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ORIGINAL RESEARCH ARTICLE

Current practice in the diagnosis and management of fetal growth restriction: An international survey

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Abstract

Introduction: The aim of this survey was to evaluate the current practice in respect of diagnosis and management of fetal growth restriction among obstetricians in different countries.

Material and methods: An e-questionnaire was sent via REDCap with "click thru" links in emails and newsletters to obstetric practitioners in different countries and settings with different levels of expertise. Clinical scenarios in early and late fetal growth restriction were given, followed by structured questions/response pairings.

Results: A total of 275 participants replied to the survey with 87% of responses complete. Participants were obstetrician/gynecologists (54%; 148/275) and fetal medicine specialists (43%; 117/275), and the majority practiced in a tertiary teaching hospital (56%; 153/275). Delphi consensus criteria for fetal growth restriction diagnosis were used by 81% of participants (223/275) and 82% (225/274) included a drop in fetal growth velocity in their diagnostic criteria for late fetal growth restriction. For early fetal growth restriction, TRUFFLE criteria were used for fetal monitoring and delivery timing by 81% (223/275). For late fetal growth restriction, indices of cerebral blood flow redistribution were used by 99% (250/252), most commonly cerebroplacental ratio (54%, 134/250). Delivery timing was informed by cerebral blood flow redistribution in 72% (176/244), used from ≥32 weeks of gestation. Maternal biomarkers and hemodynamics, as additional tools in the context of early-onset fetal growth restriction (≤32 weeks of gestation), were used by 22% (51/232) and 46% (106/230), respectively.

Conclusions: The diagnosis and management of fetal growth restriction are fairly homogeneous among different countries and levels of practice, particularly for early fetal growth restriction. Indices of cerebral flow distribution are widely used in the diagnosis and management of late fetal growth restriction, whereas maternal biomarkers and hemodynamics are less frequently assessed but more so in early rather than

Abbreviations: CTG, cardiotocography; cCTG, computerized cardiotocography; FGR, fetal growth restriction; IQR, interquartile range; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; PI, pulsatility index; PlGF, placental growth factor; REDCap, Research Electronic Data Capture; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age; SMFM, Society for Maternal–Fetal Medicine; TRUFFLE-1, Trial of Randomized Umbilical and Fetal Flow in Europe; UtA, uterine artery.

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late fetal growth restriction. Further standardization is needed for the definition of cerebral blood flow redistribution.

KEYWORDS
cardiotocography, fetal Doppler, fetal growth retardation, middle cerebral artery, surveys and questionnaires, TRUFFLE

1 | INTRODUCTION

Fetal growth restriction (FGR) is one of the most studied topics in maternal–fetal medicine. This is not only because of the association between FGR and sequelae for the newborn, but also due to unresolved questions regarding the diagnosis and management of FGR.[1,2] Several efforts have been made to standardize at least some of the clinical aspects related to FGR, resulting in the publication of Delphi procedure consensus criteria and international guidelines on the diagnosis of FGR.[3–8]

Despite this, there are still some major differences in relation to FGR definition criteria, surveillance, and timing of delivery.[9] Although fetal Doppler velocimetry and computerized cardiotocography (cCTG) are widespread in the management of fetuses affected by FGR, their inclusion in the clinical practice may depend on local facilities and expertise.[10,11] The assessment of umbilical artery Doppler is established for the surveillance of FGR, with the advantage of being relatively easy to perform and accessible.[11,12] However, its evaluation alone may not be enough to determine optimal delivery timing.

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE-1) is a randomized controlled trial of early FGR diagnosed between 26 and 32 weeks of gestation. It reported that combined monitoring by the evaluation of the ductus venosus and cCTG short-term variation improves fetal survival without neurological impairment at 2 years.[13–15] However, cCTG may not be available in all units, and the assessment of ductus venosus has not been adopted by all guidelines.[5–7] For late FGR, from 32 weeks onwards, the debate is still ongoing. Prospective observational studies have shown an association between fetal cerebral blood flow redistribution and adverse outcomes, whereas a large meta-analysis questioned this association.[16–18] There is a lack of randomized controlled trials supporting the use of signs of cerebral blood flow redistribution to time delivery in late FGR, and uncertainty remains regarding the optimal indices and thresholds to be used.[19]

All of these factors contribute to a lack of homogeneity in the management of FGR and difficulties in comparing data. The aim of this survey is to evaluate the existing clinical practice in different countries and settings regarding the diagnosis and management of FGR, to highlight discrepancies and identify topics where standardization is needed.

