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Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology

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KEYWORDS

- Fetal growth restriction • Fetal overgrowth • Intrauterine growth restriction
- Large for gestational age • Macrosomia • Placental insufficiency
- Small for gestational age

KEY POINTS

- Fetal growth is a dynamic process, whereas fetal size is a static measurement of past growth.
- Although underlying pathology is more common at the extreme ends of the spectrum of fetal size for gestational age, small or large fetal size does not necessarily indicate pathology and a seemingly appropriate size is not a guarantee for physiology.
- The challenge for the coming decade is to evaluate and implement biometrical and functional markers that identify the compromised or overgrown fetus in the complete spectrum of fetal size.

BACKGROUND

Appropriate placental supply of nutrients and oxygen is essential for fetal growth and development, neonatal health, and lifelong well-being. Conversely, abnormal placental supplies resulting in abnormal fetal growth, including fetal growth restriction (FGR) and fetal overgrowth, is associated with mortality and significant risks to health. In medical literature the terms small for gestational age (SGA) and large for gestational age (LGA) are commonly used to describe abnormal growth. Both SGA and LGA are merely defined by the statistical deviation of fetal size in relation to a reference

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population. As such, SGA and LGA describe the variation of size rather than an abnormal condition. Moreover, fetal size is frequently used as a misnomer for fetal growth. Size at a certain point in time (static) is the result of the (dynamic) process of past growth. For prenatal care, risk stratification is essential. In this respect it is important to acknowledge that the size of fetuses can be deviant yet constitutionally small or large and thus healthy, whereas fetuses with seemingly normal size can be growth restricted or overgrown. In this article we describe the differences between abnormal and normal fetal size and growth in terms of history, definition, and epidemiology. The 'placental function and the development of fetal overgrowth and fetal growth restriction' is reviewed in the article of Dumolt et al. in this issue.

Fetal growth depends on maternal factors (including maternal health status, nutritional status, smoking, drug use), fetal factors (genetic make-up), and placental function.[1] The common pathophysiologic mechanism of FGR in an otherwise healthy fetus is placental insufficiency in which, as a consequence of impaired placental function, the fetus fails to reach its intrinsic growth potential.[2,3] Placental-related FGR arises most commonly by poor remodeling of the uterine spiral arteries during early pregnancy resulting in maternal vascular malperfusion, but many other types of causal placental lesions exist.[4] In maternal vascular malperfusion the oxygen and nutrient supply is suboptimal because of high resistance flow in the fetoplacental circulation, reduced villus surface (hypoplasia), secondary damage to shear stress, and placental infarcts.[2] As a result, the placenta is unable to provide the fetal demands for appropriate growth and development throughout pregnancy, resulting in a compromised fetus. During delivery, uterine contractions combined with the impaired placental function predisposes the compromised fetus to hypoxic insults and birth asphyxia because the hypoxic stress of labor is less well tolerated. FGR is a major contributor to perinatal morbidity and mortality and carries an increased risk of long-term neurologic and neurodevelopmental complications.[5–7] Moreover, infants born with FGR are at increased risk to develop cardiovascular disease in adult life.[8,9] These long-term implications of FGR are reviewed in the article 'Short and Long Term Implications of SGA,' from Fung et al, in this issue.

On the other side of the size spectrum, the fetus can also experience growth acceleration resulting in excessive size. The Pederson hypothesis states that fetal overgrowth or macrosomia is a consequence of maternal hyperglycemia (because of obesity or diabetes), which stimulates fetal insulin production.[10] However, macrosomia may occur in pregnancies complicated by maternal diabetes despite rigorous glycemic control. It is clear that a relationship exists between maternal metabolic conditions and macrosomia, but the macronutrient metabolism cannot completely explain the phenomenon because lifestyle modification does not always reduce the incidence of macrosomia.[11] Besides glucose metabolism, several maternal and placental factors can affect the supply and uptake of nutrients to the fetus and contribute to fetal overgrowth, including physical activity, race/ethnicity, uteroplacental blood flow, and placental transfer characteristics.[12–14] Some genetic conditions are associated with overgrowth and should also be considered.[15] Fetal overgrowth is associated with a three-fold higher risk for stillbirth independent of maternal diabetes status and represents a risk factor for maternal and fetal trauma during birth and neonatal morbidity and mortality.[16–18] Overgrown newborns from mothers with and without diabetes are at risk for long-term metabolic complications, such as obesity and insulin resistance.[19,20] It is currently unknown what the effect is on neurodevelopmental outcomes because data are limited and contradictory.[21,22]

