Overlapping Pathophysiology of Preeclampsia and Fetal Growth Restriction

Marwa Ahmed Mohamed Abd Al Rahman, Mostafa Mohamed Zaitoun, Mohamed Sabry Mohamed, Wael Sabry Nossair, Basem Mohamed Hamed

Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Marwa Ahmed Mohamed Abd Al rahman

E-mail: drmarwaahmed94@gmail.com, marwaabdelrahman@medicine.zu.edu.eg

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Abstract

Preeclampsia and FGR are syndromes with multiple causative pathways that often reflect earlier placental maldevelopment, and generally become symptomatic in the third trimester. A standard utero placental circulation is necessary for the development of a normal pregnancy. Fetal birth weight less than 10th percentile for a given gestational age is called intrauterine growth restriction (IUGR). The most important thing is to identify the fetuses with hazard of compromise instead of identification of small fetus during pregnancy. Fetal growth restriction refers to a fetus that has failed to achieve its genetic growth potential, usually because of placental diseases restricting nutritional supply and fetal oxygen partial pressure. Intrauterine growth restriction affects about 10-15% of the maternal population and is a common condition affecting pregnant mothers. This condition has many risks for the babies including increased chances of fetal death, neonatal lung diseases, respiratory distress syndrome, necrotizing enterocolitis, renal diseases and chronic cardiovascular disorders. IUGR fetus has a strong connection with meconium aspiration syndrome.

Keywords: Preeclampsia, Fetal Growth Restriction

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Introduction

A standard utero placental circulation is necessary for the development of a normal pregnancy. Fetal birth weight less than 10th percentile for a given gestational age is called intrauterine growth restriction (IUGR). The most important thing is to identify the fetuses with hazard of compromise instead of identification of small fetus during pregnancy. **(1).**

Fetal growth restriction refers to a fetus that has failed to achieve its genetic growth potential, usually because of placental diseases restricting nutritional supply and fetal oxygen partial pressure. (2).

Intrauterine growth restriction affects about 10-15% of the maternal population and is a common condition affecting pregnant mothers. This condition has many risks for the babies including increased chances of fetal death, neonatal lung diseases, respiratory distress syndrome, necrotizing enterocolitis, renal diseases and chronic cardiovascular disorders. IUGR fetus has a strong connection with meconium aspiration syndrome. (3).

The placenta delivers oxygen and nutrients to the growing fetus and removes waste products; as such, it is responsible for fetal wellbeing, maintained in the background of maternal health. Events in early pregnancy can lead to different placental developmental routes.

Both epigenetic settings in the early embryo, and adaptive change in the placenta can be associated with altered fetal growth, disease in late pregnancy, and lifelong metabolic programming of the conceptus. Both conditions, via the brain, metabolic and cardiovascular effects, have effects on the lifetime health of the conceptus (4).

Placental development is effectively initiated as soon as implantation begins, about a week after ovulation, with the development of the first trophoblast lines (4).

Overlapping pathophysiology of preeclampsia and FGR:

Preeclampsia and FGR are syndromes with multiple causative pathways that often reflect earlier placental maldevelopment, and generally become symptomatic in the third trimester.

Incomplete conversion of spiral arteries during the first and second trimesters, most especially seen in the inner myometrial segments, is observed in both preeclampsia and FGR; however, the relationship between the extent of the failure, type of disease, and time of onset remains poorly understood.

This widely studied phenomenon, involves reduced trophoblast invasion of the deeper arterial segments. Mechanisms related to maternally driven disease include defective decidualization or intrinsic resistance in the spiral arteries to transformation (5).

Thus, if spiral arteries are incompletely transformed, as in early-onset FGR, blood might enter the intervillous space at elevated pressure, causing mechanical damage to the villous placenta and blood cells. In addition, hypoxia–reperfusion can occur at the villi because of blood not escaping continuously from the mouths of spiral arteries (5).

Distress signals released to the maternal circulation lead to systemic microvascular endothelial activation and the syndrome of preeclampsia. One interesting open research question is why some

cases of early-onset FGR, with placental bed abnormalities presumed to be like those in preeclampsia, do not develop the latter condition(5).