Key message

There is still some variability in the diagnosis and management of fetal growth restriction. There is good agreement among different countries and levels of practice, for early fetal growth restriction. Cerebral blood flow redistribution definition needs standardization.

2 | MATERIAL AND METHODS

Twenty-eight questions concerning the management of FGR at less than 32 weeks and at 32 weeks or more of gestation (early and late) were designed in order to explore:

- demographic characteristics of the participants;
- criteria used for FGR diagnosis, including whether a drop in fetal growth velocity (defined as the presence of a drop in abdominal circumference or estimated fetal weight at least two quartiles or more than the 50th centile) is used;
- biophysical tools used for clinical surveillance and delivery timing of early and late FGR.

Questions about early FGR management included the use of TRUFFLE-1 criteria, ductus venosus, and cCTG short-term variation, steroid prophylaxis for lung maturation, and magnesium sulfate for neuroprotection. Questions about late FGR management included the use of signs of cerebral blood flow redistribution. A series of clinical scenarios were submitted with the help of images showing various types of Doppler and/or growth abnormalities. Fetal biometry was expressed as centiles. Although there is wide variability in the type of growth charts used that could affect the definition of FGR, there is currently no consensus on which is best to use. For this reason, it was not required to indicate the type of growth chart but only the centile as per definition by published guidelines.[4–8] Fetal Doppler included evaluation of the umbilical artery pulsatility index (PI), middle cerebral artery PI, and uterine artery (UtA) PI. For middle cerebral artery, the participants were asked to indicate which index and threshold they use to define cerebral blood flow redistribution. They were also asked about their use of maternal serum biomarkers and hemodynamics for any clinical decision-making in FGR. If biomarkers were used, the participants were asked to indicate which type of biomarker was preferred between placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), or their ratio (sFlt-1/PlGF).

The survey was approved by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Clinical Standard Committee. An e-questionnaire was sent via Research Electronic Data Capture (REDCap) with "click thru" links. REDCap is a secure, web-based software platform designed to support

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data capture for research studies.[20,21] The e-questionnaire was sent in emails and newsletters by ISUOG and ultrasound manufacturers (General Electrics NYSE, MA, USA; Samsung Medison, Seoul, South Korea), following two free-to-access web seminars on FGR in 2021, to obstetric practitioners in different countries and settings with different levels of expertise. Participation in the survey was voluntary.

The survey consisted of a series of "yes/no" type questions and the simulation of specific clinical scenarios with structured question/response pairings. The full questionnaire is available as Supporting Information Appendix S1. Study data were collected and managed using REDCap electronic data capture tools hosted at IRCCS Burlo Garofolo, Trieste, Italy. Only questionnaires with more than 50% of questions answered were included in the analysis.

2.1 | Statistical analyses

The results of the survey were described using frequency and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Graphical representations of the results were performed: categorical variables through pie charts or bar plots, and continuous variables through box-plots.

2.2 | Ethics statement

As the study did not involve direct patient involvement, an approval from the internal review board was not deemed necessary.

3 | RESULTS

The total number of surveys that have been opened on the REDcap platform was 419. Of these, we received 275 replies, of which 87% (238/275) answered 100% of the questions. The remaining 13% (37/275) answered more than half the survey. Participants' demographic characteristics are reported in Table 1.

3.1 | Diagnostic criteria

Overall, 81% of participants (223/275) used Delphi consensus criteria for the diagnosis of FGR and 18.9% (52/275) used other criteria of which 21.2% (11/52) used the "Medicina Fetal Barcelona calculator"; 17.3% (9/52) used a cut-off of estimated fetal weight below the 10th centile; 11.5% (6/52) used estimated fetal weight below the 10th centile and abnormal Doppler; 9.6% (5/52) used the "Fetal Medicine Foundation calculator"; 11.5% (6/52) use national guidelines; and 28.8% (15/52) did not specify (Figure 1). Eighty-two percent of participants (225/274) considered a drop in fetal growth velocity as one of the diagnostic criteria for late FGR.

