Commentary

Current consensus on the management of fetal growth restriction

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Abstract

Fetal growth restriction (FGR) refers to a fetus that has failed to reach its biological growth potential. Clinically, FGR is described as early or late-onset. Detecting signs of growth deterioration and determining the appropriate timing of fetal rescue delivery is challenging. In early-onset FGR, problems are related to prematurity whereas in late-onset FGR difficulty in diagnosis and resulting fetal mortality are the key problems for the clinician. This review summarizes pathophysiology, recent consensus on the classification of clinical phenotypes, screening, diagnosis, assessment of deterioration and surveillance, monitoring intervals, the timing of birth, neurodevelopment outcomes, term fetal growth restriction and place of cerebroplacental ratio in fetal growth restriction.

Introduction

Optimal growth and suboptimal growth

Optimal fetal growth, i.e. a growth that is not too small and not too big, is classified as an estimated fetal weight (EFW) between the 10th and 90th centiles based on population-specific birth weight centiles corrected for gestational age at delivery, parity, and fetal sex for ease of detection and management. With this definition, growth restriction is an EFW below the 10th centile, better described as small for gestational age (SGA). Fetal growth restriction (FGR) has also been described as the process where a fetus that has a certain growth potential based on genetic criteria does not attain that growth because of environmental influence ['*pathological smallness*'][1]. It is distinct from the term SGA

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which describes both *'pathological and constitutional smallness'*[1]. Since fetal weight depends on its gestational age, fetal dating scan has to be correct to prevent discrepancies from inaccurate dating.

SGA fetus carries an increased risk for stillbirth, and antenatal detection and recognition is inaccurate and suboptimal in most[2]. Antenatal recognition of FGR can halve stillbirth risk through earlier delivery of affected fetuses [fetal rescue delivery][2].

This review addresses pathophysiology, clinical phenotypes, surveillance and current consensus and new insights into the management of FGR.

Pathophysiology

Early-onset FGR

The classical concept is poor placentation leading to insufficient delivery of nutrients and oxygen to the fetus[1]. Uterine spiral arteries are physiologically remodelled into dilated inelastic tubes escaping maternal vasomotor control between 8-18 weeks during placenta formation, which results in a low-resistance uteroplacental circulation.

The pathophysiological pathways for defective placentation include immunological factors, endogenous vascular factors, and thrombogenic factors amongst others[1]. Poor placentation is associated with early-onset phenotype of both preeclampsia and FGR. Most of the women presenting with maternal hypertensive disorders before 34 weeks gestation will also have concurrent FGR. Sharing of a common placental pathology in both conditions may explain this phenomenon and thus confirming the concept of poor placentation[1].

Late-onset FGR

In growth restriction presenting at later gestations, the previous association becomes less obvious. At or near term, most neonates from mothers with preeclampsia are of normal birth weight. Thus, both late FGR and late preeclampsia may be due to a different pathology[1].

Hypotheses proposed include;

1. Secondary placental dysfunction: 'Crowded' large placenta compromising intervillous perfusion.

2. Maternal susceptibility hypothesis: maternal constitutional susceptibility, cardiovascular dysfunction or immunological response.

Because the term fetuses have less placental reserve capacity and require comparatively more oxygen and nutrients, the interval between the onset of the disease and the subsequent adverse outcome is shorter and less predictable[1].

Late-onset FGR is a challenge to predict and harder to distinguish from pregnancies with normal growth. The defective placental maturational process leading to placental hypo-perfusion and late-onset FGR is difficult to diagnose because the size of the fetus and accompanying parameters may not be abnormal and further complicated by combinations and intermediate types[1].

Clinical phenotypes

FGR evolves from a preclinical phase to a clinically obvious phase of growth delay and may eventually lead to fetal hypoxia[3,4]. Reduced growth due to decreased transplacental nutrient supply, gas transfer, and waste removal affect reserves, reflected in reduced fetal liver size and consequently abdominal circumference (AC) first, and subsequent head growth and finally affecting the entire body[3,4]. Abnormal placental perfusion in the maternal compartment results in increased blood flow resistance in the uterine artery, which is reflected in the Doppler flow-velocity waveform[3,4]. Abnormal perfusion of the fetal villous vascular tree is associated with decreased umbilical artery end-diastolic velocity (EDV) proportional to the degree of flow impairment[3,4]. Abnormal oxygen diffusion across the villous membrane leading to lower fetal arterial oxygen saturation (PaO_2) is associated with an attempted increase of blood supply through a decrease in middle cerebral artery (MCA) blood flow resistance[3,4].

