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Fetal Growth Restriction

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Abstract

Fetal growth defect is classified into intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) fetus based on the estimated fetal weight percentile and Doppler hemodynamic parameters. IUGR pathophysiology and etiology are complex and diverse, highlighting placental insufficiency as a paradigm, which explains its association with other entities of great clinical importance such as preeclampsia. The poor long- and short-term perinatal and postnatal results associated with this context make it necessary to establish an early diagnosis and a therapeutic strategy, which can be challenging due to the compromise between the threat of intrauterine permanence and the prematurity problem. Consequently, a systematic and protocolized diagnostic-therapeutic management, based on scientific evidence, is necessary to determine whether obstetric intervention through a preterm delivery is advisable to improve the perinatal outcomes of these patients.

Keywords: fetal growth, intrauterine growth restriction, small-for-gestational-age fetus, Doppler evaluation, prematurity

1. Introduction

In general terms, fetal growth defect is considered the impossibility of achieving the genetically determined potential size [1]. In the vast majority of cases, it is related to uteroplacental insufficiency in the context of intrauterine growth restriction (IUGR). Despite its origin remains unknown, it is believed to be caused by an interaction of environmental and genetic factors with either a fetal, placental, or maternal origin. Various complications are associated with IUGR; these may include stillbirth, prematurity, neonatal morbi-mortality, endocrine and metabolic alterations, increased cardiovascular risk, and long-term neurological sequelae [2].

IUGR fetus identification is one of the main objectives of prenatal care, since proper perinatal diagnosis and management reduces perinatal morbi-mortality [3]. Most small fetuses are not diagnosed during pregnancy [4], not even in high-risk subpopulations. This is in part due to the large number of reference tables used and the lack of international standards comparable to those for child growth [5]. Therefore, it is necessary to improve the prenatal diagnosis of these cases. With this purpose, it is essential to have an agreed definition between obstetricians and neonatologists, which would allow to compare data, to conduct prospective studies, and to analyze results between different institutions [2].

2. Definitions

Fetal growth defect (FGD) is defined as an ultrasound estimated fetal weight (EFW) below the 10th percentile for gestational age and gender [2].

Among FGD fetuses, Doppler hemodynamic evaluation differentiates fetuses with higher risk of perinatal morbi-mortality [6]. Hence, fetal growth restriction definition incorporates the Doppler hemodynamic evaluation to distinguish the fetuses with placental involvement from those without that affectation. These unaffected fetuses have a better prognosis and are known as small-for-gestational-age (SGA) fetuses [2].

Fetal weight estimation is based on Hadlock's formula which includes biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) [7]. However, there is controversy about fetal weight percentile estimation in the medical literature. Percentile customization according to maternal and/or paternal features is one of the main sources of heterogeneity in the IUGR definition. The utility of customized percentiles is to a certain extent limited because factors used for customization are not powerful predictors of birth weight [8]. Maternal height, weight, and ethnicity/race are related to fetal size but do not explain the important variability in birth weight. Thus, the limitations of these parameters restrict their usefulness for IUGR definition [2]. For that reason, the Fetal Growth Longitudinal Study, part of the Intergrowth-21st Project, aimed to develop international tabulated standards for fetal growth [9]. These curves have the advantage of using fetal growth standards derived from healthy populations. This reduces the underdiagnosis that may occur when fetal growth is contrasted against references including the high-risk mothers. At the various study sites, these curves have proven to be similar for all fetal and newborn measurements showing the same growth potential regardless of the race [10]. Thus, the reported differences were probably related to nutritional problems rather than geographical location or ethnicity [2]. However, several subsequent studies have shown that individualized fetal growth tables improve the identification of patients at risk of adverse perinatal outcomes [11].

2.1. Differences between IUGR and SGA

A small fetus is associated with worse obstetric results. At least two groups of small fetuses are distinguished: IUGR and SGA [2]. **Table 1** shows its main differences:

	IUGR	SGA
Perinatal outcomes	Worse	Similar to normal fetuses
Growth delay	"True"	"Constitutional"
Doppler ultrasound	Hemodynamic redistribution	Normal
Abnormal environment adaptation	Present	Absent
Preeclampsia risk	Higher	Lower

Table 1. Differences between IUGR and SGA.

