Section 1 Basic Principles

Chapter 1

What Is Optimal Fetal Growth?

Blanka Vasak and Gerard H. A. Visser

Introduction

Normal fetal growth is usually defined as an estimated fetal weight between the 10th and 90th centiles based on population-specific birth weight centiles corrected for gestational age at delivery, parity, and fetal sex. So-called customized growth charts also correct for maternal ethnicity, weight, and length [1]. Such definitions are based on the fact that both impaired and excessive fetal growth result in an increased risk of perinatal morbidity and mortality. Indeed, in small for gestational age (SGA) fetuses, defined as a birth weight below the 10th centile, there is an increased risk of intrauterine fetal death across all gestational ages [2,3] compared with non-SGA fetuses, with the highest risk in infants with a birth weight below the 3rd centile [4]. Large for gestational age (> 90th centile, macrosomic) fetuses are at risk of labor complications and thus also of increased perinatal morbidity and mortality [5,6]. However, with a focus on too small or too big, it may be forgotten that the majority of perinatal (and especially antepartum) deaths occurs in fetuses with a "normal" weight. Moreover, the use of population-based fetal growth charts assumes that optimal size at birth for outcome is at the 50th centile.

In this chapter, optimal fetal growth/size for perinatal and long-term survival is reviewed in relation to birth weight centiles at birth. The clinical consequences are discussed.

Fetal Growth/Size and Short-Term Perinatal Survival

Several studies have been conducted on perinatal survival in relation to birth weight centiles. A study conducted in Newcastle in the United Kingdom using Z-scores for distribution of birth weight showed that the lowest stillbirth rate and infant mortality occurred in infants with a Z-score of +1, both between 1961–80 and 1981–2000, a period over which the overall stillbirth rate fell in that region of the UK from 23.4 to 4.7 per 1,000, respectively [7]. In a larger nationwide study in Norway, the lowest mortality was found for a birth weight Z-score between +1 and +2 [8]. Similar results were recently published from Australia [9] and Scotland [10]. In the latter study regarding 780,000 births, the lowest antenatal mortality occurred in fetuses with a birth weight in between the 90th and 97th centiles and in cases with unknown cause, antenatal hemorrhage, or maternal hypertensive disease. In cases of maternal diseases, including diabetes, the stillbirth rate was lowest in fetuses with a weight around the 20th centile. In the most recent study from The Netherlands, distribution of perinatal mortality according to birth weight centile and gestational age was studied in more than 1 million births from singleton pregnancies and non-malformed fetuses between 28 and 43 weeks gestation [11]. There were 5,075 (0.43%) perinatal deaths. The highest mortality occurred in infants with a birth weight below the 2.3rd centile (25.4/1,000 births), and the lowest mortality occurred in infants with birth weights between the 80th and 84th centiles (2.4/1,000 births), according to nationwide birth weight charts. Antenatal deaths were lowest with birth weights between the 90th and 95th centiles. Data were almost identical when analysis was restricted to infants born after 37 weeks or at 39–41 weeks only (Vasak et al.; Figure 1.1) [11]. In term gestations, 63% of perinatal deaths and 61% of antepartum deaths occurred in infants with a so-called normal weight between the 10th and 90th centiles. The majority of perinatal deaths occurred during the antepartum period (72%).

Data on cerebral palsy are also in line with the mortality figures; the lowest prevalence of cerebral palsy by Z-score of weight for gestation was found in infants with a Z-score of +1 [12].