TABLE 1 Demographic characteristics of participants

Participant demographics	N (%)
Reg	275
Europe	144 (52)
South America	43 (16)
South Asia	33 (12)
Asia	14 (5)
Africa	13 (5)
Middle East	12 (4)
North-America	7 (3)
Central America	6 (2)
Oceania	3 (1)
Type of practice	
Tertiary teaching hospital	153 (56)
General/Community	70 (26)
Secondary hospital	55 (23)
Qualification	
Obstetrician/gynecologist	148 (54)
Fetal medicine specialist	117 (43)
Sonographer	34 (12)
Obstetrician	21 (8)
Radiologist	15 (5)
Midwife sonographer	6 (2)

3.2 | Surveillance and management of early FGR

TRUFFLE-1 criteria were used for delivery timing by 81% of participants (223/275) but 19.9% (52/275) used different criteria: 19.2% only Doppler (10/52), 17.3% Doppler and standard CTG (9/52); 1.9% Doppler and serial growth scans (1/52); 4% clinical criteria (2/52); 4% local guidelines (2/52); 21% did not use any specific criteria (11/52); and 33% did not specify (17/52) (Figure 2). In tertiary teaching hospitals, TRUFFLE-1 criteria were used in 86% (131/153) of cases. Ninety percent (247/273) of participants considered administration of steroids for fetal lung maturation with the median maximum gestational age of 34 weeks (33–36 years). Magnesium sulfate administration for fetal neuroprotection was reported by 76% (207/273) of participants, and the median value of the maximum gestational age considered for administration was 32 weeks (IQR 32–34 weeks).

3.3 | Surveillance and management of late FGR

The use of cCTG short-term variation for late FGR surveillance was reported by 43% of participants (118/272), of which 59% (70/118) were from tertiary teaching hospitals. Indices of cerebral blood flow redistribution for surveillance of late FGR were used by 99% (250/252) (Figure 3): cerebroplacental ratio in 54% (134/250), middle cerebral artery PI in 32% (81/250), and umbilical–cerebral ratio

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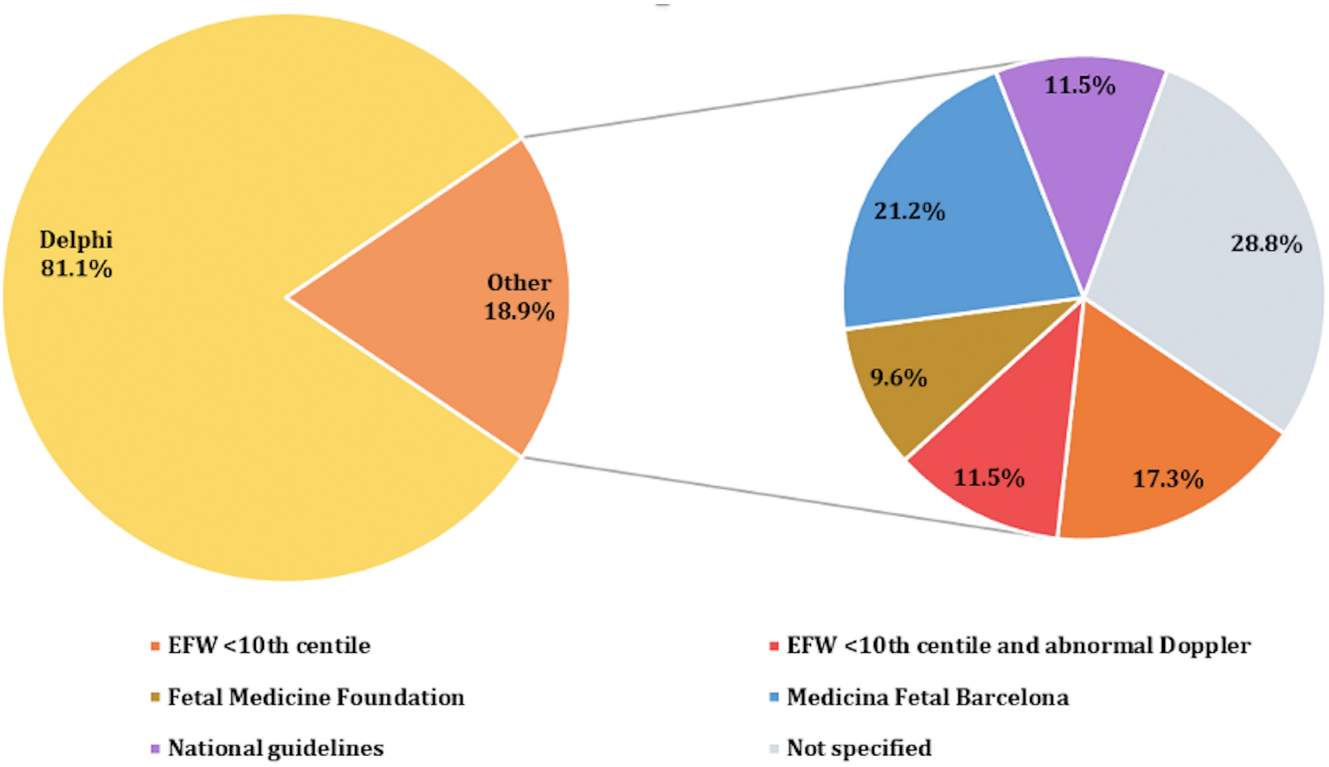