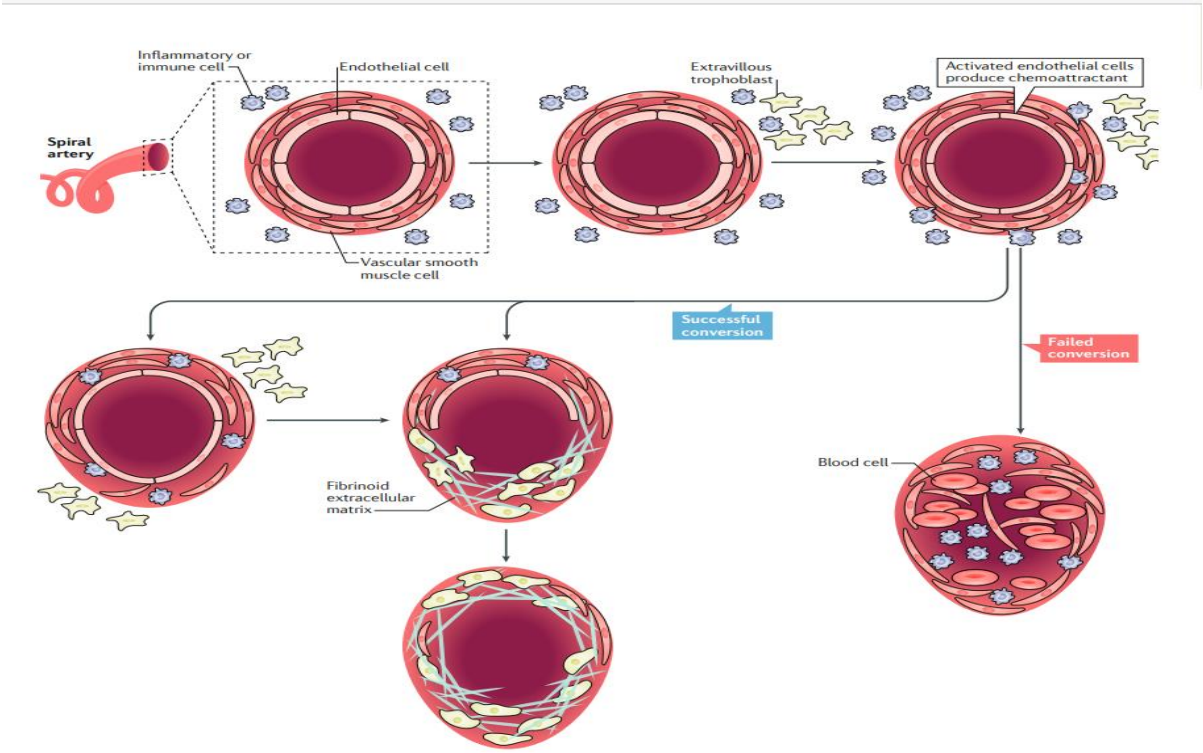

Figure (1): Steps in normal and failed spiral arterial conversion.

- Unconverted spiral arteries in the decidua are composed of endothelial cells bounded by a layer of vascular smooth muscle, and they are elastic. Decidual immune cells are numerous and at this stage are excluded from the vessel wall **(top left).**

In the process of conversion, the extravillous trophoblast begins to invade the decidual stroma surrounding the spiral artery **(top centre).**

- Subsequently, activation of endothelial cells leads to the production of chemokines. As a result, immune and/or inflammatory cells penetrate and start to disrupt the vessel media **(top right).**

- Extravillous trophoblast also plays a part in disrupting the media, including a breakdown of the normal extracellular matrix and deposition of fibrinoid **(Centre).** Some residual endothelium can remain.

- At the endpoint of the conversion process, mural trophoblast remains embedded in fibrinoid, smooth muscle is absent, and generally few inflammatory and/or immune cells are present (bottom centre).

- If the conversion fails, residual smooth muscle is present, often with intimal hyperplasia reducing the luminal profile (bottom right). Trapped blood cells might be seen.

- In some cases, atherosis occurs with macrophage-derived foam cells embedded in the vessel wall, and complete occlusion can occur.
- Note that failed conversion with an absence of trophoblast from the arterial media is most often seen in the inner myometrial arterial segments; however, failure can also occur more superficially in decidual segments

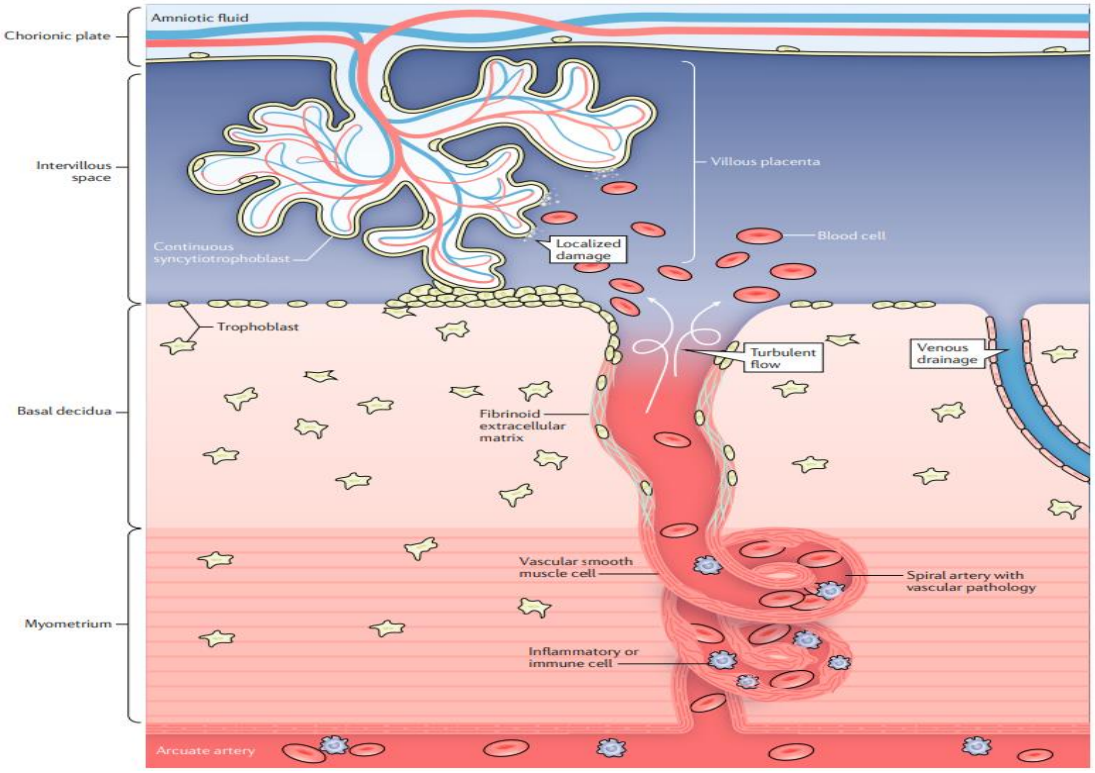

Figure (2): The near-term placenta and placental bed with spiral arterial pathology.

- **In normal near-term pregnancy,** converted spiral arteries that are free of cytotrophoblast plugs transport blood into the intervillous space.
- Note the decidual arterial segment has now lost its original spiral shape. Venous drainage (right) enables the transport of waste products away from the placenta.
- **Failure of spiral artery conversion** could result in damage to the villous syncytiotrophoblast caused by turbulent blood flow, which results from stenosis in the myometrial segment of a spiral artery that has not been fully transformed.
- **Adaptation in the arterial supply** could potentially be impaired further upstream.