HISTORY

The description of abnormal fetal growth has changed throughout history. Initially, before ultrasound was available as a diagnostic modality, the term "premature" was commonly used by pediatricians to describe children who were born with a birthweight less than 2500 g, regardless of the estimated period of gestation. In 1961 the process of intrauterine growth retardation was first described, recognizing that the growth of fetuses could be hampered in utero and that occasionally infants were born with a birth weight far less than the expected birth weight for their gestational age.[23] Because the diagnosis was made postpartum, interventions applied to live born infants in the form of special care and treatment by the pediatrician.

In 1958 the first ultrasound images of the fetus were published.[24] Imaging of the fetus in utero allowed the antenatal detection of certain conditions. In 1971 the first cephalometry graph from 13 to 40 weeks was developed and used to identify the growth-restricted fetus by showing a decline of biparietal diameter growth in the third trimester. Serial cephalometry became a standard method of the assessment of fetal growth in developing countries for many years.[25]

Seven years later the value of routine scanning of the obstetric population for accurate dating was demonstrated. It became key to accurately assess gestational age for the later assessment of fetal growth because fetal weight is inextricably linked to gestational age.[26] At the same time, real-time scanners were developed and became widely available for clinicians. Within a space of one or two decades this terra incognita became charted land as more and more fetal structures were visualized and measured and a great number of reference charts of different planes and organs were developed. In the 1980s the standard fetal biometric measurements for assessing growth included the biparietal diameter, head circumference, abdominal circumference, and femur length, which were incorporated into equations for fetal weight and growth predictions according to the models of Hadlock and colleagues,[27] still commonly used today.

Simultaneously the use of Doppler ultrasound to measure fetal flow velocities was rapidly developed and was increasingly used to evaluate fetal well-being. These technological developments led to real-time imaging and color Doppler studies to be incorporated in obstetric care to assess fetal growth and well-being, install appropriate management, and assess the timing of delivery of the compromised fetus. However, it should be noted that the body of randomized evidence to support the widespread use of these parameters is limited. For example, the Cochrane review addressing the use of any Doppler measurement for any clinical situation only reports on little more than 10,000 women.[28]

Macrosomia has also been recognized in literature for more than 100 years and the adverse outcomes related to cephalopelvic disproportion have been well described. However, unlike the rich history of investigations of cephalopelvic disproportion, little attention was paid to the metabolic aspect of large infants. Historically, only short-term and long-term health outcomes were known of infants born with a large birth weight. For instance, children born in the 1920s who were classified as large at birth seemed to have reduced morbidity and mortality in their seventh decade compared with infants with a lower birth weight.[29,30]

The focus on detecting antenatal LGA became of interest during the last four decades, during which time increased metabolic and respiratory risks of being born LGA became apparent. This transformation from being thought to have advantages to conferring risk for adverse outcomes is likely attributable to a change in population welfare, availability and composition of nutrition, and increase in diabetic

disorders in pregnancy over the intervening decades. Societal events in the past, including world wars and the great depression, were characterized by limited available nutrition to the wider population.[31,32] Fetuses were thus not likely exposed to overnourishment in utero, as shown by lower maternal weight gain and obesity rates in pregnancy during these periods compared with current rates.[33,34] Neonates classified as being LGA back then, were more likely to have been long and lean, whereas in recent decades the excess of nutrition in utero leads to long and chubby neonates.

