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Restricted Intrauterine Growth: Diagnosis, Classification and Management

Crescimento intrauterino restrito: diagnóstico, classificação e manejo
Crecimiento intrauterino restringido: diagnóstico, clasificación y manejo

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Abstract:
Objective: to review the medical-scientific literature on restricted intrauterine growth (IUGR), summarizing its main characteristics, diagnostic criteria, classification and management. Literature review: IUGR affects 5 to 10% of pregnancies and results, in most cases, from placental insufficiency. Distinguishing the small-for-gestational-age fetus from the growth-restricted fetus is essential, since only the latter carries an increased risk of adverse perinatal outcome. Obstetric ultrasound and Doppler velocimetry are the sovereign diagnostic tools, allowing IUGR to be classified as early or late and staged across four phases of deterioration, which guide fetal wellbeing surveillance and the definition of the timing and route of delivery. Prevention is restricted to lifestyle modifications and to acetylsalicylic acid in at-risk pregnancies, with no curative treatment available. Conclusion: early diagnosis, combined with an approach guided by classification and stage, is decisive in reducing fetal and neonatal morbidity and mortality.

Keywords: Fetal Growth Retardation, Ultrasonography Doppler, Prenatal Care, Placental Insufficiency, Infant Small for Gestational Age.

Resumo:
Objetivo: revisar a literatura médico-científica sobre o crescimento intrauterino restrito (CIUR), sintetizando suas principais características, critérios diagnósticos, classificação e manejo. Revisão bibliográfica: o CIUR acomete de 5 a 10% das gestações e decorre, na maioria dos casos, de insuficiência placentária. É fundamental distinguir o feto pequeno para a idade gestacional do feto restrito, pois apenas este apresenta risco aumentado de desfecho perinatal adverso. A ultrassonografia obstétrica e a dopplervelocimetria são as ferramentas diagnósticas soberanas, permitindo classificar o CIUR em precoce e tardio e estadiá-lo em quatro fases de deterioração, que orientam a vigilância da vitalidade fetal e a definição do momento e da via de parto. A prevenção restringe-se a modificações no estilo de vida e ao ácido acetilsalicílico em gestantes de risco, não havendo tratamento curativo. Conclusão: o diagnóstico precoce, aliado a uma abordagem orientada pela classificação e pelo estágio, é determinante para reduzir a morbimortalidade fetal e neonatal.

Palavras-chave:
Retardo do Crescimento Fetal, Ultrassonografia Doppler, Cuidado Pré-Natal, Insuficiência Placentária, Recém-Nascido Pequeno para a Idade Gestacional.

Resumen:
Objetivo: revisar la literatura médico-científica sobre el crecimiento intrauterino restringido (CIR), sintetizando sus principales características, criterios diagnósticos, clasificación y manejo. Revisión bibliográfica: el CIR afecta del 5 al 10% de las gestaciones y deriva, en la mayoría de los casos, de insuficiencia placentaria. Es fundamental distinguir el feto pequeño para la edad gestacional del feto restringido, pues solo este presenta riesgo aumentado de desenlace perinatal adverso. La ecografía obstétrica y la dopplervelocimetría son las herramientas diagnósticas soberanas, permitiendo clasificar el CIR en precoz y tardío y

estadificarlo en cuatro fases de deterioro, que orientan la vigilancia de la vitalidad fetal y la definición del momento y la vía de parto. La prevención se restringe a modificaciones del estilo de vida y al ácido acetilsalicílico en gestantes de riesgo, sin tratamiento curativo. Conclusión: el diagnóstico precoz, asociado a un abordaje orientado por la clasificación y el estadio, es determinante para reducir la morbimortalidad fetal y neonatal.

Palabras clave:
Retardo del Crecimiento Fetal, Ultrasonografía Doppler, Atención Prenatal, Insuficiencia Placentaria, Recién Nacido Pequeño para la Edad Gestacional.

INTRODUCTION

Alterations in fetal growth during pregnancy are strongly related to the risk of perinatal morbidity and mortality, ranging from growth restriction to macrosomia. Fetal growth restriction (FGR) occurs when environmental or genetic determinants prevent the fetus from reaching its growth potential, and can be triggered by fetal, placental, or maternal factors (CABRAL RS, et al., 2022).

