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Consensus Definition of Fetal Growth Restriction in Intrauterine Fetal Death

A Delphi Procedure

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• ***Context.***—**Fetal growth restriction is a risk factor for intrauterine fetal death. Currently, definitions of fetal growth restriction in stillborn are heterogeneous.**

Objectives.—**To develop a consensus definition for fetal growth restriction retrospectively diagnosed at fetal autopsy in intrauterine fetal death.**

Design.—**A modified online Delphi survey in an international panel of experts in perinatal pathology, with feedback at group level and exclusion of nonresponders. The survey scoped all possible variables with an open question. Variables suggested by 2 or more experts were scored on a 5-point Likert scale. In subsequent rounds, inclusion of variables and thresholds were determined with a 70% level of agreement. In the final rounds, participants selected the consensus algorithm.**

Results.—**Fifty-two experts participated in the first round; 88% (46 of 52) completed all rounds. The consensus definition included antenatal clinical diagnosis of fetal growth restriction OR a birth weight lower than third percentile OR at least 5 of 10 contributory variables (risk factors in the clinical antenatal history: birth weight lower than 10th percentile, body weight at time of autopsy lower than 10th percentile, brain weight lower than 10th percentile, foot length lower than 10th percentile, liver weight lower than 10th percentile, placental weight lower than 10th percentile, brain weight to liver weight ratio higher than 4, placental weight to birth weight ratio higher than 90th percentile, histologic or gross features of placental insufficiency/malperfusion). There was no consensus on some aspects, including how to correct for interval between fetal death and delivery.**

Conclusions.—**A consensus-based definition of fetal growth restriction in fetal death was determined with utility to improve management and outcomes of subsequent pregnancies.**

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Fetal growth restriction (FGR) is the failure of a fetus to reach its intrinsic growth potential, related to placental insufficiency as the common mechanism of many possible causes (eg, placental pathology, infections, genetic constitution).[1–3] Fetal growth restriction is a risk factor for adverse perinatal outcome, including a 3 to 7 times higher risk of intrauterine fetal death (IUFD).[4–9] Also, the recurrence risk of FGR is up to 40%.[10] If parents, family members, and care providers are aware of the cause(s) of fetal demise and the risk of recurrence, there is a potential to rationally apply better care in subsequent pregnancies.

The process and accuracy of determining if an IUFD was associated with growth restriction depends highly on whether an autopsy was performed. In individual situations, there is a variety of reasons for parents to forgo a perinatal autopsy, but it is acknowledged that an autopsy can provide additional information about the cause of death in IUFD.[11,12] If not, a regular surrogate is the use of a statistical diagnosis of small for gestational age (SGA), entailing an unadjusted birth weight lower than 10th percentile on reference charts of (live-born) infants.[13–15] However, the inability to use functional placental markers, such as ultrasound Doppler measurements, and postmortem changes can hamper the

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identification of FGR.[15] During the intervals between demise and delivery and between delivery and assessment of the size and weight of the baby, there is no fetal growth, and there is body and organ weight loss due to maceration.[15–20] Thus, using SGA parameters may lead to an erroneous overestimation of FGR due to the weight loss after demise. For that reason, adjustments may be made for effects of maceration.[19,21,22] However, FGR may also be underestimated because it can occur in appropriate for gestational age fetuses.[1,23,24] When placental insufficiency starts late in pregnancy/at advanced gestational age, or is subtle, the signs of FGR are less obvious and (decline in) size is not the best marker for the condition. If FGR occurs in late gestation, the fetus has grown and developed to a size within normal ranges; the interval that is needed to obviously decline in growth may not be reached, although hypoxia can be severe. Therefore, a decline in growth velocity is less likely to result in the fetus's size percentile to drop below the used cutoff of 50%. Dopplers may indicate a high-resistance placental vasculature, but may not be performed because the decline in growth velocity has not yet been detected.[25,26]

In 2016, a consensus definition for the antenatal diagnosis of FGR in the vital fetus was established using a Delphi procedure. This definition included functional parameters, reflecting placental function, in addition to the historically used biometrical measures. These functional parameters obviously cannot be applied in IUFD, as the placenta is no longer functional.[27] A consensus definition of how to diagnose FGR in IUFD may improve detection of FGR in stillborn babies (both SGA and appropriate for gestational age), and will assist future research projects and aid comparison of cohorts. This Delphi exercise was undertaken to come to consensus in an international expert panel on a definition for FGR in IUFD at autopsy.

