Review

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Fetal Growth Restriction: Mechanisms, Epidemiology, and Management

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Abstract

Fetal growth restriction (FGR) is the condition in which a fetus does not reach its intrinsic growth potential and in which the short-term and long-term risks of severe complications are increased. FGR is a frequent complication of pregnancy with a complex etiology and limited management options, other than timely delivery. The most common pathophysiological mechanism is placental insufficiency, due to many underlying causes such as maternal vascular malperfusion, fetal vascular malperfusion and villitis.

Identifying truly growth restricted fetuses remains challenging. To date, FGR is often defined by a cut-off of the estimated fetal weight below a certain percentile on a population-based standard. However, small fetal size as a single marker does not discriminate adequately between fetuses or newborns that are constitutionally small but healthy and fetuses or newborns that are growth restricted and thus at risk for adverse outcomes. In 2016, the consensus definition of FGR was internationally accepted to better pinpoint the FGR population.

In this review we will discuss the contemporary diagnosis and management issues. Different diagnostic markers are considered, like Doppler measurements, estimated fetal growth, interval growth, fetal movements, biomarkers, and placental markers.

Keywords: Fetal growth restriction; Growth restriction in the newborn; Placental insufficiency syndrome; Doppler measurements; Biomarkers; Placental function

Introduction

Fetal growth restriction (FGR) is the condition in which a fetus does not reach its intrinsic growth potential and in which the risk of severe complications in both the short- and the long term is increased.[1–12] FGR is a common complication of pregnancy that occurs in five to ten percent of all pregnancies.[13,14] The most common pathophysiological mechanism is placental insufficiency, caused by several underlying placental pathologies such as maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), and villitis.[15,16] Given the heterogeneous underlying pathophysiology and presentation, and in the absence of a gold standard, the disorder may best be named the placental insufficiency syndrome.[16]

In this review we discuss the underlying mechanisms, the epidemiology, consequences and the current diagnostic and management issues of placental insufficiency and FGR.

Defining growth restriction: small-for-gestational-age (SGA) *vs.* FGR

There is no gold standard for the diagnosis of FGR. Fetal smallness is a key identifier, and there is a gradual relationship between fetal size and adverse outcomes: the smaller the fetus or newborn, the higher the chance of FGR. The antenatal and postnatal screening for FGR is often based only on whether or not the fetus/newborn is SGA. SGA is often defined as an estimated size or weight below the tenth percentile (p10) of the estimated fetal weight or birth weight on a reference curve is usually chosen as the cut-off. The third percentile (p3) is usually used as the cut-off for severe SGA.

It is important to realize that small size, as a single marker, does not discriminate adequately between fetuses or newborns that are constitutionally small but healthy and fetuses or newborns that are small because of impaired placental, maternal or fetal conditions underlying a growth disorder.[17] With any cut-off, on any reference chart, small fetuses or newborns that are constitutionally small are misclassified as FGR.[18–20] This results in unnecessary monitoring and intervention for being managed as "too small." Also, fetuses or newborns that are above the 10th percentile may in fact have risks related to placental insufficiency and have not reached their individual growth potential. This group remains undiagnosed as the fetuses or newborns in it are within perceived normal size range.

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As a consequence of the SGA-FGR confusion, FGR studies based on SGA show less relation with the measured parameters as the population of pathology (true FGR) is diluted with healthy fetuses and newborns (SGA that reached the intrinsic potential).[21] The effect of SGA as the cut-off to discriminate between growth restriction and appropriate size for gestational age is schematically shown in Figure 1. SGA can be used in studies as proxy for FGR as the cut-off for p10 is very clear, the results should however be cautiously interpreted as there will be an underestimation of the effect.

In 2016 a consensus definition for FGR was developed with the aim to better pinpoint the FGR population. Since then, this definition has been adopted internationally.[22,23] Early and late FGR are demarcated at 32 weeks and in both definitions markers of placental function are taken into account. Of note is that slow fetal interval growth is also taken into account in the late FGR diagnosis. The evidence to include serum biomarkers is considered as yet too limited to include these in a universally adopted definition (Table 1).[15]

A similar approach was followed to come to a more specific definition for growth restriction in the newborn, the equivalent of FGR after birth.[24] This definition also includes antenatal and postnatal markers for placental function (Table 2).