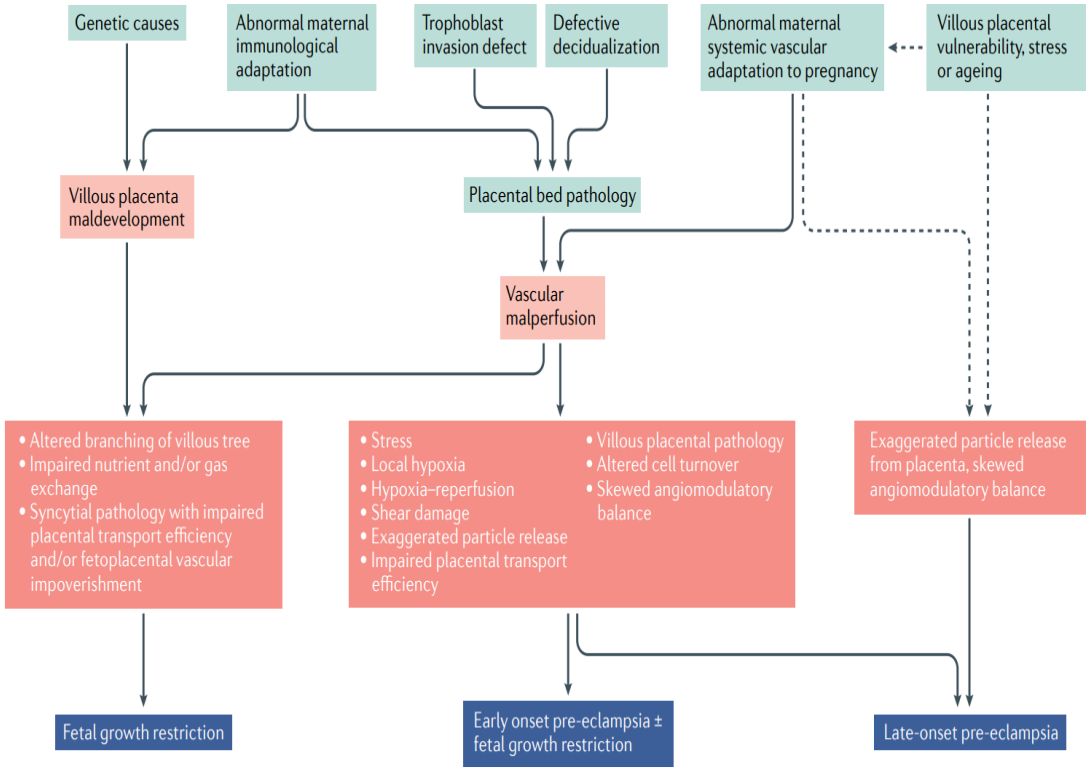

Figure (3): Fetal growth restriction — disease etiology and progression.

It is currently poorly **understood** how variations in the timing of onset, progression, extent, and **nature** of the upstream placental bed vascular pathology contribute to different disease outcomes. The figure leaves open the possibility that some late-onset disease could occur in the absence of overt placental bed pathology. Maternal malnutrition can cause fetal growth restriction

Bilateral Doppler ultrasound assessment of the proximal uterine arteries in the second trimester is associated with an increased pulsatility index and diastolic notching (an increase in resistance seen during diastole) throughout gestation in most pregnancies with early-onset FGR, and many of these pregnancies progress to preeclampsia. **(6).**

Placental villous infarcts and histopathological features such as extensive perilous fibrin deposition, villous agglutination, and elevated syncytial nuclear aggregates are associated with maternal villous malperfusion (MVM); with probable obstructive effects on molecular traffic at the villous interface **(7).**; however, the causal pathway is not always clear, and the effects are difficult to quantify at the whole-organ level.

Failure of spiral artery conversion in severe early-onset FGR might well trigger preeclampsia. Unconverted spiral arteries are vulnerable to pathological change including intimal hyperplasia and atherosis, probably leading to local hypoxia, free radical damage, and inefficient delivery of substrates into the intervillous space.

The preserved vascular smooth muscle could allow residual contractile capacity in the spiral arteries. Atherosis can also occur in basal (non-spiral) arteries that would not normally be targeted by the trophoblast. Thus, FGR and preeclampsia have overlapping pathophysiology that generates a spectrum of clinical presentations rather than being distinct disorders **(8)**.

The placental bed as a central causative component in disease remains difficult to verify in specific cohorts for several reasons. First, the efficiency and timing of ongoing spiral artery conversion cannot be assessed. Second, placental bed biopsy samples in the first and second trimesters cannot be related to what the pregnancy outcome would have been. Third, even when biopsy samples have been obtained, the importance of multiple sampling has not been universally recognized.

A critical descriptive principle is to distinguish between MVM maternal vascular malperfusion (in which placental bed abnormalities can lead to FGR with preeclampsia) and failure of the fetoplacental vascular supply in a pregnancy where the maternal supply is a normal interface **(7).**

Impairment of blood flow from spiral arteries could differentially affect oxygen and nutrient delivery because oxygen exhibits flow-limited diffusion down its concentration gradient. By contrast, hydrophilic metabolic substrates and ions require membrane channels (passive, selective, gated, and saturable) or carriers (selective, energy-dependent, and saturable **(9).**

Severe early-onset FGR, defined as being below the third growth centile before 32 weeks, is the most straightforward to recognize by combining fetal dimensions on ultrasonography with the uterine artery Doppler trace. This form of FGR has the poorest outcomes **(10).**

In less severe diseases, longitudinal scanning can identify fetuses that are not meeting their predicted growth course, allowing specification of true growth restriction as opposed to a constitutionally small for gestational age (SGA) fetus. However, 2D biometry has limited sensitivity — newer techniques might improve the accuracy of ultrasonography **(11).**

Damage to the syncytiotrophoblast that impairs the placental barrier not only affects nutrient transfer but could also trigger a reactive local regression of villous micro endothelial networks as a defense mechanism **(12),** creating a downward spiral of reduced placental efficiency.

