Consensus definition for placental fetal growth restriction: a Delphi procedure

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Abstract

Objective: To define early and late placental fetal growth restriction (FGR) through a Delphi procedure.

Method: We used the Delphi consensus methodology. An expert panel was selected and the panel members were provided with 19 literature-based parameters. The panel provided their opinion regarding the importance of these parameters for the diagnosis of both early and late FGR. Parameters were described as solitary parameters (parameters that are sufficient to diagnose FGR, even if all other parameters are normal) and contributory parameters (parameters that require other abnormal parameter(s) to be present for the diagnosis of FGR). Consensus also was sought for the cut-off values of accepted parameters.

Results: A total of 106 experts were approached, of whom 56 agreed to participate and entered the first round and 45 completed all four rounds (80%). For early FGR (<32 weeks) three solitary parameters (abdominal circumference (AC) or estimated fetal weight (EFW) <3rd percentile and absent end-diastolic flow in the umbilical artery) and four contributory parameters (AC or EFW <10th percentile combined with a pulsatility index (PI) >95th percentile of either the umbilical artery or uterine artery) were agreed upon. For late FGR (>32 weeks of gestation) two solitary parameters (AC and EFW below the 3rd percentile) and four contributory parameters (EFW or AC <10th percentile, crossing centiles on growth charts of more than two quartiles and cerebro-placental ratio (CPR) <5th percentile) were defined.

Conclusion: Consensus based definitions for early and late FGR, as well as cut-off values for parameters were agreed upon.

Introduction

Fetal growth restriction (FGR) is difficult to define. The fetus does not reach its biological growth potential as a consequence of impaired placental function, which may be due to a variety of factors[1-3]. Fetuses with FGR are at risk for perinatal morbidity and mortality[4-6], and poor long-term health outcomes, such as impaired neurological and cognitive development[7], and cardiovascular and endocrine diseases in adulthood[8]. Currently, no gold standard for the diagnosis of FGR exists. It is usually defined by the statistical deviation of fetal size from a population-based reference, with a typical threshold at the 10th, 5th or 3rd centile; such a threshold is better considered as indicative of 'small for gestational age' (SGA) fetus[9 10]. SGA however, is principally different from FGR because it also encompasses a majority of constitutionally small but healthy fetuses at lower risks for abnormal perinatal outcomes[11]. On the other hand, growth restricted fetuses with biometry >10th centile may not meet their growth potential, and remain undiagnosed despite being at increased risk of adverse outcomes[12].

Both from a clinical and a scientific perspective it is most relevant to focus on fetuses that are at risk for adverse outcomes, underscoring the need for a clear definition of FGR distinct from SGA. Several parameters are reported to distinguish FGR from SGA and may improve detection of FGR and its complications over biometric measurements alone. These include sequential ultrasound measurements focusing on (declining/crossing) growth centiles, functional parameters such as Doppler waveform analyses (umbilical artery, middle cerebral artery and ductus venosus), and serum biomarkers[13-15]. Biomarkers and Doppler measurements are termed functional parameters, as they reflect placental function at the

time of assessment, while there is latency between the onset of placental dysfunction and its effect on biometrical (size) measurements.

A definition of FGR with international consensus will help to identify fetuses at risk, assist future research projects and aid comparison of different FGR studies. The aim of this study is to reach expert-consensus on a definition of placental FGR through a Delphi procedure. We aimed to develop a consensus-based definition for both early and late gestation FGR.

Methods

Delphi procedure

We used the Delphi consensus methodology. A Delphi procedure aims for refinement of opinions by participating experts, while minimizing confounding factors present in other group response methods[16]. This procedure is a well-established instrument to reach consensus from a panel of experts for research questions that cannot be answered with empirical evidence and complete certainty[17]. It is an iterative technique based on the scoring of a series of structured statements that are revised, fed back to the participants and repeated in multiple rounds, in increasing detail, until consensus has been reached[18].

The selection of potential panel members took place on the basis of their recognized expertise on FGR, either by important publications on FGR or by suggestion of confirmed panel members. We aimed for global coverage of the expert panel. Within the Delphi process votes of all panel members are weighed equally. Experts who did not enter a particular round were not invited for subsequent rounds (Figure1).