METHODS

For this study, a semianonymous electronic Delphi survey was performed in which a modified Delphi consensus methodology was used. The Delphi procedure aims for convergence of opinions resulting in consensus of participants by multiple rounds wherein statements are weighed, summarized, and fed back on group level (individual answers are anonymous) in increasing detail. The approach minimizes some of the confounding factors present in other group response methods, such as "strong advice." The Delphi method is a well-established instrument for issues that lack a gold standard and for which empirical evidence cannot be obtained, and taps into the "wisdom of the crowd."[28]

Selection of Experts

For the expert panel, we invited perinatal pathologists who are recognized leaders in the field based on a former collaboration[29] and literature search, as well as experts recommended for inclusion by fellow expert panel members. Patients, their representatives, and other lay experts were not involved in the process, because the aim was to get to a definition of FGR in IUFD for which thorough pathologic knowledge was perceived as conditional to participate. In every round, participants had the opportunity to opt out of the procedure. Only experts who fully completed a particular round were invited for each subsequent round of the survey.

Delphi Rounds

In the first round, the expert panel members were asked to mention all variables they thought could be important in the definition of FGR in IUFD, similar to the original Delphi procedure.[28] This survey was structured into domains concerning variables for the diagnosis of FGR in IUFD, variables for determining gestational age and fetal weight at time of demise (thus correcting for retained time in utero), corrective variables that could be used to adjust biometry references of gestational age–matched liveborn infants to make them applicable in the context of IUFD, and biometry references that would need adjustment by corrective variables. After the first round, all collected variables were analyzed for duplication and overlap, and through discussion in the steering group (all authors), they were clustered into single merging variables where appropriate.

Variables mentioned by at least 2 different expert panel members in the first round were presented for rating of their importance in the second round. To rate the importance of the variables, a 5-point Likert scale was used, with a predefined cutoff for inclusion of a median score of Likert 5.

In the third round, variables that scored a median of Likert 5 in the second round were presented to confirm the inclusion. Variables that scored a median of Likert 4 or lower were presented for verification of exclusion. The cutoff level of agreement for inclusion was predefined at 70%.

In the fourth round, we presented the results of the included and excluded variables and asked the panel experts if the included variables should be "solitary variables" and/or if they should be "contributory variables." A *solitary variable* was defined as a variable that is sufficient to make the diagnosis when (strongly) abnormal, without the necessity of any other abnormal variables. A *contributory variable* was defined as a variable that, when abnormal, needs (an)other variable(s) to be abnormal as well before the diagnosis can be made. Some variables can be both solitary and contributory when a different threshold is used. All variables were presented as both solitary and contributory, at different threshold values. In principle, the proposed threshold for solitary values was more severely abnormal. Proposed threshold values were based on thresholds in the literature and discussed in the steering group. Furthermore, in this round, corrective variables that could be applied to other variables, such as effects of time and environment on size/weight measurements, were presented to the panel to determine their importance.

In the final rounds, possible algorithms to define FGR in IUFD were presented to the panel until consensus was reached.

Each round included the option for experts to explain their answers or provide other forms of feedback.

Data Collection

Data were collected using online questionnaires. In the first 3 rounds, responses were captured in the online tool LimeSurvey version 3.15.1. The fourth and fifth round were performed through the online REDCap tool, version 7.3.2, because of institutional regulations. Every participant received a unique token-secured link to participate in the online survey. Participants received 2 reminder emails and nonresponders were excluded from subsequent survey rounds.

RESULTS

For this Delphi procedure, we invited 84 experts, of whom 52 (62%) were willing to join the procedure and completed the first round. A total of 46 panel members (88%) completed all 6 rounds (Figure 1). Demographic characteristics of participating experts are shown in Table 1.

In the first round, the expert panel members proposed a total of 127 variables for the definition of FGR in IUFD, of which 66 were proposed by at least 2 panel members (Supplemental Table 1; see supplemental digital content, containing 2 tables).