Management challenges in early FGR and coexisting maternal hypertensive disease include iatrogenic prematurity whereas, in late FGR, difficulties in diagnosis and surveillance leading to unanticipated stillbirth are the primary issues.

Screening

This is based on clinical findings correlated with ultrasound fetal biometry. Traditional clinical assessment of risk is based on medical and obstetrics history, abdominal palpation for fetal size and symphysis-fundal height (SFH) marked serially over a centile chart. Risk assessment can be done through detailed history according to a recommended standard such as RCOG algorithm or Growth Assessment Protocol algorithm[2,5]. Leopold's Maneuvers are used to estimate the fetal size. However, its ability to predict fetal weight is low, only 30% SGA fetuses will be detected[6].

SFH is the most commonly used screening tool for SGA. SFH should be plotted against the gestational age starting from 24 weeks, then 28 weeks, then two weekly up to 36 weeks and weekly thereafter. SFH has a low sensitivity of 27-76% in predicting SGA, which means it potentially fails to identify over 70% of pregnancies affected by SGA[7]. This is important to consider in counselling of pregnant women[7]. In clinical practice, the SFH measurement should not be carried out in isolation and the combination of other clinical findings, medical conditions, and previous obstetric history, together will contribute to estimating the likelihood of being at risk for SGA. A higher specificity (>80%) of SFH indicates that few pregnancies which are not characterized by SGA, are referred for ultrasound evaluation[7].

Serial SFH helps to predict the need for ultrasound parameters by lagging of fundus in a plotted chart with gestation specific centile curves. The sensitivity of SFH can be improved to 48% by using the customized charts [adjusted for physiological variables such as height, weight, parity, and ethnic origin] for the particular population, which reduces referrals for ultrasound assessment[2]. Customized charts also improve EFW assessment and reduce the false-positive diagnosis of SGA[2].

World Health Organization (WHO) charts, GROW (Gestation Related Optimal Weight) charts, INTERGROWTH-21st project is all different project towards standardizing of customized charts. WHO and GROW charts are widely accepted in clinical practice[2]. GROW charts are useful when looking at subgroups within the population, e.g. maternal size. There is a better correlation between SGA defined by customized centiles and perinatal mortality than any population-based standard. GROW charts also improve the definition of SGA in multi-ethnic populations by re-classification of fetuses as normal growth according to customization[8]. These reclassified fetuses had the same perinatal mortality risk as to the general, non-SGA population further emphasizing the value of customized charts[8].

The INTERGROWTH-21st project has been introduced as a one-size-fits-all standard for birth weight[9]. The INTERGROWTH-21st project was a large-scale, multi-country study that measured fetal growth of babies in utero and at birth, in mothers in whom environmental, social, medical and pregnancy conditions were optimal[10]. It followed low risk, well-nourished mothers, in eight countries and was therefore meant to provide an optimal standard for all pregnancies[9,10]. The INTERGROWTH-21st findings challenge the acceptance of customized fetal growth charts in the UK and elsewhere[10]. Adjusting growth expectations for ethnicity has no biological basis and risks normalizing suboptimal growth in disadvantaged groups[10]. However, this concept has been challenged on theoretical grounds[1,11] and when applied to detailed multi-ethnic maternity data sets, it performed poorly compared to a customized standard[2,12].

Diagnosis

Serial ultrasound biometry and Doppler to confirm compromised circulation is the gold standard to diagnose FGR. Once diagnosed, monitoring is from umbilical Doppler flow (UAD), ductus venosus (DV) and middle cerebral artery (MCA) blood flow patterns. The combination of fetal biometry and UAD is the best available tool for the identification of an FGR fetus[5]. Uterine artery Doppler (UtAD) screening can be performed in 'high risk' cases [Thrombophilia, Previous FGR/Pre-eclampsia]. UtAD offers early evidence to prescribe low-dose aspirin in the first trimester and 85% sensitivity to predict SGA in the second trimester (22-23 weeks) in high-risk women. However, in 'low risk' mothers and after 24 weeks, it has limited predictive accuracy. Diagnosis can be based on fetal biometry alone or by considering UAD or MCA Doppler indices. Abdominal circumference (AC) less than 10th centile has the highest sensitivity for the diagnosis of SGA, whereas EFW less than the 10th centile is more specific[13]. Therefore serial EFW measurements are better than serial AC in detecting

additional FGR,[13]. However, this has to be balanced against the potential +/- 10% margin of error in estimating EFW at term using ultrasound[2].