These studies indicate that optimal fetal weight for intact perinatal survival occurs at a much higher

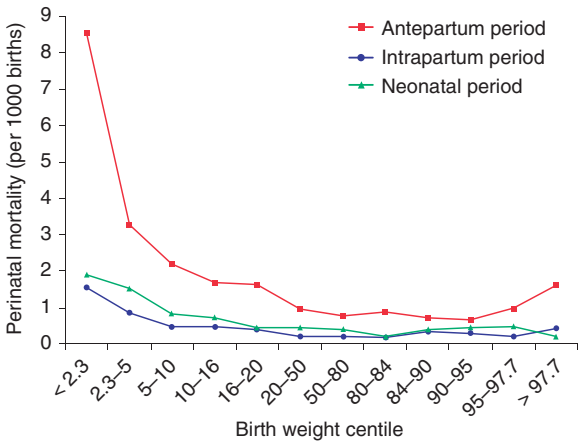

Figure 1.1 Perinatal mortality according to birth weight centile for babies delivered between 39 and 41 weeks' gestation in The Netherlands during 2002–8.

centile than the 50th centile. In fact, perinatal mortality of fetuses with a weight at the 50th centile is 34% higher than that of fetuses weighing in between the 80th and 84th centiles [11]. The lower "optimal weight" for intrapartum and neonatal survival (80th–84th centile), as compared to that of antepartum survival (90th–95th centile), may be explained by intrapartum complications in infants at the highest birth weight centiles. Regarding antepartum survival, it may be concluded that "the bigger the better" [8] and that most infants have a birth weight below optimal for perinatal survival, which seems illogical from an evolutionary perspective. However, mothers also have to survive, and the relatively small pelvis associated with bipedalism and the large human fetal head constitute major obstacles for uncomplicated childbirth. It may therefore well be that maternal factors restrain fetal growth that is below optimal for perinatal survival. In other words, a conflict takes place between mother and fetus, with a compromise as a result. Given the fact that during the whole existence of mankind women have looked after their offspring, such a compromise may have resulted in a net benefit for the infants at the end. In developing countries, this can nowadays still be seen in the poor survival of children whose mothers have died during or directly after childbirth [13,14]. These data also nicely fit with recent Doppler findings of blood flow redistribution to the fetal brain. In a large cohort of third trimester fetuses, it was shown that the cerebro-placental ratio (CPR) increased progressively with increasing fetal weight centiles whereby signs of redistribution were only consistently absent in cases of an estimated fetal weight > 90th centile [15]. The association between CPR and weight centiles has recently been confirmed in another study [16].

Fetal Growth and Long-Term Survival

The high birth weight (centile) favorable for perinatal survival is also associated with reduced risk of later non-communicable disease. Studies on the Developmental Origins of Health and Disease (DOHaD) concept have shown that birth weight is inversely related in a graded manner to risk of later cardiovascular and cerebrovascular death [17–20] and to impaired glucose tolerance and Type 2 diabetes [21]. Thus, in historical studies in the UK, the lowest risks of adult cardiovascular disease (CVD) were found in infants weighing around 4 kg at birth, approximately the 90th centile at 40 weeks of gestation [17,19]. A high birth weight, indicative of absence of intrauterine growth restraint and resulting in a low perinatal mortality, therefore is also favorable for long-term health.

Clinical Implications

Early stillbirths are generally SGA [3]. So at early gestation, identification of SGA fetuses remains of utmost importance. After approximately 32 weeks of gestation, the majority of stillbirths concerns appropriate for gestation infants [3,11]. Identification of third trimester (SGA) infants remains important since mortality may be reduced when these fetuses have been identified as being small [22,23] (see Chapters 22 and 23 of this volume). However, identification of infants at risk of stillbirth who have a weight within the normal range may prove difficult. Factors to be assessed may include:

a) Maternal characteristics. In a study from Norway, it has been shown that being SGA increases the risk for stillbirth sevenfold [24]. Other independent risk factors for stillbirth were maternal age > 35 years (RR 4.1), maternal body mass index > 25 (RR 4.7), and maternal education < 10 years (RR 3.5). A combination of risk factors resulted in a dramatic increase in stillbirth risk. For instance, SGA in combination

with maternal overweight resulted in an RR of 71 (univariate analysis). Confidence limits were large due to the relatively low number of inclusions (95% CI: 14–350), but these data indicate that a combination of risk factors may increase detection of fetuses at risk. Such a risk assessment might be made around 36–8 weeks, and if more than one of these variables is abnormal, delivery may be indicated. However, the latter policy has to be tested, preferably in a randomized controlled study.

