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Modern concepts of low birth weight and fetal growth restriction

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Abstract

The aim of this work is to study the state of the problem of the development of small-for-gestational-age fetus and fetal growth restriction over the past 5 years. A review of randomized trials of the PubMed database for the period of 2015 to 2020 was carried out. Experts reached an agreement on the definition of diagnostic criteria for small-for-gestational-age fetus and fetal growth restriction, a clinically valid classification was created, and the main monitoring strategies were developed. Due to the different pathogenesis, fetal growth restriction is divided into early and late. The observation algorithm includes tests that have shown higher sensitivity and specificity. There is no single standard for the median weight and abdominal circumference of a fetus, indicators of the reference range for fetal Doppler. Smoking cessation and taking acetylsalicylic acid at a dose of 150 mg at high risk of preeclampsia is recommended to prevent the small-for-gestational-age fetus and fetal growth restriction. The pregnancy management algorithm includes Doppler ultrasound examination of the umbilical artery, cardiotocography. If this pathology occurs before 32 weeks of pregnancy, the blood flow in ductus venosus is additionally examined, and after 32 weeks of pregnancy, the middle cerebral artery blood velocities and cerebroplacental ratio are assessed. Indicators of Doppler velocimetry and cardiotocography, which serve as criteria for early termination of pregnancy, are developed, measures are proposed to improve neonatal outcomes — prevention of respiratory distress syndrome at 24–34 weeks of gestation, as well as magnesium therapy for fetal neuroprotection. The problems of preventing fetal growth restriction and the algorithm for monitoring pregnant women who do not have risk factors for small-for-gestational-age fetus, management tactics and indications for delivery while slowing fetal weight gain remain unresolved.
Keywords: low birth weight, fetal growth restriction, management algorithm.

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Background. The incidence of a low-birth-weight fetus (LF) is 8.2–10.9% [1–3]. This pathology is the second most frequent cause of childhood morbidity and mortality after preterm birth [3, 4]. With MP, the stillbirth rate is 6 times higher than when the fetal body weight matches the gestational age (1.8 and 0.3%, respectively) [2]. An undetected LF increases the frequency of antenatal death by 8 times [5]. Infant mortality is also higher in the LF group than when the fetal body weight corresponds to gestational age (0.60 and 0.16%, respectively) [2].

Fetal growth retardation (FGR) occurs in 5.0–17.6% of pregnant women, the frequency of this syndrome in premature infants is higher (15.7–22%) [4, 6–8]. In a singleton pregnancy, FGR is a significant component of high perinatal losses (5.4%), especially at 28–31 weeks of gestation (13.2%) [4, 9]. FGR was identified in 43% of unexplained stillbirths [10]. FGR is associated with a high rate of complications in the early neonatal period: congenital pneumonia — 13.8% [hazard risk (HR) 5.4; 95% confidence interval (CI) 1.1−26.7], respiratory distress syndrome — 12.1%, intraventricular hemorrhage — 6.9% (HR 5.1; 95% CI 1.6−47.1) [7, 10, 11]. The development of metabolic syndrome characterizes children with FGR: insulin resistance, hyperinsulinemia (HR 4.75; 95% CI 1.22–18.44), arterial hypertension, and obesity [2, 5, 7, 10, 12]. We reviewed the randomized trials of the PubMed database of the US National Library of Medicine from 2015 to 2020.

The consensus was reached on the definition of LF and FGR [3, 5, 7, 13–17]. LF diagnosis is established when the fetal body weight is less than the 10th percentile [3, 4, 7, 8, 13–17]. Of these, 18–22% constitutes small children [5, 6]. A newborn with FGR can be born with a normal weight. However, during gestation (more often, it is the third trimes-

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ter), insufficient dynamics of the increase in the estimated fetal body weight (EFBW) and abdominal circumference are noted due to placental insufficiency [5, 7, 13–21].

FGR is divided into two categories: early and late [4–6, 8, 18, 19]. Early FGR (up to the 32nd week) includes a fetus with EFBW or abdominal circumference less than the 3rd percentile, as well as with EFBW or abdominal circumference less than the 10th percentile in combination with a pulsation index (PI) in the uterine artery and/or umbilical arteries (UA) more than the 95th percentile [4, 6, 18, 19]. A fetus with EFBW or abdominal circumference less than the 3rd percentile and having at least two of the following criteria is referred to as late FGR (after the 32nd week):

– EFBW or abdominal circumference less than the 10th percentile.

– EFBW or abdominal circumference more than 2 standard deviations.

– cerebro-placental ratio less than the 5th percentile.

– PI in UA is more than the 95th percentile [6, 18, 19].