Intrauterine growth restriction (IUGR) is the term used in the literature for fetal growth restriction (FGR), defined as fetal growth below the 3rd percentile (p3), or below the 10th percentile (p10) associated with abnormalities on Doppler ultrasound. It is a pathological inhibition of growth affecting 5 to 10% of pregnancies, with placental dysfunction responsible for, on average, 25 to 30% of cases. Obstetric ultrasound is fundamental for growth analysis and detection of IUGR, and early and accurate estimation of gestational age (GA) allows for the determination of fetal weight—an essential parameter in the investigation of a fetus under suspicion (BERNACHI CF, 2016; VEIGA TM, et al., 2022).

It is necessary to differentiate between a small-for-gestational-age (SGA) fetus and a fetus with IUGR. An SGA fetus is considered to be one whose biometric assessment falls below a predefined threshold for gestational age, with an estimated fetal weight (EFW) below the 10th percentile (p10) and unchanged Doppler ultrasound. The distinction is clinically crucial: an SGA fetus may be small without presenting an increased risk of adverse outcome, while a fetus with a weight above the 10th percentile may have IUGR and elevated perinatal risk (SOVIO U, et al., 2015; POON LC, et al., 2016).

The main adverse effects of IUGR affect perinatal outcomes, especially those associated with prematurity— bronchopulmonary dysplasia , mechanical ventilation, necrotizing enterocolitis, neonatal sepsis, and early fetal or neonatal death—as well as repercussions on neuropsychomotor development, mainly in placental dysfunctions. Maternal complications are associated with underlying diseases, particularly hypertensive syndrome and its severe forms,

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such as pre-eclampsia, eclampsia, and HELLP syndrome (ANTONELLI JS, et al., 2018; CORDEIRO DEF, et al., 2020).

This review is justified by the lack of consensus regarding the terminology, etiology, and diagnostic criteria for IUGR (intrauterine growth restriction), with uncertainties about the ideal management and the best time for delivery. Added to this is the challenge of distinguishing between a constitutionally small fetus, fulfilling its potential, and one that does not fulfill it due to an underlying pathological condition (ACOG, 2019; MELAMED N, et al., 2021). Therefore, the objective of this study is to review the medical-scientific literature on IUGR, addressing its main characteristics, classification, diagnosis, and management.

METHODS

This is a narrative literature review, conducted through bibliographic research in the Public Medical Literature database. Analysis and Retrieval System Online (PubMed), Scientific The Electronic Library Online (SciELO) and Google Scholar databases, covering the period from 2011 to 2023, with a few exceptions deemed necessary, are available in Portuguese and English.

Keywords in Portuguese and English were used, either alone or combined using the Boolean operators AND and OR: intrauterine growth, intrauterine growth restriction, fetal growth restriction, diagnosis, treatment and management, and their English equivalents. Review articles, prospective studies, randomized clinical trials, systematic reviews, and meta-analyses were included. Studies unrelated to the topic, duplicate works, letters to the editor, and animal research were excluded. After reading the abstracts, the selected articles were read in full, extracting the relevant content.

RESULTS AND DISCUSSION

Normal growth and etiology of IUGR

Intrauterine growth occurs in two periods: the embryonic period, in the first trimester, marked by hyperplasia and cell multiplication; and the fetal period, from the end of the first trimester to birth, characterized by cellular hypertrophy and growth of organs and systems. For proper development, mother-fetus interaction and placental support are essential; when maternal or placental determinants compromise this interaction, IUGR (Intrauterine Growth Restriction) develops (CABRAL RS, et al., 2022).

In approximately 60% of cases, fetal, maternal, or placental risk factors are identified, while the etiology remains unknown in the remainder. Among the maternal conditions, vasculopathies stand out— pre -gestational diabetes, hypertensive diseases, antiphospholipid

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antibody syndrome— , collagenoses , nephropathies, inflammatory bowel diseases, and thrombophilias, in addition to maternal malnutrition, substance use (tobacco, alcohol, cocaine), and exposure to teratogens. Among the fetal causes are congenital infections, twin pregnancies, aneuploidies, genetic syndromes, and malformations (MARTINELLI S, et al., 2018; FERNANDEZ-GONZALEZ S, et al., 2020). IUGR due to placental dysfunction is associated with adverse neurological outcomes in up to 50–60% of cases, requiring special attention given the limited regenerative capacity of the developing brain (ANTONELLI JS, et al., 2018).