Growth of the individual fetus, charts, and standards

Measurement (or rather estimation) of fetal size (a reflection of past growth) is a cornerstone of prenatal care. Measurements of the individual fetus or newborn are compared to a reference population. The references in use vary significantly between countries and have different characteristics. The most commonly developed are descriptive charts. These are a collection of measurements of (nearly) all fetuses or newborns from a certain population. The development is relatively easy because there is typically no stringent or only limited selection of normal pregnancies. The descriptive charts are therefore a reflection of how fetuses *have grown*. Particularly at the extreme ends of the spectrum and in preterm gestational ages, pathological pregnancies skew the results.[25,26]

In contrast, prescriptive charts, or "standards" are intended to describe how fetuses should grow. They are developed using only measurements of apparently healthy, low risk women and their offspring. Exclusion criteria involve risk factors that pathologically influence fetal growth such as smoking, pre-eclampsia, hypertensive disease, obesity, congenital anomalies, or other maternal disease. Good examples of birth weight standards are the INTERGROWTH standard and the World Health Organization standard.[27]

The INTERGROWTH standard, published in 2014, was developed to establish international standards for birth weight to enable global use. Cohorts of pregnant women with a low risk of having a pregnancy with impaired fetal growth were prospectively followed. 20,486 children from sites in eight different countries were included for whom sex- and gestational age specific INTERGROWTH birth weight standards were made.[27,28] The INTERGROWTH standard observed

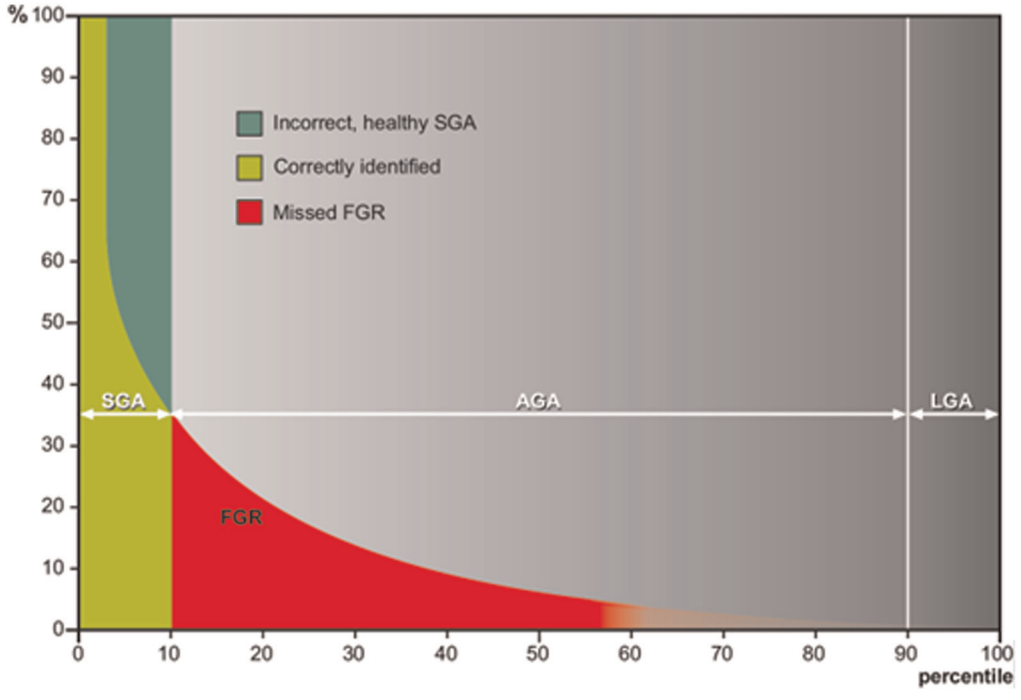

Figure 1. Schematic overview of the limitations when SGA is used as a definition for FGR. The green area represents SGA fetuses. The area highlighted in light green represents the SGA fetuses who are correctly identified as being growth restricted. The dark green area includes constitutionally small yet healthy fetuses who are thus incorrectly identified as being growth restricted. The area highlighted in red represents growth restricted fetuses who will be missed if the definition of SGA is applied. Reprinted from American Journal of Obstetrics and Gynecology, Vol 220, Wessel Ganzevoort, Baskaran Thilaganathan, Ahmet Baschat, Sanne J. Gordijn, Point, 74–82, Copyright (2019), with permission from Elsevier.[21] SGA: Small-for-gestational-age; FGR: Fetal growth restriction.

Table 1

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

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

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.
* Growth centiles are non-customized centiles.
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Table 2

Consensus-based definition of growth restriction in the newborn.

