Intra Uterine Growth Restriction

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Introduction

In the beginning of the 20th century, the only explanation that was offered to a small baby born was that of prematurity. Fetal growth was defined by birth weight alone. The concept that a fetus might suffer poor growth in utero became recognized in the 1960's. In 1963 Lubchenco and colleagues showed that the classification of neonates by birth weight percentile had a significant prognostic advantage. This classification improved the detection of neonates with intra uterine growth restriction and those at risk of adverse health events throughout life.[1]

It is widely recognized that we cannot follow a one-size-fits-all approach when assessing growth. The introduction of customized growth charts by Gardosi and colleges, based on growth potential, further improved the detection of fetal growth restriction and the ability to predict adverse perinatal outcomes.[2,3]

Although the immediate effect of disturbed fetal growth is an abnormal expression of the growth potential, the effect on outcome and fetal programming is determined predominantly by the underlying condition.[1] The mechanisms responsible for fetal growth include genetic, nutritional, placental and hormone factors. Changes in these factors, as well as interference from external factors, such as the use of medications, drugs and infections, result in inadequate fetal growth.[4]

The significance of intra-uterine growth restriction (IUGR) is clearly established and remains one of the main challenges in maternity care. We know that this condition is associated with stillbirth, neonatal death, and perinatal morbidity. The delayed effects include cerebral palsy and adult disease.[5] The risk of perinatal morbidity and mortality rises with the severity of the restriction in growth.

The detection of IUGR remains poor in high risk pregnancies and even worse in the low risk patient.

Experts are in agreement that we need better definition of IUGR, appropriate management protocols based on available evidence, as well as individualized clinical assessment to ensure good prenatal management and timely delivery.[4,5]

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Fetal growth

The concept of fetal growth is more comprehensive than fetal weight appropriate for gestational age. Fetal weight, body mass and body proportion needs to be taken into account to evaluate growth potential. (E.g. Inappropriate fetal growth is also suggested by abnormal symmetry between head and abdominal measurements.)[4]

In clinical practice, if we only identify fetuses that fall below the 3rd (WHO recommendation) or 10th percentile (ACOG guidelines) on growth charts, we cannot differentiate between the three distinct groups. These groups are the constitutionally small fetus, the growth restricted and small fetuses, and the growth restricted but not small group.

Constitutional factors include female sex, ethnicity of the parents, parity and body mass index. According to the literature the majority (70%) of fetuses who are estimated to weigh below the 10th percentile for gestational age are small due to constitutional factors. They are not at high risk of perinatal mortality and morbidity.[6]

The issue of identifying small for gestational age (SGA) infants has been addressed by the introduction of customized growth charts, which have sound physiologic and epidemiologic rationale.

A growth restricted but not small for gestation fetus is found when a fetus with appropriate weight for gestation suffered a deceleration in the rate of growth as a consequence of an intrauterine injury, with increased perinatal risk.[7]

Normal fetal growth reflects the interaction between the genetically predetermined growth potential and the presence of a healthy fetus, placenta and mother.[4]

Successful placentation is required for the coordination of key components within the maternal, placental and fetal compartments. The growing trophoblast receives the necessary nutrients and oxygen via the placental vasculature. Adherence and implantation of the blastocyst during the first trimester initiate the development of these vessels. Differentiation of placental transport mechanisms and activation of signalling pathways are established by the second trimester. Trophoblastic invasion into the maternal spiral arteries and fetal villous sprouting decrease the blood flow resistance in both vascular compartments of the placenta. Placental and fetal growth is regulated by a combination of factors including substrate availability, placental perfusion in the maternal compartment, endocrine or paracrine signalling, and perfusion and

nutrient exchange area in the fetal compartment of the placenta. In addition the design of the fetal circulation is unique because it allows for preferential streaming of nutrients via three principal shunts.