TERMINOLOGY AND DEFINITIONS

Historically there was considerable inconsistency in terms that were used to classify fetuses who do not reach their intrinsic growth potential. Many terms have been described in literature, of which intrauterine growth restriction/retardation was most commonly used for a long period of time. However, because "intrauterine" refers to a location and not to the fetus who is actually affected by the condition, and the fact that "retardation" suggests that a catch-up is possible, FGR was considered to be a more accurate term.[35] From 2016 onward this term has been widely accepted and is increasingly used in research and clinical practice. Not only has the standardization of the terminology been a hurdle, but the establishment of a widely accepted, standard definition for FGR has also been challenging.

Fetal Growth Restriction and Small for Gestational Age

In the absence of a gold standard there was, and to a lesser extent still is, large heterogeneity in the definition of FGR. FGR has been used interchangeably with SGA for decades, although small is not necessarily too small. The attractiveness of the use of SGA lies in its easy application because it is purely a statistical deviation of fetal size, often the 10th percentile, related to a reference chart to define abnormality.[36] Although there is significant overlap between SGA and FGR, the two terms principally refer to a different condition (**Figs. 1** and **2**). Approximately 40% of babies with a fetal size less than the 10th percentile are constitutionally small and healthy, whereas FGR is a pathologic condition where the fetus is deprived of oxygen (hypoxia) and nutrition (starvation), but the baby is not necessarily small.[37] An appropriate for gestational age (AGA) fetus can be growth restricted, if its intrinsic growth potential was higher. Using SGA as a definition for FGR thus leads to overestimation of FGR among SGA and underestimation or failure to diagnose FGR among AGA. In clinical studies SGA is often used as a proxy for FGR in the absence of other available indicators. The proxy concept makes use of the fact that the smaller the fetal size the higher the chance that growth restriction occurred, but it is important to realize that the population is diluted by healthy SGA fetuses and ignores FGR fetuses who are AGA (see **Figs. 1** and **2**).

A 2016 consensus definition was established by experts in the field for the antenatal diagnosis of FGR through a Delphi procedure.[38] The items that were evaluated for inclusion in the definition included parameters of placental function (eg, Doppler velocimetry measurements, decline in size percentile, and serum biomarkers) in addition to fetal biometric measurements/size. This resulted in the inclusion of abnormal Doppler flow profiles and growth trajectory (50-point decline in estimated fetal weight percentile) in the definition in addition to the biometrical measures that were used historically. This definition therefore allows FGR to be diagnosed in SGA and AGA fetuses. Also, the definition distinguishes between very small (less than the third percentile) and small (between the 3rd and 10th percentile). A fetal size less than the third percentile is an isolated criterion to define FGR at any gestational age because these fetuses are at highest risk for stillbirth and neonatal problems, such as hypothermia and

