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Consensus definition of fetal growth restriction: a Delphi procedure

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KEYWORDS: consensus; definition; Delphi; fetal growth restriction; placenta; placenta-based FGR

ABSTRACT

Objective *To determine, by expert consensus, a definition for early and late fetal growth restriction (FGR) through a Delphi procedure.*

Method *A Delphi survey was conducted among an international panel of experts on FGR. Panel members were provided with 18 literature-based parameters for defining FGR and were asked to rate the importance of these parameters for the diagnosis of both early and late FGR on a 5-point Likert scale. 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 was sought to determine the cut-off values for accepted parameters.*

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

Conclusion *Consensus-based definitions for early and late FGR, as well as cut-off values for parameters involved, were agreed upon by a panel of experts. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal growth restriction (FGR) is difficult to define. In this pregnancy condition, the fetus does not reach its biological growth potential as a consequence of impaired placental function, which may be because of 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]. At present 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 considered better as indicative of a 'small-for-gestational-age' (SGA) fetus[9,10]. SGA, however, differs from FGR principally because it also encompasses a majority of constitutionally small but healthy fetuses at lower risk of abnormal perinatal outcome[11]. On the other hand, growth-restricted fetuses with biometry > 10th centile may not meet their growth potential, and may remain undiagnosed despite being at increased risk of adverse outcome[12].

From both a clinical and a scientific perspective, it is most relevant to focus on fetuses that are at risk for adverse outcome, highlighting the need for a clear definition of FGR distinct from SGA. Several parameters

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have been reported to distinguish FGR from SGA and may improve the detection rates of FGR and its complications compared with the use of biometric measurements alone. These include sequential ultrasound measurements focusing on declining/crossing growth centiles, functional parameters such as Doppler waveform analysis (umbilical artery (UA), fetal 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 biometric (size) measurements.

A definition of FGR by international consensus should help to identify fetuses at risk, assist future research projects and aid in the comparison of different FGR studies. The aim of this study was to reach expert consensus on the definition of both early and late placental FGR through a Delphi procedure.

METHODS

Delphi procedure

For this study, 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 for reaching consensus between 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 in FGR, either by important publications on FGR or from the suggestions of confirmed panel members. We aimed for global coverage among the expert panel. Within the Delphi process, votes of all panel members are weighted equally. Experts who did not enter a particular round were not invited to participate in subsequent rounds (Figure 1).

Data collection

An online Delphi procedure was performed over four rounds. Questionnaires were completed using the online tool LimeSurvey version 2.05+ (www.limesurvey.org). 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 participants in the next round. The results were presented anonymously, on a group level. Non-responders received reminder e-mails after 10 days, and after 20 days they received a phone call. Withdrawal from the procedure was offered at all times.

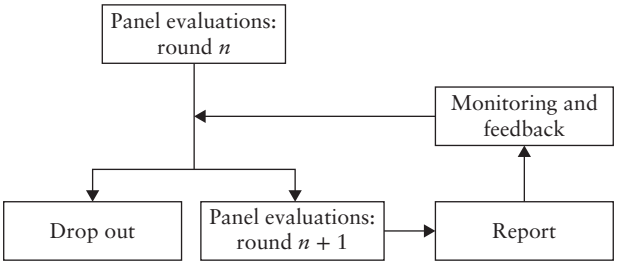

Figure 1 Overview of study design and method of incorporating survey respondents' comments for development of second round of Delphi survey.

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 FGR definition were presented to the panel for discussion. They were also given the opportunity to suggest additional parameters that they considered relevant and that were not currently listed among the 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, very important).

The predefined cut-off for inclusion of parameters in the consensus-based definition of 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 were presented in the second round for agreement on exclusion.

Second and third rounds

In the second round, parameters with a median score of 5 were presented to ascertain 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. The 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 value was sought in a similar fashion as for the parameters with a median score of 5. Parameters with

60–70% agreement were brought back for verification of acceptance or rejection in the third round, using a similar procedure.

For the determination of cut-off values for parameters, we proposed in the next round that the value with the highest level of agreement (> 70%) be 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 < 3rd centile by 35% of the panel, as < 5th centile by 50% of the panel and < 10th centile by 15% of the panel, we suggested in the next round that the panel incorporate a cut-off of < 5th centile because 85% of participants opted for < 5th centile.