b) Uterine artery pulsatility index (UtA-PI). An increased UtA-PI at 20 weeks of gestation has been found to be associated with an Odds ratio of 6.8 for third trimester stillbirth, after correction for maternal weight, body mass index, and smoking, with 50% of all stillbirth cases occurring in the 10% with an abnormal UtA-PI [25].

c) Cerebro-placental ratio (CPR). In preterm SGA fetuses, an increased PI in the umbilical artery identifies those at highest risk for perinatal death [26]. However, near term the diagnostic value of this tool is limited and significant changes are a late sign of impairment. However, subtle changes may be detected by using the ratio between middle cerebral artery and umbilical artery PI. In SGA term fetuses, it was found that a reduced CPR was associated with a poorer outcome than in cases with a normal ratio [27]. In a high-risk population of term fetuses, pH at delivery was lower in cases with an abnormal CPR, both in SGA and in normally grown fetuses [28]. This suggests that the CPR might be used to identify fetuses at risk of becoming hypoxemic, not only in SGA, but also in fetuses with a weight within the "normal" range. However, in a recent normal population of more than 6,000 fetuses assessed at around 36 weeks of gestation, no predictive value of the CPR was found regarding caesarean section for fetal distress, umbilical artery pH at birth, or Apgar score [16]. Reduced CPR immediately prior to delivery was associated with an increased risk of delivery by emergency caesarean section [29]. The value of the CPR in identifying the risks of intrauterine death or asphyxia in normally grown fetuses is therefore still uncertain.

d) Longitudinal fetal growth assessment. Single third trimester measurements of fetal growth have not been capable of identifying third trimester SGA reliably [30]. Detection of infants at risk with a weight within the normal range may only be possible by longitudinal growth assessment to identify decreasing growth velocity. Such studies are taking place at this moment.

e) Reduced fetal movements (RFM). RFM remain an important sign of fetal compromise, given the limited predictive values of the other assessment techniques. RFM have been associated with abnormal placental morphology [31]. A study from Norway has shown that structured information given to the mother at around 18 weeks of gestation on the importance of RFM may result in a more than 50% reduction of third trimester fetal deaths in nulliparous women [32].

f) Integrated risk assessment. Identification of fetuses at risk for intrauterine death is difficult. On the one hand SGA fetuses should be detected, and on the other hand the larger group of apparently normally grown fetuses at risk of dying in utero should be identified. This will require integrated risk models, including maternal characteristics (BMI, age, socioeconomic situation), Doppler measurements of the maternal and feto-placental circulation, fetal growth assessment, and measurement of biochemical markers of placental function. Most likely a contingent screening is required (e.g., to identify decreasing fetal growth velocity). Models must be first exhaustively tested in the population to which they will be applied, to obviate the risk of unnecessary intervention.

Conclusions

Optimal fetal growth for perinatal and long-term survival is a growth resulting in a birth weight in between the 80th and 90th centiles. This implies that the majority of infants will have a suboptimal fetal growth. Evolutionarily, this may be explained by a compromise between maternal survival, which will be lower in large fetuses, and fetal survival. In the third trimester of pregnancy, the majority of intrauterine deaths occurs in fetuses with a weight within the normal range. Identification of the fetuses at risk will be difficult and requires an integrated risk assessment including sequential measurements.

Key Points

- The majority of perinatal deaths occurs in fetuses with a weight within the normal range.
- Optimal fetal growth for perinatal and long-term survival is a growth resulting in a birth weight in between the 80th and 90th centiles.
- Identification of fetuses at risk, especially those with a weight within the normal range, remains difficult and requires an integrated risk assessment including sequential measurements.