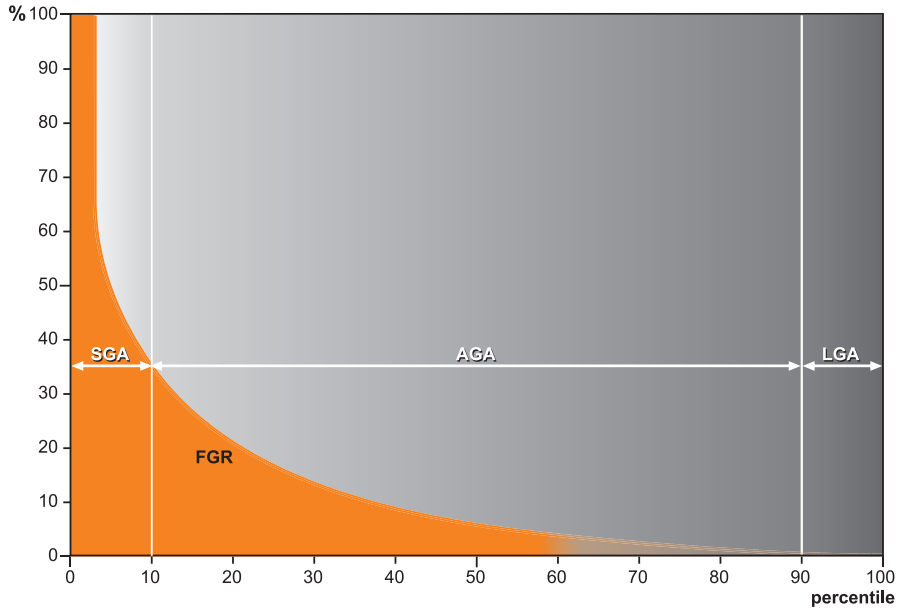

Fig. 1. Schematic depiction of the overlap and difference between FGR and SGA. SGA includes all fetuses with a weight less than the 10th percentile, which is represented in the combined *orange* and *gray* area to the left of the *vertical white line*. FGR represents the *orange* area. The *orange* area fades toward higher growth percentiles because being a little bit growth restricted might not be of clinical relevance and the consensus definition does not apply. AGA, appropriate for gestational age; FGR, fetal growth restriction; LGA, large for gestational age; SGA, small for gestational age. (*Adapted from* Ganzevoort W, Thilaganathan B, Baschat A, Gordijn SJ, Gardosi J. Fetal growth and risk assessment: is there an impasse?; with permission.)

hypoglycemia, regardless of the reason for the severe smallness. It also takes into account that small fetuses with a size between the 3rd and 10th percentile can be healthy in the absence of other indicators pointing toward placental insufficiency as shown in **Table 1**. Using this definition in clinical practice is designed to prevent unnecessary and potentially harmful interventions in the healthy-but-small fetuses and allows the clinician to pick up the compromised AGA fetus and install adequate management. Several studies (among others the DRIGITAT trial [Dutch], Truffle2 trial [European], and RATIO37 trial [Spain]) are ongoing that evaluate the efficacy of adding parameters of placental function to the management algorithm. Results from these trials may validate the theoretic benefit of using a uniform diagnostic definition apart from the obvious advantage of speaking the same language.

Furthermore, the Delphi study definition distinguishes between early and late-onset FGR. The consensus-based agreement is that early onset FGR is diagnosed at or less than 32 weeks and differs from late-onset FGR because of its association with maternal hypertensive disorders, patterns of deterioration, and severity of placental dysfunction.[39] The clinically obvious fetal and maternal manifestations make the identification of fetuses with early onset FGR simple, but this diagnosis poses a serious dilemma to the obstetrician. To solve the problem of the deprived environment the fetus needs to be delivered. However, delivery exposes the neonate to morbidity associated with prematurity, such as respiratory distress syndrome, necrotizing enterocolitis, and neonatal death. Yet, to gain maturity, the fetus should remain in