IUGR term refers to small fetuses with a higher risk of intrauterine fetal deterioration, still-birth, and, in general, a worse perinatal outcome than those with normal growth. These fetuses have a "true" growth delay and are generally associated with Doppler ultrasound signs which suggest hemodynamic redistribution due to an adaptation to fetal malnutrition/hypoxia with histological and biochemical signs of placental disease. IUGR is also associated with an increased risk of preeclampsia [2].

2.2. IUGR vs. SGA definition

Current evidence suggests that there is no superior parameter for differentiating IUGR from SGA [2]. As for the individual Doppler ultrasound study, the best candidate is the cerebro-placental ratio (CPR), which is calculated dividing the middle cerebral artery (MCA) Doppler pulsatility index (PI) (MCA-PI) by the umbilical artery (UA) Doppler PI (UA-PI). This ratio reflects small decreases in fetal cerebral vascular resistance with slight increases in placental resistance in a combined way. This relationship seems to be more sensitive to hypoxia than its individual components, correlating better with a possible adverse outcome [12]. The uterine artery (UtA) PI (UtA-PI) is a predictor of worse perinatal results in small fetuses [13]. Another poor outcome predictive factor is a very small EFW regardless of the CPR and the UtA-PI values. An EFW below the 3rd percentile indicates a much higher risk of adverse perinatal outcomes [14]. Therefore, when there are any of the three parameters mentioned above (CPR, UtA-PI, and/or EFW < 3rd percentile), the risk of adverse perinatal outcomes increases. For this reason, the definition of IUGR must include these three parameters [2].

Summarizing the definition [2, 15]:

- A SGA fetus is defined as an EFW lower than the 10th percentile and greater than or equal to the 3rd percentile for gestational age and gender with a normal Doppler hemodynamic study.

- An IUGR is defined as:

  ○ An EFW below the 3rd percentile for gestational age and gender

  ○ An EFW below the 10th percentile for gestational age and gender plus an altered Doppler hemodynamic study

2.3. Severe early onset vs. moderate late onset IUGR

The IUGR is presented in two different phenotypes according to disease onset time during pregnancy: early onset IUGR and late onset IUGR. Generally, there is a correlation between early onset and more severe IUGR forms, so two types of IUGR are defined: severe early onset and moderate late onset. The cutoff point for these forms has been arbitrarily established at 32 weeks [2]. In **Table 2**, we observe the differences between both clinical forms.

2.3.1. Severe early onset IUGR

The severe early onset IUGR represents 20–30% of all IUGR. It is related to severe placental insufficiency and chronic fetal hypoxia, and so UA Doppler is often pathological [16]. In this context, this type of IUGR is associated with early preeclampsia in up to 50% of cases [17] and with severe damage and/or stillbirth before term [18]. Besides, its clinical management is a challenge due to the necessity to balance the risks of intrauterine permanence with the complications derived from prematurity [2].

Without treatment, fetal well-being deteriorates with a progression toward hypoxia and acidosis, which is reflected in the sequence of alterations of the UA Doppler and the PI of the ductus venosus (DV). The latency period to severe fetal deterioration is variable, but it usually lasts for weeks [19] and depends on the severity of the placental compromise. The sequence of changes (**Figure 1**) is relatively constant, especially in the signs of advanced stages, except in the cases where there is an associated preeclampsia which can distort the natural history. In such cases, fetal deterioration might appear unexpectedly. These changes in fetal Doppler allow for the monitorization of the progression of fetal deterioration and the scheduling of the delivery in an elective manner [2].

		Severe early-onset IUGR	Moderate late-onset IUGR
IUGR %		20-30%	70-80%
Prevalence		1-2% (low)	3-5% (high)
Problem		Management	Diagnosis
Placental disease	Intensity	Severe	Moderate
	UA Doppler	Altered	Normal
	Preeclampsia association	High	Low
Hypoxia		++	+/-
Cardiovascular adaptation		Systemic	Central
Fetal Maturity		Immature fetus	Mature fetus
Hypoxia tolerance		High	Low
Natural history of fetal deterioration		Present	Absent (or fast evolution)
Morbi-mortality		High	Low (but common stillbirth cause). Adverse long-term outcomes