Data collection

An online Delphi procedure was performed in four rounds. Questionnaires were completed using the online tool LimeSurvey version 2.05+. In each round, panel members were e-mailed a unique link (token-secured) to the questionnaire. The results of the questionnaires for each round were reported to the participants in the next round. The results were presented anonymously, on a group level. Non-responders received reminder emails after ten days, and after twenty days they received a phone call. Withdrawal from the procedure was offered at all times.

First round

First the panel was asked to define a threshold to distinguish between early and late FGR based on the currently used cut-off values in clinical practice and study reports, in a multiple question format. Based on a literature review, potential parameters that could be part of the definition were presented to the panel for agreement. They also were given the opportunity to suggest additional parameters that they considered relevant and that were not listed in the list of potential parameters.

The panel was asked to rate the literature-based selected parameters for FGR on a 5-point Likert-scale (1 = very unimportant, 2 = unimportant, 3 = neutral, 4 = important, 5= extremely important).

The predefined cut-off for inclusion of parameters in the consensus-based definition for FGR was a median score of 5 on the Likert-scale. Parameters with a median score of 4 were considered likely candidates and were presented again in the second round along with a question as to whether they should be discarded or included in the definition. Parameters with a median score of 3 were considered for exclusion from the definition and presented in the second round for agreement to the exclusion.

<u>Second and third round</u>

In the second round, parameters with a median score of 5 were presented to define whether the parameter should be a solitary and/or a contributory parameter. A *solitary parameter* was defined as a parameter that is sufficient to diagnose FGR, even if all other parameters are normal. A *contributory parameter* was defined as a parameter that would require other abnormal parameter(s) to be present to diagnose FGR. Furthermore, the panel was asked to specify cut-off values for each parameter. Proposed cut off values were literature based. Experts were also asked to determine these cut-offs for solitary or contributory parameters separately, as these thresholds could potentially differ.

Parameters with a median score of 4 were presented for acceptance or rejection with a predefined 70% agreement for acceptance. For these parameters, specification of the cut-off values was sought in a similar fashion as for the parameters with a median score of 5. Parameters with 60-70% of agreement were brought back for verification of the acceptance or rejection in the third round using a similar procedure.

In determination of cut-off values of parameters, we proposed in the next round that the value with the highest level of agreement (>70%) was used. For continuous variables, if 70% agreement was not reached we proposed an aggregated value: for example, if a proposed cut-off value for a measurement was scored as <p3 by 35% of the panel, as <p5 by 50% of the panel and <p10 by 15% of the panel, we suggested in the next round that the panel incorporate a cut-off of <p5 because 85% of participants opted for <p5.

Lastly, the panel was asked if they agreed with rejection of parameters with a median score of 3 or lower in the first round or below 60% agreement in the second round.

The final round

Possible algorithms to define early and late FGR were presented to the panel in two multiple choice-questions. The algorithm that received the most support was considered to be the final wording for consensus definitions.

Results

We invited 106 experts to join this Delphi procedure. In the first round an expert panel of 56 participants joined the survey; of whom, 51 completed the entire questionnaire and 5 completed part of the questionnaire. Response rates in the following rounds were 86% (48/56) in round 2, 94% (45/48) in round 3 and 100% (45/45) in the final round. Thus, 80% (45/56) of participants starting the Delphi finished the complete procedure. Details

regarding the self-reported expertise, specialisation in FGR and demographic characteristics of the participants are shown in Table 1. Global coverage was reached; participants were mainly from Europe, which fairly reflects the geographical distribution of research reports concerning FGR.

In the first round we presented 18 parameters to the panel (Figure 2) and suggestions for cut-offs of early versus late FGR. The gestational age cut-off value for early versus late FGR was not ascertained with 14% voting for <28 weeks, 4% for <30 weeks, 43% <32 weeks and 39% voting for <34 weeks. For the definition of early FGR, three parameters were identified as "extremely important" (median score of 5): measurements of the abdominal circumference (AC), the estimated fetal weight (EFW), and the pulsatility index (PI) of the umbilical artery (UA). For the definition of late FGR, two "extremely important" parameters were identified: measurements of the AC and the EFW. The panel did not suggest additional specific parameters for FGR. However, they expressed a desire to expand on whether functional parameters could be solitary or contributory criteria, which was incorporated in the next round.

In the second round consensus was reached regarding the gestational age at which early and late FGR are distinguished: 89% agreed on demarcation at 32 weeks of gestation. The panel also agreed to insist that congenital anomalies should be absent for the diagnosis of both early and late placental FGR. Furthermore, participants agreed upon inclusion of functional parameters in general, with levels of agreement of 77% and 74% for early and late FGR respectively. In contrast, 70% agreed that late FGR should not be diagnosed by abnormal functional parameters alone if fetal size is not compromised.