FIGURE 1 Criteria used for the diagnosis of fetal growth restriction.

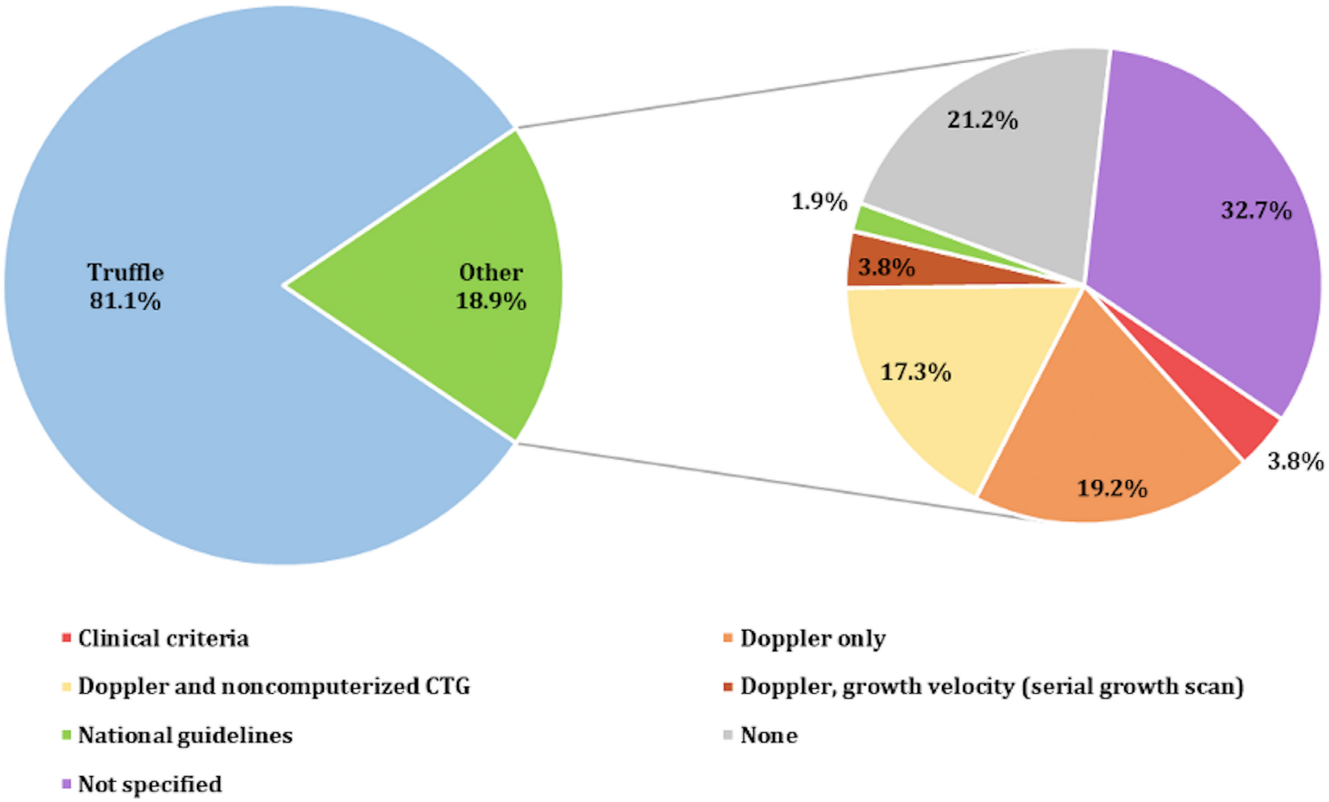


FIGURE 2 Criteria used for the management of early fetal growth restriction.