Table 2. Differences between severe early-onset IUGR vs. moderate late-onset IUGR (adapted from Ref. [2]).
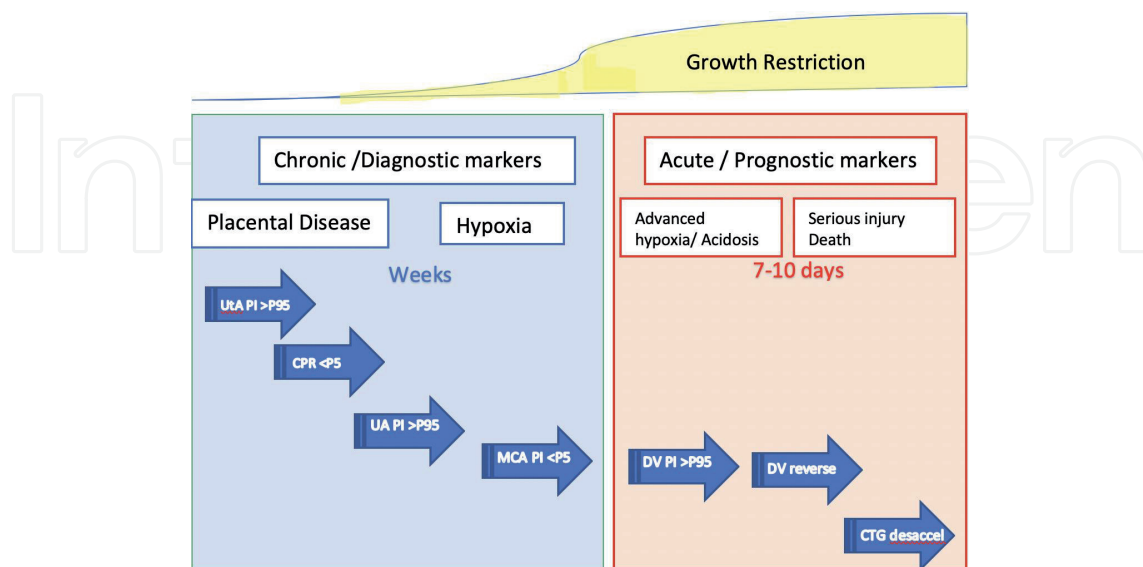
2.3.2. Moderate late onset IUGR

These fetuses represent 70–80% of cases [17]. The placental alteration is mild, and, therefore, the UA is generally normal [20] and there is low association with preeclampsia (10%) [17]. In these cases, the diagnostic rates are low, and that is what makes the late (undiagnosed) IUGR to contribute in a large proportion of late stillbirth [21].

In moderate lateonset IUGR, there is a high rate of CPR alteration [20]. In addition, in 25% of cases of late onset IUGR, a cerebral vasodilation may occur (MCA-PI below the 5th percentile), reflecting a situation of chronic hypoxia. Besides, signs of advanced fetal deterioration with changes in the ductus venosus are hardly ever observed [20]. For this reason, the sequential fetal deterioration cascade described previously does not occur (**Figure 2**). These fetuses may suffer rapid deterioration which can lead to serious injury or death. The explanation behind this fact could be a combination of factors such as the low tolerance of preterm fetuses to hypoxia (compared to preterm fetuses), the higher frequency of uterine contractions in term gestations, and some cases of acute placental failure [2]. Despite the benign nature of this type of fetus, the risk of acute fetal deterioration before delivery significantly contributes to late stillbirth [22] and to a high association with intrapartum fetal distress and neonatal acidosis [23].

2.3.3. Common problems

Both IUGR types are associated with a worse long-term prognosis in neurological, cardiovascular, and metabolic development [24–27]. This would mean that, regardless of severity, chronic exposure to an adverse intrauterine environment is essential to develop adverse fetal programming. Predictably, different stages of fetal maturation would determine different adaptive programming responses [2].