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Section 1 Basic Principles

Chapter 2

Definition of Fetal Growth Restriction and Uteroplacental Insufficiency

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Introduction

To understand any discussion, it is of paramount importance to be consistent in defining the discussed subject. This is a particular problem when dealing with impaired fetal growth. Even though the measurement of fetal size has significant challenges of its own, comparing this measurement to previously observed variation in a population provides a comparison to a reference standard that is measurable and agreed upon. However, "smallness" or being small for gestational age (SGA) in itself is not the item of interest, but rather "pathological smallness of uteroplacental origin" – otherwise termed fetal *growth restriction* (FGR). FGR is a functional problem of unmet fetal need, and the definition should include descriptions of pathological functional processes.

FGR is a descriptive term for a pathological process and not easily defined. FGR can be described as the process where a fetus that has a certain growth potential based on genetic criteria is limited in its growth because of a pathological environmental influence. It is distinct from the term *small for gestational age* (SGA). SGA is much easier to define because it is a statistical deviation from a population reference standard.

As such, many studies erroneously assume that SGA is synonymous with FGR. Because overlap between the two subgroups is significant, this is a tempting strategy that does still come up with results. However, this assumption may attenuate or even obscure important associations or identify spurious associations that may be misleading. In this chapter, the pathophysiology of FGR is shortly discussed and FGR is defined by functional parameters and compared to definitions of SGA.

Pathophysiology of Uteroplacental Insufficiency

The classical pathophysiological concept of FGR is that of poor placentation. In early pregnancy, the uterine spiral arteries are invaded by the developing endovascular trophoblast, resulting in uteroplacental blood circulation. In adequate placentation, the uterine spiral arteries are remodeled into dilated inelastic tubes without maternal vasomotor control. This is a process that probably occurs between 8–18 weeks of pregnancy [1]. The physiological consequence of vascular remodeling is that a low-resistance unit is accomplished that allows liberal blood flow. If this process is imperfect, the disturbed remodeling will not change the high-resistance unit adequately, leading to the maintenance of high uteroplacental vascular resistance. This can be measured in early pregnancy, by Doppler measurements of the upstream uterine artery. High pulsatility indices already in the first trimester reflect an increased risk for clinical disorders related to poor placentation: fetal growth restriction and preeclampsia [2,3].

The pathophysiological pathways for this defective placentation process are plentiful and none is completely explanatory in itself. Immunological factors, endogenous vascular factors, and thrombogenic factors have been shown to have consistent relationships with the process and the clinical phenotype [1]. Most of these theories were derived from work restricted to cases of preeclampsia. Since most of the pathophysiology on the placental level is shared between hypertensive disorders of pregnancy and FGR, some of this knowledge can be extended into the field of FGR.

Poor placentation is particularly associated with early-onset phenotype of both preeclampsia and FGR. Before 34 weeks' gestation, most women presenting with maternal hypertensive disorders will also have FGR – and both conditions share comparable placental pathology [4]. At later gestations, this association becomes less obvious – at or near term, neonates from mothers with preeclampsia are usually not growth-restricted [5]. Thus, both late FGR and late preeclampsia require another explanation. For this, some hypothesize a secondary placental cause based

on the evidence that slowing of placental growth in term pregnancy is more prominent in the largest placentas [1]. This finding suggests that placental growth has a physical limit, depending on size and not gestational age. At term, the placenta apparently becomes more "crowded," compromising intervillous perfusion and predisposing to dysfunction – leading to a similar process as in early-onset FGR and preeclampsia. For the maternal phenotype, the most likely etiology is maternal constitutional susceptibility, among which are (cardio)vascular dysfunction [6,7] and an excessive immunological response [8]. These findings, negating early placentation disorders as an explanation for late FGR and late preeclampsia, are consistent with the finding that the placental pathology in term FGR and preeclampsia is not very discriminative between cases and normal controls [9]. Since term fetuses have less placental reserve capacity, the interval between onset of the disease and subsequent adverse outcome is shorter. Both hypotheses explain why late-onset FGR is less easy to predict and harder to distinguish from pregnancies with normal growth.

