Early- and Late-onset Intrauterine Growth Retardation

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ABSTRACT

Aim and objective: The scope of this literature review was to synthesize the available evidence on the diagnosis and management of early and late-intrauterine growth retardation (IUGR).

Background: Intrauterine growth retardation is a common obstetric complication affecting about one out of 10 pregnancies and may be associated with both short- and long-term adverse outcomes.

Review results: Risk factors for IUGR include maternal, fetal and placental parameters like smoking, chromosomal abnormalities and placental mosaicism. Early-IUGR, usually correlated with preeclampsia, is difficult to manage, while late-IUGR may not be promptly diagnosed, but is associated with lower mortality. In addition, both entities follow different patterns of progression. For each case, ultrasound growth evaluation at 2-weeks intervals and regular Doppler monitoring are needed, along with cardiotocography. Moreover, a normal umbilical artery Doppler pattern in the third trimester endorses a normal pregnancy in the early-IUGR, but as for the clinical follow-up of late-IUGR fetuses, cerebroplacental ratio is the appropriate parameter for monitoring. Thus, timing of delivery is usually affected by these factors. Finally, the combined first-trimester screening might help in the prediction of IUGR.

Conclusion: The diagnosis of fetal hypoxia in the third trimester remains a challenge for modern obstetrics. Hence, all fetal-maternal units should adopt and follow their own protocol for the management of IUGR.

Clinical significance: IUGR remains a major problem in both developing and developed countries and several causes have been identified. More research in the field of prevention and the appropriate timing of delivery would probably improve perinatal outcomes of the affected fetuses.

Keywords: Complications, Delivery, Diagnosis, Fetal growth restriction, Intrauterine growth retardation, Management, Other, Prevention, Small-for-gestational-age, Ultrasound.

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INTRODUCTION

Fetal growth is the result of the maternal availability of nutrients, placental transfer and fetal growth potential.¹ The prevalence of intrauterine growth retardation (IUGR) is estimated 10–15% among pregnant women.² Potentially risk factors like maternal obesity, smoking in pregnancy, and fetal growth restriction together account for 56.1% of the stillbirths. Presence of fetal growth restriction has the higher risk for stillbirth and is fivefold greater if it was not detected antenatally than when it was (32.0% vs 6.2%).³ It is estimated that almost 11% of all neonates delivered in developing countries and up to 66% of them in developed countries have low birth weight.

The understanding of many aspects of IUGR is still evolving and its management continues to challenge obstetricians worldwide.⁴ Since there is no effective fetal therapy, the importance of gestational age at diagnosis and delivery as a determinant of many critical perinatal outcomes has become more apparent.^{5–9} The last decade, two different patterns of clinical presentation, determined primarily by the gestational age at the time of diagnosis have been more clearly characterized.^{10–13} Early-onset IUGR (E-IUGR) is more consistent with placental insufficiency than those presenting later in gestation called late-onset IUGR (L-IUGR).^{13,14} Distinctions between early and late clinical manifestations of the two conditions will further facilitate the understanding of the etiology, the identification of risk factors and the improvement of predictive models.¹⁵

DEFINITION—CLASSIFICATION

Small for Gestational Age

Small-for-gestational-age (SGA) mainly encompass a majority of constitutionally small but healthy fetuses at lower risk of

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abnormal perinatal outcome.¹⁶ From both a clinical and a scientific perspective, it is most relevant to focus on fetuses that are at risk for adverse outcome, highlighting the need for a clear definition of IUGR other than SGA. Several parameters have been used to distinguish IUGR from SGA and may improve the detection rates of IUGR and its complications. These include sequential ultrasound measurements focusing on declining/crossing growth centiles, functional parameters such as Doppler waveform analysis [umbilical artery (UA), fetal middle cerebral artery (MCA) and ductus venosus (DV)] and serum biomarkers.^{17–19} Doppler measurements are termed functional parameters, as they reflect placental function at the time of assessment, while there is latency between the onset of placental dysfunction and its effect on fetal measurements.