Eight parameters that were scored as “important” (median score of 4) in the first round and almost reached consensus (60-70% agreement) in the second round were brought back to the panel once more for verification in the third round (Table 2). For all accepted parameters in the first round it was determined whether the parameter would be a solitary or a contributory parameter in the definition. For early and late FGR two solitary parameters were defined. Four contributory parameters were agreed upon for early FGR and six for late FGR. Furthermore the panel agreed upon the cut-off values for the solitary as well as the contributory parameters (Table 3). Finally, consensus was reached on rejection of 13 parameters for the definition of early FGR and rejection of 11 parameters for the definition of late FGR (Table 4).

In the final round solitary and contributory parameters and their cut-offs were presented together with six possible algorithms for the definition of early and late FGR including the possible clinical scenarios that the several options of the definition would imply (Table 5).

The following definitions were agreed upon for FGR in the absence of congenital anomalies (Table 6):

Definition of early FGR (<32 weeks of gestation):

1: Abdominal circumference below the 3rd centile OR estimated fetal weight below the 3rd centile OR absent end diastolic flow in the umbilical artery

OR

2: Both of the following

- Estimated fetal weight or abdominal circumference below the 10th centile

AND

- Pulsatility index of the uterine artery above the 95th centile OR pulsatility index in the umbilical artery above the 95th centile.

Definition of late FGR (≥32 weeks of gestation):

1: Abdominal circumference below the 3rd centile, or estimated fetal weight below the 3rd centile

OR

2: At least two out of three of the following:

- Abdominal circumference below the 10th centile OR estimated fetal weight below the 10th centile
- Abdominal circumference OR estimated fetal weight crossing centiles >2 quartiles
- Cerebro-placental ratio below the 5th centile OR pulsatility index in the umbilical artery above the 95th centile.

Discussion

In this study a consensus based definition for both early and late FGR due to placental insufficiency was established through a Delphi procedure. FGR is defined in most studies by aberrations of biometrical measures of fetal size, usually with a cut-off value of estimated weight below the 10th centile. However, this encompasses many constitutionally small fetuses and may be better thought of as SGA. This distinction is important because many SGA fetuses are physiologically small and are at low risk for adverse perinatal outcomes. In contrast, FGR fetuses are pathologically small irrespective of the growth percentile (which can be >p10). Thus constitutionally small fetuses will be over-diagnosed and FGR will be under-diagnosed in fetuses with an estimated weight >p10[12].

In order to better identify the fetuses at risk and to better compare true FGR cohorts with appropriately grown cohorts there is a need to improve the definition of fetal growth restriction. While current standards for fetal growth now allow international comparisons of the prevalence of SGA to be made[19], no such consensus exists for the definition of FGR. Our study has established such a definition by consensus.

First, a distinction was agreed upon between early and late FGR with the demarcation at 32 weeks. Second, it was agreed that congenital anomalies should be absent. Third, absolute size measurements in themselves were defined at a lower cut-off than commonly used (3rd and 10th percentile respectively). Fourth, functional parameters were introduced in the definition, either as solitary (AEDF in the umbilical artery) or contributory parameters (PI in the umbilical artery or uterine artery >p95 or CPR <p5).

This is the first time that a consensus based definition has been established that includes biometrical as well as functional parameters for fetal growth restriction. The lower cut-off for absolute size measurements reflects that even in the absence of abnormal functional parameters, long-term outcomes for severe SGA fetuses are unfavourable[20]. The need for functional parameters in the definition of FGR was emphasized by the PORTO study. In this study 200 obstetricians were questioned regarding the definition and management of FGR and identified abnormal umbilical artery Doppler velicometry as a factor in the diagnosis (cut-off not specified). Other functional parameters were used in the assessment of FGR but were not deemed suitable as solitary markers to make the diagnosis; such as MCA and ductus venosus Doppler studies [21]. In another study, participants were asked for their definitions and they proposed 30 different definitions, but the survey was not designed to reach consensus.[22]