Final consensus definition of growth restriction in the newborn (% agreement)
Birth weight less than the third percentile on a population-based or customized growth chart (86%) or at least 3 out of 5 of the following: Birthweight <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 (e.g., hypertension or pre-eclampsia) (75%)

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differences in birth weight between the eight populations. Specifically, the birth weights at the Indian site (with a predominant Hindustani population) were on average some 300 grams lighter, leaving some room for thought about population variations in fetal growth. However, the differences between sites were much smaller than the differences within sites, suggesting that one generalized INTERGROWTH standard was appropriate for international use.

Ethnicity, as an ill-defined social construct is probably not sufficient to explain physiological differences in fetal growth. Ethnicity is correlated with adverse outcomes, but this is at least partly due to health disparities. We suggest that maternal height may be a better indicator of intrinsic intrauterine growth potential.[29–31] Therefore, the lower birth weight in the healthy Indian population is best explained by genetic variation. Probably the best proxy for this genetic variation is maternal height (rather than skin color).

The findings from the INTERGROWTH study support the concept that fetal growth shows physiological variation: not all fetuses grow alike. The question remains how to define (and even measure) an individual fetus's growth potential. Different concepts of individual fetal growth assessments have been proposed.[32,33] Most approaches aim to integrate factors that have an association with fetal size and use the presence or absence of these factors to predict the baby's weight. From a theoretical perspective, these approaches should not include factors that are associated with pathological growth. As an obvious example, smoking should not be corrected for since it does not explain that an individual fetus is small AND that this is without risk. Most other factors that are integrated in customized approaches also have some correlation with placental insufficiency and adverse outcomes, such as maternal body mass index and nulliparity. Again, we postulate that maternal height is the strongest customization candidate.[29–31]

Early-onset FGR *vs.* late-onset FGR

The pathways and symptomatology are different in early-onset and late-onset presentation of placental insufficiency syndrome and FGR.

The early pregnancy placental insufficiency syndrome classically is a result of abnormal placentation in the first trimester or severe other placental damage as described below. Insufficient placental development compromises the placenta's endocrine and transport functions. Early in pregnancy, the fetus has relatively high metabolic needs and relatively lower respiratory needs. In case of insufficient placenta function, the fetus puts compensatory mechanisms in place by redirecting blood towards the more vital organs. This process can be measured with Doppler ultrasound and can be reflected in asymmetrical growth restriction. The resistance in the supplying vessels of brain, heart and adrenals decreases, enabling a relatively undisturbed exchange of gases and nutrients to these organs. Inversely, the blood supply to kidneys, lungs, intestines, skin, and bones is faced with an increased vascular resistance. The process of hemodynamic redistribution is particularly well measured in the middle cerebral artery. The phenomenon of reduced vascular resistance in the middle cerebral artery in case of increased vascular resistance in the umbilical artery is called brain sparing. Brain sparing may result in a

relatively normal head size in a fetus that is otherwise growth restricted.[34–37]

Typically, in the early placental insufficiency syndrome, fetuses are easily diagnosed because of their extreme phenotype. However, therapeutic options are limited as the "maturation *vs.* nutrition/oxygenation balance" is skewed towards the need for maturation. Perinatal morbidity and mortality rates are high due to the combination of FGR and extreme prematurity.[38] In addition, early-onset FGR is associated with maternal pre-eclampsia in 50% of cases (and in early-onset pre-eclampsia FGR is diagnosed in more than 90% of cases).[38–40]

Late-onset FGR (after 32 weeks of gestation) is a condition that is more intertwined with normal placental ageing. The clinical challenge lies in the recognition of the fetus that is at risk of severe adverse outcomes. The diagnostic process is more difficult as size measurement by ultrasound and fundus symphysis measurement is more challenging. Up to 75% of cases are missed with current monitoring techniques.[41] At a later gestational age the relative increase of the respiratory needs of the fetus, means that insufficient placental function leads to hypoxia. Of note is that nutritional supply may have been sufficient up to that point. Therefore, the best-known marker of placental insufficiency, that is, fetal size, may not be abnormal by standard cut-offs. Because the fetus may not be too small by classic cut-offs, placental insufficiency in late gestation is more difficult to diagnose. Once diagnosed, the treatment option of expedited delivery is generally without severe consequences as the maturation *vs.* nutrition/oxygenation balance is skewed towards nutrition/oxygenation.[15]

When delivery is induced in cases of late-onset FGR, perinatal morbidity and mortality rates are lower than with early-onset FGR as the newborns are less premature at birth.[42] However, because the diagnostic process is more difficult, the risk of false positive diagnoses and iatrogenic premature deliveries as a result is higher.[43]