Normal placental and fetal growth across pregnancy is characterized by sequential phases that can overlap:

- *Phase one*: cellular hyperplasia (first 16 weeks of gestation)
- *Phase two*: hyperplasia plus hypertrophy, increase in cell size and number(weeks 16 to 32)
- Phase three: hypertrophy alone, (32 weeks until term) and is characterized by a rapid increase in cell size.[4,7]

Placental growth follows a sigmoid curve, plateauing earlier in gestation than fetal growth. Between 16 weeks and term human fetal weight increases 20-fold. The fetal growth curve is exponential, with maximal growth occurring in the third trimester when significant body mass and particularly adipose tissue are accumulated.[1]

Quantitatively, normal singleton fetal growth increases form approximately 5g/day at 14 to 15 weeks to 10g/day at 20 weeks and 30-35g/day at 32 to 34 weeks, after which the growth rate decreases.[8] The total substrate needs of the fetus are thus relatively small in the first half of pregnancy, after which the rate of weight gain rises precipitously. The mean weight gain peaks at approximately 230 to 285 g/week at 32 to 34 weeks of gestation, after which it decreases, possibly even reaching zero weight gain or loss, at 41 to 42 weeks of gestation. If growth rate is expressed as the percentage of increase in weight over the previous week, however, the percentage of increase reaches a maximum in the first trimester and decrease steadily thereafter.[9]

The pattern of normal fetal growth forms the basis for the clinical classification of fetal growth restriction in three types:

- ***Type I: symmetric or harmonious***

The growth is affected from early in the pregnancy, during the phase of cell hyperplasia. There is reduction in the intrinsic potential of fetal growth, with proportional decrease in all measurements. There are two subtypes:

a) *Constitutionally small fetus or normal small fetus:* A study in 2000 showed lower percentage of aneuploidy, malformations, prematurity, as well as better results in terms of neonatal morbidity and mortality when compared with type II or asymmetric growth restriction. The reduction in growth is prior to 30-32 weeks. The head circumference corresponds to the birth weight, with a 2-3 week delay to the gestational age.

b) *Fetuses with congenital abnormalities:* There is an early reduction in embryonic or fetal growth. Growth restriction presents early and can is severe. The perinatal prognosis is worse due to reduced number of neurons.

- ***Type II: asymmetric and non-harmonious***

Alteration of growth begins after 30 to 32 weeks (during the cell hypertrophy phase). The head circumference and measurements of the long bones correspond more to the gestational age than to weight. The cerebellum is an important organ for correct diagnosis of gestational age. There is a reduction only in abdominal volume and size, hence asymmetric growth. The number of cells in the organs is often normal, but there may be more severe cases with reduced cell mass especially in the lungs and kidneys. Placental insufficiency is the primary etiologic factor. Fetal hypoxemia and academia are associated with this type of growth restriction and there are studies relating it to cardiovascular diseases in adult life.

- ***Type III: fetuses with semi-harmonious growth and hypotrophic appearance***

Alterations occur during the second trimester, during the phase of hyperplasia and hypertrophy. The aetiology and pathogenesis are related to embryonic infections (rubella, cytomegalovirus, toxoplasmosis, and others) and toxic agents that affect the fetus (medications, illicit drugs, and toxins).[4]

Although the immediate effect of disturbed fetal growth is an abnormal expression of the growth potential, the effect on outcome and fetal programming is determined predominantly by the underlying condition.[1] This determines the prognosis of the fetus with growth restriction, in terms of neonatal morbidity and mortality.[4]

The mechanism of placental dysfunction determines the time of the insult or onset of disease, as well as the degree thereof. Metabolic and cellular effects of placental dysfunction leads to a combination of fetal starvation, a modified endocrine milieu, and deficient tissue stores that limit fetal growth and affects cellular and functional differentiation in many target organs. The overall effect is an improved distribution of well-oxygenated blood to vital organs, with preferential streaming of descending aorta to blood flow to the placenta for re-oxygenation. Blood flow to organs that are not vital for fetal survival is decreased. The gestational age of onset, the magnitude of injury, and the success of adaptive mechanisms determine the ultimate severity of suppression/limitation of growth.[9]

Screening options for growth restriction

Clinical assessment remains a reasonable screening tool for FGR in low risk pregnancies. Clinical assessment is based on assessment of past and present risk factors, physical examination, and ultrasound studies.[7]

The accurate determination of gestational age is paramount for suspicion and confirmation of FGR.