Figure 1. Sequence of changes in severe early-onset IUGR. Adapted from Ref. [2].
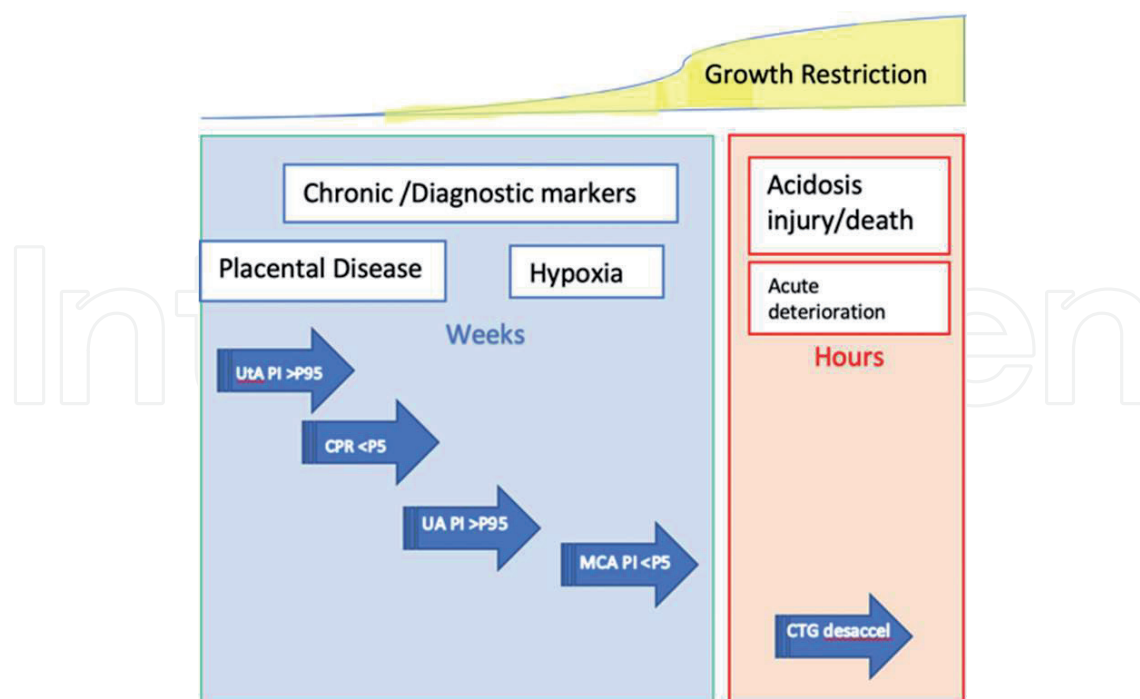
Figure 2. Sequence of changes of moderate late-onset IUGR. Adapted from Ref. [2].

The evidence suggests that both early and late onset IUGR are a consequence of a placental disease, but it is unknown to what extent they are the same type of pathology. Placental insufficiency of early onset IUGR is associated with histological signs of alteration in early implantation [28]. It is not clear, however, if late IUGR is a mild form of abnormal placental implantation at the beginning of the pregnancy or if it is an added placental damage produced in the second half of pregnancy. The latter option would be supported by the fact that part of these patients has abnormal UtA Doppler in the third trimester being this one previously normal [29].

3. Etiology

3.1. Placental disease

In general terms, IUGR with Doppler hemodynamic alteration shows fetal adaptation to a hypoxia situation and chronic malnutrition due to placental insufficiency. This placental function alteration is caused by a deficient invasion of the trophoblast in the maternal spiral arteries, with an incomplete remodeling of these vessels, and therefore a deficit in the physiological vasodilation that occurs in normal pregnancy. This phenomenon can be monitored by assessing uterine artery resistance, which increases in the cases of growth restriction associated with placental origin [2].

It is likely that in the future, biomarkers of placental insufficiency in maternal blood may be incorporated as a diagnostic criterion for IUGR as markers of placental involvement in this pathology. Recent evidence suggests that angiogenic factors predict a poor perinatal outcome in small fetuses, with predictive values similar to CPR and UtA Doppler, but without a proven

additive value [30]. An increase in anti-angiogenic factors sFlt1 and soluble endoglin (sEnd) and a decrease in pro-angiogenic factors (placental growth factor—PGF) have been observed.

3.2. Infectious disease

Cytomegalovirus: it is the first cause of congenital infection in Europe (0.3–0.6%). Most cases are asymptomatic. The risk of congenital disease is higher if the infection occurs during the first and second trimesters. In contrast, the transmission risk increases in the third trimester, but fetuses infected at this time are generally born healthy [31].

Congenital varicella: it is more frequent when the maternal disease is acquired between 8 and 20 weeks of gestation. Very rare fetal involvement is observed in the second and third trimesters. There is an affectation of the musculoskeletal system and an affectation of the autonomic nervous system [32].