The strength of a Delphi procedure is dependent on the participating experts; our aim was to perform this Delphi procedure among genuine experts. We were fortunate to have a diverse array of specialists participate, many of who conduct research on FGR. In the Delphi procedure it is ensured that all participant votes were weighed equally and the participants were blinded for the individual expert opinions of their colleagues. This minimised peer pressure from authoritative individuals and allowed for optimal use of the collective knowledge. Pre-set rules regarding acceptance or rejection of parameters were strictly adhered to, with double-checking of possible interpretation of the answers in subsequent rounds. This provided the participants with the option to change their mind in light of feedback of results of previous rounds. The weakness of a Delphi procedure is the potential of selection bias by ascertaining a group of individuals that share the same interests and

opinions and attrition of contributors with successive rounds. We included specialists with special focus on FGR and not epidemiologists, neonatologists and developmental specialists. Although this may also be a source of bias, these individuals are most familiar with the concepts and clinical implications of FGR.

In this Delphi procedure, as many potential parameters as possible were presented such as customized centiles[23] and serum biomarkers SFlt/PlGF[24]. From the answers of the expert participants we concluded that currently available evidence regarding the rejected parameters is not weighed strong enough to include these parameters in the diagnosis at this time, which does not exclude value in outcome prediction.

The proposed definition is not a prediction model for clinical outcomes. Nonetheless, similar parameters that can be used in prediction models were presented for possible inclusion in the diagnosis. The definition should be tested against other definitions (primarily SGA definitions) in prospective observational cohorts. It is likely that the new definition better identifies fetuses at risk than a solely biometrically based definition. However, the validity in reduction of adverse outcomes needs to be tested and it should be used in clinical trials of interventions.

Many research initiatives focus on establishment of good diagnostic markers for FGR and also focus on prediction models for adverse outcome in FGR with combinations of Doppler and biomarkers[24 25]. Ongoing studies are assessing the combined utility of biomarkers and ultrasound parameters for the diagnosis of FGR and as data accumulate the currently proposed definitions may need to be updated.

Now that a consensus definition for FGR has been established, it raises several questions. First, the diagnosis at delivery (neonatal growth restriction or NGR) has the same challenges as the diagnosis of FGR. The relationship between FGR and NGR needs to be evaluated using new definitions. A definition of NGR solely on the basis of size is unlikely to be optimal for identifying those at risk for adverse outcomes. Second, the diagnosis of FGR and growth restriction at delivery needs to be connected to relevant outcomes. It is not only important to use uniform and meaningful diagnosis definitions, but also to come to agreement on what the relevant outcomes are that should be reported in all trials, much like the consort statement and the CROWN initiative[26 27]. Subsequently, a similar Delphi procedure concerning growth restriction of the newborn (GRN) and outcomes will be performed.

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* full participation, with consent for acknowledgement