Pathophysiology of FGR

The differential diagnosis of a small fetus is broad and includes congenital and chromosomal abnormalities, congenital infections, maternal smoking, placental pathology and maternal disease.[13,44] These need to be considered if the fetus does not show all signs of placental insufficiency, including abnormal Dopplers and/or if there are abnormal findings on structural ultrasonography. The most common, overarching, pathophysiological mechanism of FGR is placental insufficiency.[13] Placental causes of FGR can be divided into three most common pathologies: MVM, inflammatory lesions or villitis of unknow etiology (VUE) and FVM.[45,46]

Placenta physiology

The placenta originates from the fetus as it develops from the trophectoderm, the outer layer of the embryo. The trophectoderm attaches to the endometrium and it invades into the underlying decidua. Fluid-filled spaces (lacunae) appear, and trophoblast cells rapidly proliferate to form primary villi. As a consequence of further proliferation and branching, villous trees are formed and the lacunae confluently form the intervillous space. The invasion of the extravillous trophoblast cells into the decidua is necessary to gain access to the maternal blood supply. The extravillous trophoblast invasion into spiral arteries results in a high-volume low velocity flow into the intervillous space. The simultaneous progressive branching of the villous tree results in an increasing exchange surface, formed by the syncytiovascular membrane with the underlying fetal vessel. It promotes exchange of nutrients, oxygen, and waste products, essential for normal fetal growth and development

Placenta pathology

Placenta insufficiency is the mechanism that results in fetal deprivation. Many different placental lesions and cascades can cause an insufficient placenta. In early pregnancy, deficient remodeling of the uterine spiral arteries results in high velocity maternal blood flow entering the intervillous lakes of the placenta too early. This causes uneven and intermittent perfusion of the placenta. Consequently, hypoxia-reoxygenation damage and activated immunological pathways occur. These suppress the placental growth and development and compromises the placenta's endocrine and transport functions (Fig. 2).

Maternal vascular malperfusion

The best-known placental lesion is MVM. This usually originates in early pregnancy due to deficient remodeling of the uterine spiral arteries by incomplete trophoblast

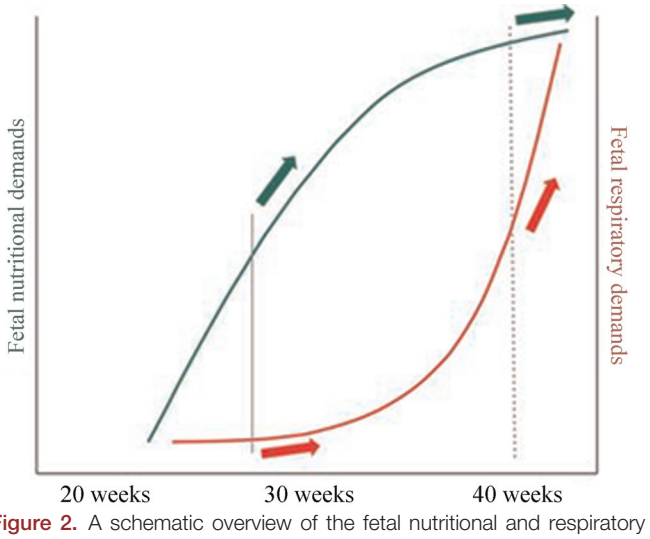

Figure 2. A schematic overview of the fetal nutritional and respiratory demands throughout pregnancy. Early-onset placental dysfunction (vertical gray solid line) will impact at a time when fetal nutritional demands (green arrows) rise exponentially and therefore will have a disproportionate effect on fetal growth compared with development of fetal hypoxemia and demise. Placental dysfunction at term (vertical gray dotted line) will impact at a time when fetal respiratory needs (red arrows) rise exponentially and therefore likely to compromise fetal wellbeing before fetal growth is impaired. Reprinted from ULTRASOUND IN OBSTETRICS and GYNECOLOGY, Vol 52, B. Thilaganathan, Ultrasound fetal weight estimation at term may do more harm than good, 5–8, Copyright (2018), with permission from John Wiley and Sons, reproduction with permission.[47]

invasion and incomplete destruction of the smooth muscle layer of the vascular intima layer. This results in a high velocity maternal blood flow entering the intervillous space of the placenta and entering it too early in pregnancy. As a result, this causes uneven and intermittent perfusion and development of the placenta. Consequently, hypoxia-reoxygenation damage and activated immunological pathways occur. Villous angiogenesis is altered resulting in high resistance elongated vessels rather than curved low resistance vessels with a large surface for exchange.[48] These changes interfere with normal placental growth and compromises the placenta's endocrine and transport functions.