Of note, placental metabolism is adaptable. FGR suggests a wide range of programming effects on fetal metabolism, neural development, and cardiovascular function, and there is a need to agree on how the spectrum of phenotypes can be classified for appropriate therapeutic attention.

Current imaging modalities allow a more advanced approach that, with appropriate resourcing, could displace the basic definition of SGA based on birthweight. By combining fetal growth surveillance, biomarkers and new disease classifications that have emerged from ‘omics strategies, clinicians could improve diagnosis of both FGR and preeclampsia subtypes **(13).**

- Different definitions of FGR

Institution / Author	FGR definition
Baschat et al 2007 [101]	Combination of small fetal AC with elevated UA Doppler blood flow resistance
Cochrane 2013 [65]	Failure to reach the growth potential
DIGITAT 2012 [38]	EFW or AC <10th centile for gestational age
ACOG 2013 [40]	Fetuses with EFW <10th centile for gestational age
RCOG 2013 [41]	Small–for–gestational age (SGA) refers to an infant born with a birth weight less than the 10th centile. Fetal growth restriction (FGR) is not synonymous with SGA.
SOGC 2013 [39]	Intrauterine growth restriction refers to a fetus with a EFW <10th centile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential.
PORTO 2013 [6]	EFW < 5th percentile & umbilical artery PI >95th percentile
TRUFFLE 2013 [3]	AC < 10th percentile & umbilical artery PI >95th percentile
Gordijin et al 2016 [43]	AC <3rd centile OR EFW <3rd centile OR AREDF OR Both of the following: 1) EFW or AC < 10th centile and 2) UtA PI >95th centile OR UA PI >95th centile.

AC abdominal circumference
AREDF absent/reversed umbilical artery end diastolic flow
EFW estimated fetal weight
PI pulsatility index
UtA uterine artery
UA umbilical artery

Table (1): Different definitions of FGR.

- GUIDELINE International Society of Ultrasound in Obstetrics and Gynecology (ISOUG 2020) OF Definition and distinction between small-for-gestational-age and fetal growth restriction:

Fetal growth is a dynamic process, and its assessment requires multiple observations of fetal size over time. Fetal size is determined through biometric evaluation of the head circumference, biparietal diameter, abdominal circumference (AC), and femur length and/or estimated fetal weight (EFW) computed by different formulae **(14).**

FGR is a condition defined as the fetus failing to reach its genetically predetermined growth potential. The identification of FGR is often not straightforward as fetal growth cannot be assessed through a single biometric evaluation of the fetal size, and growth potential is proposed.

The main distinction between SGA and FGR is that SGA fetus may be small but not at increased risk of the adverse perinatal outcome, while a fetus with size above the 10th percentile may be FGR and at increased risk of adverse perinatal and long-term outcomes**,** Fetuses with a birth weight below the 10th percentile are at increased risk of stillbirth **(3)** and perinatal mortality **(1)** with those with a birth weight below the 3rd percentile being at the highest risk.

For this reason, fetal size at the lower extreme of the growth charts, for example, AC or EFW below the 3rd percentile for given growth charts, can be used as an isolated criterion to define FGR **(10).** However, the optimal size at birth that is associated with the lowest perinatal mortality seems to

be substantially higher than the median birth weight of a normal cohort. In fact, a population-based cohort study found increased perinatal mortality even in fetuses with birth weight within the normal range, with those with birth weight between the 70th and 90th percentiles being at the lowest risk, and an inverse association between perinatal mortality and birth weight below the 80th percentile **(15).**

To differentiate between SGA and FGR in cases in which the fetal size is below the 10th percentile, additional biophysical parameters are required. Many methods have been proposed for this purpose, such as evaluation of fetal growth velocity, use of customized growth charts, Doppler velocimetric evaluation of placental and fetal circulations, and use of biomarkers. Some of these biophysical parameters are also used to monitor fetal status and/or as delivery decision criteria (e.g., umbilical artery (UA) Doppler) **(16).**

- **Late-onset fetal growth restriction:**

The pathophysiology of late FGR differs from that of early FGR. Late FGR is characterized by milder and more specific placental lesions and/or alteration in oxygen and nutrient diffusion **(17).**

Consequently, alterations in UA Doppler and venous districts are rare and fail to identify most late-FGR cases or to predict adverse outcomes in these fetuses. Several studies have found an association between MCA vasodilatation (i.e., reduction in MCA-PI) or the alteration of its ratio with UA-PI and poorer perinatal outcome, including stillbirth, higher risk of Cesarean delivery **(18),** and increased risk of abnormal neurodevelopment at birth90 and at 2 years of age.

The rationale for using the ratios of MCA-PI and UA-PI (CPR and UCR) is that they can identify indirect changes between placental and cerebral blood-flow perfusion that may not be valued by evaluation of a single parameter. Furthermore, it has been suggested that the evaluation of the CPR may improve the prediction of adverse perinatal outcomes in growth-restricted fetuses **(19).**

The biophysical abnormalities that characterize late FGR include alteration of fetal breathing, decreased amniotic fluid volume, and loss of fetal heart rate reactivity on conventional CTG.