In the second round, one new domain concerning variables that would possibly need adjustment of corrective variables was added. In this second round, 28 variables scored a median Likert of 5 (very important) and 50 variables scored a Likert 4 or lower (Figures 2 and 3, A

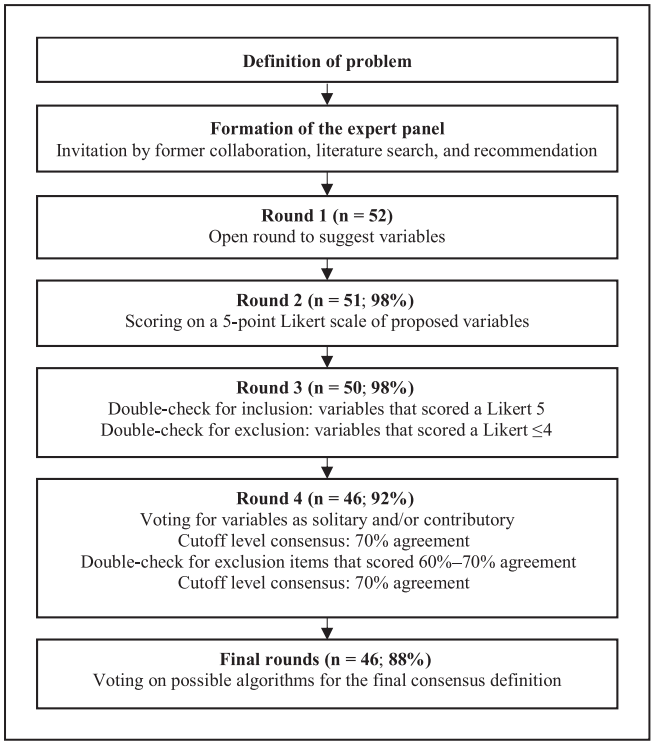

Figure 1. *Flowchart of the Delphi procedure.*

through C). In subsequent rounds, variables were brought back for consensus on inclusion and exclusion based on a Likert score of 5 and less than 5, respectively. Ultimately, a total of 11 variables were accepted for the definition (Table 2). Eight variables were identified as contributory and 2 as solitary as well as contributory at different threshold values (Supplemental Table 2).

The panel voted that 3 of these variables needed adjustment of biometry references (for the effects of the interval between demise and evaluation) in case of IUFD relative to gestational age–matched live births (Table 3). Furthermore, consensus was reached to define the histologic placental features according to the criteria of the Amsterdam Placental Workshop Group for maternal and fetal vascular malperfusion.[30]

The final rounds were used to come to consensus on the exact algorithm of the definition (Table 4).

DISCUSSION

In this study, a consensus definition of fetal growth restriction in IUFD was established using a Delphi procedure. It should first be acknowledged that consensus is not empirical evidence, but the best available synthesis of current knowledge if there is no gold standard. The strength of such a Delphi procedure highly depends on the selection of true experts for the panel.[28] We were able to include experts with a high level of expertise, as 44 (96%) of them were pathologists specialized in the field of perinatology and the other 2 were known for their (research) expertise in perinatal pathology. Although eventually 6 rounds were necessary to come to the final definition, attrition of participants was very low (88% completed the procedure). This underscores the perceived importance of this procedure by the experts in the field. The expert participants in this procedure proved to be eager to suggest variables they felt were important (127 variables were proposed in the first round among 52 expert panel members). Participants also proved to be committed to the topic and tenacious; frequently the open feedback option was used to suggest variables that had previously been voted out. The equal weighing of votes and the semianonymous approach minimized peer pressure from authoritative individuals. Predefined levels for acceptance and rejection were strictly adhered to, and responses were double-checked for confirmation.

Although we aimed for global coverage, there was no representation of Africa and South America in the final panel. This may compromise global generalizability and implementation of the results. However, it reflects the geographical distribution of perinatal autopsy rates and of research reports on this topic.