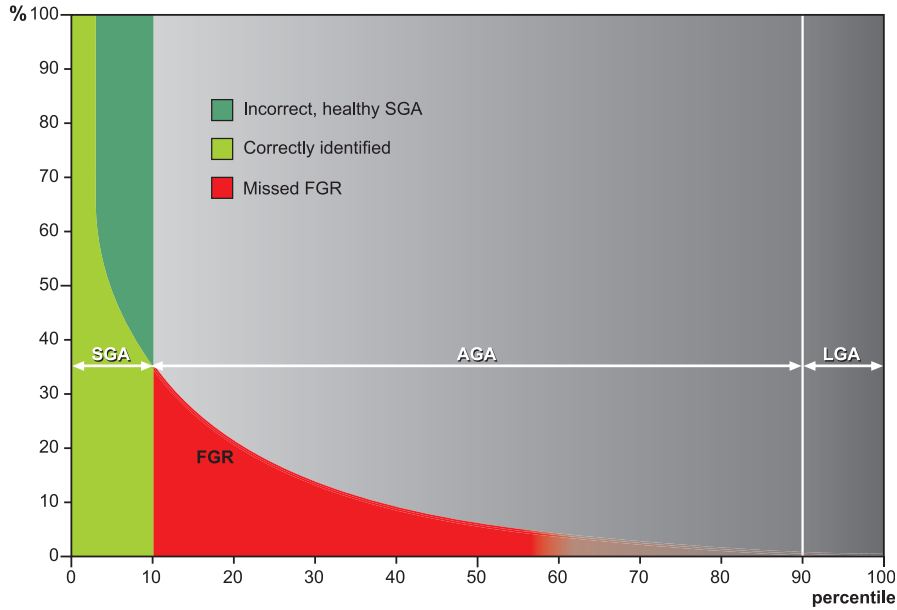

Fig. 2. Schematic overview of the limitations when SGA is used as a definition for FGR. The *dark* and *light green* area represent SGA fetuses. The area highlighted in *light green* represents the SGA fetuses who are correctly identified as being growth restricted. The *dark green* area includes constitutionally small yet healthy fetuses who are thus incorrectly identified as being growth restricted. The area highlighted in *red* represents growth restricted fetuses with a seemingly appropriate size and who will be missed if the definition of SGA is applied. AGA, appropriate for gestational age; FGR, fetal growth restriction; LGA, large for gestational age; SGA, small for gestational age. (*Adapted from* Ganzevoort W, Thilaganathan B, Baschat A, Gordijn SJ, Gardosi J. Fetal growth and risk assessment: is there an impasse?; with permission.)

the deprived environment, risking stillbirth and serious additional morbidity secondary to critical fetal hypoxia because of postponing delivery. "Treat first what kills first," the common medical doctrine, is thus difficult to apply.

Table 1
Consensus-based definitions for early and late FGR in the absence of congenital anomalies

Early FGR: GA <32 wk	Late FGR: GA ≥32 wk
AC/EFW <3rd centile or UA-AEDF	AC/EFW <3rd centile
Or	Or at least 2 out of 3 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 noncustomized centiles.

Abbreviations: 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.

From Gordijn S, Beune I, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound in Obstetrics & Gynecology 2016;48(3):333-39; with permission.

Contrary to early onset FGR, the detection and diagnosis of late-onset FGR is neither simple nor obvious, and late-onset FGR is frequently missed. Fetal sizes can be within normal ranges and the measurable cardiovascular changes are less obvious.[40,41] Fetal reserves to withstand impaired placental function are more limited in advanced gestation and acute hypoxemia (and fetal death) may occur before fetal growth has dropped below the 10th percentile for the population on reference charts.[42] Unlike early onset FGR, management of late-onset FGR is less complex because the fetal organs are more mature and the incidence of serious neonatal morbidity from prematurity is low. Thus, delivery is a more attractive option with less downside than earlier in gestation. Routine ultrasonography in the third trimester, however, is not recommended in low-risk pregnancies because it has not been shown to reduce the incidence of severe adverse perinatal outcomes compared with usual care.[43] The detection and management of FGR is described in the article 'Fetal Growth Curves: Is There a Universal Reference?,' from Grantz et al. in this issue.

FGR in singletons differs from FGR in twins and the diagnosis of FGR in stillborn babies raises specific challenges. Consensus definitions have also been established for selective FGR in monochorionic and dichorionic twin pregnancies, diagnosis of FGR in stillbirths, and also for growth restriction in the newborn.[44–46] To further facilitate standardization in growth restriction studies and enable future studies to compare and pool data between study populations, outcomes and baseline characteristics for clinical trials (known as core outcome sets and minimum reporting sets) were developed for FGR and for feeding intervention studies in growth-restricted newborns.[47–49]

Macrosomia and Fetal Overgrowth

In contrast to FGR, no consensus definition for macrosomia exists, nor have there been efforts to standardize study outcomes. In high-income countries, the most commonly used threshold is an estimated fetal weight or birth weight greater than 4500 g, but a cutoff greater than 4000 g is also frequently used.[50–52] These thresholds are not useful for identifying the preterm overgrown fetus because they are not based on population statistics and unrelated to gestational age. The statistical approach considers any fetus or infant weighing greater than the 90th percentile for gestational age as being LGA. However, it has been suggested to restrict the definition to a weight higher than the 97th percentile, because this more accurately identifies newborns who are at the greatest risk for perinatal mortality and morbidity.[53,54] As with FGR, there will be a group of LGA fetuses who are healthy and may not experience adverse effects of their nutritional status and AGA fetuses who actually have a disproportional incline in growth centiles and may be overgrown but remain undetected because their fetal size and/or birth weight remains lower than the threshold. These overgrown fetuses are at risk for metabolic and respiratory problems just after birth and should be monitored.