In conclusion, it is likely that there are two main routes to FGR based on placental dysfunction or insufficiency. The first is the classic concept of defective placentation leading to early-onset overt FGR, which is easily diagnosed because of abnormal fetal size and related biophysical/biochemical parameters. The second concept is that of a maturational process leading to placental hypoperfusion and late-onset FGR that is difficult to diagnose because size and accompanying parameters may not be severely abnormal. Combinations of the two can also occur, explaining intermediate phenotypes.

Definition of SGA

SGA is a defined statistical deviation from the population standard. Antenatal measurement variation for fetal, maternal, or observer reasons does introduce some uncertainty, but the comparison with a reference standard is a rather uniform practice. Reference ranges (as opposed to standards) are population curves constructed from observed fetal dimensions on ultrasound and birth weights. These ranges are usually normally distributed, because the majority of cases do not have pathological growth. However some skewing may occur, particularly at lower gestational ages and at the lower margin of the curve, where pathological growth is more common. When the charts are constructed prospectively using strict criteria to define an "optimal" population, then "optimal" reference standards are created, such as in the recent Intergrowth-project [10].

In obstetric populations, centiles usually describe the position of a fetus/newborn within the curve. Within a perfectly normally distributed population, this has large commonalities with the more statistically correct standard deviation scores (SD or z-scores) where the position is expressed as the number of standard deviations the fetus/newborn is from the mean. An alternative option, less statistically correct but with some clinical and statistical advantages, is the weight ratio – the ratio between the observed weight and the median weight for the gestational age (multiples of the median or MoMs).

Defining SGA is a dichotomization within the chosen curve. In most studies, the 10th and 90th centiles are chosen as the cut-off, defining those below the 10th centile as SGA. Other commonly used cut-offs are the 5th centile or the 2.3rd centile. With lowering of the chosen cut-off, the concentration of pathology within the defined group increases. However, because there are no thresholds to distinguish normal growth from pathological growth, no specific cut-off will define a totally abnormal or normal population correctly [11].

Definition of FGR

The definition of FGR is more difficult because the gold standard is not defined. Thus, all attempts focus on defining the process where a fetus with a certain genetic growth potential is limited in its growth because of a pathological environmental influence. This pathological influence is frequently termed *uteroplacental insufficiency* to express that the limitation is located in the transfer of nutrients and waste substances across the placenta. Thus, it is abnormal placental function that needs to be defined accurately in FGR. There are several candidates of measurable parameters to signal impaired placental function and abnormal fetal growth. These parameters have different statistical time relationships with the occurrence of fetal distress (Figure 2.1) [12].

Abnormal Umbilical Artery Doppler Indices

An abundance of studies has demonstrated the relationship between uteroplacental insufficiency and the consequent increased impedance in the uteroplacental

vessels and in the umbilical artery. These changes are strongly associated with hypoxemia and poor perinatal outcomes, and the associations can be described in a temporal fashion [13–15]. Among the earliest phenomenon in early-onset FGR are abnormal umbilical artery flow velocity waveforms as measured with Doppler ultrasound [12,16]. It is described quantitatively by increased pulsatility index and qualitatively by absent or reversed end-diastolic (ARED) flow. Its occurrence is specific for very early-onset fetal growth restriction and not for term or late preterm growth restriction. This phenomenon is the tip of the iceberg with respect to the fetal hemodynamic status, because an estimated 70% of the placental vascular bed is obliterated or dysfunctional before ARED flow is seen. Thus, in later gestational ages, umbilical artery waveforms do not typically become abnormal before fetal distress occurs, because fetuses have less placental reserve and fetal distress will already have become apparent. Other Doppler studies that may indicate increased impedance of the fetal central vasculature include the aortic isthmus and the descending aorta [17].

