Consensus Based Definition of Growth Restriction in the Newborn

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Objective To develop a consensus definition of growth restriction in the newborn that can be used clinically to identify newborn infants at risk and in research to harmonize reporting and definition in the current absence of a gold standard.

Study design An international panel of pediatric leaders in the field of neonatal growth were invited to participate in an electronic Delphi procedure using standardized methods and predefined consensus rules. Responses were fed back at group-level and the list of participants was provided. Nonresponders were excluded from subsequent rounds. In the first round, variables were scored on a 5-point Likert scale; in subsequent rounds, inclusion of variables and cut-offs were determined with a 70% level of agreement. In the final round participants selected the ultimate algorithm.

Results In total, 57 experts participated in the first round; 79% completed the procedure. Consensus was reached on the following definition: birth weight less than the third percentile, or 3 out of the following: birth weight <10th percentile; head circumference <10th percentile; length <10th percentile; prenatal diagnosis of fetal growth restriction; and maternal pregnancy information.

Conclusions Consensus was reached on a definition for growth restriction in the newborn. This definition recognizes that infants with birth weights <10th percentile may not be growth restricted and that infants with birth weights >10th percentile can be growth restricted. This definition can be adopted in clinical practice and in clinical trials to better focus on newborns at risk, and is complementary to the previously determined definition of fetal growth restriction. *(J Pediatr 2018;196:71-6).*

F etal growth restriction is a common pregnancy condition in which the fetus does not reach his or her biological growth potential, most often because of placental dysfunction.[1] Studies often do not differentiate between small-for-gestational-age (SGA) fetuses and fetal growth restriction, even though the 2 terms are not synonymous. SGA is a statistical definition of a deviation of size measurement, with the 10th percentile as the most commonly used threshold. An SGA fetus may be healthy, whereas pathology of growth is implicit in a diagnosis of fetal growth restriction. In an attempt to better identify fetal growth restriction (and, thus, fetuses at risk), a 2016 Delphi procedure led to new criteria for the antenatal diagnosis of fetal growth restriction that included abnormal Doppler flow profiles in addition to the biometrical measures that had been used historically.[2]

Identifying SGA, let alone fetal growth restricted babies in the antenatal period, is a major challenge in obstetrics with up to 80% not detected before birth.[3] In these undetected patients, the diagnosis must be made after birth.[4-7] No agreed definition, nor uniform term for growth restriction in the newborn exists. As in the antenatal period, there is a fundamental distinction between a birth weight that is SGA and an infant with growth restriction yet, in most studies growth restriction in the newborn is conflated with SGA.[8,9]

A consensus definition of growth restriction in the newborn would help to identify newborn infants at risk for poor outcome, facilitate future research, aid in the verification of antenatal diagnoses of fetal growth restriction and facilitate the comparison of different cohorts. The purpose of this study was to reach consensus on a clinically applicable definition of growth restriction in the newborn, building on the recently established antenatal definition of fetal growth restriction. To build broad support for a new definition, a Delphi survey was conducted among experts in the field of growth restriction of the newborn.

Methods

A Delphi procedure is a systematic interactive group communication process with multiple rounds where a series of structured statements are revised and fed back

SGA	Small for gestational age

to the participants in increasing detail until consensus is reached. This technique helps to minimize confounding factors present in other group-response methods. It is the instrument of choice to reach consensus in a panel of experts when there is the lack of a gold standard and the research question cannot be answered with scientific evidence alone.

For the expert panel, we invited published neonatologists who were recognized as leaders in the field as well as experts recommended for inclusion by fellow expert panel members. We aimed for global expertise. Sample sizes for Delphi studies are variable. In this study, we targeted a sample size of 30-100 because this would be small enough to only include true experts and maintain speed in the process, and large enough to ensure representative pooling of judgment.[10] Selecting only experts increases the likelihood that variables are selected on their scientific weight rather than opinion. Votes of all members of the expert panel were weighed equally. Responses were fed back to the panel semi-anonymously, at a group-level, and presented in the subsequent rounds. Nonresponders were excluded from subsequent rounds of the survey.

Data Collection

An electronic Delphi survey was performed through the online tool Limesurvey v 2.50 (LimeSurvey GmbH Survey Services and Consulting, Hamburg, Germany). A unique link to the questionnaire was sent to the members of the expert panel for each round. In each round, the results of the previous round were fed back to the panel. Nonresponders received a reminder email after 2 weeks and were contacted by phone after 3 weeks. There was an option to withdraw from the procedure at all times. In every round, the participants had the option to provide suggestions for the definition and regarding the procedure.