Lastly, the panel was asked if they agreed with rejection of parameters with a median score of ≤ 3 in the first round or with < 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 one for consensus-based 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 five 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 procedure completed the whole procedure. Details regarding the self-reported expertise, specialization in FGR and demographic characteristics of the participants are shown in Table 1. Global coverage was reached; participants were mainly from Europe, which reflects fairly the geographical distribution of research reports concerning FGR.

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

Table 1 Demographic characteristics of the 56 experts on fetal growth restriction (FGR) who responded to the survey

Characteristic	n *(%)*
Gender	
Female	16 (29)
Male	40 (71)
Region of practice	
Europe	30 (54)
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)

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' gestation. The panel also agreed 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 was 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 for verification in the third round (Table 2). For each parameter accepted in the first round, it was determined whether it would be a solitary or a contributory parameter for the definition of FGR. For early FGR, three solitary parameters were chosen and for late FGR two were chosen. 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 the rejection of 13 parameters for the definition of early FGR and of 11 parameters for the definition of late FGR (Table 4).

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

The definitions agreed upon for FGR, in the absence of congenital anomalies, are given in Table 6.

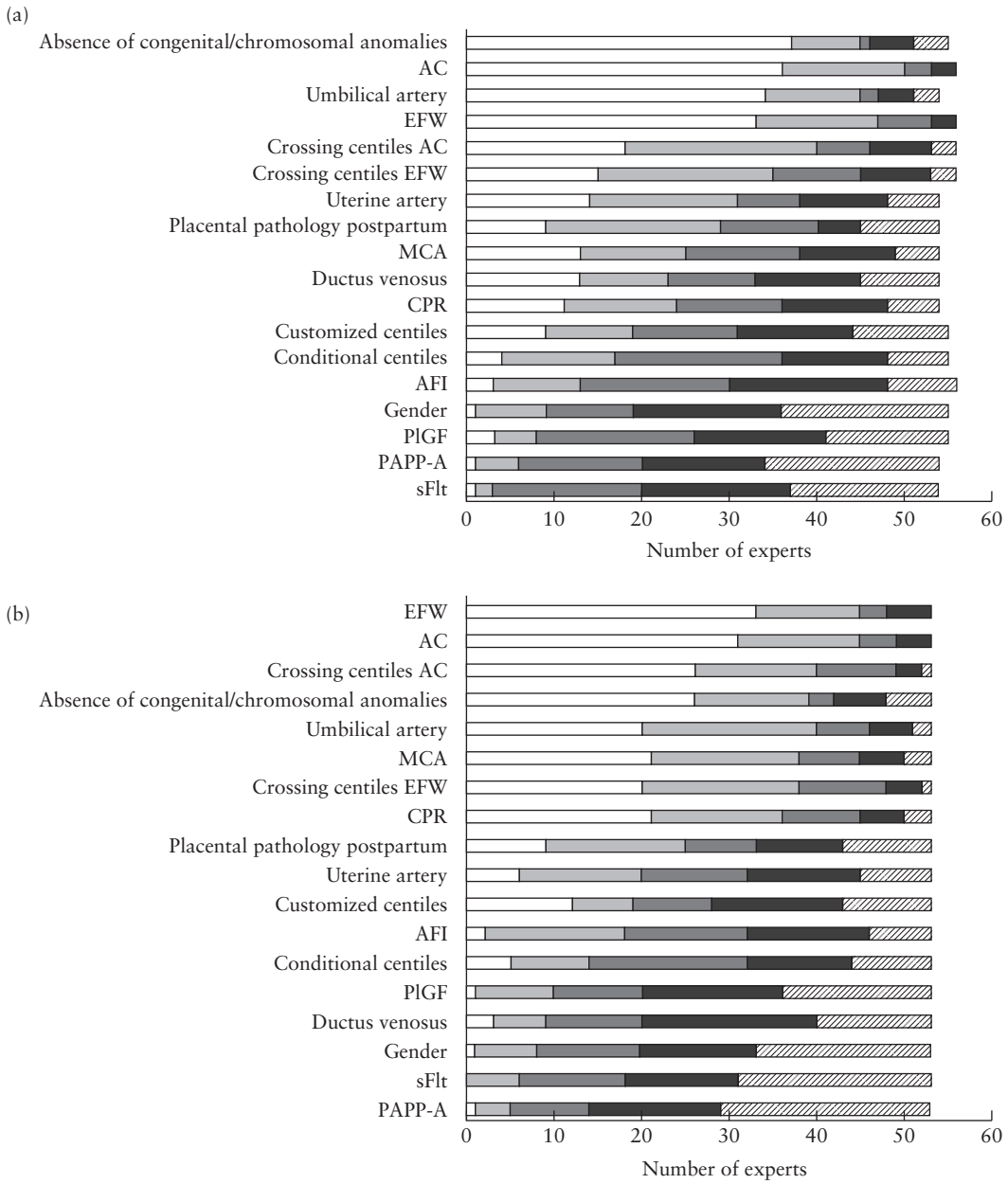

Figure 2 Importance of literature-based parameters for defining early (a) and late (b) fetal growth restriction, rated using a 5-point Likert scale: 1, very unimportant (▨); 2, unimportant (■); 3, neutral (■); 4, important (□); 5, very important (□). AFI, amniotic fluid index; CPR, cerebroplacental ratio; EFW, estimated fetal weight; AC, fetal abdominal circumference; MCA, fetal middle cerebral artery; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; sFlt, soluble fms-like tyrosine kinase.

DISCUSSION