The PEF (Peak Expiratory Flow) is calculated from biometric parameters — head circumference, biparietal diameter , abdominal circumference, and femur length. Fetuses with a PEF below the 10th percentile should be evaluated with detailed ultrasound, including amniotic fluid volume and Doppler velocimetry . In cases where these resources are unavailable, a common occurrence in some Brazilian healthcare services, constructing a fetal weight curve by gestational age helps screen cases requiring a differentiated approach (ASSIS GP, et al., 2021). The main risk factors are summarized below (**Table 1**).

Table 1 – Main risk factors for the occurrence of IUGR.

Risk factor	**Magnitude of the risk**
CIUR background	Recurrence rate of approximately 20% (if risk factors persist).
Smoking	Average weight reduction of 458 g in smokers (> 20 cigarettes/day)
Alcoholism	OR 1.1 (< 1 dose); OR 1.62 (1–2 doses/day); OR 1.96 (3–5 doses/day)
Diabetes mellitus	Incidence of ~20%
Chronic hypertension	Risk of 8.0% to 15.5%
Nephropathy	Incidence of ~23% in the presence of proteinuria.
Thrombophilia	OR 33.9 for anticardiolipin antibodies.
Systemic lupus erythematosus	28.5% employed; 7.6% inactive.
Maternal age	OR 1.28 (> 35 years); OR 1.49 (> 40 years)
BMI < 20	OR 1.37
Low socioeconomic level	OR 2.91

Source: adapted from Martinelli S, et al. (2018). OR: odds ratio ; BMI: body mass index.

Diagnosis

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Screening for intrauterine growth restriction (IUGR) begins with the medical history taken at the first prenatal visit. Measuring uterine height is no longer a diagnostic screening method but a surveillance tool, with greater value when performed serially; respecting its limitations—maternal obesity, fibroids, engaged fetus—a measurement 3 cm below the expected value indicates the need for obstetric ultrasound to assess fetal weight (BERNACHI CF, 2016). Ultrasound is the most commonly used examination for early detection of IUGR and should be performed serially when a discrepancy is identified between the observed and expected growth for the gestational age (CABRAL RS, et al., 2022).

Doppler velocimetry provides data on the fetus, placenta, and maternal circulation, and is central to diagnosis and management. It allows for the differentiation of placental-origin IUGR from other etiologies and the evaluation of maternal (uterine artery, UA), fetoplacental (umbilical artery, UA), and fetal (middle cerebral artery, MCA; ductus venosus, DV) circulation. PEF below the 10th percentile associated with abnormal flow in the UA is the best predictor of restricted fetuses susceptible to adverse perinatal effects, and its evaluation significantly reduces perinatal mortality and iatrogenic prematurity (WALTER A, et al., 2022).

In UA, increased resistance progressively reduces end-diastolic flow, potentially leading to absent or reversed diastole, findings associated with low birth weight, oligohydramnios , emergency cesarean section, and neonatal disorders. Changes in UA precede those in fetal heart rate on cardiotocography. Compensatoryly, an increase in diastolic flow is observed in the MCA with a reduction in the pulsatility index (PI) — a phenomenon called fetal centralization. The cerebroplacental ratio (CPR), the ratio between the PI of the MCA and that of the UA, has greater sensitivity than its isolated components, changing even when both are still within normal limits; values below 1.0 have a sensitivity of 66% and a specificity of 85% for adverse perinatal outcome (VEIGA TM, et al., 2022; LEAL CR, et al., 2023).

Classification and staging

IUGR is classified as early and late. Early IUGR (20–30% of cases) develops before 32 weeks, results from inadequate placental vascular remodeling with increased resistance in the uterine arteries, is associated with pre-eclampsia in about 50% of cases and chronic fetal hypoxia, and progresses with Doppler velocimetry changes in the uterine artery and ventricular septum. Late IUGR (70–80% of cases) occurs from 32 weeks onwards, is related to villous immaturity with moderate placental insufficiency, is associated with pre-eclampsia in only 10% of cases and generally presents with normal uterine artery Doppler, although it may show reduced resistance in the medullary artery in response to hypoxemia (BERNACHI CF, 2016;

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LEES CC, et al., 2022). The diagnostic criteria for each form, according to the Delphi consensus, are listed below (GORDIJN SJ, et al., 2016; FIGUERAS F and GRATACÓS E, 2014) (**Table 2**).