Based on a literature review, potential variables were presented for the definition of growth restriction in the newborn. The panel was asked to rate the variables on a 5-point Likert scale (1: very unimportant; 2: unimportant; 3: neutral; 4: important; 5: very important). In addition to the variables presented in the first round, the panel was asked to suggest additional variables for the definition. These variables were discussed by the Delphi team (the authors) for further voting in the next round.

In the second round, first-round variables that scored a median of 4 or 5 on the Likert scale were presented for confirmation for inclusion in the definition. Variables that scored a median of 3 or lower were presented for agreement for exclusion. In this process, a predefined 70% agreement was necessary for inclusion. The additional variables that were suggested by the panel in the first round also were presented and the panel was asked to rate these on the 5-point Likert-scale.

First-round variables with a median score of 4 or 5 were presented for voting for their weight in the definition. The panel was asked if the variable should be a solitary and/or a contributory variable if ultimately accepted. Solitary variables were defined as those that were sufficient to diagnose growth restriction in the newborn. Contributory variables were defined as those that that were used for diagnosis only in combination with other variables. A variable could be selected as both a solitary and a contributory variable, with the distinction that different cut-off values would apply. The experts were asked to vote separately for cut-off values for solitary and contributory variables.

In the third round, variables that scored between 60% and 70% agreement for inclusion were brought back for verification of final rejection. Confirmation for cut-off values of accepted variables was requested, with a 70% threshold for agreement. Variables that had been suggested by the panel and introduced in the second round followed the same procedure to reach consensus about rejection or acceptance as the original variables in the first round.

In the last 2 rounds, possible algorithms for the definition were presented to the expert panel. The algorithm that received the most votes was considered to be the consensus based definition for growth restriction in the newborn.

Results

Of the 122 experts invited to participate in this Delphi procedure, 57 (47%) joined the expert panel in the first round. A total of 45 panel members completed all 5 rounds, giving an overall participation rate of 79% (45/57) (**Figure 1**; available at www.jpeds.com). **Table I** shows the characteristics of the experts in our expert panel.

In the first round, we presented a total of 27 variables, and an additional 10 variables were suggested by the panel. Of these, 3 variables received a median Likert-5 (very important). Eight scored a median of 4 (important) in the first round of voting and were brought back for consensus on acceptance (**Figure 2**). Ultimately, a total of 9 variables were accepted for the definition (**Table II**).

The panel voted that all biometric measures should be measured on sex-specific growth charts (91%). There was agreement for excluding the presence both of chromosomal and congenital anomalies from the definition (**Table II**), with 72%

Table I. Demographic characteristics of the 57 experts on growth restriction in the newborn who responded to the survey