The accuracy of fundal height measurement for screening and diagnosis of FGR remains controversial, with sensitivity of symphysis-fundal height (SFH) measurements for detection of small fetuses ranging from 28 to 86 percent. The method performs best when all of the measurements are done by the same clinician. The most common criterion for demonstrating restricted growth is when there is a difference greater than 3 cm between the SFH and the number of gestational weeks.[10] Similarly, abdominal palpation for fetal size determination and detection of FGR does not perform well. (Sensitivities: 30 to 50 percent).

There is general consensus that once the suspicion of FGR has arisen, sonographic techniques should be used to try to confirm or exclude the diagnosis.

ETIOLOGY			
MATERNAL	*FETAL*	*PLACENTAL*	*UTERINE*
• Hypertensive disease (chronic, PET) • Renal disease • Severe nutritional deficiencies (IBD, inadequate pregnancy weight gain in the underweight woman, malnutrition) • Pregnancy at high altitude • Chronic maternal hypoxia (pulmonary disease, cyanotic heart disease) • Specific prescribed medications (e.g., antiepileptics) • Smoking, alcohol use, illicit drug use, toxins • Anaemia • Fever • Haematological an immunologic disorders (sickle cell disease, APLS) • Maternal age (teenaged, advanced maternal age)	• Multiple gestations • Infections • Chromosomal abnormalities (aneuploidy, partial deletions, ring chromosomes, gene mutations) • Structural abnormalities (e.g. heart disease, osteogenesis imperfecta) • Assisted reproductive technologies	• Abruption placentae, placenta previa • Uteroplacental vasculature abnormalities (maldevelopment, obstruction, disruption) • Thrombosis, infarction (fibrin deposition) • Confined placental mosaicism • Deciduitis, diffuse chronic vilifies • Distal villous hypoplasia • Placentitis, vasculitis, oedema • Chorioamnionitis • Placental cysts, chorioangioma	• Decreased uteroplacental blood flow • Atheromatosis, arteriosclerosis of decidual spiral arteries • Fibomyoma • Morphologic abnormalities

Biochemical markers

Maternal serum analyte screening is a non-invasive test of placental biochemical function. Hormone or protein markers measured in the maternal sera early in the second trimester, which are associated with subsequent IUGR, include oestriol, human placental lactogen (hPL), human chorionic gonadotropin (hCG), and α – fetoprotein (AFP). Maternal serum AFP is the most useful as a marker of abnormal placentation.[1]

The optimal way of incorporating these markers into clinical practice are still remains unclear.

Uterine artery doppler studies

Several studies have demonstrated an association between second-trimester uterine artery Doppler resistance indices (RI) that is high, persistently notched, or both and subsequent development of FGR)[11], gestational hypertensive disorders and fetal demise. The sensitivity is up to 85% when performed between 22 and 23 weeks gestation.[1] The same evidence could not be gathered for the use of uterine Doppler alone in the first trimester due to low sensitivity in clinical practice to predict FGR.

