growth included and the complete follow-up of all cases.

We chose to include SGA fetuses with abdominal circumference or EFW <10th centile and not to use other more restrictive selection criteria because a stricter follow-up and careful management are indicated in clinical practice below the 10th centile, not only at lower cutoffs. Even with these selection criteria we report the same percentage of isolated or anomalous fetuses compared with cohorts with smaller fetuses. Couples diagnosed with an SGA fetus should therefore be offered a detailed anomaly scan, genetic counseling and invasive testing, especially in the presence of fetal malformations, and serial follow-up scans. So far, these recommendations are not universally recognized

as necessary in the case of fetuses with growth <10th centile, although they are strongly suggested for those <3rd centile.[2]

5 | CONCLUSION

We report that up to one-quarter of small fetuses are not constitutionally small or related to uteroplacental insufficiency, which are widely considered the most common underlying etiology of a fetus with abdominal circumference or EFW <10th centile.[1] Malformations and chromosomal abnormalities are common etiologies that need to be discussed with couples and detailed anomaly scans and invasive testing should be offered. Parents should also be informed that there could be a postnatal diagnosis of genetic syndrome or neurodevelopmental impairment and that in 5% of live births, neonatal death might occur despite normal prenatal tests, especially in the presence of fetal growth restriction.

AUTHOR CONTRIBUTIONS

LP contributed to the conception of the work, interpretation of data, and revising the work. GM contributed to the conception of the work, analysis and interpretation of data, drafting the work. GC and TP contributed to the acquisition of data. NF and AF contributed to the interpretation of data and revising the work. FP contributed to the conception of the work, interpretation of data and revising the work.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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