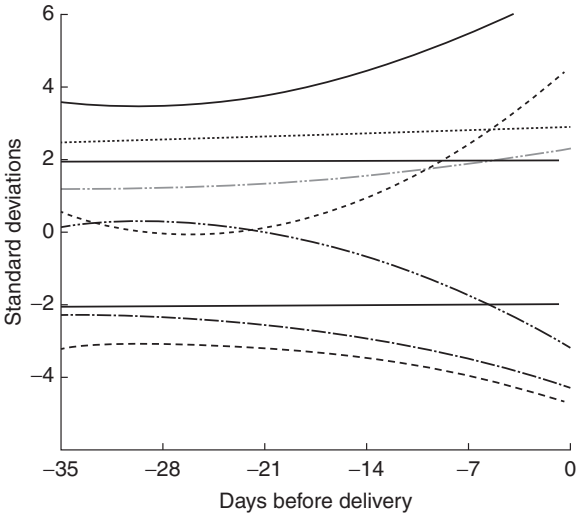

Figure 2.1 Trends over time of variables in relation to time before delivery and reference ranges (±2 SD) for Group 1 (fetuses delivered before or at 32 weeks of gestation). ——, umbilical artery; – – –, ductus venosus; ——, aorta; – – –, inferior vena cava; ——, short-term variation; – –, middle cerebral artery; – –, amniotic fluid index.
Source: Reproduce Figure 3 with permission from Hecher et al. [12].

Signs of Redistribution in the Fetal Circulation

An early response to placental insufficiency is redistribution of blood flow in the fetal circulation. Blood flow is selectively redirected to myocardium, adrenal glands, and the brain. The last phenomenon is called "brain-sparing effect" and is particularly available for measurement [18,19]. The effect is also measurable in term pregnancies [20]. Other organs may be selectively deprived of blood flow. Among these are

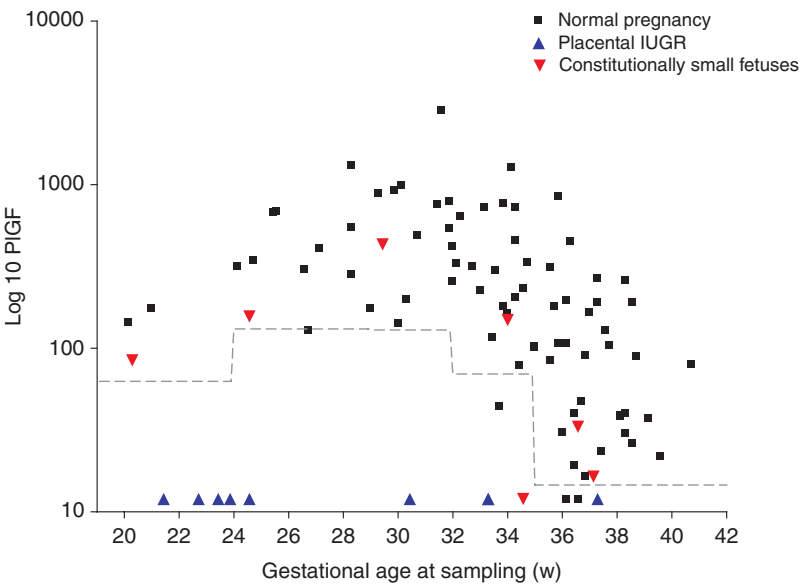

Figure 2.2 PIGF concentrations in the circulation of women with placental IUGR/FGR fetuses, constitutionally small fetuses, and normal pregnancies at the time of sampling. Constitutionally small fetuses (red triangles) and normal pregnancy controls (black squares) had increased PIGF levels compared with placental IUGR/FGR cases (blue triangles). The gray dashed black line represent the fifth percentile PIGF concentration cutoff according to the product insert. The y-axis is log transformed. Two blue triangles overlap at 33+2 weeks' gestation because of the sampling of these women occurring at the same gestational age.
IUGR, intrauterine growth restriction; PIGF, placental growth factor.
Figure reproduced with permission from Benton et al. [23].

