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Evaluation and Management of Suspected Fetal Growth Restriction

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KEYWORDS

• Fetal growth restriction • Placental insufficiency • Small for gestational age
• Doppler ultrasound • Cardiotocography

KEY POINTS

- The diagnosis fetal growth restriction (FGR) is made when the fetus has clinical signs of malnourishment and/or hypoxia owing to placental insufficiency.
- There is no available effective "cure" for FGR, other than delivery.
- In early-onset FGR ("*easy diagnosis, difficult management*"), the obstetric challenge lies in timing of delivery, whereas in late-onset FGR ("*difficult diagnosis, easy management*"), the challenge is the detection of FGR.

INTRODUCTION

Prenatal care focuses on the early detection of several pregnancy-specific conditions. Impaired fetal growth due to placental insufficiency is among the most important of those conditions because it is a major contributor to adverse perinatal outcomes. In this article, the authors focus first on the evaluation by prenatal care providers that identifies fetal growth restriction (FGR) and potential causes. Second, the authors discuss management options, including potential therapeutic strategies, monitoring modalities, and how to inform the decision for iatrogenic delivery.

EVALUATION

Primary Assessment

The evaluation of suspected FGR typically commences when it is observed that the estimated fetal size is below a defined threshold of normality for gestational age, termed small for gestational age (SGA), or when a decline in growth percentile is

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observed. In optimal conditions, the fetus grows according to its own intrinsic growth potential, determined by genetic and epigenetic factors. A fetus may be small in relation to a population reference or standard, yet be appropriate for its intrinsic growth potential. However, the more significant the deviation from the threshold of normality, the bigger the chance that a pathologic process underlies the observed smallness. This is described in Stefanie E. Damhuis and colleagues' article, "Abnormal Fetal Growth: SGA, FGR, LGA: Definitions and Epidemiology," in this issue. The core issue when confronted with a small fetus is determining if the fetal size is appropriate for this fetus. The aim of the clinical approach is primarily to discover if the fetus is compromised by placental insufficiency and at risk for morbidity or mortality.

For all diagnoses, it is important to first verify if the gestational age was calculated appropriately because this is key to the interpretation of fetal size. In high-income countries, a reliable due date will often be provided by routine first-trimester ultrasound, but this may not be the case in exceptional cases, for example, in (socially) deprived settings. If the gestational age has been reliably set, evaluation proceeds with an ultrasound to confirm the extent of abnormality of fetal size. It is important to understand that fetal size is the result of previous fetal growth. It is advisable to incorporate the results from all previous ultrasounds greater than 18 weeks of gestation in the evaluation to establish the growth pattern. Impaired placental function leads, if long-lasting or severe enough, to a decline in size centiles of biometric measurements plotted on a reference chart to "crossing centiles." As a screening tool, this is sometimes defined by a decline of 20 centiles or more, and for the diagnosis FGR, a decline of 50 centiles has been determined in consensus.[1,2]

Also, the medical, obstetric, and family history should be taken to understand if specific other factors contributing to impaired placental function can be identified. The most common are maternal or environmental smoke exposure and medical problems, such as hypertension.[3]

Placental insufficiency

The underlying pathologic mechanism of FGR is placental insufficiency, with or without maternal diseases, fetal chromosomal abnormalities, or infection. Pathologic smallness reflects malnourishment as well as hypoxia, as these processes go hand in hand.[4,5] Many causal placental lesions are known. However, the most common lesion is suboptimal remodeling of uterine spiral arteries (placentation) in early pregnancy; this is termed "maternal vascular malperfusion" (MVM). MVM occurs mostly when uterine artery remodeling is only shallow and the maternal vascular bed thereby retains smooth muscle cell vascular reactivity, which amounts to an incomplete physiologic transformation. High-resistance vessels persist, resulting in high-velocity blood flow into the intervillous space with shear stress and altered villous vascularization.[6,7]