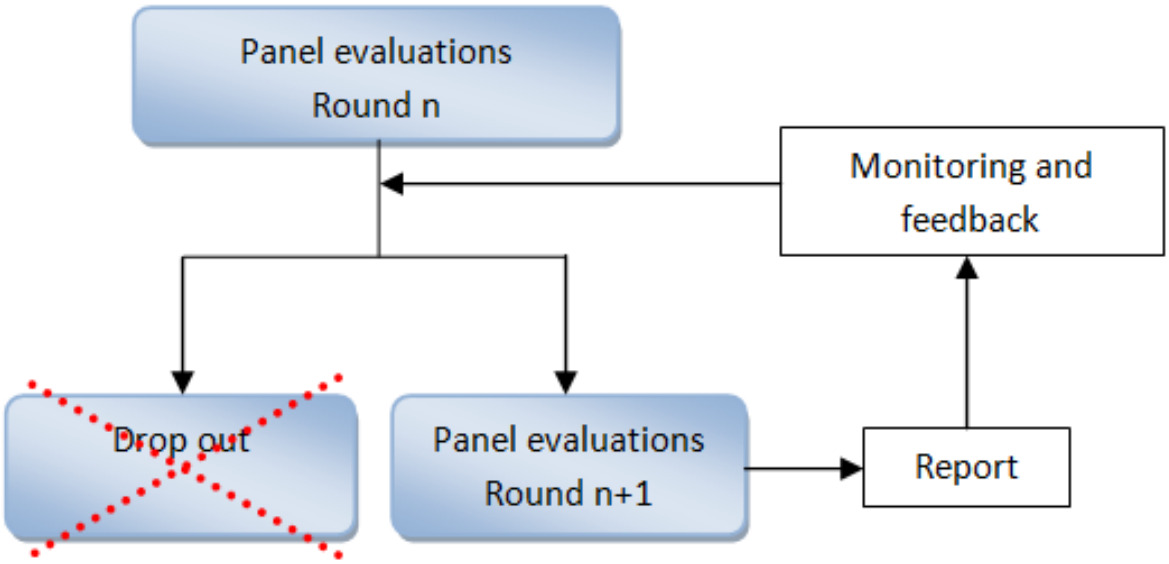
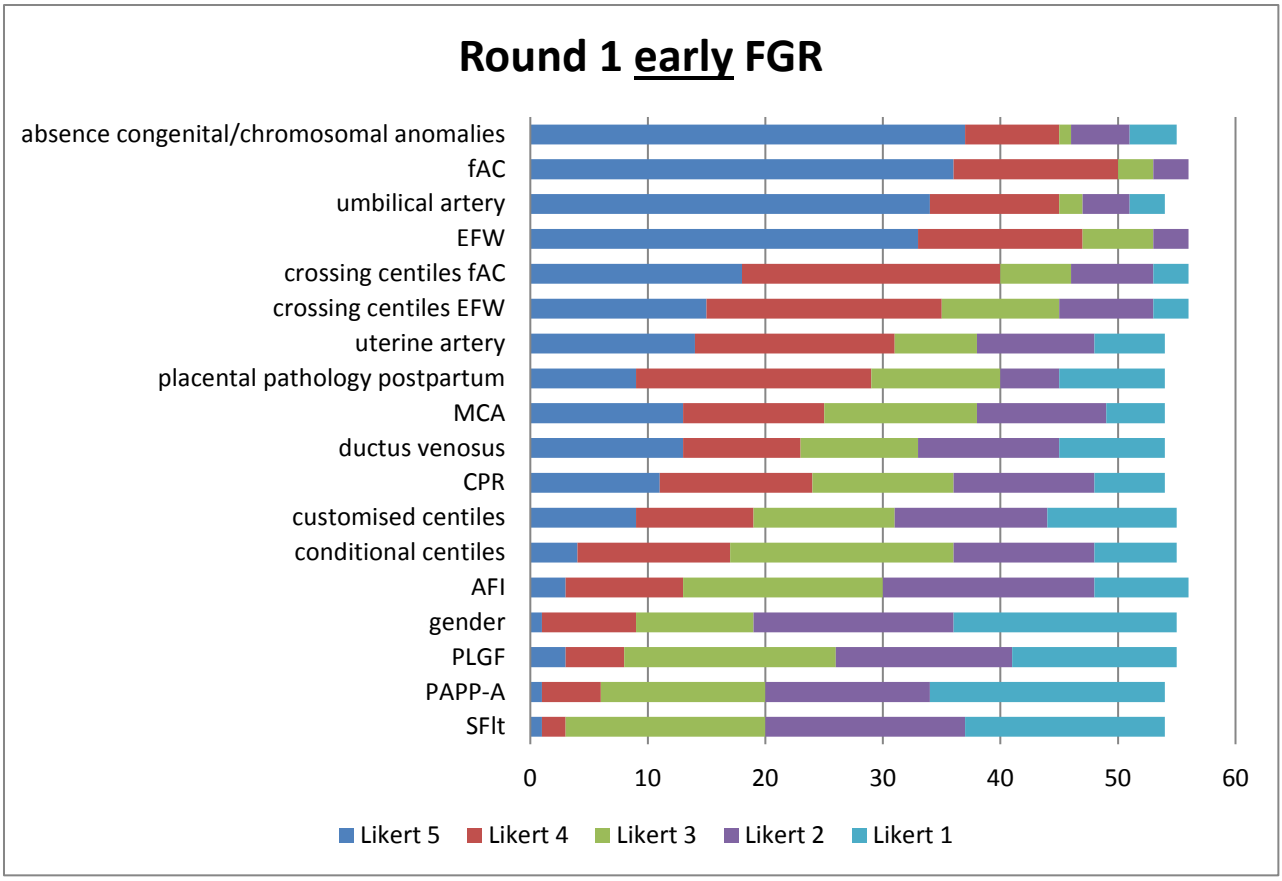


Figure 1 Delphi procedure

Table 1. Details of the expert panel participants (n=56)

