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The current state of the problem, clinical-pathogenetic approaches to the diagnosis and management tactics of fetal growth restriction

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Fetal growth restriction is a common complication of pregnancy with a complex etiology and limited possibilities of diagnosis and treatment. The relevance of this difficult obstetric problem is determined by various published diagnostic criteria, relatively low detection rates, and limited options for prevention and treatment.
Fetal growth restriction is defined as the inability of the fetus to reach its genetically determined growth potential, most often due to abnormal placentation. Forms of fetal growth restriction with early or late onset are distinguished based on the gestational age determined during prenatal ultrasound diagnosis. According to most recommendations, the 32nd week of pregnancy is set as the cut-off point for distinguishing between early and late onset fetal growth restriction.
The definition underlying this classification is based on differences between these two phenotypes of fetal growth restriction in severity, natural history, Doppler findings, association with hypertensive complications, placental features, and management. It is important to distinguish two separate conditions: fetal growth restriction and small-for-gestational fetus, which differ in short-term and long-term perinatal outcomes.
A fetus is defined as small for gestational age if the estimated weight or weight of the fetus at birth is below the 10th percentile. Fetal growth restriction is diagnosed if the estimated fetal weight is below the 3rd percentile or a combination of pathological blood flow in the umbilical arteries and/or uterine arteries in fetuses with an estimated weight below the 10th percentile. It can also occur in fetuses and newborns with a body weight above the 10th percentile.
The need to distinguish between fetal growth restriction and small-for-gestational-age fetus is related to the fact that fetal growth restriction is the main cause of stillbirth, neonatal death, higher perinatal morbidity, as well as increased risk of diseases in adulthood. The article analyzes the approaches to differentiating fetal growth restriction from small growth retardation in terms of fetal gestation period and further increasing the accuracy of diagnosis, as well as the modern concept of pathogenesis, with an emphasis on oxidant stress as a key molecular mechanism of adverse outcomes. Appropriate interventions during pregnancy to reduce perinatal complications should include antenatal monitoring and drug therapy.
Keywords: *fetal growth restriction, perinatal outcome, oxidant stress, antioxidants.*

Сучасний стан проблеми, клініко-патогенетичні підходи до діагностики і тактики ведення затримки росту плода

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Затримка росту плода належить до поширеного ускладнення вагітності зі складною етіологією та обмеженими можливостями діагностики та лікування. Актуальність цієї непростої акушерської проблеми зумовлена різними опублікованими діагностичними критеріями, відносно низькими показниками виявлення та обмеженими варіантами профілактики і лікування.
Затримка росту плода визначається як нездатність плода досягти свого генетично зумовленого потенціалу росту, частіше за все внаслідок аномальної плацентації. На підставі гестаційного віку, визначеного під час пренатальної ультразвукової діагностики, виділяють форми затримки росту плода з раннім або пізнім початком. Згідно з більшістю рекомендацій, 32-й тиждень вагітності встановлено як граничну точку для розмежування раннього та пізнього початку затримки росту плода.
Визначення, що лежить в основі цієї класифікації, ґрунтується на відмінностях між цими двома фенотипами затримки росту плода у тяжкості, природному перебігу захворювання, результатах допплерографії, зв'язку з гіпертензивними ускладненнями, плацентарними ознаками та лікуванням. Важливо виділяти два окремі стани: затримка росту плода та малий щодо терміну гестації плід, які відрізняються за короткостроковими та довгостроковими перинатальними наслідками.
Малий щодо терміну гестації плід визначають, якщо розрахункова маса або маса плода при народженні нижче 10-го процентиля. Затримку росту плода діагностують, якщо розрахункова маса плода нижче 3-го процентиля або поєднання патологічного кровотоку в артеріях пуповини та/або маткових артеріях у плодів з розрахунковою масою нижче 10-го процентиля. Також може бути у плодів та новонароджених з масою тіла вище 10-го процентиля.
Необхідність розрізняти затримку росту плода та малий щодо терміну гестації плід пов'язана з тим, що затримка росту плода є основною причиною мертвонародження, неонатальної смерті, більш високої перинатальної захворюваності, а також підвищеного ризику захворювань у дорослому віці.
У статті проаналізовано підходи до диференціації затримки росту плода від малого щодо терміну гестації плода та подальшого підвищення точності діагностики, а також сучасну концепцію патогенезу, з акцентом на оксидантний стрес як ключового молекулярного механізму несприятливих наслідків. Відповідні заходи під час вагітності, які сприятимуть зменшенню перинатальних ускладнень, повинні включати антенатальний моніторинг та медикаментозну терапію.
Ключові слова: *затримка росту плода, перинатальний результат, оксидантний стрес, антиоксиданти.*

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The purpose of the work: based on the data of the world literature, to conduct an analysis of the current state of the problem of fetal growth retardation, as well as approaches to prevention, diagnosis and management tactics depending on the period of pregnancy and taking into account the links of pathogenesis.