The diagnostic cut-off for SGA is generally accepted as below 10th centile. One disadvantage of this cut-off is the inclusion of a variable number of constitutionally small ("normal") fetuses that do not require surveillance[2]. These otherwise normal constitutionally small babies have comparable perinatal mortality to that of the normal population[2]. EFW less than 3rd centile or a decreased AC is more likely to identify "true FGR". The disadvantage of taking 3rd centile for cut-off is less severe form of FGR at risk for deterioration will be missed with the resulting risk of increased stillbirth. A combined consensus has been agreed on for diagnosis[14].

Although placental pathology does not support such clear-cut division, expert opinion considers FGR presenting before 32 weeks as "early-onset" and after 32 weeks as "late-onset" (Table 1). An estimated fetal weight less than the tenth percentile in association with an elevated umbilical artery Doppler index, a decreased middle cerebral artery Doppler index or a decreased cerebroplacental ratio (CPR) should be considered as evidence of FGR[3]. Early-onset and late-onset FGR represent two distinct clinical phenotypes of placental dysfunction. According to the Internal Society for Ultrasound in Obstetrics and Gynaecology (ISUOG) definition of FGR, "AC/EFW crossing centiles" can be defined as crossing> 2 quartiles or 50th centile as long as it occurs in a SGA fetus (AC/EFW < 10th centile) and/or in combination with a low CPR or elevated UAD Pulsatility Index[14].

Table 1. Consensus-based definitions for early and late fetal growth restriction

Early-onset growth restriction *(in the absence of fetal anomalies)*	AC or EFW <3rd centile or absent EDF in the umbilical artery or 1) AC/EFW <10th centile combined with 2) Uterine artery PI >95th centile and/or 3) Umbilical artery PI >95th centile
Late-onset growth restriction *(in the absence of fetal anomalies)*	AC or EFW <3rd centile or At least two of three of the following: 1) AC/EFW <10th centile 2) Crossing centiles* of more than two quartiles on growth centiles 3) CPR <5th centile

*AC/EFW crossing centiles can be defined as crossing > 2 quartiles or 50th centile as long as it occurs in a SGA fetus. *AC, abdominal circumference; CPR, cerebroplacental ratio; EDF, end-diastolic flow; EFW, estimated fetal weight; PI, pulsatility index.* Source: Adapted from Gordijn et al[14].

Assessment of the degree of fetal deterioration

Gestational age is a critical determinant in decision making. Fetal surveillance tests are applied in pregnancies with suspected FGR to estimate the risk for hypoxia, prelabor acidosis, and antepartum stillbirth, as well as the clinical deterioration. An accurate estimation of hypoxia/ acidosis is important to predict fetal compromise, risk of stillbirth and therefore the timing of delivery[3,4]. Doppler indices and biophysical profile (BPP) provide estimates for pre-labor acidosis.

Integrated multimodal fetal testing is probably the way forward compared to the elusive single best test of fetal well-being. Tests include kick count charts, clinical examination, Doppler parameters, and BPP. Abnormal umbilical flow patterns indicate an increased risk of hypoxia and acidosis. Fetal acidosis is directly proportional to the reduction in umbilical artery EDV with acidosis highest in reversed flow in end-diastole. However umbilical artery Doppler alone as a single test is not justified due to the wide range of pH distribution and additional Doppler indices are indicated depending on the gestation.

DV Doppler and presence of 'a' wave for forwarding blood floware indicated up to 32 weeks for fetuses with absent or reversed umbilical artery Doppler indices. MCA Doppler has limited accuracy to predict acidosis before 32 weeks and adverse outcomes and should not be used to time delivery in early FGR. Beyond 32-34 weeks, the umbilical artery waveform may be normal with developing acidosis. Therefore, better predictors for fetal hypoxia and deterioration is MCA PI and cerebroplacental ratio (CPR) beyond 32 weeks, which is considered as abnormal if less than 5th centile.