First trimester integrated screening

The most severe forms of placental dysfunction originate during the first trimester and interventional strategies appear most effective at this point. This led to an increasing focus to identify early makers of placental failure. Integrating these markers with maternal history (risk factor), physical characteristics (first trimester mean arterial pressure) and uterine artery Doppler are considered most promising. However, performance of integrated screening models appears to vary amongst populations and further research is necessary to identify optimal predictive algorithms and determine the best management strategies for patients identified as high risk.[1]

Three-dimensional (3D) ultrasound

The size of the placenta and the vascular flow patterns within the placental villous tree in early pregnancy might predict adverse pregnancy outcome, including pre-eclampsia and FGR.[12] Three-dimensional (3D) ultrasound can assess placental volume more accurately in the first trimester, and the 3D power Doppler permits assessment of the flow in thin vessels of placenta in the first trimester. A study by Hafner et al compared placental volume by 3D ultrasound at 12 weeks with uterine Doppler at 22 to predict preeclampsia and FGR. They observed similar detection sensitivities for prediction preeclampsia and FGR. Odibo et al assessed the placental volume and vascularisation at 11-14weeks in the prediction of adverse pregnancy outcomes. They found the vascular indices significantly lower in pregnancies that developed pre-eclampsia. New studies are necessary to prove the real importance of volume and vascularisation of placenta by 3D ultrasound in the prediction of FGR.[4]

Ultrasound assessment

Currently, ultrasonographic evaluation of the fetus is the preferred and accepted modality for the diagnosis of inadequate fetal growth. It offers the advantages of reasonably precise estimations of fetal weight, determination of interval fetal growth velocity, measurement of several fetal dimensions to describe the pattern of growth abnormality, and assist in the investigation of the aetiology of restricted growth. The

interpretation of ultrasonographic findings requires accurate knowledge of gestation age, and a skilled sonographer.

Measurements of biparietal diameter, head circumference, abdominal circumferences, and femur length allow estimation of fetal weight and determine whether a fetal growth aberration represents an asymmetric, symmetric, or mixed pattern.13

Abdominal circumference is the most sensitive measurement for the detection of IUGR. Specificity 89.9% and negative predictive value 90,7%. The decrease in the circumference is due to a smaller liver, diminished accumulation of glycogen, and depletion of adipose tissue in the abdominal region.[14]

Distinguishing between symmetric and asymmetric IUGR is also of considerable clinical significance and may provide useful information for both diagnostic and counselling purposes.[9] Determining prognosis will further assist in decisions regarding fetal evaluation, appropriate timing of delivery, and the need of skilful neonatal management.

In many developed countries, three ultrasound tests are recommended. The first performed between 11 and 14 weeks, in order to confirm gestation, screen for aneuploidy, and to determine the number of fetuses. The second examination between 20 and 24 weeks, have the objective to morphological evaluate the fetal growth, placental location, determination of quantity of amniotic fluid, and evaluation of the cervical canal. At the beginning of the third trimester (30-32 weeks), again the fetal growth curve is checked in addition to the quantity of amniotic fluid and fetal vitality by means of biophysical parameters.[4]

Introduction of a third examination has been motivated as a tool to identify and diagnose late onset growth restriction.

Routine or intermittent third trimester ultrasound biometry and the effectiveness thereof in diagnosing growth restriction and its impact on perinatal outcome remain uncertain. Currently there is insufficient evidence to support routine third trimester ultrasound in low risk pregnancies.

For pregnancies at risk, serial assessment of estimated fetal weight or abdominal circumference is the best predictor of FGR. Therefore serial biometry is the recommended gold standard for assessing pregnancies that are high risk, either on the basis of past history or because of complications that arose during the current pregnancy.[5]

Furthermore, the use of 3D ultrasound and volume estimation can assist in more accurate weight determination.

Doppler velocimetry

Doppler (maternal - uterine arteries, fetal-placental - umbilical arteries, and fetal - middle cerebral artery, abdominal aorta, renal arteries, ductus venosus, transverse sinus provides a unique possibility of identifying placental insufficiency and of evaluating fetal hemodynamic alterations that occur in response to oxygen deficiency in a non-invasive form. It also promotes the differential diagnosis between pathological restrictions, that is, fetus with a deficit of nutrients and hypoxemia that require intensive monitoring from those that are constitutionally small, in whom a more conservative treatment can be adopted. In addition, it aids in the investigation of other etiologic factors that might be involved, such as aneuploidy and congenital syndromes. There is consensus regarding the fact that its use significantly reduces perinatal mortality, as well as iatrogenic prematurity and its complications.[15]

Placental insufficiency remains the most common cause of growth restriction and evaluation of placental function by umbilical artery Doppler remains the gold standard. Although it is a good predictor of poor perinatal outcome in early-onset disease, this may not be true for late-onset cases.