According to the 2020 Human Capital Index, Ukraine has one of Europe's worst indicators of life. An alarming trend in the 21st century is a decrease in the number of newborns in Ukraine from 387,890 in 2000 to 260,502 in 2021, which was accompanied by a negative trend of the objective criterion of a healthy start of the progeny – an increase in the frequency of low-weight and premature children, which are characterized by morphological, physiological and metabolic features, neurological disorders, somatic and immune status, increased risk of neonatal morbidity and mortality [1]. The greatest risk of perinatal morbidity, mortality, and long-term adverse consequences is for new-borns with a very low birth weight of less than 1500 g.

Fetal growth restriction (FGR) refers to a common complication of pregnancy [2–6], which is the main cause of stillbirth, neonatal mortality, short-term and long-term neonatal morbidity worldwide [7–9]. The relevance of this complex obstetric problem is due to various published diagnostic criteria, relatively low detection rates and limited options for prevention and treatment [3, 10–13]. The prevalence of FGR varies between countries, populations, and races and increases with increasing gestational age [5, 12, 14].

In high-income countries such as the United States and Australia, the incidence of FGR is approximately 11%, but in low- and middle-income countries, approximately 32.5 million infants are born with FGR, and the majority of these infants are estimated to be 53% (16.8 million) were born in South Asia [12, 15, 16]. The frequency of preterm delivery varies among populations, also due to the rate of concomitant preterm birth (from 7 to 13%). Both FGR and premature birth are more common in countries with limited resources [17, 18].

Currently, the rate of FGR is the highest in the last 20 years and is likely to increase further due to the increase in the number of cases of infertility treatment, multiple pregnancies, occupational workload, older mothers, and exposure to factors that cause FGR, such as stress, nicotine, malnutrition [19]. Half of stillbirths are due to fetal growth restriction, and perhaps a quarter of live births in low- and middle-income countries are due to fetal growth restriction [13]. More than 80% of neonatal deaths occur in small-for-gestational-age (SGA) newborns, of which two-thirds are preterm and one-third are full-term with SGA [20].

According to Blencowe H. at al., in 2015, 20.5 million newborns were born with low body weight for gestational age [21]. The birth rate of low-weight fetuses in low- and middle-income countries is six times higher than in highly developed countries. In Ukraine, according to various authors, the frequency of this pregnancy complication ranges from 3% to 24% among full-term infants, and from 18% to 46% among premature newborns [22].

The high frequency of a negative trend of low-birth-weight newborns in recent years is maintained due to this category of newborns' higher share and growth rate. It should be noted that the change in the structure of births by body weight was accompanied by a stable excess of the number of low-weight children over the number of premature ones, which reflects the disadvantage of women's reproductive health and quality of life at the population level [2]. Fetal growth restriction is a problem that obstetrician-gynecologists face almost every day, and the American College of Obstetricians and Gynecologists considers FGR as "the most pressing and complex problem in modern obstetrics" [4].

Today, there are several classifications of FGR in the world. According to the nature of changes in fetometric parameters, symmetric and asymmetric forms of pregnancy are distinguished, and according to the term of formation - early and late. Until recently, the most common and well-known division was based on the anthropometric data of the fetus during ultrasound fetometry [2, 23, 24].

Depending on the mass and the mass-growth index, it was proposed to classify the fetal growth retardation syndrome based on the regularity of the normal development of the fetus. The classification is based on the ratio of head circumference to abdominal circumference to distinguish symmetric, or proportionally small, fetuses from asymmetric fetuses, i.e., with disproportionately slower growth, and classifies FGR into types I (asymmetric), II (symmetric), and III (mixed) [2, 24–26].

Traditionally, the symmetry of the proportions of the fetal body was considered the main sign of the etiology of FGR. Moreover, symmetric FGR was considered associated with fetal aneuploidy, and progressive asymmetric FGR indicated placental insufficiency. However, it has been found that fetal aneuploidy can lead to an asymmetric FGR, and placental insufficiency can lead to a symmetric FGR. In addition, the symmetry of body proportions by itself is not a consistent prognostic indicator.

Therefore, today it is considered that the terms «symmetric form», and «asymmetric form» of FGR do not provide additional information regarding the etiology and prognosis of the state of the fetus, therefore it is not advisable to use them in clinical practice [24].