BPP shows a reliable and reproducible relationship with the fetal pH, irrespective of gestational age[3,4]. Each component in BPP is independently altered by hypoxia and it takes minimum 30 minutes of work to assess one fetus[3,4]. It can be combined with computerized CTG (cCTG). Abnormal CTG is associated with a wide range of pH values, unlike cCTG. However, cCTG as a stand-alone test in FGR offers limited accuracy. BPP parameters (especially loss of tone) have a narrower pH distribution in acidosis when compared to Doppler[3,4]. BPP alone has limited utility in the prediction of longitudinal deterioration, which is better assessed with Doppler[15,16].

Selection of the monitoring intervals

Fetal surveillance is indicated to prevent stillbirth and irreversible fetal deterioration by early detection of prelabor acidosis and carry out a fetal rescue delivery balancing against neonatal morbidity and mortality of preterm birth. The consensus is based on expert opinion due to a lack of high-quality evidence to guide practice[3]. Once FGR is diagnosed, longitudinal surveillance starting at 24 to 26 weeks with integrated multimodal fetal testing, including multi vessel Doppler assessment, fetal heart rate analysis, and BPP is considered best practice[3,4]. It is expected that the combination of these tests improves the prediction of acidosis and stillbirth compared with single tests as outlined above.

In early FGR, fetal needs are less and allow a relatively chronic course leading to a small baby. Fetal deterioration typically evolves from abnormal umbilical artery Doppler studies to brain-sparing, then abnormal ductus venous Doppler, abnormal cCTG, and finally, abnormal BPP. The rate of progression is determined by the interval between diagnosis to loss of umbilical artery EDV which typically takes four to six weeks. Once forward velocities in the DV Doppler become absent or reversed, fetal survival of longer than one week is unlikely[17].

In late FGR, risk of terminal deterioration and unanticipated stillbirth is high, warranting closer surveillance. There are no evident Doppler changes in the precordial veins [pre-load to the fetal heart] and brain sparing may be the only observed Doppler sign of hypoxia. The new onset of Doppler abnormalities signals to expedite the birth[3,4]. Closer surveillance is required after 34 weeks because more fetal needs, less placental reserve and less time to adapt.

Planning birth

Gestational age should be the intervention threshold. Neonatal survival, more importantly neurologically intact survival, improves with gestational age. Planning birth is a decision taken after balancing the risks and benefits of birth compared to the continuation of pregnancy.

1. 24 to 26 weeks: Even with the best available care, the survival rate of growth-restricted neonates average less than 50%[18]. In the

surviving babies, risks for major neonatal morbidity is high as 80%. The survival rates exceed 50% once the EFW exceeds 500 g and/or when 26 weeks have reached. Delivery at this age is more commonly due to maternal life-threatening conditions such as severe pre-eclampsia than FGR.

2. 26 to 28 weeks: Neonatal survival exceeds 50%. However, intact survival (survival without prematurity-related morbidity) at 26 to 27 weeks remains around 30%. Ductus venous Doppler abnormalities are not considered as an indication to birth until 28 weeks[3] while abnormal BPP ($< 6/10$) is an indication for delivery. Each day in utero increases neonatal survival by a median of 2%[3].

3. 28 to 32 weeks: Neonatal survival exceeds 70% at 28 weeks and increases to more than 90% at 32 weeks. Fetal deterioration of venous Doppler parameters may be tolerated as long as DV flow is forward. Reversal of the DV a-wave before delivery reduces the chance of neonatal survival. Persistence of this abnormality beyond one week carries a significant risk for stillbirth. For this reason, the presence of a DV reversed a-wave is generally considered an indication of inter-vention from 28 weeks. However, birth before 30 weeks gestation still carries a significantly higher risk for adverse neurodevelopment at age two because of neonatal complications and their impact on motor development. Each day in utero increases neonatal survival by a median of 1%. These conclusions were based on TRUFFLE and GRIT trials and their follow up data[19,20,21,22]. Although there is no difference in neonatal mortality between immediate and deferred deliveries, due to a significant difference in morbidity in an immediate delivery group of early FGR, delaying at least up to 32 weeks is generally advocated based on these TRUFFLE and GRIT data[19,20,21,22].