Currently a variable but significant proportion (15%–60%, depending on which of the more than 30 classification systems is used) of IUFD remains unexplained despite postmortem examinations being undertaken in specialist centers.[31] In particular, the unexplained cases are frequently associated with FGR.[9,32–34] The prevalence of FGR among IUFD cases varies, with percentages up to 47%.[35] An autopsy examination combined with placental investigations remains the gold standard postmortem investigation and can reveal the underlying cause of death.[36] However, poor consent rates to autopsy are found in the literature.[37] When a (full) autopsy cannot be performed, usually placental examination and external measurements are still possible. The placenta can be an invaluable factor in such cases to identify FGR.[38] Many, if not all, known placental lesions have been found in association with FGR: abnormalities of placentation, macroscopic vascular anomalies, microscopic lesions, and umbilical cord anomalies.[39] Whether an autopsy is performed or not, the pathologist or the death review panel usually aims to determine a probable sequence of events resulting in death. All conditions (like FGR and maternal hypertensive disease), the cause of death, and the subsequent future implications for monitoring and management in the next pregnancy are considered. The newly developed consensus definition supports the pathologist who is confronted with a difficult task: to determine at autopsy whether there has been FGR or not. It also allows for parameters or variables that can be measured without a dissection and measurement of visceral organs. Of the 10 contributory variables, only 3 require dissection and weighing (of the brain and liver). It is noteworthy that the consensus definition does not exclude FGR occurring in appropriate for gestational age stillbirths, in keeping with the definition of FGR in liveborn infants.[27]

Historically, a distinction between symmetrical and asymmetrical growth restriction has been made. In this study, all suggested variables for asymmetrical growth restriction (Supplemental Table 1) were ultimately rejected by the expert panel. This is in line with the observations that in early severe FGR there is already an adaptation to the pathologic condition in very early pregnancy and asymmetrical growth does not necessarily occur.[26]

Consistent with previous publications, the panel agreed that postmortem changes depend on the intrauterine interval, maceration grade, degree of organ autolysis, degree of hydrops, and fixation procedures, and on the need for them to be taken into account when defining FGR in IUFD.[15] In these adjustments, birth weight needs to be considered in light of the intrauterine interval, maceration

Table 1. Demographic Characteristics and Self-Reported Expertise of the 52 Experts Who Participated in the Survey

	No.	%
Characteristics		
Gender		
Male	25	48
Female	27	52
Region of practice		
Europe	21	40
North America	20	39
Asia/Australia	11	21
Occupation		
Pediatric/obstetric/perinatal pathologist	50	96
General pathologist with special interest for stillbirth	1	2
Obstetrician with a special interest in stillbirth	1	2
Level of experience		
Professor	25	48
Assistant/associate professor	7	13
Consultant	19	37
Trainee	1	2
Level of care		
Secondary care	9	17
Tertiary care	43	83
Referral center for perinatal autopsies	46	89
Fetal autopsies performed at expert's center[a]		
<50	7	13
50–100	17	33
101–150	9	17
151–200	2	4
201–250	3	6
>250	14	27
Full fetal autopsies at expert's center[a,b]		
<50	16	31
50–100	11	21
101–150	9	17
151–200	0	0
201–250	4	8
>250	12	23
Fetal autopsies performed by individual expert[a]		
None	5	10
<25	10	19
25–50	12	23
51–75	11	21
76–100	2	4
>100	12	23
Fetal autopsies supervised by individual expert[a]		
None	3	6
<25	14	27
25–50	12	23
51–75	11	21
76–100	4	8
>100	8	15
Placentas examined at expert's center[a]		
<50	9	17
50–100	16	31
101–150	6	12
151–200	2	4
201–250	1	2
>250	18	35
Placentas examined by individual expert[a]		
None	1	2
<25	8	15
25–50	13	25
51–75	7	13
76–100	4	8
>100	19	37
Autopsy rate in case of IUFD, %		
<20	5	10
20–39	12	23
40–59	9	17
60–79	8	15
>80	6	12
Unknown	12	23
Factors for not performing autopsy in expert's country		
Lack of parental permission	47	90
(Un)availability of perinatal pathologist	8	15
Financial consequences for the parents	3	6
Other	8	15

Abbreviation: IUFD, intrauterine fetal death.

[a] On annual basis.