In this study, consensus-based definitions for both early and late FGR due to placental insufficiency were established through a Delphi procedure. FGR is defined in most studies by aberrations of biometric measures of fetal size, usually with a cut-off value of EFW < 10th centile. However, this encompasses many constitutionally small fetuses and may be better thought of as SGA. This distinction is important, because although many SGA fetuses are physiologically small they are at low risk for adverse perinatal outcome. In contrast, FGR fetuses are pathologically small, irrespective of the growth centile (which can be > 10th centile). Thus, constitutionally small fetuses will be overdiagnosed and FGR will be underdiagnosed in fetuses with an EFW > 10th centile[12].

In order to better identify fetuses at risk and to better compare true FGR cohorts with appropriately grown cohorts, there is a need to improve the definition of FGR. 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' gestation. Second, it was agreed that congenital anomalies should be absent. Third, absolute size measurements in

Table 2 Parameters for defining early and late fetal growth restriction (FGR) that were considered important in the first round, almost reached consensus (60–70% agreement) in the second round and were brought to the panel for re-examination in the third round of the Delphi procedure

Parameter	*Agreement in second round (%)*
Early FGR	
UtA Doppler	63
Absence of congenital anomalies	63
Late FGR	
AC crossing of centiles	64
EFW crossing of centiles	66
UA Doppler	66
MCA Doppler	64
CPR	62
Absence of congenital anomalies	60

AC, fetal abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight; MCA, fetal middle cerebral artery; UA, umbilical artery; UtA, uterine artery.

Table 3 Solitary and contributory parameters and their cut-off values for defining early and late fetal growth restriction (FGR) that were agreed upon by a panel of experts

	Solitary		*Contributory*	
Parameter	*Cut-off*	*Agreement (%)*	*Cut-off*	*Agreement (%)*
Early FGR				
AC	< 3rd centile	84	< 10th centile	75
EFW	< 3rd centile	82	< 10th centile	81
UA-PI	AEDF	80	> 95th centile	88
UtA-PI			> 95th centile	96
Late FGR				
AC	< 3rd centile	71	< 10th centile	74
EFW	< 3rd centile	71	< 10th centile	85
UA-PI			> 95th centile	93
CPR*			< 5th centile	64
AC CC			> 2 quartiles	76
EFW CC			> 2 quartiles	78

*Consensus reached in last round with > 50% preference. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CC, crossing centiles; CPR, cerebroplacental ratio; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

themselves were defined at lower cut-offs (3rd centile) than are commonly used (10th centile). Fourth, functional parameters were introduced into the definition, either as solitary (absent end-diastolic flow in the UA) or contributory parameters (UA-PI or UtA-PI > 95th centile or CPR < 5th centile).