Congenital rubella: there is a higher incidence of the disease in developing countries [33]. Fetal involvement is observed in the vast majority of cases in which maternal infection occurs in the first trimester, being infrequent beyond 17 weeks.

HIV: a relationship between HIV seropositivity and the increased risk of spontaneous abortion, stillbirth, IUGR, low birth weight, premature delivery, and neurodevelopmental alteration [34] has been observed. The association between premature birth and low birth weight has also been related to the use of highly active antiretroviral therapy (HAART) [35]. In these patients, an increased risk of placental insufficiency has been described [36].

Malaria: this infection causes a massive sequestration of erythrocytes in the syncytiotrophoblast. Multiple mechanisms contribute to fetal growth restriction, including abnormal vascularization, impaired growth hormone expression, difficulty in transporting nutrients, and a process of inflammation and activation of the immune response [37].

3.3. Genetic disorders

Only 2% of the cases with fetal growth restriction without structural abnormalities are associated with alterations in the karyotype [38]. The risk of a genetic syndrome with cognitive repercussion is increased if there are malformations, microcephaly, and/or progressive flattening of biometrics.

3.4. External factors

Smoking is the main contributor to fetal growth restriction in our environment. The odds ratio for developing IUGR in pregnant smokers is 1.9 (95% confidence interval (CI): 1.69–2.13). The risk is directly proportional to consumption [39].

4. Fetal well-being assessment

Fetal well-being assessment is based on determining whether the fetus is suffering from any chronic affectation (due to a progressive increase in hypoxemia and/or hypoxia) or an acute

involvement (acute changes in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis) whose alteration usually precedes fetal death within a few days.

UA Doppler: it is the only measure that provides both diagnostic and prognostic information for IUGR management. The progression of the Doppler patterns of the UA toward an absent or reverse diastolic flow correlates with the risk of fetal injury or death [2].

MCA Doppler: it reports the presence of cerebral vasodilation, a subrogated hypoxia biomarker. Its alteration is considered a late manifestation. Fetuses with an altered MCA-PI have a six times higher risk of urgent cesarean section due to suspected loss of fetal well-being than fetuses with a normal PI [40].

CPR: it has mainly a diagnostic value. It significantly improves the sensitivity of the UA and the isolated MCA, since the increase in placental impedance (UA-PI) is usually combined with a decrease in brain resistance (MCA-PI) [41].

Ductus venosus (DV) Doppler: it is the parameter that, by itself, has the greatest capacity to predict the risk of short-term stillbirth in early onset IUGR. The absent/reverse flow during atrial contraction is associated with perinatal mortality, regardless of gestational age [42], with a risk ranging from 40 to 100% in the cases of early onset IUGR [43].

Aortic isthmus (AoI) Doppler: it is associated with an increase in fetal mortality and neurological morbidity in the cases of early onset IUGR. This vessel reflects the balance between cerebral impedance and the systemic vascular system [44]. Longitudinal studies show that alterations in AoI precede those of DV in 1 week [45] and, therefore, it is not a good predictor of short-term stillbirth risk. In contrast, AoI seems to improve the prediction of neurological morbidity [46].

Uterine artery Doppler (UtA): the study of the uterine artery flow has mainly focused on predicting the risk of preeclampsia and fetal growth restriction. However, this flow has also been considered both as diagnostic and fetal well-being assessment tool in SGA fetuses. There is a statistically significant correlation among the Doppler alteration in the UA, the Doppler alteration in the UtA, and an adverse perinatal outcome. Both vessels are comparable in their prediction ability [43].

Computerized cardiotocography (CTG): it provided with new knowledge about the pathophysiology and management of IUGR. It evaluates the short-term variability (STV) of fetal heart rate, a parameter that cannot be subjectively evaluated. Current evidence suggests that computerized CTG is sensitive for the detection of advanced fetal impairment, and that provides a value similar to that of DV with a reverse atrial flow for the prediction of short-term fetal death. A low variability of fetal heart rate is correlated with the presence of acidosis and severe hypoxia, a fact that has been demonstrated with cord blood collected at the time of cesarean section. Despite the high implementation of conventional CTG in all clinical control protocols, it has not been shown to reduce mortality in high-risk pregnancies given its high inter- and intra-observer variability in interpretation [47].