Consequently, the term SGA represents a subgroup of small fetuses, which has no signs of placental disease and no adaptation to an abnormal environment, with perinatal outcomes similar to those of normally grown fetuses.²⁰

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR), or intrauterine growth retardation and fetal growth restriction (FGR) define the same clinical entity. As this is a rather vague definition, several other definitions and terminologies have been used in the literature to define IUGR, including the statistical deviation of fetal size from a population-based reference, with a typical threshold at the 10th, 5th or 3rd centile; such a threshold is considered better as indicative of an SGA fetus.²¹

One of the most acceptable definitions has been suggested by the American College of Obstetricians and Gynecologists (ACOG) describing "a small fetus that is not fulfilling its growth potential because of an underlying pathologic condition".²

Symmetric-asymmetric Intrauterine Growth Retardation

Intrauterine growth retardation fetuses may be classified according to their anthropometric parameters into types I, II and III.

- Type I, symmetrical IUGR fetuses exhibit a proportional decrease in all measurements, especially in the size of head and abdomen. Etiological factors affect the growth pattern of these fetuses during the cellular hyperplasia phase, at the second trimester (early IUGR) and accounts for about 20–30% of the total IUGR cases.²² The prognosis for those, born with symmetric IUGR is poor compared with asymmetric IUGR regarding perinatal mortality and morbidity.²³
- Type II, asymmetrical IUGR is characterized by late onset of changes in growth, in the cellular hypertrophy phase, resulting in asymmetry and disharmony, especially in abdominal circumference (AC), while biparietal diameter (BPD), head circumference (HC) and femur length (FL) measurements are normal. This type accounts for about 70–80% of IUGR cases and the main etiological factor is placental insufficiency.^{22,24}
- Type III IUGR includes an association of the previous mechanisms (types I and II). The change occurs in the second trimester and it is associated with embryonic infections, as well as with toxic agents that affect the fetus.

Early-late Intrauterine Growth Retardation

Placentation is the determinant factor in the development of early or late IUGR.²⁵ Due to this common pathway, IUGR presents under two different phenotypes when the onset is earlier or later than 32 weeks. In general, there is a correlation between early-onset and the most severe forms of IUGR. Differentiating between early- and late-onset IUGR has a clear value in understanding the different presentations of the disease. Recent studies both in humans and lamb models suggest that the way the fetus reacts depends on the gestational age.²⁶

Early-onset IUGR: In E-IUGR, the typical pattern of deterioration progresses from abnormalities in the uteroplacental and fetal-placental circulation, to abnormal fetal biophysical profile.^{7,11,13,27–30} The degree of deterioration of Doppler parameters determines the overall speed of deterioration, often necessitating preterm delivery.^{11,13} E-IUGR presents in association with early pre-eclampsia in up to 50% of cases³¹ and is also frequently encountered in

patients with autoimmune disorders or other conditions that can affect the placental vasculature.³² In severe cases, early-onset group is associated with high incidence of severe injury and/or fetal death before term.⁶

The classical sequence of Doppler deterioration is usually observed in E-IUGR.¹³ Thus, the UA flow is the first to be affected followed by the cerebral artery flow.¹³ Until the terminal lesions of the fetal brain or severe fetal stress signs, a sequence of Doppler modifications will develop: an augmented UA vasodilation with peripheral vasoconstriction leading to an increased resistance and a high pulsatility index (PI), cerebral vasodilation with reduction of the MCA PI, then an absent or reverse end-diastolic flow in the UA, absent "a" wave in the DV, cardiac diastolic and systolic insufficiency and overload of the precordial venous system with negative "a" wave in the DV²⁹ (Table 1 and Figs 1 and 2). Studies have also reported an association between abnormal changes in aortic isthmus (Aoi) velocimetry and neonatal morbidity and mortality in E-IUGR,³³ however abnormal Aoi-flow precedes abnormal DV-flow by a week.^{34–36} The rapidity of the above-mentioned PI progression tends to be faster in E-IUGR.^{13,37}

Late-onset IUGR: L-IUGR represents a failure of the fetus to achieve its optimal growth potential, likely secondary to placental insufficiency and it constitutes up to 70% of all IUGR cases.^{38,39} L-IUGR has a much weaker association with late-onset pre-eclampsia⁴⁰ and placental findings are generally less specific.⁴¹ Several studies have determined a lower incidence of uteroplacental lesion and in the majority of cases they were deemed unremarkable.⁴² Despite a more benign nature of pathway, late-onset IUGR group may undergo rapid deterioration, leading to severe injury or stillbirth without detectable late-stage signs^{43,44} (Table 1 and Figs 2 and 3).