[b] Full autopsies include brain dissection.

grade, and degree of hydrops. A hydropic fetus can have a birth weight at the 80th percentile and be severely growth restricted, because in these cases weight is largely driven by extracellular fluids.[21] Currently, empirical evidence is lacking for determining the intrauterine interval. It remains unclear how adjustment of these variables should be done, as we were unable to create consensus on this topic. The different corrections that individual pathologists apply to the variables proved too difficult to decide and to implement in an ultimate consensus definition. For clinical application, the steering group agreed that based on these results, the executive pathologist should be aware of the difficulties in examination caused by these postmortem changes and adjust the findings accordingly by his or her own judgment or state in the report that there is reason to assume that there is FGR based on the postmortem changes that warrant correction for weight of unknown magnitude. To address this absence of a strict algorithm, we thus advise the executive pathologist to report how variables are weighed to come to the diagnosis.

There are some interesting findings of this Delphi procedure that merit discussion. One is that the expert panel included the variable "clinical antenatal information including scan results and Doppler studies" as both a solitary and contributory variable (and voted the similar variable "premortem antenatal suspicion of FGR" out), but was not able to reach consensus on a more detailed description. In order to provide an applicable definition, a distinction was made between solitary and contributory by

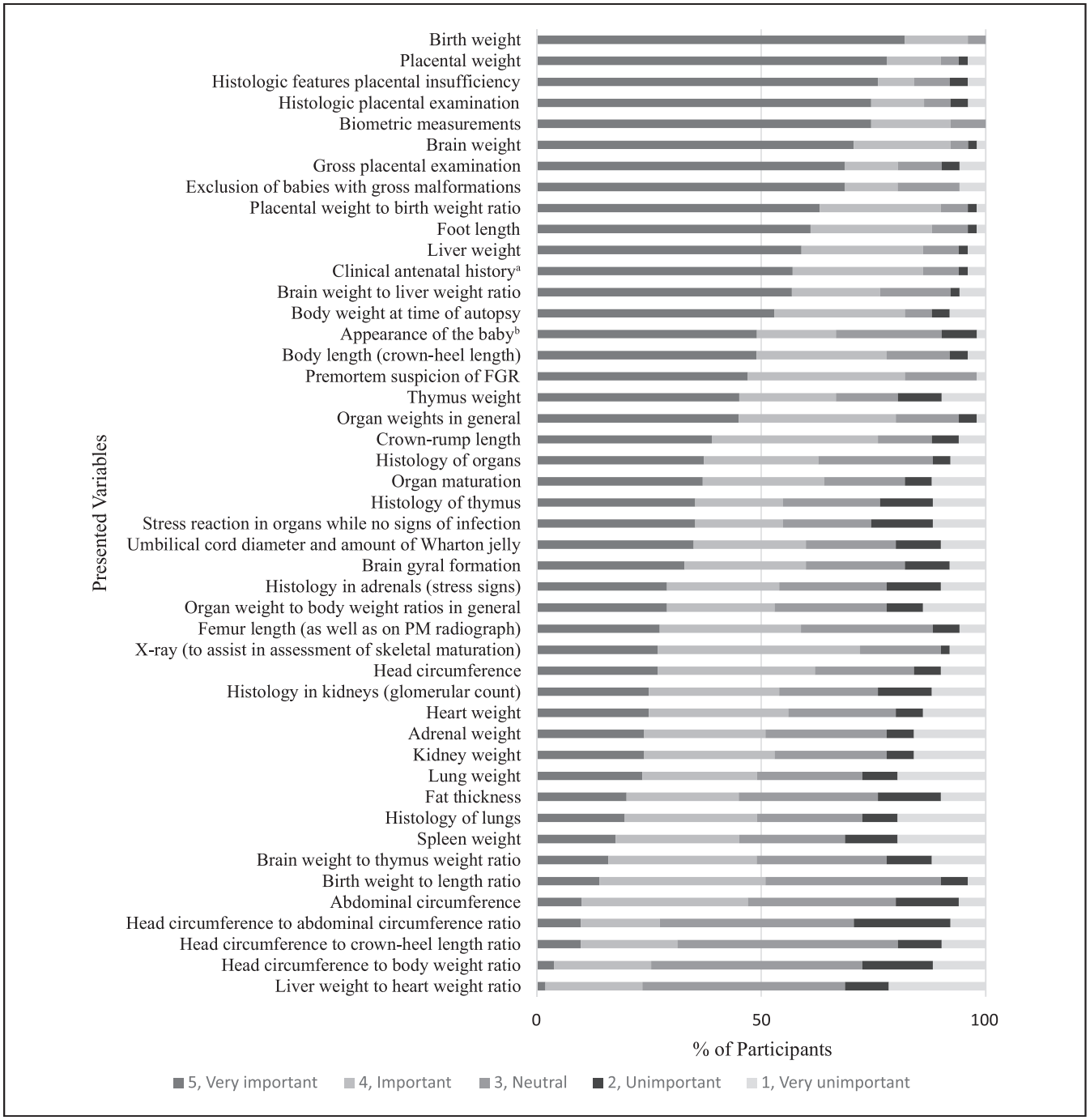

Figure 2. *Rated importance of the variables for the definition of fetal growth restriction (FGR) in intrauterine fetal death, in the second round.* [a]*Thin, loose skin, large head, narrow body, lack of fat deposit.* [b]*Including scan results and Doppler studies. Abbreviation: PM, postmortem.*

the steering group. The solitary variable was considered to be an antenatal clinical diagnosis of FGR diagnosed by an obstetrician or perinatologist, whereas the contributory variable was considered to be "risk factors in the clinical antenatal history including scan results and Doppler studies suggestive for FGR." Table 5 illustrates 2 example cases to aid in this distinction. In the case of an IUFD, there has been an unwanted major event during pregnancy. If the antenatal caregivers and pathologist disagree about whether the fetus should be considered growth restricted, it would be preferable to err on the side of caution, accepting the diagnosis of growth restriction and monitoring subsequent pregnancies with extra care for recurrence.

Furthermore, the variable "foot length below the 10th percentile" is included in the definition. However, foot length is in general little influenced in FGR and is one of the items recognized to be a relatively accurate measure to determine gestational age at time of death.[39]

CONCLUSIONS

In conclusion, we established a consensus definition of FGR in IUFD through a Delphi procedure. This definition