Biophysical profile (BPP): it is obtained by combining ultrasound evaluation of fetal tone, respiratory movements, and body movements with amniotic fluid and conventional CTG. A

systematic review [48] found that the use of BPP does not reduce perinatal mortality (relative risk (RR) 1.33, 95% CI 0.60–2.98) or APGAR less than 7 at 5 min (RR 1.27, 95% CI 0.85–1.92). An increased risk of cesarean section was also found (RR 1.60, 95% CI 1.05–2.44). It is currently not recommended to perform a BPP for the control of the preterm SGA fetus.

Amniotic fluid index (AFI): it is basically used as part of the BPP. There is limited evidence on the role of oligoamnios as a predictor of perinatal complications in IUGR fetuses with Doppler follow-up, its inclusion being questionable in management protocols [2].

5. Diagnosis

5.1. Clinical diagnosis

Uterine height will be performed at each visit from 26 weeks. The methodology will be supine position, from fundus to pubis, and masked observation of the previous exploration. If the uterine height is less than the 10th percentile for gestational age and no EFW is available in the previous 2 weeks, an ultrasound EFW is required.

5.2. Ultrasound diagnosis

Fetal weight estimation requires three steps:

- First step: gestation dating according to crown-rump length.

- Second step: calculation of EFW according to fetal biometrics—algorithm that includes BPD, HC, AC, and FL [49]. If the cephalic measurements are not valuable, an alternative algorithm with FL and AC will be used [50].

- Third step: calculation of the growth percentile according to reference tables.

5.3. Diagnosis of the type of alteration

5.3.1. Study protocol

Detailed anamnesis:

- Toxic habits: tobacco, alcohol, drugs, medication, and work [51]

- Maternal and paternal weight and size, weight of the patient at birth, and measurement of blood pressure (BP) at the beginning of pregnancy

- Sexual history of the couple: relationship time. Type of contraception. Artificial fertilization techniques

- Previous obstetric clinical history: neonatal weight of previous children (the history of a previous SGA doubles the risk in successive pregnancies) [52], history of fetal death, preeclampsia, growth restriction, repeated abortions, placental abruption, and premature deliveries [15]

- Medical history: diabetes with vascular disease, moderate and severe nephropathy, cyanotic congenital heart disease, arterial hypertension, antiphospholipid syndrome, and systemic lupus erythematosus [53]

Maternal physical examination: weight, height, uterine height, limb examination in search of chronic vascular disease, blood pressure.

Complementary explorations:

- **Ultrasound:** detailed anatomical assessment. 20–60% of congenital malformations are accompanied by growth disturbance [54], and approximately 10% of fetuses with growth restriction have an associated congenital anomaly [55]. It is also important to assess Doppler study (UA, MCA, UtA, and CPR), placenta, amniotic fluid, and chromosomopathy markers.

- **Neurosonography and echocardiography**: for a growth below the 3rd percentile.

- Proteinuria study.

- **Complete blood test** with hemogram, coagulation, and basal biochemistry (with liver and kidney profile).

- **Amniocentesis:** it is advisable to perform an amniocentesis to rule out chromosomal abnormalities when the diagnosis of IUGR is made at early gestational ages. The rate of chromosomal abnormalities in IUGR fetuses is approximately 20% if diagnosed before 23 weeks, being practically null afterward [56]. Genetic studies in amniotic fluid are recommendable if any of the following criteria is met:

  ○ Quantitative fluorescence-polymerase chain reaction (QF-PCR) and molecular karyotype (array CGH):

  ○ IUGR diagnosis prior to 24 weeks and severe (below the 3rd percentile)

  ○ IUGR diagnosis prior to 28 weeks and severe (below the 3rd percentile) accompanied by ultrasound markers (excluding oligoamnios), minor structural anomaly, or biometrics (FL or HC) < −3 standard deviations (SD)

  ○ EFW lower than the 10th percentile accompanied by any major structural anomaly

  ○ Study of bone alterations (add it to QF-PCR and molecular karyotype)

  ○ Achondroplasia and hypochondroplasia study if bone biometrics < −3 SD or femur/foot ratio < 0.85.

  ○ Genetic counseling to assess skeletal dysplasia study if malformations associated with dysplasia, bone morphological alterations (fractures, curvatures, hypomineralization), or long bone length below the 1st percentile.