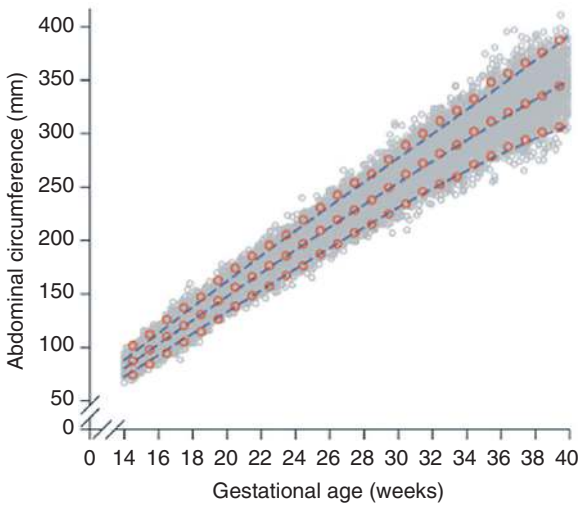

Figure 2.3 Fitted 3rd, 50th, and 97th smoothed centile curves of fetal measurements.
Fitted 3rd (bottom dashes line), 50th (middle dashed line), and 97th (top dashed line) smoothed centile curves for fetal abdominal circumference measured by ultrasound according to gestational age. Open red circles show empirical values for each week of gestation and open grey show actual observations.

the renal arteries – explaining the phenomenon of oligohydramnios.

Venous Doppler Changes

Other changes, usually later in the temporal sequence of deterioration of placental function, are in the fetal venous circulation. Both abnormal ductus venous measurements and pulsations in the umbilical vein are related to fetal hypoxemia and adverse perinatal outcomes [12,15,21].

Uterine Artery

Uteroplacental insufficiency is also signified by increased impedance in the uteroplacental vessels. In physiological pregnancy, the uterine arteries demonstrate a transition from a unit of high resistance to very low resistance. The opening of the spiral arteries into low-resistance units causes the upstream resistance of the uterine artery to decrease to levels where the notching of the uterine artery disappears around 24 weeks. If this does not occur sufficiently, the notching continues to be measurable, and/or the pulsatility index remains high. This situation significantly increases the risk for placental dysfunction later in pregnancy in both low- and high-risk populations. As a predictor this phenomenon does not distinguish between various placentally mediated disorders such as preeclampsia, placental abruption and stillbirth, but it may help in the diagnosis of FGR.

Type of Growth Measurements

Asymmetrical measurements of growth in the antenatal period may hint at the diagnosis of FGR. The brain-sparing effect causes the measurements that signify brain growth (biparietal diameter, head circumference) to be less affected than the measurements of the other organs (abdominal circumference, femur length). Particularly the abdominal growth is heavily influenced by liver size, which is the predominant location of fetal energy storage. In energy-deprived situations, the liver will consequently grow less fast and the abdominal circumference will be typically smaller in the curve than the cerebral measurements. Another suggestive finding is when consecutive measurements of the fetus show the measurements as "crossing centiles." This may signal FGR even when the measurements are not officially SGA, or even below the median for gestation. Such an approach, by definition, may be the optimal method for identifying suboptimal fetal growth. However, there are significant resource implications to routinely undertaking serial growth scans in all pregnancies, and the clinical interpretation of when crossing centiles becomes clinically relevant is yet to be determined.

PlGF

Placental dysfunction is reflected in several serum markers, the most predominant of which is Placental Growth Factor (PlGF). It has strong associations with early-onset hypertensive disorders of pregnancy and its clinical manifestations [22]. There are increasing suggestions it may have significant benefit in identifying FGR fetuses [23–25], although the effect is diluted significantly if SGA rather than FGR is chosen as the endpoint [26].