Other well-described FGR-related placental lesions include fetal vascular malperfusion (FVM) and villitis of unknown etiology (VUE).[8] FVM is most often caused by obstructed fetal blood flow because of thrombosis or other lesions, such as those occurring in the cord (high- or low-coiling index) and hypercoagulability with and without thrombosis. VUE is only considered present when a nonspecific inflammatory process results in villitis.[8]

Antenatal detection of placental insufficiency

The increased vascular resistance in MVM can be detected by use of Doppler ultrasound to measure the blood flow patterns of both maternal and fetal arteries (**Fig. 1**). Many vessels, including the uterine artery, umbilical artery (UA), and middle cerebral artery (MCA), can be assessed throughout pregnancy and can provide an

indication of actual placental function. Abnormal flow patterns can be used to identify the compromised fetus that is deprived of oxygen and nutrients. It is noteworthy that Doppler abnormalities are not necessarily seen in other placental lesions (**Table 1**).[9]

Uterine artery

In normal pregnancy, the uterine arteries, as an indirect measure of resistance in the spiral arteries, demonstrate a transition from a unit of high resistance to very low resistance in the first trimester.[6] 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. If this does not occur sufficiently, the notching continues to be measurable, and/or the pulsatility index (PI) remains high. Retained high resistance of the uterine artery in the second trimester of pregnancy is associated with an increased risk for the development of especially early-onset preeclampsia and FGR.[10]

Umbilical artery

Many studies demonstrate the relationship between uteroplacental insufficiency and consequent increased impedance in the UA. Among the earliest phenomenon in early-onset FGR are abnormal UA flow velocity waveforms.[11,12] It is described quantitatively by increased PI and qualitatively by absent or reversed end-diastolic (ARED) flow. ARED-flow is specific for very-early-onset FGR and less so for term or late preterm FGR.[13] This phenomenon is merely the "tip of the iceberg" because ARED-flow is only observed when a larger proportion of the placental vascular bed is dysfunctional.[14] In later gestational ages, fetuses have little placental reserve, and UA waveforms do not typically become severely abnormal. Fetal distress in advanced pregnancy can become apparent through reduced fetal movements, abnormal

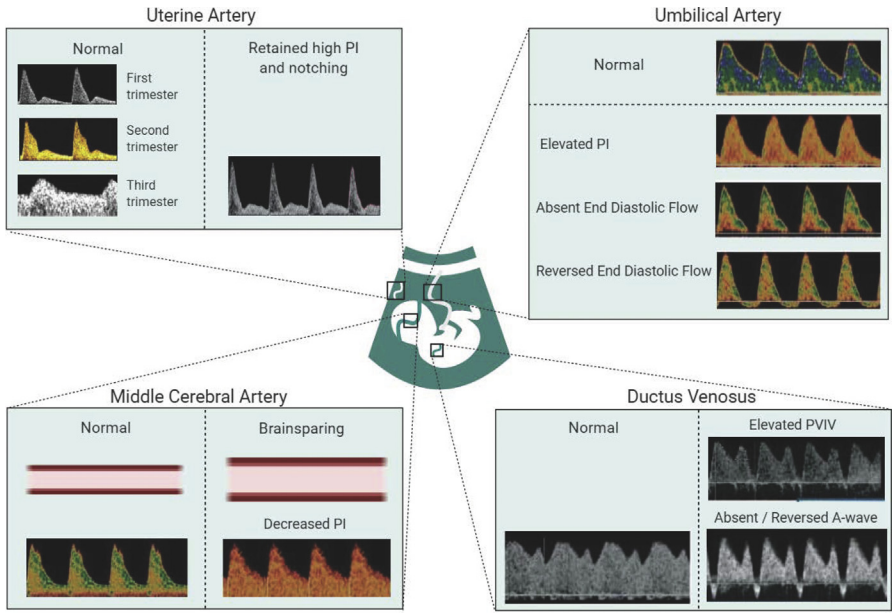

Fig. 1. Different Doppler flow patterns in maternal and fetal vessels relevant to placental function. PVIV, peak velocity index for the vein.