Recently, most specialists have divided the forms of FGR, considering the pathophysiological mechanisms of their development [2, 5, 11, 12]. This clinical classification of FGR is based on a normal fetal growth trajectory, which is based on the time of occurrence. It is this classification that has greater clinical applicability, as it provides both management tactics and the prognosis of fetal development [1–6, 24].

In 2016, with the aim of better defining the population of FGR, a consensus definition of FGR was developed [26]. Items evaluated for inclusion in the definition included measures of placental function (Doppler velocity measurement, size percentile reduction, and serum biomarkers), in addition to fetal biometric measurements/size. This led to the inclusion of abnormal Doppler blood flow profiles and growth trajectory (50-percent percentile reduction in predicted fetal weight) in the definition, in addition to the biometrics used historically.

Thus, this definition makes it possible to diagnose FGR both in fetuses with SGA and fetuses with appropriate gestational weight. In addition, the proposed definition criteria distinguish between very small (less than the 3rd percentile) and small (between the 3rd and 10th percentile) fetuses. Fetal size less than the third percen-

tile is the isolated criterion for defining SGA at any gestational age, as these fetuses have the highest risk of stillbirth and neonatal problems such as hypothermia and hypoglycemia, regardless of the cause of the low birth weight.

It is also considered that small fetuses from the 3rd to the 10th percentile can be healthy in the absence of other signs indicating placental insufficiency [3, 5, 8]. Since then, this very definition has been adopted at the international level [3–6]. Based on the gestational age determined during prenatal ultrasound diagnosis, forms of FGR with early or late onset are distinguished [2, 13, 19].

According to most recommendations [3, 5, 6, 8, 10], the 32nd week of pregnancy is set as the cut-off point for distinguishing between early and late onset of FGR. The definition underlying this classification is based on the differences between these two phenotypes of FGR in severity, natural history, Doppler findings, association with hypertensive complications, placental features, and treatment [27–29].

The early form of FGR makes up 20-30% of all cases of FGR, the manifestation of which occurs before 32 weeks of gestation. It has a prevalence of 0.5–1% of the total number of births in the population [27]. As a rule, it is more severe, in contrast to the late-onset FGR, and is more likely to be associated with abnormal umbilical artery Doppler. Early FGR is mostly associated with impaired blood supply to the placenta, abnormal transformation of the spiral arteries of the uterus, pathological features of the placental villi, and multifocal infarctions.

Chronic ischemia of placental villi impairs placental growth factor (PlGF) secretion and leads to excessive release of soluble fms-like tyrosine kinase-1 (sFlt-1) by syncytial nodules. This is manifested in the form of an increase in the ratio of sFlt-1/PlGF, which is characteristic of a high risk of developing preeclampsia (PE), and also, probably, of an early form of FGR [30–32].

The underlying placental pathology is often similar to that seen in cases of early PE, which explains the close association of early-onset FGR with PE. A significant disturbance in the implantation of the placenta, which manifests itself in an increase in the resistance of the uterine artery, leads to an increased risk of developing PE (with PE with an early onset, FGR is diagnosed in more than 90% of cases) [12, 33–35].

The rate of change in blood flow in the umbilical cord arteries from high to low resistance reflects the rate of fetal deterioration. During a Doppler examination, it is expressed as a low blood flow rate in the umbilical artery, zero or reverse blood flow in the ductus venosus. These changes precede or occur in parallel with a low value of short-term variability (Short Term Variation – STV), the appearance of decelerations according to cardiotocography (CTG), and violations of the fetal biophysical profile (BPF) [36].

High rates of perinatal morbidity and mortality are inherent in the early form of FGR [5, 35, 37–39]. Thus, early-onset FGR is usually easier to detect, and the natural course tends to follow a predictable sequence of Doppler changes in the umbilical artery and ductus venosus [5, 6, 36, 37].

The late form of FGR makes up 70-80% of all cases of FGR and manifests itself after 32 weeks of gestation. Late-onset FGR is more common than early-onset FGR with a prevalence of 5–10%. With this form of FGR, there is a slight degree of placental disturbance, which leads to mild hypoxia and requires minor adaptation of the fetal cardiovascular system. It is less likely to be associated with maternal hypertensive disorders and usually has less extensive placental histopathological findings of insufficient perfusion.

This form is caused to a greater extent by violations of the maturation of the villi than by a decrease in their surface area, as a result of which gas exchange and the exchange of nutrients between the mother and the fetus become difficult. As a result of the greater prevalence of villous diffusion anomalies and the lesser degree of perfusion anomalies of late-onset FGR, blood flow disturbances in umbilical cord arteries are not often observed [38–40].