Details of expert panel	Number (%)
Gender	
Female	16 (29)
Male	40 (71)
Region of practice	
Europe	30 (53)
North America	8 (14)
South America	3 (5)
Asia/Australia	10 (18)
Africa	5 (9)
Specialty	
Obstetrician	54 (96)
Gynecologist	2 (4)
Level of experience	
Professor	27 (48)
Assistant/associate professor	11 (20)
Consultant	16 (29)
Fellow	2 (4)
Level of care	
Secondary care	3 (5)
Tertiary care	53 (95)
Referral center for FGR	55 (98)


Round 1 early FGR
absence congenital/chromosomal anomalies
fAC
umbilical artery
EFW
crossing centiles fAC
crossing centiles EFW
uterine artery
placental pathology postpartum
MCA
ductus venosus
CPR
customised centiles
conditional centiles
AFI
gender
PLGF
PAPP-A
SFlt
0
10
20
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40
50
60
Likert 5
Likert 4
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Likert 1

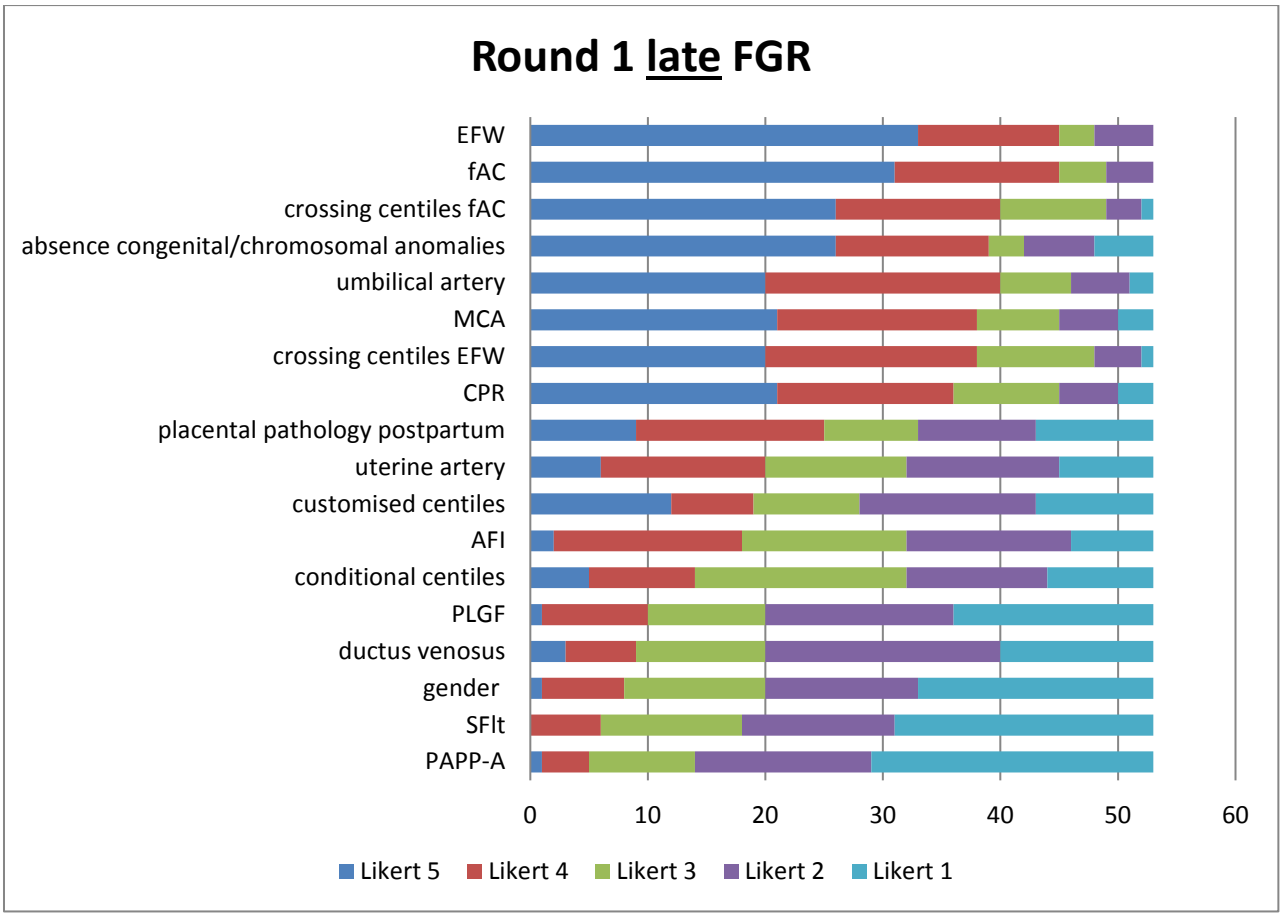
Round 1 late FGR
EFW
fAC
crossing centiles fAC
absence congenital/chromosomal anomalies
umbilical artery
MCA
crossing centiles EFW
CPR
placental pathology postpartum
uterine artery
customised centiles
AFI
conditional centiles
PLGF
ductus venosus
gender
SFlt
PAPP-A
0
10
20
30
40
50
60
Likert 5
Likert 4
Likert 3
Likert 2
Likert 1