Table 1
Overview of relevant ultrasound parameters and their implications

Doppler Parameters	Indication	Abnormal Findings	Indicative for
Uterine artery	Screening high-risk FGR pregnancies	UtA-PI >95th centile[a]	Risk stratification for development of PE and FGR
Umbilical artery	(Suspected) FGR maternal hypertensive disorders	UA-PI >95th centile[a] AEDF REDF	Very early-onset FGR
Middle cerebral artery	(Suspected) FGR	MCA <5th centile[a] PSV	Fetal adaptation to hypoxemia Fetal anemia
Cerebroplacental ratio	(Suspected) FGR	CPR <5th centile[a]	Fetal redistribution
Ductus venosus	Severe early-onset FGR	PVIV >95th centile[a] Reversed A wave	Fetal cardiac compromise

Abbreviations: AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; PE, preeclampsia; PSV, peak systolic flow; REDF, reversed end-diastolic flow; UtA, uterine artery.
[a] Most often used cutoff for abnormal.

cardiotocogram (CTG), or death before deterioration of Doppler flows, partly because the indication to measure flow patterns is often only small size.[15]

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 the most important organs, including the heart, brain, and, in utero, the adrenal gland. This phenomenon has been dubbed the "brain-sparing effect" and can be expressed in an abnormal ratio between the PI of the UA and the MCA, the so-called cerebroplacental ratio.[16] Other organs may be selectively deprived of blood flow, such as the renal arteries, explaining the phenomenon of oligohydramnios. Asymmetrical measurements of size signify brain growth (biparietal diameter, head circumference) is less affected than the measurements of the other organs (abdominal circumference, femur length). 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 relative to cerebral measurements.

Venous Doppler changes

Signs of FGR can also be observed in the fetal venous circulation. Both abnormal ductus venosus (DV) measurements and pulsations in the umbilical vein are related to fetal hypoxemia and adverse perinatal outcomes.[12,17] Because these changes typically occur late in the sequence of deterioration of placental function, this parameter is more useful for the monitoring strategy to determine timing of delivery rather than for the diagnosis of FGR.

Serum biomarkers

Placental dysfunction is also reflected in serum markers; of these, placental growth factor (PlGF) is the best studied and most potentially useful. It has strong associations with early-onset hypertensive disorders of pregnancy and its clinical manifestations, particularly if combined with soluble fms-like tyrosine kinase-1 (sFlt-1).[18] These

markers may be useful in identifying FGR fetuses,[19,20] although utility is diluted significantly if SGA is chosen as the endpoint rather than FGR.[21]

Decreased fetal movements

When placental insufficiency deteriorates to the extent whereby the fetus experiences hypoxemia, a decline in fetal activity can occur.[22] This phenomenon is one that can be recognized by the mother, and as such, can be considered an additional monitoring tool. Although efficacy is uncertain, most authorities recommend additional antenatal testing in cases of decreased fetal movement.

Differential diagnosis and maternal comorbidities

Clinicians, when confronted with a suspected small or growth-restricted fetus/newborn, must explore all possible pathophysiologic mechanisms besides and/or relating to placental insufficiency. These mechanisms are, among others, fetal infections, congenital anomalies, syndromes, genetic abnormalities, and maternal diseases. Each of these conditions requires different management and treatment strategies and should therefore be considered.

Fetal infections

An uncommon, but clinically important alternative diagnosis underlying SGA is congenital infection. The microorganisms that are the main contributors are toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex virus, and malaria, as they have the potential to cause a placental and/or congenital infection.