However, the degree of tolerance to hypoxia is low. Cardiovascular adaptation in fetuses with late-onset FGR is usually limited to cerebral circulation and is associated with normal umbilical artery Doppler [15, 41, 42]. Unlike the early form of FGR, the fetus cannot withstand this oxygen deficiency for a long time [43]. The main problem associated with the late onset of FGR is early diagnosis since the results of umbilical artery Doppler in most cases will be normal, thereby masking the disease [5, 6, 9, 10, 43].

Fetuses with late FGR are at risk of acute hypoxia before delivery, as evidenced by the increased frequency of antenatal death in late pregnancy and neonatal acidosis. The low percentage of diagnosis of late FGR in the antenatal period leads to an increase in the frequency of antenatal death of the fetus in the late stages of pregnancy [42, 43].

Despite the different course of early and late FGR, both forms are associated with adverse pregnancy outcomes and diseases of the cardiovascular system, renal system, and metabolic disorders in the future in a child born with a diagnosis of FGR [5, 8, 18, 19, 44–46].

Under optimal conditions, the fetus grows according to its internal growth potential, which is determined by genetic and epigenetic factors. The fetus may be small compared to the standard population but meets its internal growth potential. However, the greater the deviation from the normal threshold, the greater the probability that the observed smallness is the basis of a pathological process [11, 18, 47].

Many terms are described in the literature, among which the term «intrauterine growth retardation» was most often used over a long period. However, since «intrauterine» refers to the location, and not to the fetus, which is affected by the pathological condition, and the fact that «retardation» indicates that there is a possibility of «catch-up» of growth, FGR is considered today to be a more accurate term [3, 6, 19].

FGR is a frequent complication of pregnancy with a complex etiology and limited treatment options [7, 13, 48, 49], and is defined as the failure of the fetus to reach its genetically determined growth potential, resulting in

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increased short- and long-term risks of severe complications [3, 12, 14, 19]. Clinically, this is reflected by a decrease in fetal size percentiles during gestation. However, fetal growth potential is difficult to determine, and serial assessments of fetal size to detect a decrease in fetal weight percentile are usually not available [3, 6].

This is why the identification of stunted fetuses is often a challenging task, as fetal growth cannot be assessed by a single biometric assessment of fetal size, and growth potential is a hypothetical definition [2, 6, 8]. In addition, fetal growth is a dynamic process, and its assessment requires multiple observations of fetal size over some time. The current measurements focus on the nutritional component of fetal deprivation as it is derived from measurements of size.

By using the term FGR, it is implied that the food component of deprivation is the greatest threat. However, the most important consequences, which is perinatal mortality, are caused exclusively by insufficient oxygen status of the fetus, and not by starvation. Unfortunately, it is currently impossible to measure the oxygen level in fetal serum [48]. Therefore, early prenatal identification of fetuses with growth retardation is extremely important for the health of the child.

The accurate identification and treatment of cases of FGR should be key to reducing mortality and morbidity. In practice, currently, more than 50% of cases of FGR go undiagnosed even in high-income countries [50], and more than 70% of children with FGR who die before birth are not diagnosed at all [51]. They are first recognized only at very late stages of pregnancy or at birth [39, 40], which leads to a lack of adequate short- and long-term follow-up of these newborns [7, 9, 52].

In addition, even if the FGR is correctly defined, there are only limited tools to monitor the severity of fetal hypoxia and thus attempt to balance the risks of stillbirth or fetal malformation [53, 54]. A quarter of live births with FGR occur in low- and middle-income countries [13], making FGR screening a cornerstone strategy to reduce fetal loss before delivery [12]. Unfortunately, only a small part of newborns with FGR are suspected of having this pathology before birth [13]. Almost half of all stillbirths are associated with FGR [46].

The goal of the clinical approach in the diagnosis of FGR is, first of all, the need to find out whether the fetus is affected by placental insufficiency with an increased risk of morbidity or mortality. To establish a diagnosis, it is important to first check that the gestational age has been correctly calculated, as this is key to interpreting the appropriateness of fetal size. In high-income countries, a reliable date of delivery can often be determined by routine ultrasound in the first trimester [48].

In early pregnancy, fetal size is assessed by measuring the length of the caudal-parietal dimension of the fetus using ultrasound. Later, head circumference, biparietal diameter, abdominal circumference, and fetal femur length are measured [48, 55]. If the gestational age is reliably established, further ultrasound examination determines the degree of fetal size lag. It is important to understand that the size of the fetus is the result of its previous growth. Therefore, after 18 weeks of pregnancy, to determine the nature of fetal growth, it is advisable to include the results of all previous ultrasounds in the assessment [47].

The detection of FGR is based on the identification of a fetus, the size of which is smaller than expected, using a physical examination, namely, measuring the height of the uterine fundus (UFH) or conducting ultrasound biometry [6]. Measurement of UFH using a centimeter tape is a simple, inexpensive, and widely used screening strategy for FGR [56]. Measurements are performed in a lying position using an inelastic centimeter tape after the woman has emptied her bladder.