Recently, the PORTO study in 2013, identified multiple possible patterns of Doppler sequence alteration in IUGR.¹⁶ In L-IUGR the majority of adverse outcomes occur in fetuses with normal UA Doppler;⁴⁵ a substantial proportion of L-IUGR with normal UA Doppler may have true growth restriction and be at risk for adverse perinatal outcome.^{46–48} Furthermore, due to a milder degree of placentation deficiency, cardiovascular adaptation does not extend beyond the cerebral circulation.^{12,49} However, L-IUGR fetuses, due to the increased oxygen requirements of their brain⁵⁰ react with an

Table 1: Summary of the main differences between early- and late-onset forms of intrauterine growth retardation (IUGR)

Early-onset FGR (1–2%)	Late-onset FGR (3–5%)
Problem: management	Problem: diagnosis
Placental disease: severe (UA Doppler abnormal, high association with preeclampsia)	Placental disease: mild (UA Doppler normal, low association with preeclampsia)
Hypoxia ++: systemic cardiovascular adaptation	Hypoxia +/-: central cardiovascular adaptation
Immature fetus = higher tolerance to hypoxia = natural	
History	Mature fetus = lower tolerance to hypoxia = no (or very short) natural history
High mortality and morbidity; lower prevalence	Lower mortality (but common cause of late stillbirth); poor long-term outcome; affects large fraction of pregnancies

FGR, fetal growth restriction; UA, umbilical artery

Fig. 1: Fetal deterioration in early-intrauterine growth retardation (IUGR). AEDV, absent end-diastolic velocity; Aol, aortic isthmus; BPP, biophysical profile; CPR, cerebroplacental ratio; CTG, cardiotocography; DV, Ductus venosus; MCA, middle cerebral artery; PI, pulsatility index; REDV, reversed end-diastolic velocity; STV, short-term variation; UA, umbilical artery; Uta PI, uterine artery Doppler PI

Fig. 2: Pattern of clinical progression in intrauterine growth retardation (IUGR). FGR, fetal growth restriction; FHR, fetal heart rate; AFI, amniotic fluid index

alteration of brain metabolism⁵⁰ establishing MCA Doppler studies particularly valuable for the identification and prediction of adverse outcomes.^{12,51,52} In contrast with E-IUGR, in L-IUGR advanced signs of deterioration with abnormal DV-waveforms were not observed.^{53,54}

RISK FACTORS

Causes of IUGR are generally described under three main categories: maternal, fetal and placental.⁵⁵

Maternal Risk Factors

Women at the upper and lower limits of reproductive age, of low socioeconomic status, as well as those with substance abuse are at increased risk for IUGR.⁵⁶⁻⁵⁹ Maternal weight at birth, low pre-pregnancy weight and poor weight gain during pregnancy are positively associated with increase in the risk of IUGR.^{60,61} The use of artificial reproductive technologies is a risk factor for IUGR both independently in singleton pregnancies and also as a result of higher prevalence of multiple gestation pregnancies.⁶² Moreover, smoking during pregnancy is associated with low birth weight.^{63,64} Finally, the use of heroin or cocaine is associated with high rates of for SGA infants, 50% and 30% respectively.^{65,66}

Fig. 3: Fetal deterioration in late-intrauterine growth retardation (IUGR). Aol, aortic isthmus; CPR, cerebroplacental ratio; CTG, cardiotocography; MCA, middle cerebral artery; PI, pulsatility index; UtA PI, uterine artery Doppler PI