Decreased Fetal Activity

When placental insufficiency deteriorates to the extent where the fetus experiences hypoxemia, a decline in fetal activity can occur [27]. This is a phenomenon that the mother can recognize and is as such an important monitoring tool.

Maternal Manifestations – Hypertensive Disorders of Pregnancy

Especially in earlier gestational ages [5,28], hypertensive disorders of pregnancy have a very high prevalence of FGR. Up to 94% are SGA, and those above the 10th centile may also be FGR [29]. The association is reciprocal [30].

Fetal Distress during Uterine Contractions

One of the defining revealing symptoms of fetuses that are growth-restricted is the incapacity to cope with the challenges of uterine contractions in overt labor or subclinical contractions. In previous times, subclinical contractions were elicited by oxytocin administration to test the fetus's reserve. This was termed the *stress test*, as opposed to the *non-stress test*, the current form of cardiotocography.

Postpartum Neonatal Morbidity

Neonatal jaundice, disordered glucose metabolism, and insufficient temperature regulation are forms of maladaptation to the extra-uterine milieu. These transitional problems are associated with FGR and can also be used as differentiators between FGR and SGA.

Absence of an Alternative Diagnosis

Clinicians, when confronted with a fetus/newborn that is SGA, must consider different causes of smallness. These are uncertain dating of pregnancy, fetal viral infections, congenital anomalies, and constitutional smallness. The absence of additional ultrasound findings of a viral infection or congenital anomaly in an appropriately dated pregnancy leaves the clinician with the scenario of pure SGA/FGR.

Together, the aforementioned signs may help form a diagnosis of FGR. It may be stated that if there are several signs associated with uteroplacental insufficiency and signs of other diagnoses are absent, the case for FGR may be made. In a recent consensus procedure, a more apt definition was agreed upon that encompasses some of these functional parameters [31]. This may, however, still leave ample room for diagnostic doubt, especially in later gestations where measurements are less sensitive and specific.

Differences between SGA and FGR

It is increasingly apparent that not all FGR babies are SGA, and vice versa. The clinical significance of this distinction is important because children with a pathological process are at risk for severe adverse outcomes, whereas this is probably not the case for constitutionally small children.

There is considerable overlap between the two populations, since many fetuses with significant growth restriction will also be statistically deviant from the norm population, and the further deviant a fetus/infant is from the population norm, the bigger the chance it is caused by a pathological process [11]. Because of the easier identification, most studies on FGR identify their patients on a statistical basis (for instance, birth weight or estimated fetal weight) and as such define an SGA population. As a result, most studies on FGR are undermined by the inclusion of physiological SGA pregnancies.

The likeness between the two populations and the distinct differences pose significant clinical problems and scientific challenges. First, there is the group of fetuses/newborns who are SGA but not FGR. Especially near the cut-off values chosen, many of the SGA children/fetuses will actually not be FGR. This has significant consequences. In clinical management, once identified, fetuses in this group will be subjected to more intensive surveillance and consequently more (unnecessary) interventions and adverse effects from these interventions. In the interpretation of findings from studies, the conflation of FGR with SGA may mask significant associations or identify associations that in fact are not important for FGR [26].

Second, there is the group of fetuses/newborns who are not SGA, but still FGR. There are strong arguments to suggest that fetuses with optimal intrauterine growth within a population are those eventually born as above average. In a Dutch registry study, the highest perinatal mortality occurred in the lowest birth weight percentiles, decreasing with every decile even beyond the median birth weight in the population [32]. The nadir was at the 80th–84th percentile, suggesting that this is the optimal birth weight for children. This implies that the majority of fetuses may be subjected to some form of growth restriction. This is further substantiated by the findings from the Intergrowth study [33]. In eight populations across the globe, optimal growth curves were established in