Ultrasonographic abnormalities that are associated with these infections are fetal ventriculomegaly, intracranial calcifications, ascites, and hyperechogenic bowel. In severe fetal smallness, screening for CMV infection can be considered because this is the most common congenital viral infection, with a prevalence of 0.2% to 2% (average, 0.65%).[23]

Other infections should only be assessed if there is a specific pattern of ultrasound abnormalities or specific clinical risk factors, because the incidence of these infections in the absence of ultrasonographic abnormalities is very low.[24,25]

Syndromal abnormalities

In the case of early-onset FGR, an advanced obstetric sonogram can help to screen for chromosomal abnormalities, especially if other signs of placental insufficiency are absent. Structural anomalies can suggest an underlying syndrome and may justify invasive prenatal testing with amniocentesis or chorionic villus sampling. Noninvasive prenatal testing is currently only useful to screen for a small number of chromosomal abnormalities. Because placental insufficiency is more common in the context of chromosomal abnormalities, diagnostic testing (rather than screening) should be considered in early-onset FGR, especially when other ultrasound abnormalities are seen.[26]

Maternal comorbidities

The presence of maternal comorbidities may increase (or sometimes decrease) the likelihood that the observed fetal smallness is caused by placental insufficiency. Most noticeable are disorders that have impact on endothelial cell function, such as chronic hypertension, diabetes mellitus, renal disease, lupus, and cardiovascular disease, all of which can have an impact on early placental development.[27]

Maternal preeclampsia

Most of the pathophysiologic processes of hypertensive disorders of pregnancy are similar in FGR. Therefore, some of this knowledge can be extended into the field of

FGR. Preeclampsia is a serious complication of pregnancy, characterized by hypertension and proteinuria in the second half of pregnancy because of endovascular inflammation.[28] Poor placentation is particularly associated with the early-onset phenotype of both preeclampsia and FGR. Especially in earlier gestational ages, hypertensive disorders of pregnancy and FGR have a reciprocal association.[29]

MANAGEMENT

In this section, the authors discuss potential therapies influencing the root cause of the placental insufficiency. Next, they discuss how the main therapeutic approach remains determining the timing of delivery and how this is different in early-onset FGR and late-onset FGR. In early-onset FGR ("*easy diagnosis, difficult management*"), obstetric management focuses on timing of delivery, whereas in late-onset FGR ("*difficult diagnosis, easy management*"), the focus lies on the detection of FGR.

Therapeutic strategies

Particularly in early-onset FGR, MVM with retained smooth muscle cell function of the spiral arteries appears to be the predominant pathophysiologic pathway. This suboptimal remodeling of uterine spiral arteries has led to pharmacologic strategies that influence uteroplacental vascular function through the endothelial nitric oxide pathway and vasodilatation, depicted in **Fig. 2**.[30] No strategy with established efficacy is currently available. Such an intervention is particularly wanted for the severe phenotype of early-onset FGR, because any option that can prolong pregnancy and decrease the consequences of prematurity after iatrogenic delivery can have a tremendous impact on perinatal outcomes.

Sildenafil

Early evaluations of phosphodiesterase-5 inhibitors (sildenafil) as therapeutic treatment for early-onset severe FGR with high risk of fetal demise appeared promising.[31,32] However, in an international collaboration (acronym STRIDER), randomized controlled trials (RCTs) of antenatal sildenafil citrate for FGR showed no benefit and possible harm.[33–35]

Antioxidants: arginine

An increasing number of studies on the therapeutic use of antioxidants, such as L-arginine, have become available.[36] This option is appealing, as it is a nutritional supplement, unlikely to have unexpected unwanted side effects, such as seen with sildenafil exposure in the Dutch STRIDER RCT.[35] A recent cross-species meta-analysis combining all available data from human and nonhuman studies suggests that arginine family supplementation, in particular, arginine and nitrogen carbamoyl glutamate, improves fetal growth in complicated pregnancies.[37] Rigorous research in complicated human pregnancies is needed before determining efficacy in the treatment of FGR.