Fetal Risk Factors

Fetal chromosomal abnormalities account for 5–20% of total IUGR infants born, with trisomies 13, 18 and 21 being the most common.⁶⁷ Other chromosomal abnormalities include autosomal deletions, ring chromosomes and uniparental disomy.⁶⁸ Congenital infections account for around 5% of the total IUGR cases. *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex virus, varicella-zoster virus and treponema the most common pathogens;⁶⁹ IUGR is also frequently observed in infants born to HIV-affected women.⁷⁰

Placental Risk Factors

Placental insufficiency accounts for many causes of IUGR and can affect 3% or more of all pregnancies. Heinonen et al. and Yu et al. reported that the placenta of SGA infants was smaller in size than that of appropriate for gestational age infants.^{71,72} Confined placental mosaicism refers to chromosomal mosaicism found in the placenta, but not in the fetus and occurs significantly more often in the placental associated with IUGR than in controls of normal weight.⁷³ Velamentous cord insertion, single umbilical artery, true umbilical cord knot, placental abruption and placental infarct occur more frequently in the IUGR group, as they lead to decreased transfer of nutrients to the fetus.^{74–76}

COMPLICATIONS

Growth-restricted fetuses exhibit a higher incidence of mortality and morbidity.^{77,78} IUGR fetuses tend to be delivered preterm and thus many of the complications are associated with prematurity.²³ Necrotizing enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, stillbirth and neonatal death are adverse perinatal outcomes associated with IUGR.^{77,79} IUGR neonates are also found to have an increased incidence of low Apgar scores, umbilical cord pH less than 7.0, need for intubation, seizures and sepsis.^{80,81}

Intrauterine growth retardation fetuses are at higher risk for adverse perinatal and neonatal outcomes, as well as complications in early infancy.²⁴ Moreover, IUGR fetuses and neonates are at increased risk for cesarean section, convulsions, meconium obstruction and cerebral palsy, whereas their long-term development may be complicated by higher rates of neurological impairment and growth delay.^{23,80,82} David Barker pioneered the idea of “fetal origins of adult disease”.¹⁷ Especially, he stated that the 20th century epidemic of coronary heart disease in Western countries might have originated in fetal life. In adult life, individuals who had been growth restricted in utero were noted to have a higher incidence of hypertension, diabetes, obesity, coronary artery disease, stroke and metabolic syndrome.⁸³

DIAGNOSIS

Clinical Evaluation

There are still controversies over methods and antenatal screening for the early detection of IUGR.⁵ The traditional screening methods for restricted fetal growth using abdominal palpation or measurement of symphysis-fundal height are recommended by the ACOG, the Royal College of Obstetricians and Gynecologists (RCOG) and the Society of Obstetricians and Gynecologists of Canada (SOGC) for low risk pregnancies, but both have poor diagnostic rate for IUGR fetuses;^{2,84} this is in accordance with the findings from a recent systematic review where the sensitivity of symphysis-fundus height measurement for SGA prediction ranged from 0.27 to 0.76 and specificity ranged from 0.79 to 0.92.⁸⁵ A discrepancy of more than 3 weeks between dates and the estimated gestational age based on the fundal height measurement has been proposed as indicative of a fetus that may be growth restricted.⁸⁶

Ultrasound Evaluation

If IUGR is suspected, ultrasonography should be used to confirm the diagnosis. Initially, the exact gestational age should be identified

according to fetus' crown-rump length measurement during the first-trimester screening test.⁸⁷ The AC measurement is the most specific parameter for detecting IUGR with specificity 89.8% and negative predictive value 90.7%.^{88–90} The sensitivity of isolated estimated fetal weight (EFW) to predict IUGR and related adverse outcomes is higher for fetuses with severe growth restriction and EFW below the 3rd centile.¹⁶ However, IUGR could be over- or underestimated by using conventional population-based cut-offs. Therefore, customized fetal weight charts taking in account maternal variables such as weight, height, parity and ethnicity should be used.⁹¹ In addition, functional parameters, either as isolated finding (AEDF-UA) or multiple parameters [UA-PI >95th centile or uterine arteries (UtA)-PI >95th centile or cerebroplacental ratio (CPR) between MCA-PI and UA-PI <5th centile] should be used for the diagnosis of IUGR.⁵⁴