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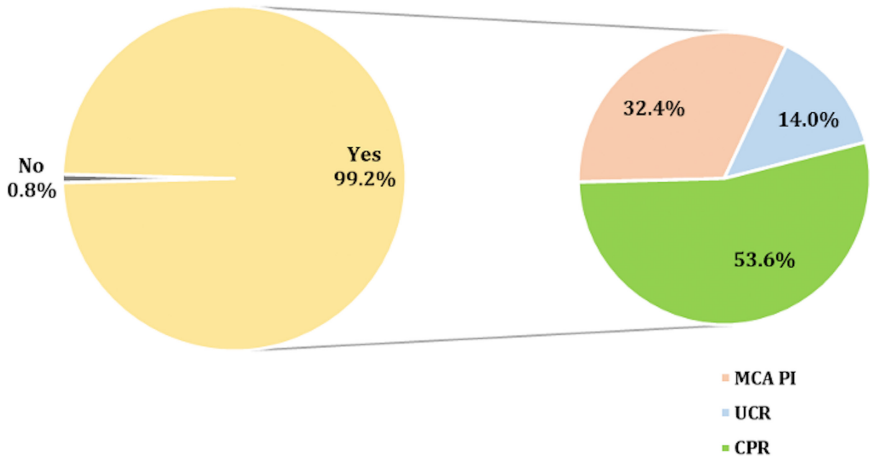


FIGURE 3 Use of indices of cerebral blood flow redistribution in the surveillance of late fetal growth restriction. CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; UCR, umbilical cerebral ratio.

in 14% (35/250) of cases. in all, 244 participants answered question no. 19: "Do you decide delivery timing in case of late FGR based on signs of cerebral blood flow redistribution?". The presence of cerebral blood flow redistribution was reported by 72% of participants (176/244) as a trigger for delivery timing in late FGR. The Doppler indices and the thresholds used to define cerebral blood flow redistribution are reported in Table 2.

Figure 4 shows the box-plot analysis of gestational age epochs at which the participants would offer delivery for women with a pregnancy showing late FGR based on different clinical scenarios. The median gestational age at which the majority of participants would deliver a woman with a pregnancy showing late FGR was 37 weeks, and this was true for different patterns of growth and Doppler velocimetry parameters (i.e. estimated fetal weight below the 3rd centile combined with a drop in abdominal circumference, umbilical artery PI above the 95th centile with present end-diastolic flow, UtA PI above the 95th centile, and signs of cerebral blood flow redistribution). The highest heterogeneity in reported gestational age epochs was observed for signs of cerebral blood flow redistribution (IQR 34–37 weeks). For small-for-gestational-age (SGA) fetuses the median gestational age at which the majority of participants would deliver the woman was 39 weeks (IQR 38–40 weeks).

Forty-five percent (125/275) of participants reported that they use UtA Doppler for late FGR diagnosis, 40% for late FGR surveillance (109/275), and 24% (66/275) for the decision on the delivery timing.

3.4 | Maternal biomarkers and hemodynamics

Answers regarding the use of maternal serum biomarkers and hemodynamics are displayed in Table 3. Eight-four percent (232/275) of the participants gave a response on the use of maternal serum biomarkers. Out of these, 44% would like to use them, but stated that the biomarkers were either unavailable or too expensive (103/232), 34% did not use biomarkers (78/232), and 22% included the biomarkers in clinical practice (51/232). Among those that used maternal serum biomarkers, 78% (40/51) used them for

TABLE 2 Reported indices and thresholds to define cerebral blood flow redistribution

Indices of cerebral blood flow redistribution	*N* (%)
Cerebroplacental ratio	134 (54)
Centile	76 (57)
5th centile	33 (43)
Not specified	43 (57)
Multiple of the median	14 (10)
1.5	7 (50)
Not specified	7 (50)
Ratio	14 (10)
<1	14 (100)
Z score	1 (0.75)
Not specified	1 (100)
Middle cerebral artery	81 (32)
Centile	44(54)
5th centile	18 (41)
Not specified	26 (59)
Multiple of the median	10 (12)
Not specified	10 (100)
Pulsatility index	3 (4)
0.8–1.2	1 (33)
1.49–1.94	1 (33)
1.5	1 (33)
Z score	1 (1)
Not specified	1 (100)
Umbilical cerebral ratio	35 (14)
Centile	16 (46)
95th centile	5 (31)
Not specified	11 (69)
Multiple of the median	4 (11)
Not specified	4 (100)
Ratio	6 (17)
>1	6 (100)
Z score	1 (3)
Not specified	1 (100)