As in FGR, macrosomia also confers an increased risk for perinatal asphyxia, although the underlying placental and mechanical mechanisms are completely different. In FGR the oxygen supply is insufficient, whereas in macrosomia it is postulated that hyperglycemia and hyperinsulinemia leads to increased intrauterine oxygen demands, especially in infants of mothers with diabetes.[55] Another contributing factor includes the mechanistic complication of cephalopelvic disproportion (leading to prolonged labor and shoulder dystocia), which increases the percentage of women undergoing operative delivery. To assess the risk for operative delivery and assist in the decision making, a grading system has been developed based on absolute weights independent of gestational age. This system suggests that grade 1

(>4000 g) is useful for the identification of increased risks of labor and newborn complications, grade 2 (>4500 g) is predictive of neonatal morbidity, and grade 3 (>5000 g) is an indicator for mortality risk.[53] Timely delivery based on these absolute weights is an intuitive but unproven approach to prevent adverse outcomes from cephalopelvic disproportion. However, relying on an absolute weight cutoff alone will not adequately identify all overgrown fetuses who are at risk for metabolic adverse outcomes. Research is urgently needed to optimize prenatal identification and clinical management of excess fetal growth.

REFERENCE CHARTS

Parameters reflecting placental function (eg, Doppler indices and serum biomarkers currently under investigation) are gaining more importance in the detection of abnormal growth. Nonetheless, the assessment of estimated fetal weight and birth weight for gestational age, and the expression in percentiles to compare current size with a reference or standard population, will remain a significant element of assessing growth. The use of these percentiles requires an appropriate reference. However, as in all aspects of FGR, there is inconsistency with regard to the reference charts used to determine abnormal fetal weight and birth weight. Different reference charts for fetal growth are extensively described in the article 'Evaluation and management of suspected FGR,' from Bruin et al. in this issue.

EPIDEMIOLOGY

The overall incidence of FGR depends on the definition used, and the population being examined. It is estimated that between 3% and 9% of pregnancies in the developed world, and up to 25% of pregnancies in low- and middle-income countries are affected by FGR. In contrast, the incidence of SGA by definition is around 10% and only partly overlaps with FGR.[56,57] The estimated prevalence of FGR throughout the percentile ranges is shown in **Fig. 1** and emphasizes that the lower the weight the higher the chance that FGR occurred. Also, a significant part, if not 50% of all FGR, occurs in AGA. Factors that influence FGR rates in communities include maternal nutritional status, smoking rates, alcohol and drug use, socioeconomic status, maternal activity, maternal disease, air pollution, and genetic make-up.[57] The incidence of FGR is significantly higher in low- and middle-income countries, and this is mainly attributed to a large number of FGR infants born in the Asian continent, which accounts for approximately 75% of all FGR in the world, followed by Africa and South America.[58] Firm statements regarding incidence and timing of FGR are hampered worldwide because of diagnostic inaccuracy. This is exacerbated by the fact that in developing countries, pregnant women do not receive a standard ultrasound for accurate pregnancy dating. When the gestational age is not known with reasonable certainty, a birth weight cannot be used to determine whether there has been growth restriction. This is a problem even when SGA is used as a proxy for FGR, because this may well be caused by preterm birth. The incidence of FGR in sub-Saharan countries may be higher because contributors to FGR, such as maternal malnourishment, and conditions, such as placental malaria and syphilis, are common.[59]