A prospective study using decision tree analysis in more than 700 cases determined that 32 weeks at the time of diagnosis best classified early and late groups of IUGR.²⁵ It is thought that early IUGR due to reduction of the villus vascular area, occurs in about 30% of fetuses during the second trimester, resulting in increased resistance to the UA flow.⁴ This usually affects fetal biometry which, in conjunction with raised UA resistance, constitutes the diagnosis of early IUGR.⁹² A survey on 45 experts reached good agreement that before 32 weeks abnormal UA Doppler is a criterion for IUGR.⁵⁴ The defect in placentation exerts a great negative effect on fetal growth, with the AC affected more than the fetal head's BPD and the FL.^{93,94}

Despite late-onset IUGR represents 70–80% of IUGR fetuses, the diagnosis is more difficult, due to the large variability of fetal parameters on growth charts in the third trimester.^{16,95} L-IUGR may be suspected when the individual growth curve decreased more than two quartiles on growth centiles or becomes flat.⁵² In this group, the degree of placental disease is mild, thus UA Doppler can be normal.¹² Although normal UA-PI Doppler, there is a high association with abnormal CPR values.¹² The CPR improves remarkably the sensitivity of UA and MCA alone, because increased placental impedance (UA) is often combined with reduced cerebral resistance, due to advanced brain vasodilation. Thus, the CPR is already decreased when its individual components suffer mild changes but are still within normal ranges.^{96,97}

In 2016, consensus-based definitions for both early and late IUGR were established, according to AC and EFW under the 3rd centile or Doppler evaluation (Table 2).⁵⁴

MANAGEMENT

Monitoring

Once a growth restricted fetus has been detected by ultrasound measurements, further evaluation must include frequent anthropometric measurements, Doppler studies, cardiotocography (CTG) and biophysical profile (BPP) assessment.⁹⁸

For growth restricted fetuses, serial assessment of AC, BPD, HC and FL measurements is the best predictor of fetal growth rate.⁸⁹ There is no clear evidence and consensus about the frequency and timing of repeated scans. However, evaluation of growth rate in intervals less than 2 weeks is not indicated because the scan error is likely to exceed the increment in size.⁹⁹ Progressive changes of EFW during time should be mentioned and documented.

As already mentioned, there is evidence that the use of UA Doppler in IUGR improves perinatal outcomes.¹⁰⁰ In more than 80% of IUGR fetuses, abnormal UA-waveforms have been reported

Table 2: Consensus based criteria for early and late intrauterine growth retardation (IUGR)

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

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery

to be present almost 2 weeks before the acute deterioration.^{28,29} In addition, end-diastolic UA velocities are present approximately 1 week before acute deterioration and therefore UA Doppler studies is used for the surveillance and obstetrical management of early IUGR.²⁹ Furthermore, this UA abnormal waveforms are also associated with higher risk of neurodevelopment disorders.¹⁰¹

The MCA Doppler may be useful in tracking L-IUGR independent of UA Doppler findings. In L-IUGR fetuses, an abnormal CPR is present before delivery in 20–25% of the cases.¹⁰² Hecher et al. first provided evidence that near-term fetuses with isolated MCA vasodilation are at risk of adverse outcomes.¹⁰³ Despite being less sensitive, MCA PI has been suggested to be more specific.¹⁰⁴ On the other hand, the CPR is more sensitive to hypoxia than its individual components and it correlates better with adverse outcomes.^{96,97,104} A value of CPR <1 or <0.6765 multiples of the median (MoM) is used for the diagnosis of brain sparing.^{98,105,106}

The CPR should be used as an additional tool in fetuses undergoing ultrasound assessment, regardless of the results of the UA and MCA measurements.⁹⁸ In E-IUGR an abnormal CPR is associated with a higher incidence of early gestational age at birth, low birthweight centile, high rate of adverse neonatal outcome and a greater incidence of perinatal death.^{52,96,104,107–110} It has been shown that in E-IUGR, the CPR is highly correlated with ante- and postpartum outcome,⁹⁸ but other studies support a superior role of UA in these cases. In addition to predicting adverse fetal and neonatal outcome, an abnormal CPR was a better predictor of adverse outcome than the BPP, suggesting that CPR changes may occur before the deterioration of this test.^{108,109} Also, Baschat et al. showed that umbilical and cerebral Doppler, gestational age and other circumstances during delivery are the most powerful predictors of clinical outcomes.³⁷