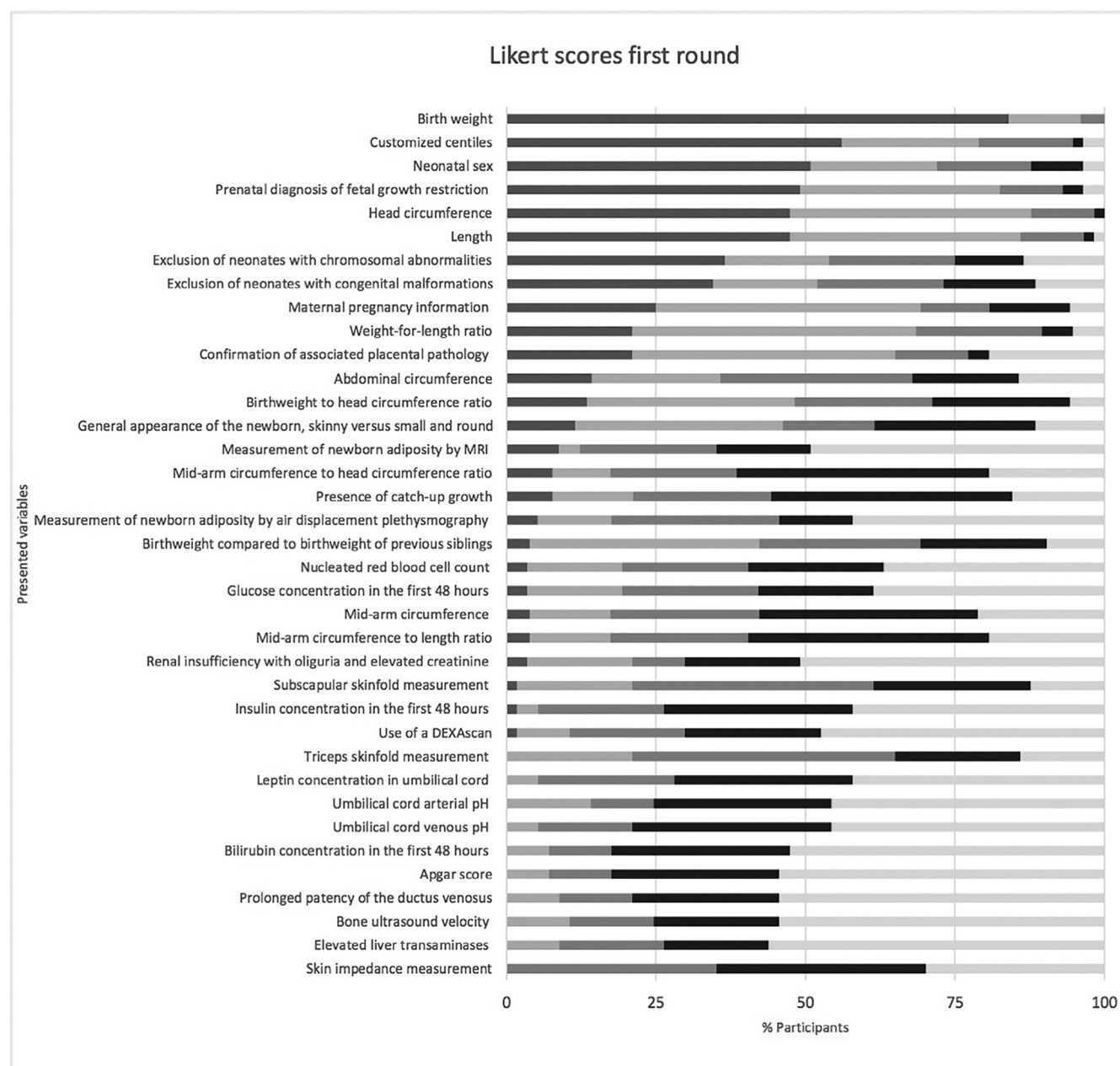| Characteristics	n (%)
Sex	
Male	32 (56)
Female	25 (44)
Region of practice	
Europe	31 (54)
North America	11 (19)
South America	1 (2)
Asia/Oceania	14 (25)
Level of experience	
Professor	30 (53)
Assistant/associate professor	13 (23)
Consultant	13 (23)
Trainee	1 (2)
Level of care	
Secondary care	6 (11)
Tertiary care	51 (89)

Figure 2. Importance of literature-based variables for defining growth restriction in the newborn, rated using a 5-point Likert scale; 1, very unimportant (□), 2, unimportant (■), 3, neutral (■), 4, important (□), and 5, very important (■). On the y-axis are the variables, and on the x-axis the percentage of the participants presented.

and 74% agreement that the definition should be applicable for newborns with chromosomal abnormalities and congenital anomalies. Ultimately, 1 variable was identified as solitary and 5 as contributory variables (**Table III**).

The final rounds were used to come to consensus on the algorithm (**Table III**). Consensus was reached that a birth weight <10th percentile was not mandatory to diagnose growth restriction of the newborn (consensus score 82%). For example, a neonate with a length <10th percentile, maternal hypertension during pregnancy, a prenatal diagnosis of fetal growth restriction and a birth weight >10th percentile would be defined

as growth restricted using this new consensus definition. A majority of the participants voted that 3 out of 5 contributory variables are needed to diagnose growth restriction in the newborn (**Table III**).

Discussion

Using the Delphi procedure, we were able to establish a consensus definition for growth restriction of the newborn that is not solely based on birth weight below a certain percentile, but also incorporates other fetal and neonatal variables

Table II. Ultimately accepted and rejected variables for the consensus definition of growth restriction in the newborn