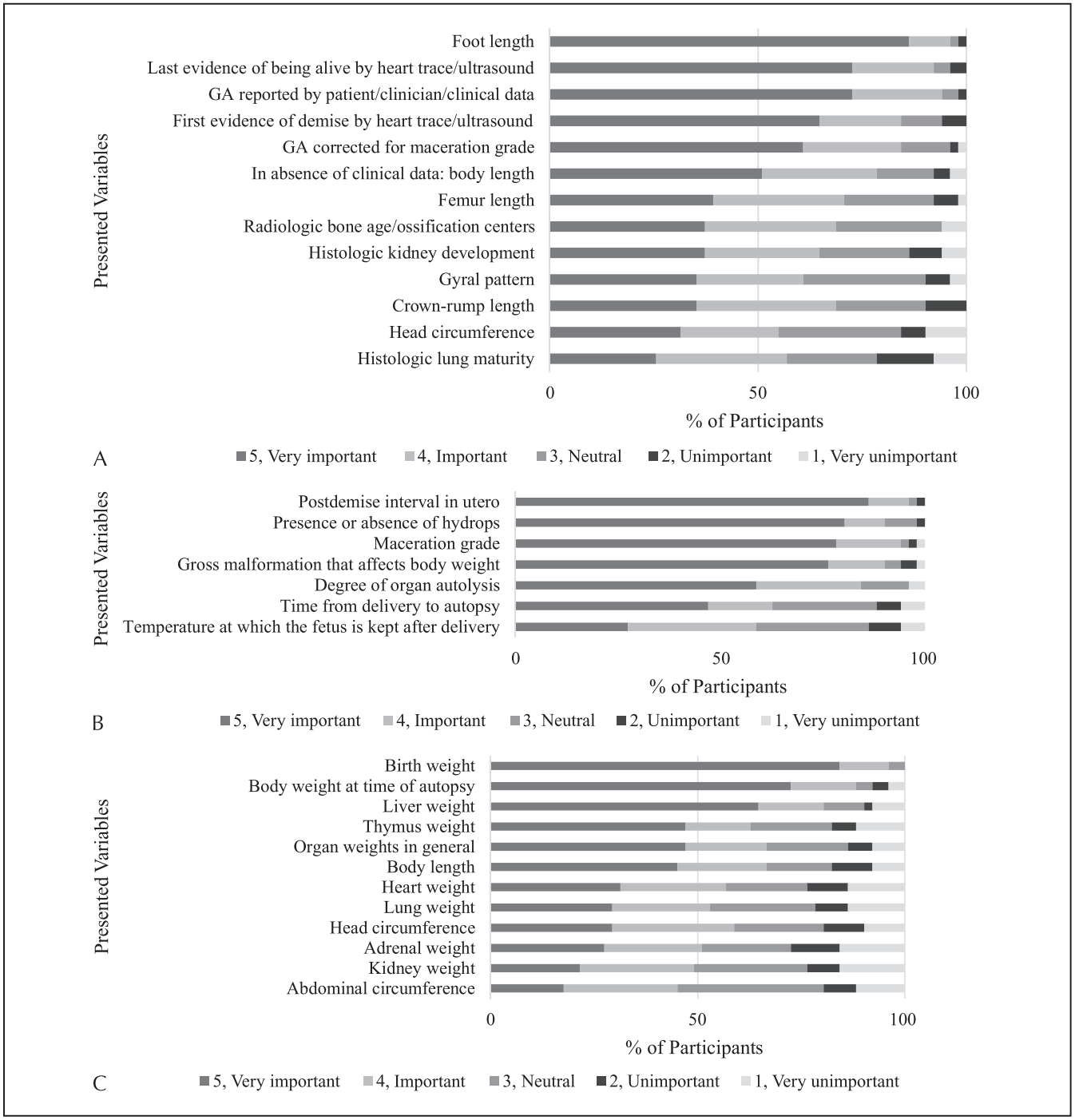

Figure 3. *A, Rated importance of the variables to determine the postmortem intrauterine interval and the gestational age at time of demise in the second round. B, Rated importance of the corrective variables in the second round. C, Rated importance of the variables that needed correction if included in the definition in the second round. Abbreviation: GA, gestational age.*

may improve the detection of FGR in both SGA and appropriate for gestational age IUFD. Because FGR is a condition with potential severe adverse outcomes that can be averted by timely interventions if diagnosed, this may have implications for interpretation of postmortem investigations, for calculations of recurrence risks, and in litigation. This consensus definition should be validated for identification of FGR in IUFD, for example by looking at recurrence of FGR in subsequent pregnancies. Also, there is a need for studies to provide formulas with empirical evidence to estimate the intrauterine interval and how to adjust weight variables. We hope that awareness of the fact that SGA is not similar to FGR will improve and that with this definition another step toward individual management for subsequent pregnancies will result in better outcome.

We would like to acknowledge the participants (full participation with consent for acknowledgment) of this Delphi procedure (in alphabetical order): S. M. Arbuckle (Westmead, Australia), I. Ariel (Jerusalem, Israel), R. N. Baergen (New York, New York), R. W.

Table 2. Accepted and Rejected Variables for the Consensus Definition of Fetal Growth Restriction (FGR) in Intrauterine Fetal Death (IUFD)