Several studies have demonstrated that DV flow is the strongest parameter to predict the short-term risk of fetal death in E-IUGR and absent or reversed velocities are strongly associated with perinatal mortality independently of the gestational age.^{34,111,112} In about 50% of cases, an abnormal DV precedes the loss of short-term variability in computerized CTG¹¹ and in 90% of cases becomes abnormal 48–72 hours before the BPP.²⁷ Additionally, Aol Doppler is associated with increased fetal mortality and neurological morbidity in E-IUGR.³³ Aol flow may also be found to be abnormal in a small proportion of L-IUGR.³⁵ Aol precedes DV abnormalities by

1 week and consequently it is not ideal in predicting the short-term risk of stillbirth.^{34–36} As there are studies suggesting that reverse Aol could be incorporated in clinical protocols as a sign of severe placental insufficiency, more data are required.

Numerous studies on high-risk pregnancies showed that CTG has a 50% rate of false positives for the prediction of adverse outcomes.¹¹³ A meta-analysis on high-risk pregnancies failed to demonstrate any beneficial effect in reducing perinatal mortality.¹¹⁴ As a result, there is no evidence to support the use of traditional fetal heart rate monitoring or “non-stress” tests in IUGR fetuses, as abnormal DV-waveform precedes the loss of short-term variability.^{11,115–117}

The BPP reflects the fetal acid-base status and it has been used for monitoring IUGR fetuses. Observational studies showed an association between abnormal BPP and perinatal mortality and cerebral palsy.¹¹⁸ Unfortunately, BPP has a high false-positive rate (50%)¹¹⁹ and a meta-analysis showed no significant benefit of its use in high-risk pregnancies.¹²⁰ The amniotic fluid index (AFI) as a part of the BPP progressively decreases among E-IUGR.^{11,28} In a large study about late IUGR fetuses, about one-third had oligohydramnios.^{121,122} Finally, a meta-analysis showed that a reduced AFI is associated with an abnormal 5-min Apgar score, but no association with acidosis or perinatal death was identified.¹²³

Furthermore, the UtA Doppler studies reflect placental insufficiency from the maternal side and may also capture placental insufficiency secondary to other pathophysiologic mechanisms beyond abnormal early trophoblastic invasion.¹²⁴ Doppler examination of the UtA in the first and second trimester may confirm the presence of vascular pathology and also predict its evolution.¹²⁵ Thus, there is agreement for this parameter to be included in the definition of E-IUGR.⁵⁴ Furthermore, there is evidence that placental disease in L-IUGR may develop late in pregnancy, as suggested by a proportion of patients developing abnormal UtA-waveform in the third trimester, after having previously demonstrated normal values.¹²⁴ A recent retrospective study reported that high UtA-PI at term is independently associated with increased risk of adverse perinatal outcome regardless of fetal size.¹²⁶ Figure 2 represents the pattern of the clinical progressions of early and late IUGR as evaluated by different diagnostic tools.

Timing of Delivery

Since no treatment has been proved to be beneficial when IUGR is already diagnosed, time of delivery remains the main goal of fetal assessment.^{127–131} The timing of delivery should be determined taking into account the gestational age, Doppler studies of UA, MCA and DV, CTG and BPP.^{2,84,132} Mortality among SGA fetuses is reduced if IUGR is diagnosed, antenatal surveillance initiated, and delivery managed according to guidelines.^{2,84,133–136}

The growth restriction intervention trial (GRIT) randomly assigned pregnant women with IUGR to immediate or delayed delivery, in order to assess the timing of delivery of the early preterm IUGR.⁵ Delaying delivery of the very preterm IUGR in the setting of uncertainty resulted in some stillbirths, but immediate delivery produced an almost equal number of neonatal deaths. As a result, there was insufficient evidence to support either immediate or delayed delivery.⁵