An epidemiologic distinction between early and late-onset FGR is commonly made. The prevalence of early onset FGR is far less (0.5%–1%) compared with late-onset FGR (5%–10%), but the clinical impact is high because there is a high mortality and morbidity rate.[41] Late-onset FGR is associated with lower mortality and morbidity rates, but causes a large absolute number of adverse outcomes because of its higher

incidence.[41,60] Moreover, approximately one-third of medically indicated late preterm births may be complicated with FGR.[61]

At the other end of the spectrum, the incidence of women giving birth to large infants has increased in the last four decades.[62–66] The current proportion of macrosomia (≥4000 g) worldwide is approximately 9% and 0.1% for birth weight greater than the 5000 g with a wide variation among countries. Variation is influenced by contributing factors, such as genetics, gestational diabetes, and obesity rates.[67] The highest prevalence is found in Nordic countries where around 20% of the newborns have a birth weight at or greater than the 4000 g.[66] In developing countries the prevalence of macrosomia (≥4000 g) is typically 1% to 5% ranging from 0.5% to 14.9%.[68] Similar to SGA the incidence of LGA by definition is 10%. In the absence of a clear distinction between macrosomia, LGA, and overgrown fetuses and also in the absence of an accurate diagnostic tool to differentiate the overgrown fetuses from healthy LGA, little is known about the incidence throughout the percentile spectrum, but it is plausible that the inverted curve of FGR applies (see **Fig. 1**).

DISCUSSION

Because approximately 9% of pregnancies are affected by FGR and another 9% by fetal overgrowth, the clinical and societal impact of abnormal fetal growth is significant. To make matters worse, accurate detection of FGR and fetal overgrowth is challenging technically (ultrasound is imperfect)[69] as in the way we define the compromised and overgrown fetus.

At present there is no effective treatment to reverse the course of FGR and macrosomia except delivery. FGR is probably the condition among the obstetric entities with the greatest variation in clinical practice, in terms of monitoring, management strategies, and gestational age at delivery. Prenatal recognition of FGR remains a major challenge in daily obstetric practice. Current focus of measurements lies on the nutritional component of fetal deprivation because this is inferred from size measurements. By using the expression FGR it is implied that the nutritional component of the deprivation is the biggest threat. However, the most important outcomes, including the devastating outcome of perinatal mortality, are caused by a deprived oxygen status of the fetus rather than starvation and, unfortunately, fetal serum oxygen levels currently cannot be measured. New techniques for in vivo assessment of fetal oxygenation, such as the magnetic resonance blood oxygen level dependent effect, are currently being investigated as part of the National Institutes of Health–sponsored Human Placenta Project.[70]

Similarly, methods to distinguish healthy large fetuses from overgrown fetuses or to identify overgrown fetuses with appropriate weight are lacking, especially in the absence of maternal diabetes. Beyond the obvious obstetric concerns of obstructed labor, detecting the latter group with normal size is necessary so interventions can be developed to mitigate the associated long-term health risks for the overgrown newborn. Future efforts should focus on the development of a more accurate diagnostic approach that considers fetal body proportion, composition, and metabolic characteristics.

SUMMARY

Abnormal fetal growth has been subjected to different terms and definitions, resulting in varying epidemiology throughout history. Gold standards to detect growth-restricted fetuses and overgrown fetuses are lacking. However, knowledge and understanding about both pathologic conditions has improved significantly in the past

years. Better identification of the fetuses at risk, independent of size, is essential to prevent potential harmful interventions in healthy but small fetuses and allow clinicians to appropriately intervene for fetuses with seemingly normal size but who are growth restricted or overgrown.

CLINICS CARE POINTS

- Assessment of fetal growth and defining abnormality is complex. Being of small or large fetal size does not necessarily reflect pathology but puts the fetus at a higher risk and an appropriate size is not a guarantee of normal outcomes.
- Implementation of the established consensus definitions in clinical practice and research facilitates the improvement of accurate identification of compromised fetuses.

DISCLOSURE

The authors S.J. Gordijn and W. Ganzevoort report the in-kind contribution of study materials from Roche Diagnostics for investigator-initiated studies. Author S.E. Damhuis has nothing to disclose.

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