Gene therapy

A promising and more radical approach is vascular endothelial growth factor (VEGF) gene therapy, in which adenoviral vectors encoding for proteins, such as VEGF, are introduced to the maternal uterine artery.[38] In preclinical studies, it has been shown to increase uterine blood flow and reduce vascular contractility. These functional findings correspond with the anatomic findings of vascular remodeling with increased endothelial cell proliferation in the perivascular adventitia of treated uterine arteries. This method is anticipated to be safe, because no vector seems to spread to the fetus, and no adverse effects on either the mother or fetus have been observed. However,

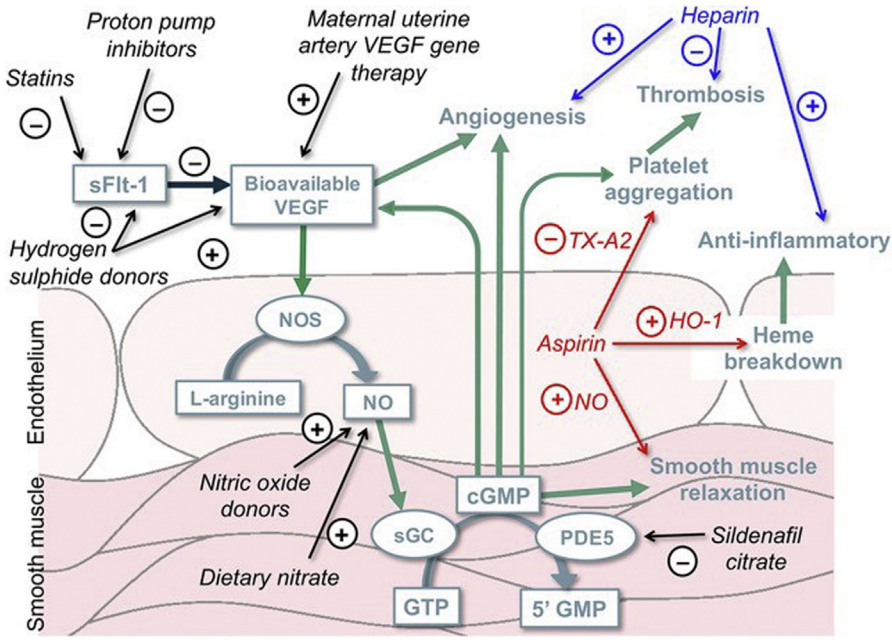

Fig. 2. Possible interventions to treat FGR by site of action influencing the vascular smooth muscle and endothelium metabolism. 5′ GMP, guanosine monophosphate; cGMP, cyclic guanosine monophosphate; GTP, guanosine-5′-triphosphate; HO-1, heme oxygenase-1; NO, nitric oxide; NOS, nitric oxide synthase; PDE5, phosphodiesterase type 5 inhibitor; sGC, soluble guanylate cyclase; TX-A2, thromboxane A2. (*From* Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. Am J Obstet Gynecol. 2018;218(2S):S829-S840.)

this bold strategy still requires many steps, including extensive clinical trials, before it can be implemented into clinical practice. Furthermore, the high cost associated with gene therapy may restrict this option to high-income health care settings.

Monitoring for delivery in early-onset fetal growth restriction

Although the term "fetal growth restriction" implies that the fetus suffers most from poor nutritional exchange, sustained starvation is rarely the cause of fetal demise. It is the lack of oxygen supply to the fetus, resulting in chronic or acute hypoxia that leads to perinatal death. Obstetric management aims to minimize the risk of fetal demise. The only management that "treats" placental insufficiency is delivery, which prevents stillbirth but predisposes to postnatal death from prematurity. Despite the fact that early-onset FGR is rare (0.3% of all pregnancies), this extreme phenotype has significant societal and individual impact owing to the aggravated effects of prematurity: death or survival with severe impairment.[39] All severe morbidities are essentially expressions of underdeveloped organ function, including lungs (bronchopulmonary dysplasia, respiratory distress syndrome), bowels (necrotizing enterocolitis), immune system (sepsis and meningitis), and cerebral blood vessels (intracerebral hemorrhage, periventricular leukomalacia).