To reduce interobserver variability, a standardized measurement technique should be followed. UFH is defined as the distance from the upper edge of the pubic symphysis to the upper part of the uterine fundus. UFH, measured in centimetres between 24 and 38 weeks of pregnancy, approximately corresponds to gestational age. However, the accuracy of UFH measurement in predicting FGR is limited, and no randomized controlled trials are comparing UFH measurement with serial ultrasound assessment of fetal biometry.

In a meta-analysis of 34 observational studies [6], UFH was reported to have a sensitivity of 58% and a specificity of 87% for predicting birth weight below the 10th percentile. It is important to recognize that factors such as maternal obesity, uterine leiomyoma, and polyhydramnios may further limit the accuracy of UFH as a screening tool. Despite this, in the majority of foreign clinical recommendations, the measurement of UFH, as before, remains in the list of diagnostic measures [2, 6, 10].

Ultrasound biometry is currently the most accurate method of diagnosis of FGR. Fetal size is determined by biometric assessment of head circumference, biparietal diameter, abdominal circumference, and femur length and/or derivation of estimated fetal weight calculated by various formulas [14, 10, 24]. Several studies have compared the accuracy of different equations. Most studies have concluded that equations based on 3–4 biometric parameters provide the most consistent and accurate results.

A recent systematic review found that the Hadlock equation based on three indices: head circumference (HC), abdominal circumference (AC) and femur length (FL): Log10 weight = 1.326 – 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158* FL), provided the greatest accuracy [57].

Identification of FGR in utero and even after birth is often a difficult task, with an indicator such as estimated fetal weight often used as a surrogate indicator. The probability of FGR is associated with the degree of expressiveness of the body weight deficit of newborns before the gestation period. For example, 30% of infants with a birth weight < 10th percentile is considered SGA, while 70% of infants with a birth weight < 3rd percentile is considered SGA [58].

Therefore, in clinical practice, the term «small size for gestational age», which is associated with the probability of FGR, is most often used when FGR is suspected. A fetus is considered SGA if its size (biometric assessment) falls below a pre-set threshold for its gestational age. The most common definition of SGA is an estimated fetal

weight or fetal abdominal circumference below the 10th percentile based on reference range data [3–6].

However, other thresholds have been described, such as the 5th and 3rd percentile (the latter approaching 2 SD) or a Z-score of –2 [3, 44, 59]. SGA is determined by the statistical deviation of the size of the fetus concerning the control population. Thus, SGA describes a change in size rather than an abnormal condition. In addition, fetal size is often used as a misnomer for fetal growth. The size at a certain point in time (static) is the result of the (dynamic) process of past growth. Importantly, risk stratification is an essential task for prenatal care [53].

The attractiveness of using the SGA is its ease of application, as it is a purely statistical deviation of fetal size that is linked to a control chart for the determination of growth abnormality [10].

The birth of children with low gestational weight is a serious challenge for the health care system in every country because it is associated with several serious, both short-term [12, 17, 44, 60] and long-term health consequences. Newborns with FGR at any period of life [15, 58]. Low birth weight infants are associated with an increased risk of adverse perinatal outcomes [9, 44, 60].

For fetuses at any gestational age with a weight below the 10th percentile, the stillbirth rate is approximately 1.5%, which is twice the rate for fetuses with a normal weight for gestational age. If the fetal weight is below the 5th percentile, the stillbirth rate can be as high as 2.5% [4, 6], but fetuses with a birth weight below the ≤ 3rd percentile have the highest risk of stillbirth [3]. Currently, a birth weight < 10th percentile, either by population or by special charts, is the most accepted definition for SGA infants [9, 14].

This mathematical threshold was chosen because of the increased neonatal mortality observed in this group compared to those born between the 10th and 90th percentiles [53, 59]. However, several researchers [60–63] have expressed concern that some of these infants are «constitutionally small» and are not at higher risk of (neonatal) adverse outcomes even at a lower cut-off for SGA such as ≤ 5 [19], ≤ 3 or even ≤ 2 percentile.

However, little is known about the long-term final health indicators of «constitutionally small» newborns [17]. Thus, the 10th percentile seems to be the most acceptable threshold for both epidemiological and clinical purposes [3, 4]. SGA babies are divided into two main groups: constitutionally normal SGA babies and SGA babies due to growth restriction with a birth weight lower than the expected optimal weight – the actual FGR.