  ○ Study of specific genetic panels or exome sequencing (request genetic counseling to assess these studies)

○ If IUGR with more than one structural anomaly of two systems (except hypospadias) of high syndromic risk

○ Biometrics (FL or HC) < −4 SD with no signs of placental insufficiency and normal molecular karyotype result

- **Infections study:** it is estimated that around 5% of SGA fetuses have an infectious cause. The most frequently implicated pathogen is CMV, followed by toxoplasma and syphilis [2]. Facing IUGR diagnosis, it is necessary to request:

○ Rubella study.

○ Syphilis study: treponemal and reaginic test in maternal blood.

○ Malaria study: for populations at risk (from endemic areas) [57].

○ CMV study: in the case of indication of invasive technique, it is necessary to perform CMV PCR in amniotic fluid. In the case of non-indication of invasive technique, maternal serologies (IgG and IgM) will be requested only in IUGR (excludes SGA). If IgG and IgM are negative, the infection is discarded. If IgG and IgM are positive, it is recommended to perform an amniocentesis for CMV PCR in amniotic fluid. If IgG is positive but IgM is negative, it is advisable to perform an amniocentesis only if there is an ultrasound marker compatible with CMV infection (except an isolated oligoamnios).

5.3.2. Classification

IUGR is classified into stages, as shown in **Table 3**:

Stage	Pathophysiological Correlation	Criteria
I	Very small EFW or moderate placental insufficiency	EFW < p3 EFW < p10 + any of these criteria: • CPR < p5* • PI MCA < p5* • PI UtA > p95
II	Severe placental insufficiency	EFW < p10 + absent diastolic flow in UA**
III	Low suspicion of fetal acidosis	EFW < p10 + any of these criteria: • Reverse diastolic flow in UA** • PI-DV > p95 or absent diastolic flow in the DV***
IV	High suspicion of fetal acidosis	EFW < p10 + any of these criteria: • Reverse diastolic flow in the DV*** • Pathological CTG

*on two separated occasions > 12h.
** > 50% of cycles, in free cord loop in both arteries on two separated occasions > 12h.
*** on two separated occasions > 6-12h.

Table 3. IUGR stages (adapted from Refs. [2, 15]).

5.4. Follow-up

Follow-up visits for Doppler study will be adapted to the degree of fetal involvement [15]:

- SGA: control every 2–3 weeks

- IUGR stage I: control every 1–2 weeks

- IUGR stage II: control every 2–4 days

- IUGR stage III: control every 24–48 h

- IUGR stage IV: control every 12–48 h

During visits, Doppler control and CTG will be carried out. EFW assessment will be carried out at intervals equal to or greater than 15 days. When IUGR is accompanied by severe preeclampsia, the follow-up should correspond to the follow-up of the immediately superior IUGR stage.

6. Obstetric behavior

6.1. Prenatal obstetric behavior

6.1.1. General recommendations

- Avoid complete rest, as it does not improve fetal growth or perinatal outcome [58].

- Promote the elimination of possible external factors, such as tobacco. Quitting smoking reduces the risk of having SGA fetus. Although the benefit is greater if tobacco is abandoned before 15 weeks [59], smoking cessation should be advised when diagnosing SGA fetus at any gestational age [60].

- Work leave is advisable [15].

- Lung maturation only if termination criteria are met and gestational age is greater than 26 weeks (26–34.6 weeks).

- The criteria for neuroprophylaxis with magnesium sulfate will be <34 weeks and whenever possible >4 h before birth.

6.1.2 Termination of pregnancy: gestational age and delivery

The optimal moment of termination requires a balance between the risks of prematurity with those of intrauterine permanence (death and multiple organ damage due to inadequate tissue perfusion) [61]. The objective of IUGR vigilance is to evaluate fetal and neonatal risks to optimize intervention times, as well as to choose the best route of delivery. **Table 4** shows the recommended gestational age and delivery according to fetal growth defect.

	Gestational age	Delivery
SGA	≥ 40 gestation weeks	Vaginal delivery not contraindicated
IUGR stage I	≥ 37 gestation weeks	Vaginal delivery not contraindicated (If MCA-PI < p5, the risk of urgent caesarean section is 50%)
IUGR stage II	≥ 34 gestation weeks	Elective caesarean section
IUGR stage III	≥ 30 gestation weeks	
IUGR stage IV	≥ 26 gestation weeks	

Table 4. Recommended gestational age and delivery according to fetal growth defect.