MVM occurs in one in 12 nulliparous women and increases the risk of pre-eclampsia and a SGA newborn by 4.5 times.[49,50] As such, it is the underlying mechanism in 25% to 30% of FGR and pre-eclampsia cases, and even more so in the early-onset variants of the clinical disorder.[13]

Inflammatory lesions and VUE

Chorioamnionitis is the most common inflammatory lesion, related to infectious pathogens. It typically results in preterm birth and not in FGR. Non-infectious inflammation has a stronger association with placental insufficiency. VUE is characterized by lympho-histiocytic infiltrates within the villous stroma and it is associated with late-onset FGR and stillbirth. It can be divided into low- and high grade VUE and especially high grade VUE is associated with FGR and other adverse outcomes.[46]

Fetal vascular malperfusion

FVM characterizes a group of lesions that cause reduced perfusion of the villous parenchyma. The incidence is reported to be 0.3%–6.4% in literature.[51] It is often caused by placental vascular and/or umbilical cord obstruction or vascular damage in the placenta. In severe cases FVM can result in FGR or even stillbirth.[52] In a larger Pakistani study, FVM had a relative risk of 4.09 in fetal deaths *vs*. live term births and a relative risk of 1.77 in preterm neonatal deaths *vs*. live term births.[53]

Obstruction of the umbilical cord is most often the result of mechanical problems such as a marginal or velamentous insertion or a true knot. The obstruction can also be caused by thrombi, for example in cases of fetal thrombosis/coagulopathy or an abnormal coiling index. The umbilical coiling index (UCI), expressed in coils per cm of umbilical cord normally lies between 0.10 and 0.30. Both hypocoiling (UCI below 0.10) and hypercoiling (UCI above 0.30) are associated with adverse neonatal outcomes such as fetal heart rate abnormalities, preterm labor and perinatal hypoxia.[54] Other causes of FVM are maternal diabetes, fetal cardiac insufficiency or hyperviscocity.[52]

Birthweight placenta weight ratio

The birthweight-placental weight ratio depends on many factors. It is a consequence of developmental factors at the implantation phase and the latest maturation phase. There is no linear relation between placental and fetal weight as the exchange capacity is only partly dependent on the volume of the placenta. However, there is a significant correlation between the fetal-placental weight ratio and the consequences of placental insufficiency. At both extreme ends of the ratio is associated with growth restriction and adverse perinatal outcomes.[55,56]

Literature regarding the clinical relevance of antenatal assessment of placenta morphometry is scarce. Different studies show that abnormal placental shape (placental thickness >4 cm or >50% of placental length) were predictive for FGR. Another study showed an association with small placental size (linear placental length <10 cm).[57] However antenatal and postnatal placenta imaging regarding FGR is not implemented in a routine and standardized way in daily practice.

Maternal pathways of FGR

Maternal (pre-existent) conditions that can have a negative influence on fetal growth include chronic diseases such as coagulopathy disease, (pre)gestational diabetes mellitus, renal insufficiency and pregnancy induced hypertension. These conditions are important risk factors for the placental insufficiency syndrome. Multiple gestation, teratogen exposure, infectious disease and substance abuse such as smoking, alcohol and cocaine are also risk factors for FGR.[58] Women who smoke during pregnancy have a two- to threefold higher risk of FGR.[59] Other maternal risk factors include an inter-pregnancy interval of less than 6 or more than 120 months, maternal age below 16 or above 35, maternal body mass index below 20, previous delivery of a growth restricted or SGA newborn, nulliparity, severe anemia, maternal hypoxia for example due to living on high altitude, low socioeconomic status and heavy physical work.[11]

Fetal and infectious causes

Fetal conditions that may be a cause for fetal smallness include chromosomal abnormalities, genetic syndromes, intrauterine infections, fetal cardiac disease, and inborn errors of metabolism. In these cases, there is often early-onset FGR, and it may be related to placental abnormalities but are not necessarily. Infections that may cause FGR include malaria, rubella virus, cytomegalovirus, and the varicella zoster virus. Errors of metabolism can also cause impaired fetal growth but are rare.