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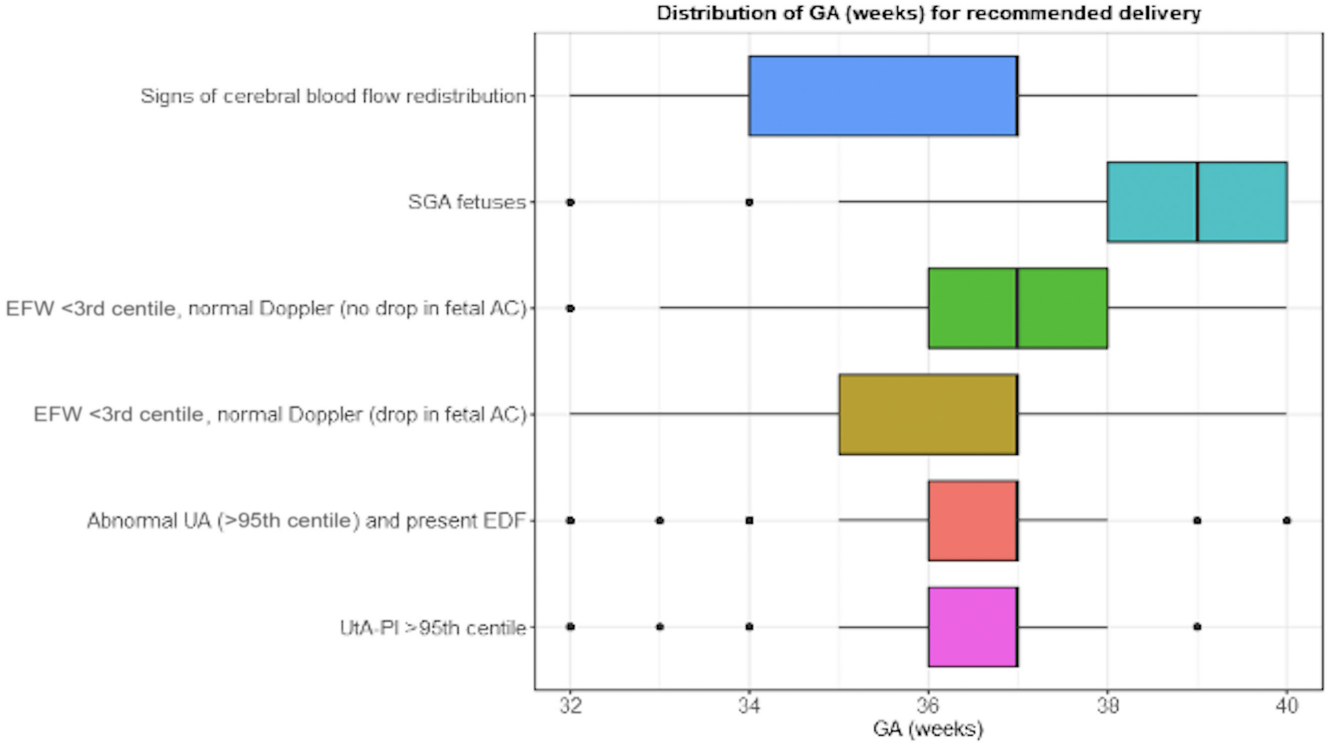


FIGURE 4 The box-plot analysis shows the gestational age epochs at which the participants are willing to deliver the woman with a pregnancy showing late fetal growth restriction according to the different clinical scenarios. Data are represented as median and interquartile range. AC, abdominal circumference; EDF, end-diastolic flow; EFW, estimated fetal weight; GA, gestational age; SGA, small for gestational age; UA, umbilical artery; UtA, uterine artery.

early FGR, while 39% (20/51) used them for late FGR, and the use was mainly for monitoring frequency (49%, 25/51) or diagnosis (45%, 23/51), but less for delivery timing (35%, 18/51). The most commonly used maternal serum biomarker was sFlt-1/PlGF ratio (55%, 28/51), followed by PlGF alone (25%, 13/51). Twenty percent indicated "others" (10/51).

Regarding the use of maternal hemodynamic assessment, 84% of participants responded (230/275) and of those 46% (106/230) used hemodynamic assessment in clinical practice, 39% (89/230) did not use it, and 15% (35/230) would use it but it was either unavailable or too expensive. Among those that used maternal hemodynamic assessment, 64% (68/106) used it for early FGR and 46% (49/106) used it for late FGR, mainly for delivery timing (59%, 63/106) and monitoring frequency (51%, 54/106); it was used least for diagnosis (39%, 41/106).