Accepted variables	Agreement	Rejected variables
Likert 5		Length to weight ratio
Birth weight on population based charts		Subscapular skinfold measurement
Birth weight on customized charts		Triceps skinfold measurement
Sex		Skin impedance measurement
Likert 4		Apgar score
Head circumference	91%	Umbilical cord arterial pH
Length	85%	Umbilical cord venous pH
Prenatally diagnosed growth restriction (according to the previously determined definition[2])	87%	Blood glucose concentration in the first 48 h
Maternal pregnancy information	75%	Serum bilirubin concentration in the first 48 h
Exclusion of neonates with chromosomal abnormalities	74%	Plasma insulin concentration in the first 48 h
Exclusion of neonates with congenital anomalies	74%	Leptin concentration in umbilical cord blood
		Elevated liver transaminase concentrations
		Renal insufficiency (oliguria and elevated plasma creatinine concentration)
		Prolonged patency of the ductus venosus
		Nucleated red blood cell count
		Bone ultrasound velocity
		Use of a Dexa-scan
		Measurement of newborn adiposity by magnetic resonance imaging
		Measurement of newborn adiposity by plethysmography
		Confirmation of associated placental pathology
		Presence of catch-up growth
		General appearance of the newborn, skinny vs small and round
		Birth weight to head circumference ratio
		Mid-arm circumference
		Mid-arm circumference to length ratio
		Mid-arm circumference to head circumference ratio
		Birth weight compared with birth weight of previous siblings

The percentage of agreement for acceptance is presented for accepted variables that scored a Likert 4 (important) in the first round.

relevant to growth. It has been customary to define growth restriction in the newborn as a birth weight that is SGA. Using an SGA definition, infants who are small but healthy may be subjected to unnecessary interventions. In addition, growth-restricted infants who have a birth weight above the 10th percentile may be falsely classified as normally grown.[11] Correct identification of growth restriction may lead to improved surveillance and adequate treatment of complications such as hypoglycemia and hypothermia. This may avoid a "second hit" over and above the intrauterine starvation, thereby improving long-term outcomes.[12,13] Accurate diagnosis in the newborn is also important for correlation with a prenatal diagnosis of fetal growth restriction. Thus, an accurate definition of growth restriction in the newborn is relevant both for clinical and scientific purposes.

Table III. Final consensus definition of growth restriction in the newborn

Final consensus definition growth restriction in the newborn (% agreement)

Birth weight less than the third percentile on population-based or customized growth charts (86%) or at least 3 out of 5 of the following:
- Birth weight <10th percentile on population-based (78%) or customized growth charts (94%)
- Head circumference <10th percentile (82%)
- Length <10th percentile (82%)
- Prenatal diagnosis of fetal growth restriction (88%)
- Maternal pregnancy information (eg, hypertension or pre-eclampsia) (75%)

Agreement of the panel for including the variables as solitary and/or contributory is presented.

Variables other than birth weight and size measurements have been reported in previous studies to aid distinction between SGA and growth restriction in the newborn, including: signs of malnutrition of the newborn by skinfold measurements; pregnancy information, such as hypertension or pre-eclampsia; diagnosis of fetal growth restriction during pregnancy; and serum markers that indicate poor nutritional status during pregnancy.[14-16] Many of these variables have not been implemented in practice for defining growth restriction, largely for reasons of applicability and costs. This the first consensus-based definition for growth restriction in the newborn that includes prenatal information. This is the first international consensus definition of growth restriction in the newborn.

The strength of a Delphi procedure is highly influenced by the selection of experts for the panel. Although the overall participation rate was less than 50% of the invited experts, those who entered the questionnaire phase of the procedure had a high level of expertise and attrition was low, as 79% completed the process. We were able to include many academic pediatricians: 75% of the panel described themselves as professors or associate professors. We only included experts with a special focus on growth restriction in newborns. We chose to invite predominantly pediatricians in this procedure. Although this might be a source of bias, pediatricians are most familiar with clinical implications and variables used for newborns.

We aimed for global participation and invited experts from all continents, but in the final panel there was an underrepresentation of Africa and South America. This reflects the geographical distribution of research reports on the topic.

The fact that the panel suggested 10 variables to the definition suggests that the panel members were engaged and critical. The free text answers revealed that rejected variables were not included in the definition mostly because of lower weighting of currently available evidence. The participant panel made some decisions that needed clarification, and discrepancies were resolved by careful adherence to the procedure with group-feedback and the predefined consensus rules. For example, a head circumference <10th percentile was accepted as a contributory variable. Asymmetrical growth can be an indicator for brain sparing, which means that the head circumference is large in comparison with other size measurements, especially the abdominal circumference. A small head circumference can be a symptom of a pathologic growth process, as might a disproportionately large head circumference.[17]

Variables that indicated asymmetrical growth were rejected by the panel. Although widely applied in clinical practice, the weight-for-length ratio was not voted into the definition. Confirmation of placental pathology also was rejected by the panel, although placental histology can identify a pathological process. Birth weight is strongly correlated with placental weight, and abnormal birth weight/placental weight ratio can indicate growth restriction.[18]