Depending on the gestational age when we proceed to termination, we will have various degrees of prematurity:

- Extreme prematurity (24–28 weeks). In this period, each additional day of pregnancy represents an increase of 1–2% in the chances of survival [2]. Less than 26 weeks will be considered in the periviable infant with chances of survival without severe sequelae below 50% [15].

- Moderate prematurity (28–34 weeks). The presence of reverse flow in the umbilical artery is associated with a RR of 10.6 for the development of perinatal morbi-mortality [2].

- Late prematurity (34–36 weeks). There is not neither a high mortality rate nor severe morbidity, but there is a worse perinatal and cognitive outcome [62]. The decrease in diastolic velocities of the umbilical artery correlates with fetal nutritional deterioration [63] and its neurodevelopment [64]. The fetus with absent telediastolic flow of the umbilical artery presents four times greater risk of severe morbidity and perinatal mortality [65].

- Full-term gestation (>37 weeks). Cerebral hemodynamic redistribution is associated with worse perinatal and cognitive outcome [13].

Labor in fetuses with growth restriction is associated with an increase in the rate of urgent cesarean sections. Therefore, in the presence of signs of severe fetal deterioration such as absent or reverse umbilical diastolic flow, an elective cesarean section is advised.

6.1.3. Termination methods

Cervical maturation will begin with a PGE2 slow-release device, mechanical methods, or oxytocic induction depending on cervical conditions and uterine dynamics [66].

6.2. Intrapartum obstetric behavior

Continuous monitoring is necessary and an adequate resuscitation according to the baby's weight. It is also important to carry out a placental anatomo-pathological study in all cases.

6.3. Postpartum obstetric behavior

6.3.1. Immediate postpartum

- Protein/creatinine ratio and hepatic and renal profile: in those cases not studied prenatally and with IUGR criteria [15].

- CMV maternal serologies (IgG): to perform breast milk processing before administration and to avoid vertical transmission. It should be carried out in those cases with no prenatal studies and with IUGR criteria with delivery before 32 weeks or birth weight below 1500 g.

6.3.2. Quarantine

- Thrombophilic study: early onset IUGR, preeclampsia, or placental abruption.

- Explanation of the anatomo-pathological report of placenta. The massive deposit of perivillositary fibrin is associated with a risk of recurrence of 40–60%. The patient should be informed of the possibility of prophylaxis with heparin in a subsequent pregnancy to reduce this risk.

7. Conclusion

FGD is an important cause of perinatal morbidity. Its diagnosis, management, and monitoring according to clinical evidence are very important to improve perinatal outcomes in these cases.

7.1. Recommendation and future directions

1. It is very important to improve the diagnosis of fetuses with FGD. For this reason, the first trimester ultrasound is essential to date the pregnancy correctly. A second trimester ultrasound should be performed to detect fetal anomalies and to detect the most severe and early cases of FGD and a third trimester ultrasound to increase the diagnosis of late FGD.

2. In those cases with risk factors for growth defects, additional ultrasounds are recommended in the third trimester.

3. A careful etiological diagnosis should be done to rule out malformations, infections, or genetic alterations.

4. The management and follow-up of these gestations must be based on systematic protocols based on clinical evidence that facilitate the unification of clinical practice.

Abbreviations

IUGR	intrauterine growth restriction
SGA	small for gestational age

FGD	fetal growth defect
EFW	estimated fetal weight
BPD	biparietal diameter
HC	head circumference
AC	abdominal circumference
FL	femur length
CPR	cerebroplacental ratio
MCA	middle cerebral artery
PI	pulsatility index
UA	umbilical artery
UtA	uterine artery
HIV	human immunodeficiency virus
HAART	highly active antiretroviral therapy
DV	ductus venosus
CTG	computerized cardiotocography
BPP	biophysical profile
STV	short-term variability
RR	relative risk
CI	confidence interval
AFI	amniotic fluid index
BP	blood pressure
QF-PCR	quantitative fluorescence-polymerase chain reaction
PCR	polymerase chain reaction
SD	standard deviation
IgG	immunoglobulin G
IgM	immunoglobulin M
PGE_2	prostaglandin E_2

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