Constitutionally normal babies have a birth weight of less than the 10th percentile, which is normal for them due to such inherent factors as the mother's height and weight, and ethnicity [47]. Many babies with SGA have signs of FGR, and many babies with FGR also have SGA. However, SGA cannot be used as a marker for FGR, as some infants with FGR will have a birth weight that exceeds the 10th percentile for gestational age [48].

The still frequent interchangeability of the terms «fetal growth rectriction» and «small size for gestational age» complicates the interpretation of some studies that may cover both categories of infants and consider as FGR also newborns who are usually constitutionally small [31, 38, 59, 61]. Understanding that newborns with SGA and FGR differ in terms of condition and status allows us to realize that the most adverse consequences are inherent in children diagnosed with FGR.

These newborns have an increased risk of such neonatal complications as asphyxia during childbirth, emergency cesarean delivery, meconium aspiration, persistent pulmonary hypertension, hypothermia, hypoglycemia, polycythemia, jaundice, feeding difficulties, necrotizing enterocolitis, late sepsis, and neonatal mortality [9, 50, 59].

In most guidelines, a fetus with FGR is diagnosed in cases of expected weight below the 10th percentile before the corresponding gestational age in combination with ultrasound markers of impaired placental function [2–4, 12, 62]. It is important to realize that any size threshold that does not consider the pattern of fetal growth carries the risk of losing fetuses whose growth trajectory slows down, and who are therefore at risk of an adverse outcome, even if their absolute size exceeds the 10 percentiles [24, 63]. In addition, using the definition of SGA as an FGR, only one-third of infants who are stillborn at or near term would be considered stunted [40, 50, 51, 54].

Over the decades, national and international societies, as well as experts, have proposed numerous definitions of FGR [2, 36]. The American College of Obstetricians and Gynecologists (ACOG) [4], and the Society for Maternal-Fetal Medicine (SMFM) [10] define FGR as a predicted fetal weight less than the 10th percentile. The Royal College of Obstetricians and Gynecologists (RCOG) uses fetal abdominal circumference or predicted fetal weight <10th percentile for the diagnosis of fetal FGR [26].

Other authors have proposed a cut-off at the 3rd percentile level to identify pregnancies with an increased risk of adverse outcomes [3, 33]. Small fetal size, as a single marker, does not make it possible to adequately distinguish between fetuses or newborns that are constitutionally small but healthy, and fetuses or newborns that are small due to placental, maternal, or fetal abnormalities and underlying growth impairment [3, 4, 48].

With any cut-off value, on any control table, small fetuses or neonates who are constitutionally small will be misclassified as having an FGR [62, 64]. This can lead to unnecessary monitoring and intervention. On the other hand, fetuses or neonates above the 10th percentile may have risks associated with placental insufficiency and fail to reach their individual growth potential. This group will remain undiagnosed because the fetuses or newborns in it are within the limits of normal sizes [57, 64].

Because of this, FGR should be attributed to fetuses with pathologically small dimensions caused by an underlying functional problem, and therefore a definition that includes not only biometric cut-off but also Doppler indices of fetoplacental function is currently agreed upon by most fetal medicine societies [26, 63].

At present, additional biophysical parameters are needed to distinguish FGR from SGA [3, 65, 66]. For better risk stratification, in addition to redefining estimated fetal weight for very small (weight < 3rd percentile) and small (> 3rd to < 10th percentile) babies and assessing maternal comorbidities, additional assessment variables

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include placental, umbilical, and fetal blood flow, fetal heart blood flow velocity analysis, fetal biophysical profile assessment, longitudinal growth trajectories, and diagnostic and/or prognostic biochemical markers [14, 26, 67, 68].

Doppler measurements help to depict the pathophysiological sequence of events that occur in the placenta and the fetus in cases of FGR [26, 39, 69]. The rationale for using Doppler to assess fetal growth is that it can identify uteroplacental function by assessing the nature of blood flow in the uterine and umbilical arteries. Uteroplacental insufficiency is likely mediated by maladaptation of the spiral artery and changes in the villous vascular tree. From the side of the fetus, dopplerometry makes it possible to evaluate the middle cerebral artery (MCA) and the ductus venosus, as the adaptation of the fetal cardiovascular system progresses from hypoxia to acidemia [3].

It should be noted that the results of dopplerometry of the umbilical artery may be normal in the early stages of FGR. Thus, a normal Doppler study of the umbilical artery does not rule out placental dysfunction, and therefore consistent monitoring is recommended in all cases of suspected FGR [6, 63, 68]. The Doppler index of pulsation (PI) of the uterine artery (UtA) mainly takes place in the identification of inadequate trophoblastic invasion of spiral arteries, which is reflected in the form of blood circulation with high vascular resistance. A persistently elevated uterine artery pulsatility index (above the 95th percentile) is associated with placental insufficiency and placental vascular malperfusion [70, 71].