Screening and diagnosis of FGR

Biometric measurements

The most common screening method for FGR is by measuring volume/size and relate this to a reference. This can be done by measuring the fundal height of the uterus or using ultrasound to estimate the abdominal circumference and estimated fetal weight. The diagnosis FGR is highly dependent on accurate pregnancy dating, ideally done in the late first trimester. In early pregnancy, fetal size is estimated by measuring the crown rump length of the fetus using ultrasound. Later, the head circumference, biparietal diameter, abdominal circumference and the femur length of the fetus are measured.

Slow(ed) and decline in fetal growth

Although scientific evidence is still scarce, it is thought that slow fetal growth can help to identify fetuses at risk for morbidity and mortality by distinguishing between truly growth restricted fetuses (often due to placental insufficiency) and small but healthy fetuses.[60,61] Interval growth between sequential measurements is therefore of importance. An example of a definition of slow(ed)/declined fetal growth is the decline of the abdominal circumference or estimated fetal growth of more than 20 or 50 percentiles between two measurements in the third trimester such as proposed by Sovio *et al*. of the pregnancy outcome prediction (POP) study.[62] The predictive value of slow or declined fetal growth as compared to size in the second trimester in the IUGR risk selection study (IRIS study) is currently being studied by our team.[63]

Doppler ultrasound

In addition to monitoring fetal growth by sequential size measurements, impaired placental function can be detected using Doppler velocity measurements that indicate vascular resistance. Doppler measurements aid in the reflection of the pathophysiological sequence of events that occur within the placenta and the fetus in cases of FGR.[15,56] Doppler measurements in the maternal uterine artery (UtA) reflect the maternal circulation resistance, the umbilical artery (UmbA) Dopplers the placental circulation resistance and the middle cerebral artery (MCA) Doppler reflects the fetal cerebral circulation resistance.

The uterine artery

The uterine artery Doppler pulsatility index (UtA PI) predominantly has a place in identifying incomplete placentation. It reflects the downstream placental resistance that is reduced in physiological placentation. It is therefore most useful as a diagnostic tool in early-onset FGR. However, the UtA PI may provide useful information throughout the entire pregnancy. There may be a place for the uterine artery in first-trimester prediction of pre-eclampsia and FGR and there are also suggestions that it may have value in late pregnancy.[64]

Although approximately one third of the pregnancies with an abnormal uterine Doppler in the third trimester had a normal uterine resistance during the first trimester, this is still associated with a high incidence of placental related diseases (30%).[61]

The umbilical artery

Reference values of the umbilical artery pulsatility index (UmbA PI) gradually decrease during pregnancy. An increased mean UmbA PI (above the 95th percentile of the reference) indicates abnormal high resistance which is a proxy for placental insufficiency. Specifically in fetuses below the 10th percentile or fetuses that are experiencing slow growth a high UmbA PI can indicate placental insufficiency.[13,15,65]

In (early) FGR the UmbA PI typically increases until there is a loss of the diastolic component: absent end-diastolic flow (AEDF) and ultimately reversed end-diastolic flow (REDF). Median time between the onset of AEDF and REDF and acute deterioration of the fetal well-being as signed by repeated spontaneous deceleration on cardiotocography, is three and two weeks.[66] The UmbA PI does not become abnormal until more than half of the placenta is dysfunctional. At term, the fetus does not have that much placental reserve so at that point the UmbA PI is not very discriminative.[65]

Since the use of Doppler measurements in obstetric ultrasound there has been a decrease in neonatal deaths. This is likely due to the fact that UmbA Doppler prevents unnecessary iatrogenic preterm deliveries in high-risk pregnancies.[67]

The middle cerebral artery

The middle cerebral artery pulsatility index (MCA PI) can detect a relatively low vascular resistance in the brain. This low vascular resistance suggests fetal brainsparing which is a sign of chronic hypoxia. A lowered MCA PI is considered a late manifestation of FGR, and it is valuable for the prediction of adverse perinatal outcomes, especially in late-onset FGR. The cerebroplacental ratio (CPR) (the ratio of MCA PI and UmbA PI) is a measure for brainsparing and it improves the sensitivity of Doppler monitoring because it already increases when its two components are still within the normal range.[2,68] It is not known how to use CPR in the monitoring management strategy for suspected FGR, for this reason multiple trials are underway such as DRIGITAT (NL6475, NTR 6663), CEPRA (NL 7557), RATIO37, TRUFFLE2 (IRAS Project ID: 266400).[69,70]

The ductus venosus

In early FGR the ductus venosus (DV) can be used as a parameter to predict the short-term risk of fetal death. The DV flow waveforms only become abnormal in advanced stages of fetal compromise. Reversed or absent velocities have a risk of perinatal mortality ranging from 40% to 100% in early FGR, independent of gestational age.[71] In the detection and management of late FGR the DV is not used.