Figure 2 Likert scores of parameters for early and late FGR. The distinction between early versus late has not been presented for a likert scores and is not incorporated in this table.

Table 2: parameters for re-examination

Early FGR	**% agreement**
Uterine artery	63
The absence of congenital anomalies	63
Late FGR	**% agreement**
Crossing of centiles FAC	64
Crossing of centiles EFW	66
Doppler umbilical artery	66
Doppler MCA	64
Doppler CPR	62
The absence of congenital anomalies	60

Table 3. Accepted parameters and their cut-offs for early and late FGR

Late FGR Parameter	Cut-off value solitary	%	Cut-off value contributory	%
Abdominal Circumference	< 3rd centile	71	< 10th centile	74
Estimated Fetal Weight	< 3rd centile	71	< 10th centile	85
PI umbilical artery			PI > 95th centile	93
CPR *			< 5th centile	64
Crossing centiles fAC			> 2 quartiles	76
Crossing centiles EFW			> 2 quartiles	78

Early FGR Parameter	Cut-off value solitary	%	Cut-off value contributory	%
Abdominal Circumference	< 3rd centile	84	< 10th centile	75
Estimated Fetal Weight	< 3rd centile	82	< 10th centile	81
PI umbilical artery	Absent ED-flow	80	PI > 95th centile	88
PI uterine artery			PI > 95th centile	96

* consensus reached in last round with determined >50% preference

Table 4. Rejected items

Parameter
Early FGR
crossing centiles fAC
crossing centiles EFW
Doppler MCA
cerebro-placental ratio
use of customised centiles
use of conditional centiles
volume amniotic fluid
fetal gender
Doppler ductus venosus
Placental growth-factor (PLGF)
PAPP-A
SFlt
confirmation placental pathology post-partum
Late FGR
Doppler MCA
use of customised centiles
use of conditional centiles
volume amniotic fluid
fetal gender
Doppler uterine artery
Doppler ductus venosus
Placental growth-factor (PLGF)
PAPP-A
SFlt
confirmation placental pathology post-partum

Table 5. Possible algorithms

Early FGR	**Late FGR**
Solitary Biometrical: FAC <3rd percentile Biometrical: EFW <3rd percentile Doppler: AEDF in the umbilical artery	**Solitary** Biometrical: FAC <3rd percentile Biometrical: EFW <3rd percentile
Contributory Biometrical: FAC or EFW <10th percentile Doppler: PI umbilical artery >95th percentile Doppler: PI uterine artery >95th percentile	**Contributory** Biometrical: FAC or EFW <10th percentile Biometrical (relative): crossing centiles FAC or EFW more than 2 quartiles Doppler: PI umbilical artery >95th percentile abnormal CPR
Algorithms for contributory parameters **A** 2 out of 3 contributory parameters are required irrespective of which parameter **B** 2 out of 3 parameters are required including a biometrical parameter (AC/EFW) **C** all contributory parameters are required	**Algorithms for contributory parameters** **A** 2 out of 3 contributory parameters are required irrespective of which parameter **B** 2 out of 3 parameters are required including an absolute biometrical parameter (AC/EFW) **C** all contributory parameters are required

Table 6. Consensus based definitions for early and late FGR.

Early FGR: gestational age <32 weeks, in the absence of congenital anomalies AC/EFW <p3 or AEDF in the umbilical artery **Or** 1. AC/EFW <p10 **combined with** 2. PI in the uterine artery >p95 **and/or** 3. PI in the umbilical artery >p95
Late FGR: gestational age ≥32 weeks, in the absence of congenital anomalies AC/EFW <p3 **Or** At least 2 out of 3 of the following 1. AC/EFW <p10 2. crossing centiles of more than 2 quartiles on growth centiles* 3. CPR <p5

* Growth centiles are non-customised centiles

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