Thus, it is most useful as a diagnostic tool for early-onset FGR. However, UtA PI can provide useful information throughout pregnancy. Uterine artery Doppler in the first trimester is important in predicting pre-eclampsia and FGR [32, 72]. Although uterine artery Doppler is promising, especially for predicting early-onset FGR, current evidence does not support routine screening with uterine artery Doppler for FGR in low- or high-risk pregnancies [73, 74].

During the physiological course of pregnancy, the reference values of PI of the umbilical artery gradually decrease with the progression of pregnancy. An increase in the PI of the umbilical artery (above the 95th percentile) indicates an abnormally high resistance in the vessels and corresponds to a progressive decrease in the placental surface area available for gas and nutrient exchange, as well as an increase in the resistance of the compensatory mechanisms of the fetus after the load associated with the placental vascular insufficiency In particular, in fetuses with an index below the 10th percentile or fetuses with slow growth, a high PI of the umbilical artery may indicate placental insufficiency [7, 26].

In early FGR, the PI of the umbilical artery usually increases due to the loss of the diastolic component: absence of end-diastolic blood flow (AEDF) and reversible end-diastolic blood flow (REDF). The average time between the appearance of AEDF and REDF and the sharp deterioration of the fetal condition is, on average, three and two weeks, respectively.

The PI of the umbilical artery becomes abnormal when more than half of the placenta ceases to function. At full-term pregnancy, the fetus does not have so much placental reserve, therefore, in the late form of FGR, PI of the umbilical artery is not very discriminatory [14, 26, 31, 75].

Fetal distress in late pregnancy may be evident by decreased fetal movements, abnormal CTG, or death before worsening Doppler blood flow, in part because the indication for measuring blood flow patterns is often only small in fetal size [46, 52, 62].

A decrease in the middle cerebral artery pulsatility index is a consequence of vasodilation, the so-called «brain-sparing» effect. This is a hemodynamic response to fetal hypoxemia due to the direct effect of oxygen tension on vessels in the cerebral circuit [76]. In other vascular channels, the subsequent redistribution of cardiac output of the fetus occurs mainly in the direction of the coronary arteries and adrenal glands [3].

A reduced PI of the MCA is considered a late manifestation of FGR and is valuable for predicting adverse perinatal outcomes, especially in the late onset of FGR. The cerebroplacental ratio (CPR) (ratio of PI MCA and UmbA PI) is a measure of brain preservation and improves the sensitivity of Doppler monitoring, as it increases even when its two components are still within normal limits [3, 6,10, 27, 76].

An early response to placental insufficiency is the redistribution of blood flow in the fetal circulation. Blood flow is selectively redirected to the most important organs, including the heart, brain and, in utero, the adrenal glands. Other organs can be selectively deprived of blood flow, such as the renal arteries, which explains the phenomenon of oligohydramnios.

Asymmetric measurements of size indicate that brain growth (biparietal diameter, head circumference) is less affected than measurements of other organs (abdominal circumference, femur length). The growth of the abdominal cavity is strongly influenced by the size of the liver, which is the main place for storing the energy of the fetus. In energy-deficient situations, the liver will consequently grow less rapidly, and the abdominal circumference will tend to be smaller compared to the size of the brain [47].

Biophysical tools, such as ductus arteriosus flow pattern, BPF assessment, and CTG assessment of STV, are not used as diagnostic criteria for FGR but are relevant for monitoring and management of pregnancies with the established diagnosis of FGR [3].

Although scientific evidence is still scarce, it is believed that the identification of fetal growth retardation can help identify a fetus at risk of morbidity and mortality by differentiating between a fetus with FGR (often due to placental insufficiency) and a small but healthy SGA fetus [68, 72, 75].

An example of the definition of fetal growth retardation is a decrease in abdominal circumference or estimated fetal weight of more than 20 or 50 percentiles between two measurements in the third trimester, as suggested by the Prediction of Pregnancy Outcome trial [77] and the IRIS trial [78].

Clear and well-defined diagnostic criteria for FGR due to placental insufficiency are important for two broad reasons, namely early detection of FGR in infants who are at significantly increased risk of neonatal complications, and early identification of infants with FGR

who would benefit from intervention to improve neonatal outcomes [51].

Thus, early-onset FGR is defined when: (i) predicted fetal weight and/or abdominal girth is less than the 3rd percentile or (ii) absent diastolic blood flow in the umbilical artery detected by Doppler. Early-onset FGR can also be diagnosed if two of the following three parameters are present: (1) estimated fetal weight and/or abdominal circumference < 10th percentile, (2) uterine artery PI > 95th percentile, and (3) PI umbilical cord > 95th percentile [3, 4].