4 | DISCUSSION

This survey shows that there is good agreement among different countries and levels of practice in the diagnosis and management of FGR, particularly for early FGR. The Delphi consensus criteria, used by approximately 80% of our respondents, concurred largely with the combined biometric and maternal–fetal Doppler definition of FGR agreed through consensus by the TRUFFLE group and the Irish PORTO consortium.[3,22,23] These criteria have been adopted by the ISUOG and FIGO (International Federation of Gynecology & Obstetrics) guidelines, but not by the Society for Maternal–Fetal Medicine (SMFM) guidelines, and this may explain why around 20% of the respondents use different criteria for the diagnosis of FGR. The criteria used to define FGR are important, although it has been shown that the application of different criteria has an impact on the prevalence of FGR and association with adverse outcomes. In a study by Roeckner et al., the use of SMFM and Delphi consensus criteria defined 13% and 5% of fetuses as FGR, respectively.[24] The higher sensitivity of SMFM criteria were at the expense of the specificity, which was higher for Delphi consensus criteria. Regarding the concept of fetal size below the 10th centile as the only criterion to define FGR, our survey showed that even among those participants that did not use the Delphi consensus criteria, the majority (83%) were keen to include additional evaluation, such as Doppler parameters.

Surprisingly, 45% of the participants stated that they consider UtA Doppler in the diagnosis of late FGR. Previous studies have shown that the presence of a mean UtA PI at the 95th centile or above, despite normal cerebral indices, increases the risks of adverse perinatal outcome and ISUOG guidelines consider the inclusion of UtA Doppler in the surveillance of SGA fetuses.[4] The results of our survey highlight that the role of UtA Doppler in the diagnosis and surveillance of late FGR should be further explored.

Eighty-one percent of participants used the criteria of the TRUFFLE-1 randomized controlled trial for delivery timing in early

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FGR.[13] Despite the fact that the results of the trial have shown the best 2-year outcome for surveillance strategies based on combined monitoring by ductus venosus and cCTG short-term variation, there are still some differences regarding the management of early FGR.[13–15] One of the possible reasons might be that cCTG is not available in all maternity services because of the higher costs implied or different local policies. Moreover, the superiority of computerized over visual assessment has not been proven in clinical practice, although it allows an objective and reproducible analysis.[25]

Forty-three percent of respondents used cCTG for the surveillance of late FGR and 99% used indices of cerebral blood flow distribution for surveillance of late FGR. The explanation for this finding might be that several observational cohort studies have found an association between the presence of cerebral blood flow redistribution and increased risk of adverse short- and long-term outcomes.[16–19] It has to be highlighted, however, that these studies cannot prove a causal link. Moreover, it emerges from the survey that there are still some major discrepancies regarding the indices and thresholds used to define cerebral blood flow redistribution, that could potentially influence the clinical management. A simulation study on the historical consecutive cohort of SGA fetuses showed that even in the case of the same management protocol, the proportion of labor induction in pregnancies with an SGA fetus at term could vary from 1.1% to 13.3% and from 5.6% to 23.3% depending whether the highest or the lowest published reference values for middle cerebral artery-PI below the 5th centile and cerebroplacental ratio below the 5th centile are used, highlighting the importance not only of the Doppler reference charts but also of the indices used.[26]

Despite the lack of randomized controlled trials evaluating the optimal delivery timing in fetuses affected by late FGR based on Doppler velocimetry, this survey showed that there is a good broad consensus in the management of these pregnancies, across different clinical scenarios. Overall, the median gestational age considered for delivery in FGR is 37 weeks, which is slightly lower than the gestational age proposed by the DIGITAT study.[27] However, differences in management depending on degree of fetal smallness and Doppler characteristics were encountered, as participants were willing to deliver earlier in the case of estimated fetal weight less than the 3rd centile combined with a drop in growth velocity, umbilical artery PI above the 95th centile with present end-diastolic flow, increased UtA PI, and signs of cerebral blood flow redistribution. The highest heterogeneity was encountered for late FGR with signs of cerebral blood flow redistribution, reflecting the current debate on the topic. The TRUFFLE-2 randomized controlled trial, currently ongoing, aims to explore this question.[28]