Other vascular examinations that can be helpful in all forms of growth restriction are the middle cerebral artery Doppler. Studies have shown that a reduced resistance are found in up to 20% of SGA fetuses, and this sign is also associated with poorer perinatal outcome and suboptimal neurodevelopment at 2 years of age. Umbilical and cerebral artery Doppler can be combined in the cerebroplacental ratio. This ratio has been demonstrated in animal and clinical models to be more sensitive to hypoxia and correlates better with adverse outcome.[5]

Late onset growth restriction

Current thinking on the natural history of growth restriction differentiates between early-onset and late-onset forms, which have different biochemical, histological, and clinical features. Whereas the former is usually diagnosed with an abnormal umbilical artery Doppler and is frequently associated with preeclampsia, the latter is more prevalent, shows less change in umbilical flow pattern, and has a weaker association with preeclampsia.[5]

Further differences were pointed out by Baschat and colleagues. The main challenge in early-onset growth restriction remains timely and correct management, whereas diagnosis remains the biggest challenge in the late-onset counterpart. In early-onset IUGR, the degree of placental disease is high and frank hypoxia illicit cardiovascular adaption. The degree of placental disease is much lower in late-onset growth restriction, with cardiovascular adaptation possible even with subtle hypoxia, therefore showing much less tolerance to hypoxia. The early-onset variant has high morbidity and mortality whereas late-onset disease has lower mortality, but higher risk of neurologic morbidity and of a greater magnitude.[16]

Management

Because no treatment has been demonstrated to be of benefit for FGR, the assessment of fetal well-being and timely delivery remains as the main strategy for management. Fetal well-being tests could be classified as chronic or acute. Whereas the former becomes progressively abnormal because of increasing hypoxemia and/or hypoxia, the latter correlates with acute changes, occurring in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis, and usually precedes fetal death by a few days.

Because a fixed sequence of fetal deterioration does not exist, integration of several well-being tests into comprehensive management protocols is required.

- *Chronic tests*: Umbilical artery Doppler, Middle Cerebral artery Doppler, Amniotic fluid volume
- *Acute markers*: Ductus venosus Doppler, Fetal heart rate analysis, Biophysical profile score;

Timing of delivery

The only current treatment for IUGR remains to be delivery. The challenge remains balancing the risk of potential iatrogenic morbidity and continued exposure to an unfavourable intra-uterine environment.[5]

With regard to late-onset IUGR, studies are still ongoing and prospective trials are underpowered to determine the value of elective induction after 36 weeks gestation.

The multicentre Growth Restriction Intervention Trial compared outcome after randomization with early or delayed delivery in early-onset growth restriction and concluded that it was safe to wait, especially at preterm gestation. The study design has been criticized for having clinical selection bias (preferentially included the less severe cases) in which it would be safe to wait anyway. Therefore, such results cannot be extrapolated to all cases of IUGR.

The TRUFFLE Trial (trial of umbilical and fetal flow in Europe) is an on-going randomized clinical trial aimed at evaluating the role of Ductus venosus Doppler assessment over standard management based on cardiotocography for timeous delivery of early-onset IUGR cases.

Current best practice would indicate that from the time fetal pulmonary maturity can be inferred, delivery is indicated if good fetal growth cannot be demonstrated. However, each case needs to be carefully assessed and individually considered, in consultation with the parents.