Table 2 – Diagnostic criteria for early and late IUGR (Delphi consensus).

Parameter	Early IUGR (< 32 weeks)	Late IUGR (≥ 32 weeks)
Prerequisite	Absence of fetal malformations	Absence of fetal malformations
Largest isolated parameter	CA or PFE < p3; or zero/reverse diastole in AU	CA or PFE < p3
Smaller parameters	PFE or CA < p10 with average IP of the AU > p95 and/or IP of the AU > p95	Drop in PFE or CA > 2 quartiles; RCP < p5 or AU IP > p95

Source: adapted from Figueras F and Gratacós E (2014) and Gordijn SJ, et al. (2016). CA: abdominal circumference; PFE: estimated fetal weight; IP: pulsatility index ; AU: umbilical artery; AUt : uterine artery; RCP: cerebroplacental ratio .

Regarding severity, fetuses with IUGR are categorized into four stages of deterioration, which guide the frequency of monitoring and the timing and route of delivery. Stage I meets the diagnostic criteria for IUGR, excluding zero or reversed diastole in the fundal height; Stage II is defined by zero diastole in the fundal height; Stage III, by reversed diastole in the fundal height or absent "a" wave in the ventricular septum; and Stage IV, by spontaneous decelerations of the fetal heart rate or reversed "a" wave in the ventricular septum (FIGUERAS F and GRATACÓS E, 2014; CORDEIRO DEF, et al., 2020) (**Table 3**).

Table 3 – Staging of IUGR, monitoring and resolution of pregnancy.

Internship	Doppler velocimetry finding	Surveillance	Resolution
I	Criteria for IUGR without zero/reverse diastole in the AU (AU/ AUt > p95; RCP < p5)	Weekly Doppler	≥ 37 weeks (via obstetric delivery)
II	Zero diastole in AU	Doppler twice a week	≥ 34 weeks (cesarean section)
III	Reverse diastole in the AU or absent "a" wave in the DV.	Daily Doppler	≥ 30 weeks (cesarean section)
IV	Decelerations of the heart rate (HR) in the central axial tilt (CTG) or reverse "a" wave in the digital vertex (DV).	Doppler/CTG every 12 hours	≥ 26 weeks (cesarean section)

Source: adapted from Figueras F and Gratacós E (2014) and Cordeiro DEF, et al. (2020). AU: umbilical artery; AUt : uterine artery; RCP: cerebroplacental relationship ; DV: ductus venosus; FCF: fetal heart rate; CTG: cardiotocography.

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Prevention and conduct

Currently, there are no proven effective drug interventions to prevent IUGR in high-risk populations, with recommendations limited to lifestyle modifications. In women at risk of pre-eclampsia, acetylsalicylic acid (ASA) is recommended, with evidence suggesting it also reduces the risk of IUGR; a meta-analysis demonstrated that starting ASA within 16 weeks reduces the risk of IUGR by almost 50%, with most guidelines favoring doses of 100–150 mg/day (ROBERGE S, et al., 2017; ROLNIK DL, et al., 2017; MCCOWAN LM, et al., 2018). Low molecular weight heparin, alone, has not demonstrated benefit in preventing IUGR and should be restricted to research settings (GROOM KM, et al., 2017; MCLAUGHLIN K, et al., 2018).

Management begins prenatally and prioritizes lifestyle modifications: relative—not absolute—rest is recommended in cases of placental insufficiency, along with control of obesity, smoking, diabetes, and blood pressure, and nutritional supplementation in cases of maternal malnutrition. The risk of pre-eclampsia/IUGR should be screened by assessing maternal factors combined with Doppler ultrasound of the uterine arteries in the first trimester. Consideration should be given to aspirin (150 mg/day, from the 16th to the 36th week), corticosteroid therapy for lung maturation at the appropriate gestational age, and neuroprophylaxis with magnesium sulfate when indicated (MEHER S, et al., 2017; BARMPAS DS, et al., 2020).

Assessment of fetal vitality relies on Doppler velocimetry (PI of the AU, ACM and RCP; mean PI of the AUt at diagnosis; PI and "a" wave of the DV in more advanced stages) and, from 28 weeks and stage II, on antepartum cardiotocography and fetal biophysical profile. The frequency of examinations varies among international guidelines and is proportional to the severity of Doppler velocimetric impairment (LEAL CR, et al., 2023) (**Table 4**).