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) recruited pregnant women between 26 weeks and 32 weeks of gestation with AC <10th centile and UA-PI >95th centile. The main outcome was a composite of fetal or neonatal death or

severe morbidity.¹³⁷ The intervention was delivery of the fetus according to the criteria of the randomization group, determined by the CTG criteria of reduced short-term variation, early abnormalities of the DV (PI >95th centile) or late DV changes (absent or negative a-wave). As for the outcome, perinatal death was uncommon and 70% survived without severe neonatal morbidity, reinforcing that when a protocol is in place there is an improvement in perinatal care. In a *post hoc* analysis of their data, the TRUFFLE group concluded that both DV and CTG evaluation are warranted, since the majority of infants in the DV groups were delivered for reduced short-term variability or spontaneous decelerations in fetal heart rate, rather than PI changes in the DV.¹³⁸

The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) randomly assigned 650 pregnant women over 36 weeks of gestation with suspected IUGR to induction of labor or expectant monitoring.¹²¹ This study found equivalent fetal and maternal outcomes for induction and expectant monitoring at IUGR at term, indicating that both approaches are acceptable.¹²¹

The simplest approach, using AC, EFW, and UA, is according to Royal College of Physicians of Ireland, where in a fetus with an EFW less <10th centile, UA Doppler should be performed. Once UA-PI values are within normal limits, repeated scans every 2 weeks and delivery between 37 weeks and 40 weeks is recommended. If UA-PI is greater than 95th centile with positive end-diastolic flow, weekly sonogram, 2-weekly biometry assessment, timed corticosteroids before 34 weeks and assessment of AFI are recommended. Delivery is recommended at 37 weeks or earlier if the growth interval is poor. In cases of absent UA end-diastolic flow, sonogram in twice weekly intervals, timed corticosteroids, assessment of UA-PI and AFI and delivery not later than 34 weeks are recommended. If UA end-diastolic flow is reversed, thrice weekly sonogram, assessment of UA-PI and AFI, timed corticosteroids and delivery not later than 30 weeks are recommended. It should also be noted that in all cases with an abnormal CTG, delivery is indicated (Flowchart 1).¹³⁶

The SOGC recommends delivery according to the onset of IUGR. Thus, if IUGR is diagnosed before 34 weeks, delivery should be based on UA, MCA, DV, non-stress test and BPP. When the onset of IUGR is later than 34 weeks of gestation, if Doppler studies and the BPP are normal, delivery should be offered after 37 weeks. If there are abnormal Doppler studies, BPP or oligohydramnios, delivery should be considered earlier.¹³⁴

Figuera et al. recently suggested a stage-based protocol for managing fetal growth retardation.²⁰ According to this there are four stages of severity of IUGR with a different suggested management: Stage I (Severe smallness or mild placental insufficiency): At this stage, UtA, UA, MCA Doppler or the CPR is abnormal. Labor induction beyond 37 weeks is acceptable with weekly monitoring. Stage II (Severe placental insufficiency): This stage is defined by UA-AEDV or reverse Aol. Monitoring twice a week and delivery at 34 weeks by cesarean section should be recommended. Stage III (Advanced fetal deterioration, low-suspicion signs of fetal acidosis): This stage is defined by UA-REDV or DV-PI >95th centile. Monitoring every 24–48 hours and delivery by cesarean section at 30 weeks should be suggested. Stage IV (High suspicion of fetal acidosis and high risk of fetal death): There are spontaneous fetal heart rate decelerations, reduced short-term variability in the cCTG or reverse a-wave in DV. At this stage, monitoring every 12–24 hours and emergency cesarean section after 26 weeks should be recommended (Table 3).²⁰

Flowchart 1: Management of intrauterine growth retardation (IUGR). EFW, estimated fetal weight (Hadlock-4); UA, umbilical artery; EDF, end-diastolic flow; AEDF, absent end-diastolic flow; REDF, reversed end-diastolic flow; AFI, amniotic fluid index; AREDF, absent or reversed end-diastolic flow index in UA; CTG, cardiotocography; MCA, middle cerebral artery; GA, gestational age; LMWH, low molecular weight heparin