Timing of delivery is therefore based on the estimated balance of the risks of ongoing intrauterine hypoxia versus the consequences of iatrogenic premature delivery. In the previable/periviable period, consideration of expectant management is warranted even when fetal death is expected because delivery often confers near

certainty of postnatal death.[40] In scenarios whereby severe fetal compromise is present before viability, pregnancy termination should be made available, especially when continued expectant management is associated with maternal risk. Of note is that viability may occur at later gestational ages for fetuses with FGR, and the determination of the moment of esteemed viability depends on the expertise of the obstetric and neonatal staff along with local resources. Once a viable gestation is reached, the main clinical dilemma is which surveillance test should guide the decision on timing of birth: CTG, fetal Doppler ultrasound, and/or serum biomarkers.[12,41,42] At the moment, published national guidelines on the matter vary considerably.[43]

Indication for delivery

Umbilical Artery. The finding of ARED flow in the UA in FGR is a telltale sign of severely impaired placental perfusion, and it has been consistently shown to be an indicator of adverse outcomes, including death.[17,44] The use of UA Dopplers as a direct indicator for fetal well-being is supported by recent study results,[45] but a study comparing the use of UA Doppler with a management protocol that remains expectant until other parameters of fetal condition become abnormal is lacking. Currently, UA Doppler is variably part of management protocols as a direct indicator for delivery in the extremely preterm period. The most recent Society for Maternal-Fetal Medicine Guideline for FGR recommends general timing of delivery at 37 weeks' gestational age in the case of UA Doppler PI > p95, delivery at 33 to 34 weeks if there is absent end-diastolic flow, and delivery at 30 to 32 weeks if there is reversed end-diastolic flow. However, in the case of repetitive late decelerations on CTG tracing, delivery is advised after the fetal viability.[25]

Cardiotocography. Fetal heart rate (FHR) is a function of the autonomic nervous system. At the onset of hypoxia, FHR variability decreases, whereas progressive hypoxia and acidemia result in spontaneous decelerations. When repeated decelerations occur, unprovoked by uterine contractions, there is strong consensus that imminent delivery is warranted because hypoxia is likely present, and the risk of stillbirth is high.[43]

The importance of low FHR variability is less clear. Short-term variation (STV) is a measurement of FHR variability that is calculated by computer analysis, which avoids the high interobserver and intraobserver variability of visual CTG observation.[46] It has recently been made available as freeware.[47] STV has been established as a reflection of fetal acid-base status.[48] However, no studies exist with sufficient power to detect an association of STV at any threshold with the most important outcomes, stillbirth, and long-term infant health.[49]

In an indirect comparison of visual CTG versus STV assessment with computerized CTG (cCTG) using data from the GRIT and TRUFFLE trials, it was suggestive that monitoring with cCTG improved outcomes.[41] Notwithstanding the lack of conclusive comparative evidence, some advocate that cCTG should be the gold standard.[50] However, clinical practice shows variable implementation: although STV has been adopted as a standard of care in many European centers (but far from all), it has not been adopted in the United States. Because of these firm beliefs and practice variation, cCTG needs to be tested rigorously to determine whether its use improves outcomes compared with visual CTG interpretation.

Ductus Venosus. Use of the DV Doppler waveform in addition to CTG to determine timing of delivery appears to improve neurocognitive outcome at the age of 2 among surviving infants, although this finding is nonsignificant when stillbirths and perinatal deaths are included in comparison groups.[42] It is likely that intrauterine malnutrition

and hypoxia affect some fetal organs before others. In fetuses with early-onset FGR, cardiac dysfunction (as reflected in abnormal DV assessment) can precede cerebral dysfunction (as reflected in low STV).[51] The combination of CTG and Doppler evaluation of the DV as monitoring modalities to time delivery is likely to be synergistic in achieving optimal results. The findings of the TRUFFLE trial are difficult to generalize to practice settings in the United States, where cCTG has not been widely adopted and Doppler evaluation of the DV waveform has not been endorsed by professional societies.[25]

Biophysical Profile. The biophysical profile score (BPS) is a crude composite score of a combined assessment of fetal movements, reactivity of the CTG, and assessment of amniotic fluid. The association of an abnormal BPS with the adverse outcomes of interest is not as good as other available parameters.[52] Nevertheless, in the difficult decision of iatrogenic preterm delivery in the context of borderline abnormal findings of cCTG, the presence or absence of fetal movements may sometimes sway decisions in practice.