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

Table 4 Parameters that were rejected by a panel of experts for defining early and late fetal growth restriction (FGR)

	Rejected for:	
Parameter	*Early FGR*	*Late FGR*
AC crossing centiles	Yes	No
EFW crossing centiles	Yes	No
Middle cerebral artery Doppler	Yes	Yes
Ductus venosus Doppler	Yes	Yes
Uterine artery Doppler	No	Yes
Cerebroplacental ratio	Yes	No
Use of customized centiles	Yes	Yes
Use of conditional centiles	Yes	Yes
Amniotic fluid index	Yes	Yes
Fetal gender	Yes	Yes
Placental growth factor	Yes	Yes
PAPP-A	Yes	Yes
sFlt	Yes	Yes
Postpartum confirmation of placental pathology	Yes	Yes

AC, fetal abdominal circumference; EFW, estimated fetal weight; PAPP-A, pregnancy-associated plasma protein-A; sFlt, soluble fms-like tyrosine kinase.

The strength of a Delphi procedure depends 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 whom conduct research on FGR. In the Delphi procedure, all participants' votes were weighted equally and the participants were blinded to the individual expert opinions of their colleagues. This minimized peer pressure from authoritative individuals and allowed for optimal use of the collective knowledge. Predefined rules regarding acceptance or rejection of parameters were strictly adhered to, with double-checking of possible differing interpretations 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 for selection bias by gathering together a group of individuals that share the same interests and opinions and attrition of contributors with successive rounds. We included specialists with a special focus on FGR and not epidemiologists, neonatologists and developmental specialists. Although this may also be a source of bias, these specialists are most familiar with the concepts and clinical implications of FGR.

Table 5 Possible algorithms of solitary and contributory parameters for defining early and late fetal growth restriction (FGR), as determined by a panel of experts

Early FGR (< 32 weeks)	*Late FGR (≥ 32 weeks)*
Solitary	Solitary
Biometric: AC < 3rd centile	Biometric: AC < 3rd centile
Biometric: EFW < 3rd centile	Biometric: EFW < 3rd centile
Doppler: absent end-diastolic flow in UA	
Contributory	Contributory
Biometric: AC < 10th centile	Biometric: AC < 10th centile
Biometric: EFW < 10th centile	Biometric: EFW < 10th centile
Doppler: UA-PI > 95th centile	Biometric (relative): AC or EFW crossing centiles more than 2 quartiles
Doppler: UtA-PI > 95th centile	Doppler: UA-PI > 95th centile or abnormal CPR
Algorithms for contributory parameters	Algorithms for contributory parameters
(A) 2/3 contributory parameters required irrespective of which parameter	(A) 2/3 contributory parameters required irrespective of which parameter
(B) 2/3 parameters required including a biometric parameter (AC/EFW)	(B) 2/3 parameters required including an absolute biometric parameter (AC/EFW)
(C) all contributory parameters required	(C) all contributory parameters required

AC, fetal abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

Table 6 Consensus-based definitions for early and late fetal growth restriction (FGR) in absence of congenital anomalies

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3rd centile *or* UA-AEDF	AC/EFW < 3rd centile
Or	*Or at least two out of three of the following*
1. AC/EFW < 10th centile *combined with*	1. AC/EFW < 10th centile
2. UtA-PI > 95th centile *and/or*	2. AC/EFW crossing centiles >2 quartiles on growth centiles*
3. UA-PI > 95th centile	3. CPR < 5th centile *or* UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

In this Delphi procedure, as many potential parameters as possible were presented, such as customized centiles[23] and serum biomarkers soluble fms-like tyrosine kinase and placental growth factor[24]. From the answers of the expert participants, we concluded that currently available evidence regarding the rejected parameters is not weighted strongly enough to include these parameters in the diagnosis at this time – which does not exclude their 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 definitions of SGA) in prospective observational cohorts. It is probable that the new definition will better identify fetuses at risk than does a solely biometrically based definition. However, its validity in regard to a reduction in adverse outcomes needs to be tested and it should be used in clinical trials of interventions.

Many research initiatives focus on the establishment of good diagnostic markers for FGR and also focus on prediction models for adverse outcomes in FGR with combinations of Doppler ultrasound 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 definitions proposed here may need to be updated.

Now that a consensus definition of FGR has been established, it raises several questions. First, diagnosis at delivery (neonatal growth restriction (NGR)) presents the same challenges as does the diagnosis of FGR. The relationship between FGR and NGR needs to be evaluated using the new definitions. A definition of NGR based solely on size is unlikely to be optimal for identifying those at risk for adverse outcome. Second, the diagnoses of FGR and growth restriction at delivery need to be connected to relevant outcomes. It is important not only to use uniform and meaningful diagnostic 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 and outcomes will be performed.

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