Reduced fetal movements

Reduced fetal movements (RFM) can occur when the fetus installs mechanisms to reduce energy consumption in a hypoxemic intrauterine environment.[72] Monitoring of fetal movements has an important role in (maternal) antenatal surveillance, especially in the management of FGR. Although research has been done there are currently no tools that objectively assess fetal movements and improve the perinatal outcomes.[72] The AFFIRM trial introduced a package of interventions with strategies for increasing pregnant women's awareness of RFM. However, there was no reduction in the incidence of stillbirth or perinatal mortality.[73] Maternal perception of RFM occurs in 6%–15% of pregnancies.[74] It has a 2.4–5-fold increase in stillbirth and other adverse outcomes such as asphyxia, neurodevelopmental impairment and maternal hypertensive disease.[75] Women experiencing RFM are at increased risk for preterm birth or FGR.[76] Currently the CEPRA trial investigates the role of Doppler measurements for timing of delivery in case of RFM at term.[69]

Biomarkers

In recent years, several metabolites have been identified in maternal serum that could enhance the accuracy of FGR diagnosis and fetal monitoring.[77–79] The oldest of these are the placental growth factor (PlGF) and the soluble fms-like tyrosine kinase-1 (sFlt-1).

PlGF has a pro-angiogenic effect and supports the growth of trophoblasts. Physiologically, the concentration of the PlGF peaks between 26 and 30 weeks. Low PlGF is associated with early-onset hypertensive disorders and other signs of the placental insufficiency syndrome.[78]

sFlt-1 is an anti-angiogenetic factor that is released by hypoxic placental tissue. sFlt-1 causes increased maternal blood pressure and intervillous space blood flow velocity through peripheral vasoconstriction, thereby being central in the development of pre-eclampsia. Clinical trials are underway to investigate how PlGF and the PlGF/sFlt-1 ratio can be used to predict and monitor the consequences of abnormal placentation.[79]

Another candidate for clinical use is the metabolite ratio that, in conjunction with ultrasonic imaging at around 36 weeks' gestation, is a good identifier of FGR in the authoritative prospective POP study, a finding that should be further evaluated in clinical trials for screening, diagnosis and intervention.[77]

Currently no consensus exists regarding the best combination of markers for the detection of impaired fetal condition. It should always be borne in mind that high specificity of any combination of markers is important to avoid overdiagnosis (and unnecessary interventions) in healthy fetuses.

Remarks about FGR screening

The practice variation/measurement error in estimating fetal weight and abdominal circumference range from an average of 10% to 15% although it can be as high as 25%.[80] The highest risk of error is found within the groups of fetuses for which the estimates are most relevant, the very small and very large fetuses.[63,80,81] In previous trials, routine third trimester ultrasonography generally increased the detection of SGA, but it did not reduce the rate of Severe adverse perinatal outcomes (SAPO) compared to clinically indicated ultrasonography to detect and treat FGR.[63,62,82]

Prediction rates for FGR screened by fetal biometry between 35 to 37 weeks of pregnancy have false positive rates around 10%.[83] If a woman has certain risk factors such as maternal and obstetric conditions, advanced maternal age, nulliparity, high or very low body mass index before pregnancy and smoking, the chance that FGR will be detected prior to delivery of the child increases due to increased awareness. Unfortunately, the number of false positives of FGR also increases with the presence of maternal and obstetric risk factors and overall, the detection rates remain low.[84]

Outcomes of FGR

Short-term effects of FGR

Ten percent of perinatal mortality cases and 52% of stillbirths are estimated to be related to, partly unrecognized, growth restriction.[85] The risk of neonatal complications such as birth asphyxia, emergency delivery, meconium aspiration, persistent pulmonary hypertension, hypothermia, hypoglycemia, polycythemia, jaundice, feeding difficulties, necrotizing enterocolitis, late-onset sepsis, and neonatal mortality is also increased.[11,13,15] Because of these risks and the increased risk of a poor adaptation to extra-uterine life, a pediatrician should be consulted after the birth of a growth restricted newborn.