4. 32 to 34 weeks: Cerebral circulation gains an additional structural layer reducing cerebral haemorrhage risk during this period. This reduction has a measurable impact on motor development at age three. Administration of antenatal steroids has an added benefit in reducing respiratory morbidity and cerebral haemorrhage, and babies who have received steroids have improved survival. Evidence suggests that neurodevelopment is also improved by the administration of steroids[23]. Umbilical artery absent/reversed EDV is generally considered an indication for birth from 32 weeks onwards.

5. 34 to 38 weeks: Gain in survival as well as neonatal morbidity is minimal. However, up to 38 weeks gestation, the rate of neonatal admissions to the NICU is still significantly greater for FGR infants. Umbilical artery absent/reversed EDV is an indication of delivery from 34 weeks onwards. MCA Doppler is considered the best predictor of fetal adaptation to hypoxia, and some guide-lines recommend the use of this parameter to time delivery in fetuses with normal umbilical artery Doppler[5].

6. After 38 weeks: Neonatal adverse events in SGA infants are negligible and, accordingly, on-going pregnancy must be weighed carefully against the risks of unanticipated stillbirth if the patient remains undelivered. DIGITAT study has shown among women with sus-pected FGR at 36-41 weeks, a policy of labour induction affects neither the rate of adverse neonatal outcomes nor the rates of instru-mental vaginal delivery or caesarean delivery, indicating that both approaches are acceptable[24]. PROBAAT study group has shown that the use of Foley catheters for labour induction offers a better outcome compared to prostaglandins for FGR fetuses[25]. The consensus from the DIGITAT trial is that the optimum time for induction in SGA with normal Doppler study is around 38 weeks because it is associated with the lowest neonatal morbidity and seems to minimize the risk of stillbirth[26].

Between 24 and 34 weeks, a single course of steroids should be given over 48 hours if birth is being considered in the next seven days. Magnesium sulphate for fetal neuroprotection needs to be considered before

34 weeks which halves the risk of cerebral palsy. Birth should be planned at a centre with neonatal intensive care facilities and mode of delivery depends on the severity of fetal compromise, along with other maternal and obstetric factors. In FGR cases with abnormal UAD, induction of labour can be offered, but the rate of emergency caesarean birth is high. Because of the increased risk of intrapartum asphyxia in FGR, continuous FHR monitoring is recommended from the onset of uterine contractions.

Neurodevelopmental outcomes in FGR

In early FGR, particularly before 28 weeks, gestational age at birth and birth weight are the most important predictors for poor neurodevelopment, advanced cardiovascular deterioration, and ICH leading to psychomotor retardation. Whereas in late FGR, gestational age at birth is a smaller contributor and other main predictors have yet to be defined. It mainly affects behavioral rather than motor development.

Cerebroplacental ratio and 'term FGR'

Many groups have suggested the CPR as a functional marker of failure to reach growth potential at or near term[26]. Low CPR, regardless of the fetal size, is independently associated with the need for operative birth for presumed fetal compromise and neonatal unit admission at term[26]. Rising evidence proposes that CPR as a marker of impaired fetal growth velocity and adverse pregnancy outcome, even in fetuses whose size is considered "appropriate for gestational age" using conventional fetal biometry[26,27]. Therefore it is wise to apply CPR at 40 weeks assessment of low-risk pregnancies with fetal biometry to assess the suitability to wait a few more days without intervention.

Conclusion

Early FGR is associated with significant uteroplacental blood flow abnormalities and abnormal cardiovascular findings with evolving deterioration. In contrast, late FGR is not dominantly associated with placental vascular blood flow abnormalities and shows minimal signs of deterioration making it difficult to predict. EFW below the 10th centile with co-existing UAD and/ or MCA Doppler flow and/or CPR abnormalities can identify a small fetus with pathological growth restriction requiring antenatal surveillance and planning

delivery. Gestational age is the primary determinant as the threshold for intervention in planning delivery. Decision of timing of delivery is a balanced decision after considering fetal risks of continuing pregnancy and neonatal risks after delivery.

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