Late-Onset Fetal Growth Restriction: From Diagnosis to Delivery

In late-onset FGR when placental reserve is already challenged, the interval between the onset of nutritional deprivation and life-threatening hypoxia is typically shorter than in early-onset FGR. In this gestational age period, the concept is "easy to manage, difficult to diagnose." This concept is reflected in the fact that a significant number of fetuses suffer from the consequences of hypoxia without apparently being challenged in growth, as they are not small.[53,54]

The Small for Gestational Age Approach

Because the aforementioned signs of placental insufficiency are unlikely to be observed in late-onset FGR, differentiation between FGR (failure to meet growth potential) and SGA (constitutionally small but healthy) is difficult. Despite the low absolute risk, adverse outcomes are devastating and include stillbirth and short- and long-term effects of hypoxia (neonatal intensive care unit admission, hypoxic-ischemic encephalopathy). On the other hand, unnecessary iatrogenic (relatively) preterm birth in women with small but healthy infants also confers low absolute risk of postnatal morbidity but translates into significant societal impact.

Because serious perinatal morbidity from delivery in the late preterm pregnancy is unlikely,[55] clinicians may have a low threshold for delivering small fetuses relatively later in gestation. Imperfections with approaches that depend exclusively on assessments of fetal size lead to "undertreatment" of fetuses of normal size but who are affected by FGR and "overtreatment" of fetuses who are small but healthy. The DIGITAT study randomized women with fetuses suspected to have FGR at 37 weeks' gestation to delivery or expectant management and showed no difference in the primary outcome of short-term perinatal morbidity.[56] However, more fetuses in the expectant management were in the lowest birth weight percentile group, and these were the fetuses at risk of later developmental delay.[57] This study shows that selection of "the fetus at risk" is still imperfect, and the ideal approach is still not known.

The individual risk approach

Further risk stratification is necessary to identify the fetus that should be delivered early.[58] The same variables that are identified in early-onset FGR can be used for an individualized risk approach. The most commonly used marker is the brain-sparing phenomenon.[59] Cohort studies have consistently shown that abnormal MCA Dopplers (low PI) are associated with adverse outcomes.[13,60] However, in a

recent individual patient data meta-analysis, it was found that, if continuous data of UA and MCA Doppler indices were used, the diagnostic performance of both UA and MCA variables and their ratio (cerebroplacental ratio) was similar.[61] Ongoing studies are further evaluating these discrepancies and whether UA Doppler velocities that were previously considered normal may actually represent evidence of compromised placental function.

Management: other aspects

Prevention of Fetal Growth Restriction/Acetyl Salicylic Acid

Low-dose aspirin (acetyl salicylic acid 80–150 mg) has long been recognized as effective for reducing the risk of developing preeclampsia, provided it is started in early pregnancy.[62] Considering the fact that preeclampsia and FGR share risk factors with MVM as the most common pathologic underlying lesion, these data have been extrapolated to FGR by some. Its use in decreasing the risk of FGR is studied with mixed results[63] and will be reviewed in more detail in Nathan Blue and colleagues' article, "Recurrence Risk of Fetal Growth Restriction: Management of Subsequent Pregnancies," in this issue. Also, the risk of SGA infants is reduced with low-dose aspirin, although this was assessed as a secondary outcome in most studies. One approach is to offer it to women with the highest risk of developing the disorder, using algorithms provided by the Fetal Medicine Foundation algorithm, or US Preventive Services Task Force.[64,65]

Mode of Delivery

Severe fetal compromise often affects mode of delivery planning. In situations where it is unlikely that the fetus will be able to withstand the challenges of uterine contractions, a cesarean section without a trial of labor should be considered. If it is estimated that the placental reserve will allow vaginal delivery, continuous fetal CTG is warranted. Because it can be difficult to accurately predict whether a fetus will tolerate labor, shared decision making is critical.