Neonatal outcome

The growth restricted fetus can experience numerous complications in the neonatal period. This may relate to the aetiology of the growth insult as well as antepartum and intrapartum factors. These include neonatal asphyxia, meconium aspiration, metabolic abnormalities (including hypoglycaemia), and polycythemia. After correction for gestational age, a large population-based outcomes analysis showed that the premature IUGR infant is at increased risk of mortality, necrotizing enterocolitis, and need for respiratory support at 28 days of age. This observation becomes more significant as prematurity and IUGR coexist.[9]

Beyond the neonatal period, data by Low *et al*[18] showed that fetal growth restriction has a deleterious effect on cognitive function, independent of other variables. They found that almost 50% of SGA children had learning deficits at age 9 to 11 years. A strong association was found

Temporal sequence of fetal deterioration[1,9,21]

Decrease in umbilical venous volume flow (precedes clinical recognition) = no blood flow redistribution			
Umbilical venous flow redistributed away form liver, towards heart. Liver size decreases, AC decreases (first biometric sign of FGR)	• Asphyxia extremely rare • ↑Risk for intra- partum distress	IUGR WITH NO BLOOD FLOW REDISTRIBUTION	• Deliver for maternal or obstetric indications • Fortnightly Doppler, Weekly BPS
Increase in umbilical artery Doppler index (diminished end diastolic flow due to increased resistance in placental vasculature	• Hypoxemia possible • Asphyxia rare • ↑Risk for intra- partum distress	IUGR WITH BLOOD FLOW REDISTRIBUTION	• Delivery if maternal or obstetric indications • Weekly Doppler • Twice a week BPS
Middle cerebral artery index decreases (increased end diastolic flow) = brain sparing effect (preferential perfusion of the brain)	• Hypoxemia common • Academia or asphyxia possible • Onset of fetal compromise	SIGNIFICANT REDISTRIBUTION, UA: A/REDV	• Deliver if > 34 weeks • <32 weeks: give antenatal steroids, daily testing
Myocardial dysfunction due to chronic hypoxia and nutritional deprivation. Increased fetoplacental arterial impedance, increased ductus venosus indices. Cardiac performance deteriorates, absent or reversed end diastolic flow in the ductus venosus and pulsatile umbilical venous flow may develop, can be pre-terminal events	• Cardiovascular instability • Metabolic compromise • Stillbirth imminent ↑perinatal mortality irrespective of intervention	FETAL DECOMOPENSATION (Ductus venosus – absent/ reversed a wave, pulsatile Umbilical vein, BPS 6, oligohydramnios)	Delivery at tertiary care centre with highest level of NICU care

AC= abdominal circumference; FGR= fetal growth restriction; BPS=biophysical profile score; UA=umbilical artery; A/REDV=absent/reversed end diastolic flow

between IUGR and spastic cerebral palsy in newborns, which was highest in IUGR infants who were short, thin, and had a small head size. Danish investigators observed a significantly lower cell number in the cortex of IUGR fetuses and infants compared with normal controls, which in part explain the clinical explanation.[19]

There is currently a substantial research effort to explore the role of IUGR and adult disease: the so-called 'fetal origins of disease' hypothesis. The epidemiologic studies of Barker's group have indicated that IUGR is a significant risk factor for subsequent development of chronic hypertension, ischemic heart disease, type 2 diabetes, and obstructive lung disease.[20] Maternal and fetal malnutrition seem to have both short- and long-term effects. The concept of programming during intrauterine life, needs to include a host of other factors, such as the genotype of mother and fetus, maternal size and obstetric history, and postnatal and lifestyle factors.

Conclusion

Revisiting aetiological and pathogenic routes involved in growth restriction of the fetus helps us to appreciate the complexity of this challenging obstetric problem. There is still room for improvement in all the aspects of this condition: diagnosis, management and timely delivery. We are still discovering different manifestations of this disease, as evidenced most recently by the acknowledgement of late-onset growth restriction. While we are awaiting guidance from further studies on management protocols and timing of delivery we need to remain alert and sensitive to this challenge in our obstetric practises.

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