Long-term effects of FGR

Catch-up growth in weight usually occurs within six months and for length within a year.[86] FGR is associated with many long-term effects such as hypertension, coronary heart disease, obesity and diabetes mellitus.[5] Changes in the cardiovascular risk profile can already be detected in school age children.[8] Other long term effects of FGR include a higher risk of cerebral palsy and neuro-developmental impairment.[59] Neuro-developmental impairment is most present in cognitive and behavioral development. This is due to the fact that when the blood is redistributed to the brain during intrauterine hypoxia it is not spread evenly across the brain but in favor of certain areas such as the basal ganglia. The cognitive and behavioral impairment often worsens as the children become older and are faced with increasingly complex cognitive demands. If growth restricted newborns are not identified as such, they will not be targeted for interventions during early childhood that from which cognitive and behavioral development may benefit.

Interventions for FGR

Prevention

Primary prevention of FGR has remained rather illusive. Low-dose antiplatelet agents such as acetylsalicylic acid can be given to women at high risk for placental insufficiency syndrome. Acetylsalicylic acid delays the onset of pre-eclampsia and possibly FGR and therefore increases the gestational age at birth. The number needed to treat is 38 for pre-eclampsia <37 weeks gestational age and 16 for birth weight <10th percentile.[87] Women with a high a prior risk for pre-eclampsia or FGR are therefore prescribed aspirin according to national guidelines.[88–90]

Other kinds of medication such as L-arginine supplements and heparin have not been proven to be useful. Some agents are being studied for specific lesions such as (combinations) of anticoagulants immunoglobulins, hydroxychloroquine, and pravastatin for chronic histiocytic intervillositis and villitis of unknown etiology.[46]

Therapy

To date the only intervention that is effective for the prevention of adverse outcomes if FGR is suspected is timing of the delivery. Many intervention strategies such as treatment with aspirin, heparin and sildenafil have been under investigation but no treatment has been proven effective to improve fetal growth after FGR has been diagnosed.[91]

Timing of delivery based on risk assessment

Delivery is timed carefully balancing the risks of the severity of the FGR and prematurity. A protocol has been suggested by Figueras *et al.* in which SGA and FGR have been divided into five stages of severity (SGA and FGR stage I to V).[71] For each stage the proper planning of the delivery is determined to prevent both adverse neonatal outcomes and mortality. According to this protocol the SGA fetuses should be monitored fortnightly, and induction is only justified from 40 weeks onwards. For stage V FGR fetuses, who have the most severe growth restriction and spontaneous fetal heart rate decelerations and reduced short term variability on the cardiotocography and reversed atrial flows delivery after 26 weeks is justified.[68]

Overall, close fetal monitoring should be applied and in general it is advised to deliver a growth restricted fetus based on REDF from 32 weeks onward, based on AEDF from 34 weeks onward, and with an UmbA PI >p95 from 36 weeks onward. However, the timing of the delivery should be individualized.[92,93] Between 24 and 34 weeks of gestation antenatal corticosteroids should be given when delivery is considered, in order to accelerate lung development and reduce the risk of intracranial hemorrhage.[13]

In a group of low-risk SGA fetuses with normal umbilical artery Doppler it was found that an increase in monitoring frequency resulted in an increase in interventions. A group that was monitored twice a week with Dopplers was compared to a group that was monitored fortnightly. The first group was subjected to more inductions of labor, but the perinatal outcomes were not significantly different.[94]

FGR in the newborn

FGR often remains undetected before birth which means that many fetuses do not receive adequate intrapartum monitoring. Once a growth restricted fetus is born there is a second chance to diagnose the growth problem and to install proper monitoring and support in the postnatal period. As with FGR, it is difficult to differentiate between healthy but small newborns and growth restricted newborns. Usually, the 10th percentile on a birth weight standard is used as cut-off. As mentioned before, in 2016 a Delphi procedure was done to establish a more accurate definition of growth restriction in the newborn.[24]

Appropriate monitoring strategy when growth restriction is suspected should include, regular temperature and glucose checks and close monitoring of feeding problems. Glucose monitoring is very important as a single episode of hypoglycemia can result in substantial neurological morbidity.[95] Support of warmth and breastfeeding/additional artificial feeding could be installed.

Conclusions

FGR is a common complication of pregnancy with a broad clinical spectrum, a complex and variable etiology and limited management options. To date, the only effective treatment to prevent severe morbidity and mortality is timely delivery, which has the disadvantage of iatrogenic premature birth.

The search for sensitive markers identifying suboptimal conditions in utero and impaired fetal growth and development is ongoing. Functional antenatal parameters for placental function, if available, may be added to the biometric measurement.[96] A prediction model that includes multiple markers for fetal growth and placental function could contribute to the accuracy of prediction and the effectiveness of management of FGR.

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Conflicts of Interest

None.

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