Table 4 – Frequency of fetal vitality assessment according to the main guidelines.

Situation	FIG / ISUOG	SMFM / FCOG
Early changes in Doppler (IP AU > p95 or IP ACM < p5)	Doppler ultrasound 1–2 times/week and biophysical profile; or weekly Doppler ultrasound.	Doppler ultrasound every 2–3 weeks; or weekly.
Absence of end-diastolic flow in the AU	Doppler ultrasound 3 times/week and daily biophysical profile (BPP); or 2–3 times/week	Doppler ultrasound 2–3 times/week and daily CTG.

Situation	FIG / ISUOG	SMFM / FCOG
Reverse end-diastolic flow in AU	Daily Doppler and biophysical profile twice a day; or 2–3 times a week.	CTG daily
Changes in DV (IP > p95, wave "a" missing/reversed)	Daily Doppler and biophysical profile twice a day.	—

Source: adapted from Leal CR, et al. (2023). UA: umbilical artery; MCA: middle cerebral artery; DV: ductus venosus; PBF: fetal biophysical profile; CTG: cardiotocography; IP: pulsatility index .

Drug treatment and resolution of pregnancy

There is no curative treatment for IUGR; suggestions such as inhaled oxygen, aspirin, corticosteroids, and beta-mimetics have not proven satisfactory and lack randomized trials (MARTINELLI S, et al., 2018). For the prevention of acute respiratory distress syndrome, corticosteroid therapy is recommended . Antenatal neuroprotection is indicated when delivery is expected before 34 weeks — up to 35 weeks and 6 days according to the RCOG (Regional Control of Occurrence) — with intensified monitoring in fetuses with absent or reversed diastolic flow in the fundal height (MAGANN EF, et al., 2017; MCCOWAN LM, et al., 2018). Magnesium sulfate for neuroprotection has recognized efficacy in preterm labor, although variations persist among protocols regarding the gestational age limit, and its application is recommended according to local protocols (VAYSSIÈRE C, et al., 2015; STOCKLEY EL, et al., 2018; WOLF HT, et al., 2020).

In fetuses with IUGR (intrauterine growth restriction), the most important prognostic factor is gestational age at birth, and the risks of prematurity should always be weighed against those of prolonged gestation. Based on fetal viability, serial monitoring becomes the main tool in determining the timing of delivery. Resolution recommendations vary among guidelines (**Table 5**): generally, fetuses with PEF (peak expiratory flow) between p3 and p10 and normal Doppler are managed close to term, while the presence of reversed diastolic flow in the AU (ausal valve) or abnormalities in the DV (diastolic flow) anticipates delivery. Cesarean section is consensually indicated in the absence or reversal of end-diastolic flow in the AU, in the presence of maternal indication, or in a non-reassuring fetal status; in other cases, induction with continuous intrapartum monitoring is permitted. Histopathological examination of the placenta is recommended, as it can indicate the risk of recurrence (MELAMED N, et al., 2021; LEAL CR, et al., 2023).

Table 5 – Recommended timing for termination of pregnancy according to the main guidelines.

Clinical scenario	FIG / ISUOG	SMFM / ACOG
PEF p3–p10, no changes on Doppler.	37–39 weeks / 38–39 weeks	38–39 weeks / 38 weeks
PEF < p3, normal Doppler	36–38 weeks / 36–37 weeks	37 weeks / 37 weeks
Early changes in Doppler	34–37 weeks / 36–37 weeks	37 weeks / —
Absence of end-diastolic flow in the AU	32 weeks / 34 weeks	33–34 weeks / —
Reverse end-diastolic flow in AU	30 weeks / 32–33 weeks	30–32 weeks / —
Changes in DV (IP > p95, wave "a" missing/reversed)	26 weeks / 26 weeks	26 weeks / —

Source: adapted from Leal CR, et al. (2023). PFE: estimated fetal weight; AU: umbilical artery; DV: ductus venosus; sem: weeks.

CONCLUSION

IUGR remains an obstetric challenge, despite advances in perinatal care; early diagnosis, supported by ultrasound and Doppler velocimetry , and a classification- and stage-oriented approach are crucial to reducing fetal and neonatal morbidity and mortality, while further research is needed to clarify the effectiveness of therapeutic options for this complex condition.

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