Accepted Variables	Inclusion Agreement, %	Rejected Variables
Definition of FGR in IUFD		
Birth weight	98	Abdominal circumference
Body weight at time of autopsy	78	Adrenal weight
Brain weight	82	Appearance of the baby[a]
Brain weight to liver weight ratio	76	Birth weight to length ratio
Clinical antenatal history[b]	92	Body length (crown-heel length)
Exclusion of babies with gross malformations	88	Brain gyral formation
Foot length	96	Brain weight to thymus weight ratio
Histologic or gross placental examination	84	Crown-rump length
Liver weight	78	Fat thickness
Placental weight	88	Femur length (as well as on postmortem radiograph)
Placental weight to birth weight ratio	86	Head circumference
		Head circumference to abdominal circumference ratio
		Head circumference to body weight ratio
		Head circumference to crown-heel length ratio
		Heart weight
		Histology of adrenals (stress signs)
		Histology of kidneys
		Histology of lungs
		Histology of thymus
		Kidney weight
		Liver weight to heart weight ratio
		Lung weight
		Organ to body weight ratios
		Premortem suspicion of FGR
		Spleen weight
		Thymus weight
		Umbilical cord diameter/amount of Wharton jelly
		X-ray
Determine intrauterine interval and gestational age at time of demise		
CI: first evidence of demise[c]	94	Body length (crown-heel length)
CI: last evidence of being alive[c]	98	Crown rump length
Foot length	98	Femur length
Gestational age corrected for maceration grade	82	Gyral pattern
Gestational age reported by patient/clinician	100	Head circumference
		Histologic kidney development
		Histologic lung maturity
		Radiologic bone age/ossification centers
Applicable for correction		
Degree of organ autolysis	82	Temperature at which the fetus is kept after delivery
Fixation procedures (formalin)	91	Time from delivery to autopsy
Maceration grade	94	
Postdemise interval in utero	96	
Presence or absence of hydrops	98	
Need correction		
Birth weight	85	Abdominal circumference
Body weight at time of autopsy	78	Body length
Liver weight	91	Brain weight
		Head circumference
		Kidney weight
		Organ weights in general[d]
		Placental weight
		Specific organ weights

Abbreviation: CI, clinical information

[a] Thin, loose skin; large head; narrow body; lack of fat deposit.
[b] Including scan results and Doppler studies.
[c] By heart trace or ultrasound.
[d] Adrenal, lung, heart, thymus.

Table 3. Included Variables That Need Adjustment of Corrective Variables in Order to Appropriately Diagnose Fetal Growth Restriction in Intrauterine Fetal Death, %[a]

Variable	Corrective Variable				
	Intrauterine Interval	Maceration Grade	Degree of Hydrops	Degree of Organ Autolysis	Fixation Procedures (Formalin)
Birth weight	**85**	**83**	**96**	52	46
Body weight at time of autopsy	**87**	**87**	**94**	**76**	67
Liver weight	**87**	**85**	54	**80**	**76**

[a] Bolded percentages are indicated by 70% or more of the expert panel for the need for adjustment (for example, 85% indicated the need for adjustment of birth weight for the intrauterine interval).

Table 4. Consensus-Based Definition for Fetal Growth Restriction (FGR) in Intrauterine Fetal Death (IUFD)[a]

FGR in IUFD is defined as

Evident antenatal clinical diagnosis of FGR

Or

Birth weight <third percentile

Or

At least 5 of the following:

1. Risk factors in the clinical antenatal history including scan results and Doppler studies suggestive for FGR
2. Birth weight <10th percentile
3. Body weight at time of autopsy <10th percentile
4. Brain weight <10th percentile
5. Foot length <10th percentile
6. Liver weight <10th percentile
7. Placental weight <10th percentile
8. Brain weight to liver weight ratio >4
9. Placental weight to birth weight ratio >90th percentile
10. Histologic or gross placental features of placental insufficiency/vascular malperfusion[b]

[a] Babies with gross malformations are excluded from the definition and need to be considered separately.

[b] According to the statement of the Amsterdam Placental Workshop Group for maternal and fetal vascular malperfusion.

Table 5. Two Clinical Case Illustrations to Clarify the Distinction Between Antenatal History as Solitary and Contributory Variable

Variable	Description
Case 1	
Gestational age	28 wk
Biometry	Abdominal circumference and estimated fetal weight below the third percentile
Doppler	Absent umbilical arterial end-diastolic flow
Conclusion	Antenatal clinical diagnosis of FGR
Case 2	
Gestational age	Beyond 34 wk
Biometry	A downward deflection of the growth velocity from the 80th percentile to the 40th percentile on the growth chart within a 4-wk interval
Doppler	The pulsatility indexes of the umbilical artery and the middle cerebral artery are both borderline abnormal
Conclusion	Risk factors in the clinical antenatal history suggestive for FGR

Abbreviation: FGR, fetal growth restriction.

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