Late-onset FGR is defined by only one parameter, namely: estimated fetal weight and/or abdominal circumference < 3rd percentile. A diagnosis of late-onset FGR can also be made if two of the following three parameters are present: (1) estimated fetal weight and/or abdominal girth < 10th percentile, (2) fetal growth retardation by two «quartiles» during fetal monitoring, and (3) CPR < 5th percentile [3, 11, 17, 33].

Although the Delphi procedure [26] reached a consensus on the definition, classification, and diagnosis of FGR, it is now recognized that accurate identification of FGR and thus risk determination requires a broader set of measures suggested by the criteria of this consensus [14, 26]. Implementation of this definition is limited by the lack of guidance on which growth chart should be used to define the 10th and 3rd percentiles for calculated fetal weight and fetal abdominal circumference [3, 6, 48, 57]. Furthermore, further studies are needed to correlate this definition with adverse perinatal outcomes [6, 13].

FGR has long been associated with oxidative stress caused by an increase in reactive oxygen species (ROS) and/or a lack of antioxidant availability and activity. Both in cases of FGR with and without abnormal Doppler findings, e.g., due to maternal malnutrition, maternal and neonatal plasma concentrations of antioxidants have been shown to be relatively low, whilst oxidant concentrations are relatively high [79].

Oxidative stress is generally high in the placenta due to its high mitochondrial activity, which leads to endogenous ROS production. A large amount of the proteins differentially expressed in placentas of late-onset FGR pregnancies are involved in the oxidative stress response [80]. The exact origin of oxidative stress in the placenta remains unknown. It is thought to be largely due to inadequate perfusion and metabolic disorders [81].

More recently, a cohort study comparing term and preterm FGR infants with their controls at birth showed increased serum levels of reactive oxidative metabolites in SGA infants. Moreover, the amount of oxidative stress was inversely correlated with the severity of growth restriction [82]. In addition, environmental factors may aggravate oxidative stress. It is well known that smoking is a major risk factor for the development of FGR. Recently, it has been shown that altered antioxidant defense mechanisms might contribute to this observation [83]. Similarly, air pollution has been shown to induce oxidative stress in the placenta and alter placental function [84].

Since oxidative stress has increasingly been recognized as a major pathomechanism in the development of FGR, the question of appropriate prevention approaches arises. Intervention strategies aiming to reduce oxidative stress whenever it is reaching a pathological threshold have been studied [79]. A large meta-analysis has recently shown that antioxidant therapy might reduce the risk of FGR when administered after diagnosis of preeclampsia [85].

However, the studies included in this analysis were very heterogeneous using different antioxidant compounds. In addition, the studies partially contradict each other, with some showing a beneficial effect of one substance, whilst others show no effect of the same substance [86].

Antioxidants might be a therapeutic option to avoid oxidative stress in pregnancy, but this needs further study to allow for successful implementation in the clinical setting [79].

Based on the above data, it is important to understand that FGR is a biological continuum. The time of the onset of the development of FGR is an important variable. About 20–30% of cases of FGR have an early onset (onset < 32 weeks of pregnancy) [49, 57, 65, 67]. These fetuses have a much higher risk of mortality and morbidity [15, 20, 28, 44]. Late FGR (≥ 32 weeks) is still associated with a risk of adverse perinatal events and outcomes, including late preterm birth, sudden fetal distress, hypoxia, and stillbirth [18, 47, 49, 68, 75].

Further work is needed to better risk stratify pregnancies at risk for placental insufficiency and stillbirth. So far, no consensus has been reached yet as to the properties, timing, and dosage of antioxidant therapy.

CONCLUSIONS

Fetal growth retardation remains a common complication of pregnancy all over the world today, despite the significant amount of data that has been collected to study the features of pathogenesis, diagnosis, and clinical course. Although a consensus has been reached in the last decade in the diagnostic criteria for fetal growth retardation, differences remain in the recommended management of pregnancies.

Today, the main controversial issues that need to be agreed on are the diagnostic criteria for fetuses with suspected FGR in low-risk pregnant women, the use of Doppler parameters for monitoring fetuses with diagnosed FGR, and decision-making about delivery dates. The data of recent studies that were focused on the study of oxidative stress as the leading pathogenetic mechanism for the development of placental aetiology FGR identified new targets that can be used as targets for cytoprotective therapy. Further research strategies should be focused on the search for biological markers to predict complications in fetuses and newborns with FGR and transfer these approaches to clinical practice.

Regarding the prevention strategy, pregnant women with a high risk of placental insufficiency should be given prophylactic antioxidant therapy. In the near future, it is desirable to obtain practical markers for a reliable assessment of the prenatal state of the fetus and the risk of both short- and long-term perinatal complications.

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