Both population-based and customized percentiles for birth weight were accepted in the definition. Customized growth charts are population growth charts that have been adjusted using statistical modeling for factors predicting term birth weight such as maternal height and weight or ethnic group.[19] When customized fetal percentiles are used for the diagnosis of fetal growth restriction, the birth weight also should be plotted on customized percentiles. It is important to note that the diagnosis of fetal growth restriction does not necessarily diagnose growth restriction in the newborn, but correlation of these indicators can be used to evaluate tools that are used for antenatal detection of fetal growth restriction. Customized charts are based on the principle that a genetic smaller couple would also have smaller children. Ethnicity, which is not synonymous to a biological identity, is one of the variables used in customized growth charts. The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) project study has shown that ethnic background does not influence healthy fetal weights as much as the variation within populations.[20] Also, genetic studies show only a limited relationship between genetic factors and birth weight.[21] Nevertheless, customized charts continue to be used worldwide. In the previously developed definition of fetal growth restriction,[2] only population-based percentiles were included. A benefit of including both population-based and customized percentiles in the definition is that the definition is applicable both in institutions that use customized percentiles and in those that do not. This may promote greater uptake of the definition.

Although the definition excludes congenital and chromosomal abnormalities, consensus was reached that the definition should be applicable for this group. This makes the definition broadly applicable in clinical management.

The equal weighing of votes and semi-anonymous approach minimized peer pressure from authoritative individuals. This ensured that collective knowledge was used optimally. Predefined levels for acceptance and rejection were strictly adhered to, and responses were double-checked to avoid misinterpretation of given answers. This also prompted a final fifth round to make absolutely sure there could be no misinterpretation of the results. Because of the additional round, the level of drop-out slightly increased.

For this definition, consensus was reached regarding the fact that newborns with a birth weight >10th percentile can be identified as growth restricted, providing that length or head circumference also is <10th percentile. Birth weight less than the third percentile was included as a solitary variable, and, thus, a lower cut-off value was chosen. This recognizes the fact that extremely SGA newborns have an unfavorable outcome even in absence of other abnormalities.[22]

A Delphi procedure is a method to reach consensus on an opinion-based definition. This means that the definition was not developed as a prediction model for adverse outcome. Its validity should be tested for adverse outcome against other used definitions. This includes testing the importance of use of the 10th percentile selected for biometric variables (apart from birth weight less than the third percentile as a solitary variable) and the use of customized percentile charts in the newborn. When new evidence arises in the future, the procedure should be repeated to update the definition and again establish consensus.

We propose the term "growth restriction in the newborn" to differentiate growth-restriction of the newborn from fetal growth restriction and SGA because although these terms overlap, infants defined by these terms are not the same. Use of a unique term will promote clarity in the categorization of infants, both in clinical practice and research, and will prevent conflation and confusion with SGA. ∎

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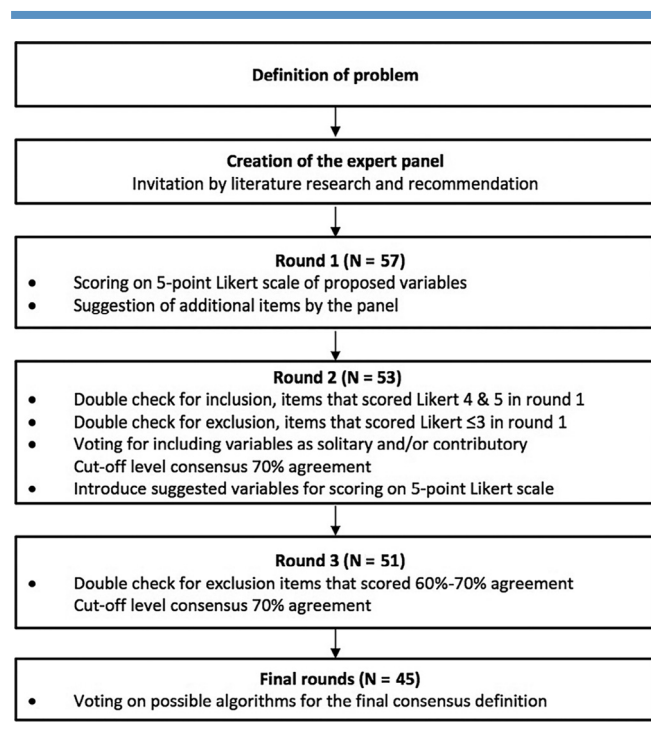
Figure 1. Flowchart of the Delphi procedure. For each step of the procedure the method and participation is presented.