Despite presenting with a milder clinical form than early FGR, late FGR is still associated with poor perinatal outcomes and longer-term educational attainment. In the TRUFFLE study, the risk of poor neurodevelopmental outcomes in babies that were delivered after 32 weeks' gestation remained static until term. This may be due to several factors **(20).**

The pathophysiology of late FGR is still not completely understood and this may determine a lower identification rate of fetuses exposed to growth restriction near term. Moreover, fetuses near term seem to have reduced tolerance to hypoxemia100, possibly because of their relatively high metabolic rate, compared with fetuses at an earlier gestation. Thus, frequent monitoring of pregnancies with late FGR is warranted in the same way as for those with early FGR **(21).**

How to monitor

At present, MCA-PI and its ratios to UA-PI are the most important Doppler parameters in the surveillance of late FGR. In the presence of UA-PI > 95th percentile, monitoring at least once or twice a week is indicated.

A large retrospective study showed that, in FGR pregnancies after 34 + 0 weeks of gestation, the median interval between a low MCA-PI and stillbirth was ≤ 5 days, suggesting that, if delivery has not been indicated by that time, twice-weekly Doppler surveillance may be required after 34 weeks. Moreover, in the same study, almost 90% of stillbirths occurred within 1 week of a normal BPP score in the presence of cerebral vasodilatation, suggesting that BPP may have poor value in determining the frequency of fetal monitoring **(22).**

Since some concerns have been raised regarding the interobserver reliability of MCA-PI measurement, when an alteration in MCA-PI, Cerebroplacental ratio (CPR), or umbilical cerebral ratio (UCR) is encountered, the measurement should be confirmed within 24 h to avoid false-positive results, especially when the timing of delivery is based on this finding **(23).**

*** Corticosteroid prophylaxis**

There is a lack of consensus between guidelines with respect to corticosteroid prophylaxis between 34- and 36-weeks' gestation. Most guidelines on FGR recommend corticosteroid prophylaxis if the birth is likely to occur before 34 + 0 weeks70–74, however, the RCOG recommends corticosteroid prophylaxis up to 35 + 6 weeks **(24).**

Magnesium sulfate prophylaxis

There is good evidence for the efficacy of magnesium sulfate for fetal neuroprotection in the context of preterm delivery, however, the exact gestational-age threshold at which this decrease remains unclear **(25).**

- **Diagnosis 0f fetal growth restriction**

There are several methods to evaluate fetal growth velocity, including the use of longitudinal growth, assessment of deviation from growth-velocity charts18, and individualized growth assessment. Overall, the objective is to evaluate the fetal growth course and identify those fetuses that are deviating from their individual course, indicating a failure to reach their growth potential **(26).**

Reduced growth velocity is normally taken to be a fall between consecutive ultrasound scans of > 50 percentiles for AC or, more commonly, EFW.

- Customized growth charts

In customized charts, the fetal weight and growth are adjusted for variables known to impact fetal size. These can include maternal height, weight, age, parity and ethnicity, and fetal sex.

- Doppler velocimetry

The rationale behind the application of Doppler velocimetry in fetal growth assessment is that it can identify uteroplacental function through evaluation of the uterine and umbilical arteries. Uteroplacental insufficiency is mediated through spiral artery maladaptation and alterations in the villous vascular tree. On the fetal side, Doppler velocimetry allows evaluation of the middle cerebral artery (MCA) and ductus venosus as fetal cardiovascular adaptation progresses from hypoxia to acidemia. A lack of physiological transformation of the uterine arteries from high- to low-resistance vessels is thought to reflect the inadequate trophoblastic invasion of the spiral arteries, leaving a high-resistance circulation. The persistence of high uterine artery mean pulsatility index (PI) (above the 95th percentile) is associated with placental insufficiency and maternal vascular malperfusion of the placenta Progressively increasing PI in the UA corresponds to a progressive reduction in the placental surface area available for gas and nutrient exchange and increased fetal afterload resistance and is associated with placental vascular insufficiency reflected by absent and, in the end-stage phase, reversed end-diastolic flow (EDF) in the UA. **(27).**

This represents a hemodynamic response to fetal hypoxemia, via direct vascular detecting of oxygen tension in the cerebral circuit, and in other vascular beds a consequent redistribution of fetal cardiac output occurs preferentially to the coronary arteries and adrenal glands. Others consider that absent or reversed a-wave in the ductus venosus is a consequence of increased intra-atrial pressure due to high cardiac afterload (increased vascular placental resistance) and/or a direct effect of fetal acidemia on myocardial cell function **(28).**

Doppler velocimetry plays a central role in the identification, surveillance, and management of FGR because it allows for the identification of uteroplacental insufficiency and/or fetal cardiovascular adaptation to hypoxemia. Importantly, the two phenotypes of FGR, early-onset and late-onset, are characterized by different Doppler velocimetry patterns.

- Biophysical profile scoring

The BPP score consists of the combined evaluation of fetal tone, gross body movement, breathing movement, amniotic fluid volume and heart-rate reactivity. BPP score can predict both fetal pH and outcome. The relationship between altered BPP score and fetal pH seems to be consistent across gestational ages. A score of ≤ 4 is associated with a fetal pH ≤ 7.20, while a score of < 2 has a sensitivity of 100% for acidemia. This correlation remains highly significant even when using a simplified BPP that is based on an assessment of only fetal heart rate and amniotic fluid volume **(29).**

- Cardiotocography and short-term variation STV

A reactive CTG virtually excludes fetal hypoxemia. The fetal heart rate STV is a biophysical parameter obtained by computerized CTG (cCTG) that reflects autonomic nervous system function. FGR and the accompanying presence of severe hypoxemia, the fetal sympathetic and parasympathetic activity is altered, resulting in reduced fetal heart rate variation, and, thus, reduced STV.

cCTG and evaluation of STV have been validated against invasive testing in fetal hypoxemia and academia and represent the only objective measure of fetal heart rate. **(30).**