Delivery is, instead, delayed until 39 weeks in the case of a small fetus but with normal Doppler studies (i.e. SGA), but it is expedited if there is also a drop in the fetal growth. These data suggest that the concept of fetal growth velocity or trajectory is starting to be integrated into clinical practice, even if not universally so by all guidelines.[7]

TABLE 3 Use of maternal biomarkers and hemodynamics in the management of early and late fetal growth restriction

Maternal biomarkers and hemodynamics	*N* (%)
Biomarkers for clinical decisions (answer provided)	232 (84)
No	78 (34)
Would like to, but not available/too expensive	103 (44)
Yes	51 (22)
If yes, which clinical decision?	
Early fetal growth restriction	40 (78)
Late fetal growth restriction	20 (32)
Diagnosis	23 (45)
Frequency of monitoring	25 (49)
Delivery timing	18 (35)
Biomarkers	
PlGF alone	13 (25)
sFlt-1/PlGF ratio	28 (55)
Others	10 (20)
Maternal hemodynamics for clinical decisions (answer provided)	230 (84)
No	89 (39)
Would like to, but not available/too expensive	35 (15)
Yes	106 (46)
If yes, which clinical decision?	
Early fetal growth restriction	68 (64)
Late fetal growth restriction	49 (46)
Diagnosis	41 (39)
Frequency of monitoring	54 (51)
Delivery timing	63 (59)

Abbreviations: PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

To date, the role of maternal biomarkers and hemodynamics in the management of FGR is mainly confined to clinical research. There is a link between low maternal serum concentrations of biomarkers, such as PlGF and sFlt-1, and pregnancy complications secondary to the presence of placental dysfunction. However, if their performance is good in the prediction of preterm pre-eclampsia, the same has not yet been proven for FGR, even more so for late FGR, typically characterized by less severe degrees of placental dysfunction.[29] In fact, only one-quarter of participants considered the use of maternal serum biomarkers, and mainly in the field of early FGR, but just under one-half of participants would like to use them, suggesting that there is a strong interest in including maternal biomarkers in the clinical management of FGR.

Similarly, fewer than half of participants evaluated maternal hemodynamics in the presence of FGR. Pregnancies complicated by placental insufficiency are characterized by a specific maternal hemodynamic profile that appears to be more marked in the case of severe FGR.[30] Despite this emerging evidence, this evaluation is still not recommended nor it is widespread in the clinical setting. It is surprising that almost half of the participants gave a positive answer

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regarding maternal hemodynamic evaluation in pregnancies complicated by FGR. A plausible explanation might be that the participants interpreted the question to mean Doppler of UtA as reflective of maternal hemodynamic evaluation.

There are some limitations of the survey. Around 60% of participants were obstetrician/gynecologist and fetal medicine specialists working in a tertiary teaching hospital, who had attended a web seminar on FGR promoted by ISUOG in 2021. This might have influenced the answers and the observed agreement. However, it has to be acknowledged that FGR, especially in its early forms, is usually managed in tertiary referral centers and mostly by experienced operators in the field.[13] The majority of the respondents were from Europe, and alignment with European guidelines is certainly reflected in the results.[9] We aimed to reach a representative response from different countries and continents by using three different international channels, but the response from some parts of the world, including North America, was very low. Finally, despite these limitations, our survey highlights the areas that are still critical in daily practice, in which standardization is needed, and that are open for further research.

5 | CONCLUSION

This survey showed that there is a general consensus in the management of FGR, particularly in its early forms. At the same time, it highlights the points that need standardization and that are still open for further research, mainly in the field of late FGR. Although indices of cerebral blood flow redistribution are considered in daily practice, there is a wide heterogeneity in the type of index and threshold adopted that could affect the clinical management. Prospective randomized trials, currently ongoing, could address this issue. Finally, the role of maternal biomarkers and hemodynamics is still marginal in the management of FGR, and it should be confined to research until more robust data become available.

AUTHOR CONTRIBUTIONS

TS, IF, and CL developed the survey; IF and GZ collected and analyzed the data; IF, GZ, and TS wrote the manuscript; BM-F, LM, EM, and FP contributed to the scientific contents and revised the manuscript.

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CONFLICT OF INTEREST

CL and TS were part of the ISUOG Practice Guideline on the Diagnosis and Management of Small for Gestational Age and Fetal Growth Restriction published in 2020. TS and FP are part of the ISUOG Clinical Standards Committee. The other authors have no conflict of interest to declare.

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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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