Corticosteroids and Magnesium Sulfate

Once it is estimated that the antenatal risks surpass the neonatal risk and intensive monitoring is underway with the intent to deliver a fetus, it is also important to optimally anticipate imminent delivery. The benefit of a single course of antenatal corticosteroids to accelerate fetal lung maturation for spontaneous premature delivery has been unequivocally established remote from term.[66] Whether this is also valid in the context of severe early-onset FGR is uncertain, as these high-risk pregnancies were often excluded from trials included in meta-analyses. Nonetheless, it is appropriate to offer this potentially potent preventive therapy, as it is endorsed by professional societies.[25]

A serendipitous finding from studies assessing magnesium sulfate for prevention of eclamptic seizures was a reduction in the risk of cerebral palsy, and several studies have since confirmed that magnesium sulfate has a neuroprotective effect and can reduce the incidence of cerebral palsy when given to women at risk of early preterm (<32 weeks) birth.[67–69]

Postnatal Pediatric Care

The need for specialized pediatric care is self-evident if birth is very preterm. Given the potential for the need of specialized postnatal pediatric care, clinicians should be prompted to consider referral to a center where such specialized care is available. Specific attention should be given to the problems associated with long-standing metabolic challenges, such as an increased risk of necrotizing enterocolitis and difficulties in achieving full enteral feeding. However, if growth restriction is suspected in a neonate born at term, transitional problems above and beyond those associated with

preterm birth should be anticipated. These problems include neonatal hypoglycemia and jaundice.

Summary and future perspectives

Currently, there is no proven therapeutic option in FGR other than timed delivery. In early-onset FGR, Doppler assessment of UA, MCA, and DV, along with visual or computerized CTG assessment can be used to guide delivery timing. However, the optimal combination of how to use these modalities remains unclear. Some may be indicative in themselves (recurrent FHR decelerations) but most seem to be interdependent. In the future, the integration of these variables in decision support tools is likely to be of great value. The development of such tools would require a collaborative effort to analyze prospectively collected data that include all known prognostic factors: cCTG, fetal sex, gestational age, Doppler measurements of fetal (UA, MCA, DV) and maternal (uterine artery) blood vessels, and maternal characteristics (age, body mass index, blood pressure) as well as serum biomarkers (PlGF, sFLT). In the development of such a model, several sources of bias, including intervention bias and competing risks, need to be accounted for. Moreover, before implementation of decision support, the approach needs to be prospectively evaluated with a randomization element with outcomes that include long-term neonatal follow-up.

In late-onset FGR, identifying the fetus that is at risk for immediate hypoxia and benefits from expedited delivery is the challenge. In most cases, available parameters have imperfect correlation with important outcomes, particularly when considered dichotomously and as stand-alone prognosticators. It is likely that studies in the next decades will provide evidence on how to use estimated fetal size in combination with other identifiers of placental insufficiency in risk models that include these identifiers as continuous variables.

CLINICS CARE POINTS

- The most common mechanism in fetal growth restriction is suboptimal remodeling of uterine spiral arteries, leading to smooth muscle cell vascular reactivity of the maternal vascular bed, resulting in high-resistance placental circulation without a constant large amount of low-velocity maternal blood flow into the intervillous space.
- Doppler ultrasound of the uterine artery, umbilical artery, and middle cerebral artery can be measured throughout pregnancy and provides an indication of placental function.
- The main obstetric decision for fetal growth restriction remains timing of delivery. In early-onset fetal growth restriction, management hinges on weighing the risk of prematurity versus the risk of fetal hypoxia; in late-onset fetal growth restriction, the clinical challenge is the correct diagnosis of the fetus at risk for hypoxia.

DISCLOSURE

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

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