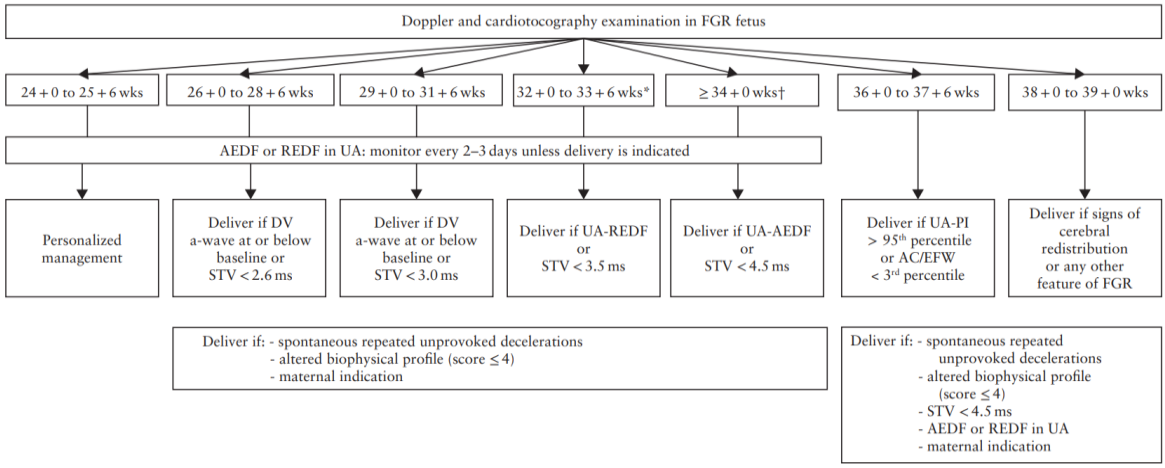

Figure (3): Summarizes the proposed management of FGR pregnancies based on cCTG and Doppler findings.

Recommended management of pregnancies with fetal growth restriction (FGR), based on computerized cardiotocography and Doppler findings. *Permitted after 30 + 0 weeks. †Permitted after 32 + 0 weeks.

***AC**, fetal abdominal circumference; **AEDF**, absent end-diastolic flow; **DV**, ductus venosus; **EFW**, estimated fetal weight; **PI**, pulsatility index; **REDF**, reversed end-diastolic flow; **STV**, short-term variation; **UA**, umbilical artery; **wks**, gestational weeks.*

When and how to deliver *

There is no international consensus on the timing of delivery in late FGR, due to the lack of interventional management randomized trials based on Doppler indices in these pregnancies. In fact, national guidelines for the management of FGR are highly variable.

The only randomized interventional trial on FGR at or close to term is the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT) study **(31)**. The study compared the effect of induction of labor vs expectant monitoring in singleton pregnancies beyond 36 + 0 weeks

of gestation with suspected FGR. The study did not consider any Doppler assessment and the only Doppler parameter reported was absent EDF in the UA (present in 14/650 pregnancies).

The induction-of-labor policy, compared with expectant management, did not affect the rate of adverse neonatal outcome or neurodevelopmental and behavioral outcome at 2 years of age, except for in children with birth weight below the 2.3rd percentile. Moreover, it did not affect the rates of instrumental vaginal delivery and Cesarean section. **(23).**

In pregnancies with late FGR and UA-PI above the 95th percentile, expert opinion is that delivery should be considered when the gestation is beyond 36 + 0 weeks and not later than 37 + 6 weeks. Though cerebral redistribution is associated with adverse short- and long-term perinatal outcomes there is currently no evidence as to how cerebral Doppler should be utilized in the delivery timing of FGR. **(32).**

It is important that each unit predisposes and follows a precise devoted monitoring protocol, based also on local experience and resources. Depending on the clinical situation (parity, EFW, cervical findings), induction of labor may be undertaken, but this is not recommended in the context of critical UA Doppler findings (i.e., absent, or reversed EDF) Continuous fetal heart rate monitoring during labor should be undertaken. **(33).**

***Recommendations The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG Guidelines 2020) {Late FGR}**

• In pregnancies with late FGR, delivery should be based on biophysical assessments or maternal indication as follows:

◦ At any gestational age, deliver if one of the following is present:

- Spontaneous repeated persistent unprovoked fetal heart rate decelerations (GOOD PRACTICE POINT); - Altered BPP (score ≤ 4) **(GOOD PRACTICE POINT);**

- Maternal indication (e.g., severe preeclampsia, HELLP syndrome) or obstetric emergency requiring delivery **(GOOD PRACTICE POINT).**

- cCTG STV < 3.5 ms at 32 + 0 to 33 + 6 weeks and < 4.5 ms at ≥ 34 + 0 weeks **(GOOD PRACTICE POINT).**

- Absent or reversed UA-EDF (GOOD PRACTICE POINT); ◦ 36 + 0 to 37 + 6 weeks: deliver if UA-PI > 95th percentile or AC/EFW < 3rd percentile **(GOOD PRACTICE POINT).**

◦ 38 + 0 to 39 + 0 weeks: deliver if there is evidence of cerebral blood-flow redistribution or any other feature of FGR **(GOOD PRACTICE POINT).**

• In the absence of contraindications, induction of labor is indicated **(GOOD PRACTICE POINT).**

Grades of recommendation

A At least one meta-analysis, systematic review, or randomized controlled trial rated as 1++ and directly applicable to the target population; or systematic review of randomized controlled trials or body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results

B Body of evidence including studies rated as 2++ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+

C Body of evidence including studies rated as 2+ applicable directly to the target population and demonstrating overall consistency of results; or evidence extrapolated from studies rated as 2++

D Evidence of level 3 or 4; or evidence extrapolated from studies rated as 2+ Good practice point Recommended best practice based on the clinical experience of the Guideline Development Group

- Small-for-gestational age.