Table 3: Stage-based classification and management of fetal growth restriction (FGR)

Stage	Pathophysiological correlate	Criteria (any of)	Monitoring*	GA/mode of delivery
I	Severe smallness or mild placental insufficiency	EFW <3rd centile CPR < p5 UA PI > p95 MCA PI < p5 UtA PI > p95	Weekly	37 weeks LI
II	Severe placental insufficiency	UA AEDV Reverse AoI	Biweekly	34 weeks CS
III	Low-suspicion fetal acidosis	UA REDV DV-PI > p95	1–2 days	30 weeks CS
IV	High-suspicion fetal acidosis	DV reverse a flow cCTG <3 ms FHR decelerations	12 hours	26 weeks** CS

All Doppler signs described above should be confirmed at least twice, ideally at least 12 h apart. *Recommended intervals in the absence of severe preeclampsia. If FGR is accompanied by this complication, strict fetal monitoring is warranted regardless of the stage. **Lower GA threshold recommended according to current literature figures reporting at least 50% intact survival. Threshold could be tailored according to parents' wishes or adjusted according to local statistics of intact survival.

GA, gestational age; LI, labor induction; CS, cesarean section; EFW, estimated fetal weight; CPR, cerebroplacental ratio; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; UtA, uterine artery; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity; DV, Ductus venosus; CTG, cardiotocography; FHR, fetal heart rate

PREDICTION AND PREVENTION

Intrauterine growth retardation prediction rate values range between 12% and 47% with false positive rate values about 10%.¹³⁹ Several predictive markers have been proposed. Velauthar et al. in a meta-analysis using the Uta Doppler studies during the first trimester, showed a prediction rate of 15.4%; for E-IUGR the prediction rate was higher, with a sensitivity of 39.2%.¹²⁵ Cignini et al. observed that a low level of PAPP-A and a high level of free β -hCG are associated with SGA newborns.¹⁴⁰ Crovetto et al. developed an algorithm in the first trimester for predicting early- and late-onset IUGR; the detection rate was 86.4% for E-IUGR and 65.8% for L-IUGR.¹³⁹ Screening with maternal characteristics, fetal biometry and Uta Doppler in the second trimester may also be useful.¹⁴¹

Several evidence-based interventions have been shown to reduce the incidence of IUGR, through multiple interventions that have been carried out over the world.¹⁴² A Cochrane meta-analysis of 12 trials suggested balanced energy and protein supplementation for the prevention of IUGR.¹⁴³ In addition, a Cochrane systematic review suggests multiple micronutrient supplementation.¹⁴⁴ Mosquito avoidance and preventive treatment of malaria in pregnancy reduce also placental malaria and incidence of IUGR.¹⁴²

In a meta-analysis of 45 randomized trials of low dose aspirin for the prevention of preeclampsia and IUGR in women at a high risk, aspirin prophylaxis markedly reduced the incidence of IUGR compared to placebo or no treatment.¹⁴⁵ On the other hand, anticoagulation with unfractionated heparin or low molecular weight heparin does not reduce the risk of growth retardation.¹⁴⁶

The SOGC and RCOG advocate smoking cessation as a preventative strategy in a subsequent pregnancy.^{84,134} Finally, dietary changes and supplements, antihypertensive therapy of hypertensive women, betamimetics and bedrest do not prevent IUGR.^{128,147–149}

CONCLUSION

Intrauterine growth retardation remains a major problem in both developing and developed countries and several causes have been identified. Current evidence suggests that two different phenotypes of IUGR exist, early and late, associated with dissimilar perinatal morbidity and mortality. The diagnosis of fetal hypoxia in the third trimester remains a challenge for modern obstetrics. The approach that a normal UA Doppler pattern in the third trimester endorses a normal pregnancy in the E-IUGR comes in contrast with clinical follow-up in L-IUGR fetuses, where CPR is the appropriate parameter for monitoring. Despite all the above-mentioned useful parameters, all fetal-maternal units should adopt and follow their own protocol for the management of IUGR.

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