SGA is often considered as a constitutionally small fetus that is otherwise healthy; it is frequently the case that the SGA categorization is applied to a small baby that is structurally normal and has normal Doppler findings. In these cases, the adoption of customized growth charts has been suggested to reduce the proportion of SGA **(1).** However, there is evidence suggesting that SGA with normal fetoplacental Doppler can be associated with accelerated placental aging **(17)**, signs of placental under perfusion, lower umbilical vein blood flow volume altered maternal hemodynamics and greater incidence of Cesarean section for fetal distress compared with AGA fetuses. there might be a subgroup of SGA fetuses that do in fact suffer from 'stunted' fetal growth, which adapts to a poor nutritional environment and are not identified by standard biophysical diagnostic tools **(34).**

*** How to monitor**

At the diagnosis of SGA, fetal Doppler indices (UA-PI, MCA-PI, and their ratios) and uterine artery Doppler should be evaluated. In the case of late SGA (after 32 weeks), once uterine artery Doppler has been assessed at diagnosis, there is no need for uterine artery Doppler to be re-evaluated at each visit as, usually, it remains unchanged from diagnosis of SGA to delivery. Fortnightly assessment of fetal growth is recommended **(35).**

*** When and how to deliver**

Reports suggest that universal induction of labor at term may be more beneficial than expectant management in terms of reduced perinatal mortality **(35)** without increasing the rate of Cesarean

section or operative vaginal delivery. This is true for both nulliparous women aged ≥ 35 years and unselected populations. Considering that the major cause of perinatal death at term is the stillbirth and that some SGA fetuses might suffer some degree of stunted growth that is not adequately identified by current biophysical tools, it is reasonable to consider delivery after 38 + 0 weeks of gestation, and the pregnancy should not exceed 39 + 0 weeks, to reduce the risk of severe growth restriction or stillbirth in fetuses identified as SGA **(36).**

* **Recommendations The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG Guidelines 2020) {SGA}**

• Fetal Doppler velocimetry should be performed both at the diagnosis of SGA and during follow-up **(GOOD PRACTICE POINT).**

• In case of late SGA, fortnightly assessment of fetal growth and weekly assessment of UA-PI, MCA-PI, CPR, and UCR is recommended **(GOOD PRACTICE POINT).**

• When SGA has been identified, delivery should be planned from 38 + 0 weeks and the pregnancy should not exceed 39 + 0 weeks of gestation **(GRADE OF RECOMMENDATION: A).**

• Continuous fetal heart rate monitoring during labor is indicated **(GOOD PRACTICE POINT).**

Grades of recommendation

A At least one meta-analysis, systematic review or randomized controlled trial rated as 1++ and directly applicable to the target population; or systematic review of randomized controlled trials or body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results

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No Conflict of interest.

References:

1. **Gardosi J, Giddings S, Buller S, Southam M, Williams M. (2014):** Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health.;128:698–702.

2. **Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. (2011):** Cognitive function after intrauterine growth restriction and very preterm birth. Pediatrics; 127: e874–882.

3. **Moraitis AA, Wood AM, Fleming M, Smith GC. (2014):** Birth weight percentile and the risk of term perinatal death. ObstetGynecol; 124: 274–283.

4. **Lane-Cordova AD, Khan SS, Grobman WA, Greenland P, Shah SJ. (2019):** Long-term cardiovascular risks associated with adverse pregnancy outcomes: JACC review topic of the week. J. Am. Coll. Cardiol.; 73: 2106–2116.

5. **Burton GJ, Jauniaux E (2018):** Pathophysiology of placental-derived fetal growth restriction. Am. J. Obstet. Gynecol.; 218: S745–S761.

6. **Kaya B, Nayki U, Nayki C, Ulug P, Oner G, Gultekin E, Yildirim Y. (2014):** Proliferation of trophoblasts and Ki67 expression in preeclampsia. Arch Gynecol Obstet. 2015 May;291(5):1041-6. doi: 10.1007/s00404-014-3538-4. Epub Nov 11. PMID: 25384521.

7. **Redline RW. (2008):** Placental pathology: a systematic approach with clinical correlations. Placenta. Mar;29 Suppl A: S86-91.

8. **KuzminaI Y, Hubina-Vakulik GI, Burton GJ. (2005):** Placental morphometry and Doppler flow velocimetry in cases of chronic human fetal hypoxia. Eur. J. Obstet. Gynecol. Reprod. Biol.; 120:139–145.

9. **Junaid TO, Brownbill P, Chalmers N, Johnstone ED, Aplin JD. (2014):** Fetoplacental vascular alterations associated with fetal growth restriction. Placenta; 35: 808–815.

10. **Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. (2016):** Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound ObstetGynecol; 48: 333–339.

11. **Simcox LE, Myers JE, Cole TJ, Johnstone ED. (2017):** Fractional fetal thigh volume in the prediction of normal and abnormal fetal growth during the third trimester of pregnancy. Am J Obstet Gynecol.; 217(4): 453.e1-453.e12.

12. **Collins SL, Grant D, Black RS, Vellayan M, ImpeyL. (2011):** Abdominal pregnancy: a perfusion confusion? Placenta; 32:793–795.

13. **Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones DS, Smith GCS. (2018):** Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study. Lancet Child Adolesc Health; 2: 569–581.

14. **Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, Glanc P, Khalil A, Lee W, Napolitano R, Papageorghiou A, Sotiriadis A, Stirnemann J, Toi A, Yeo G. (2019):** ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound ObstetGynecol; 53: 715–723.

15. **Vasak B, Koenen SV, Koster MP, Hukkelhoven CW, Franx A, Hanson MA, Visser GH. (2015):** Human fetal growth is constrained below optimal for perinatal survival. Ultrasound ObstetGynecol; 45: 162–167.

16. **Iliodromiti S, Mackay DF, Smith GC, Pell JP, Sattar N, Lawlor DA, Nelson SM. (2017):** Customized and non-customized birth weight centiles and prediction of stillbirth and infant mortality and morbidity: a cohort study of 979,912 term singleton pregnancies in Scotland. PLoS Med; 14: e1002228.

17. **Parra-Saavedra M, Crovetto F, Triunfo S, Savchev S, Peguero A, Nadal A, Parra G, Gratacos E, Figueras F. (2013):** Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. Placenta; 34: 1136–1141.

18. **Cruz-Mart´ınez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. (2011):** Fetal brain Doppler to predict cesarean delivery for non-reassuring fetal status in term small-for-gestational-age fetuses. ObstetGynecol; 117: 618–626.

19. **Habek D, Salihagic A, Jugovi´c D, Herman R. (2007):** Doppler Cerebro-umbilical ratio and fetal biophysical profile in the assessment of perinatal cardiotocography in growth-retarded fetuses. Fetal Diagn Ther; 22: 452–456.

20. **Van Wassenaer-Leemhuis AG, Marlow N, Lees C, Wolf H; TRUFFLE investigators. (2017):** The association of neonatal morbidity with long-term neurological outcome in infants who were growth restricted and preterm at birth: secondary analyses from TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe). BJOG; 124: 1072–1078.

21. **Caradeux J, Martinez-Portilla RJ, Peguero A, Sotiriadis A, Figueras F. (2019):** Diagnostic performance of third-trimester ultrasound for the prediction of late-onset fetal growth restriction: a systematic review and meta-analysis. Am J ObstetGynecol; 220: 449–459.e19.

22. **Fabjan-Vodusek V, Kumer K, Osredkar J, Verdenik I, Gersak K, Premru-Srsen T. (2019):** Correlation between uterine artery Doppler and the sFlt-1/PlGF ratio in different phenotypes of placental dysfunction. Hypertension Pregnancy; 38: 32–40.

23. **Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, van der Salm PC, van Pampus MG, Spaanderman ME, de Boer K, Duvekot JJ, Bremer HA, Hasaart TH, Delemarre FM, Bloemenkamp KW, van Meir CA, Willekes C, Wijnen EJ, Rijken**

M, le Cessie S, Roumen FJ, Thornton JG, van Lith JM, Mol BW, Scherjon SA. (2010): Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ; 341: c7087.

24. **American College of Obstetricians and gynaecologists Committee on Practice Bulletins-Obstetrics and the Society for Maternal-Fetal Medicine (2019):** ACOG Practice Bulletin No. 204: Fetal Growth Restriction. ObstetGynecol; 133: e97–109.

25. **Wolf HT, Huusom LD, Henriksen TB, Hegaard HK, Brok J, Pinborg A. (2020):** Magnesium sulphate for fetal neuroprotection at imminent risk for preterm delivery: a systematic review with meta-analysis and trial sequential analysis. BJOG; 127(10):1180-1188.

26. **MacDonald TM, Hui L, Tong S, Robinson AJ, Dane KM, Middleton AL, Walker SP. (2017):** Reduced growth velocity across the third trimester is associated with placental insufficiency in fetuses born at a normal birth weight: a prospective cohort study. BMC Med; 15: 164.

27. **Levytska K, Higgins M, Keating S, Melamed N, Walker M, Sebire NJ, Kingdom JC. (2017):** Placental pathology in relation to uterine artery Doppler findings in pregnancies with severe intrauterine growth restriction and abnormal umbilical artery Doppler changes. Am J Perinatal; 34: 451–457.

28. **Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G.** Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growthrestricted fetus. Ultrasound ObstetGynecol 2002;19:140–6.

29. **Turan S, Turan OM, Berg C, Moyano D, Bhide A, Bower S, Thilaganathan B, Gembruch U, Nicolaides K, Harman C, Baschat AA. (2007):** Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. Ultrasound ObstetGynecol; 30: 750–756.

30. **Baschat AA. (2018):** Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin ObstetGynaecol; 49: 53–65.

31. **van Wyk L, Boers KE, van der Post JA, van Pampus MG, van Wassenaer AG, van Baar AL, Spaanderdam ME, Becker JH, Kwee A, Duvekot JJ, Bremer HA, Delemarre FM, Bloemenkamp KW, de Groot CJ, Willekes C, Roumen FJ, van Lith JM, Mol BW, le Cessie S, Scherjon SA; DIGITAT Study Group. (2012):** Effects on (neuro)developmental and behavioral outcome at 2 years of age of induced labor compared with expectant management in intrauterine growth-restricted infants: long-term outcomes of the DIGITAT trial. Am J ObstetGynecol; 206: 406.e1–7.

32. **Meher S, Hernandez-Andrade E, Basheer SN, Lees C. (2015):** Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review. Ultrasound ObstetGynecol; 46: 398–404.

33. **Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. (2012):** Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound Obstet Gynecol.; 39:299–303.

34. **Roberts LA, Ling HZ, Poon LC, Nicolaides KH, Kametas NA. (2018):** Maternal hemodynamics, fetal biometry and Doppler indices in pregnancies followed up for suspected fetal growth restriction. Ultrasound ObstetGynecol; 52: 507–514.

35. **Knight HE, Cromwell DA, Gurol-Urganci I, Harron K, van der Meulen JH, Smith GCS. (2017):** Perinatal mortality associated with induction of labour versus expectant management in nulliparous women aged 35 years or over. an English national cohort study. PLoS Med; 14: e1002425.

36. **Walker KF, Bugg GJ, Macpherson M, McCormick C, Grace N, Wildsmith C, Bradshaw L, Smith GC, Thornton JG; 35/39 Trial Group. (2016):** Randomized Trial of Labor Induction in Women 35 Years of Age or Older. N Engl J Med; 374: 813–822.