Several researchers consider it reasonable to distinguish a high-risk group of LF/FGR (HR > 2.0) and a low-risk group (HR < 2.0) [9, 22].

High-risk includes a history of stillbirth (HR 6.4; 95% CI 0.78–52.56), antiphospholipid syndrome (HR 6.22; 95% CI 2.43–16.0), overt diabetes mellitus (HR 6.0; 95% CI 1.5–2.3), renal failure (HR 5.3; 95% CI 2.8–10) [9]. The birth of low-birth-weight children in the past (HR 3.9; 95% CI 2.14–7.12), an indication of the weight of the child's father at birth less than the 10th percentile (HR 3.47; 95% CI 1.17–10.27) or the pregnant woman (HR 2.64; 95% CI 2.28–3.05) [9] are considered significant. Older reproductive age (HR 3.2; 95% CI 1.9–5.4) was more significant than chronic arterial hypertension (HR 2.5; 95% CI 2.1–2.9) [9].

The following factors are referred to the low-risk group: values of pregnancy-associated protein A in blood plasma less than the 10th percentile (HR 1.96; 95% CI 1.58–2.43), unbalanced maternal nutrition (HR 1.9; 95 % CI 1.3–2.8), first birth (HR 1.89; 95% CI 1.82–1.96), in vitro fertilization (HR 1.6; 95% CI 1.3–2.0), obesity (HR 1.55; 95% CI 1.3−1.7), smoking (HR 1.54; 95% CI 1.39–1.7), history of preeclampsia (HR 1.31; 95% CI 1.19–1.44), intergenetic interval less than 6 months (HR 1.26; 95% CI 1.18–1.33) or more than 60 months (HR 1.29; 95% CI 1.2–1.39) [9, 22–24].

Early-onset of FGR is detected in 30% of cases [11]. Early FGR is caused by defective invasion of the trophoblast in the myometrial segment of the spiral arteries and a vascular anomaly of the tertiary cotyledons, resulting in systemic endothelial dysfunction and preeclampsia [4, 6, 8, 18]. Early severe FGR leads to severe hypoxia and/or antenatal fetal death [4, 8, 11]. Therefore, pregnancy management becomes a difficult task and aims to achieve the best balance between the risk of finding a fetus in the uterus and complications due to prematurity [4, 6, 8]. Up to 20% of cases of early FGR are associated with fetal pathology or chromosomal abnormalities, which requires a detailed ultrasound examination and a solution to the issue of chromosomal typing of the fetus [3, 9, 11, 18].

The leading pathogenetic mechanism of late FGR (70%–80%) is impaired uteroplacental blood flow, which manifests itself in the redistribution of fetal blood flow with predominant perfusion of the fetal brain, dilation of cerebral vessels [4, 6, 8, 10, 18]. Late FGR becomes the main cause of unexplained stillbirths in pregnancies with an initially low perinatal risk [4, 6, 8]. Later, FGR is characterized by abnormal Doppler measurements in the middle cerebral artery with normal or minimally increased resistance in the UA [6, 11, 25]. A study revealed that a violation of blood flow in the UA accounts for only 46% of cases of late FGR [6].

For a comprehensive assessment of the condition of the fetus, several methods have been proposed. Notably, the measurement of the height of the fundus of the uterus has limited accuracy for the detection of a fetus with LF / FGR (sensitivity 19%–21%, specificity 98%) [22]. Assessment of fetal movements is widely used to monitor its well-being and is most often carried out based on the subjective perception of the mother [6, 9, 15]. However, most national agreements did not include a fetal movement assessment test in the observation algorithm [1, 4, 5, 10, 19, 22, 25–27].

Computerized cardiotocography has a high false-positive rate (up to 50%) for predicting adverse outcomes and is more likely to detect acute hypoxic events than chronic conditions [4, 28]. Nevertheless, it is recommended to carry it out regularly in the antenatal period if placental insufficiency is suspected [4, 23, 28, 29]. Several schemes of ultrasound observation for high-risk pregnant women have been proposed:

– two additional studies at 28–30 weeks and 34–36 weeks of pregnancy [9].

– scanning every 2–4 weeks before delivery from the 24th week of pregnancy [19, 22].

– scanning every 2–3 weeks, starting from 28 weeks of gestation [4, 15, 23].

Doppler study of blood flow in the uterine artery reveals up to 60% of the risk of placental complications [15, 30, 31]. Several national guidelines do not include Doppler blood flow in the uterine artery

in the diagnostic and monitoring algorithm in the third trimester of pregnancy [4–6, 15, 25, 27]. Management of pregnant women with LF/FGR needs to include Doppler blood flow in the UA, as this reduces perinatal mortality in high-risk pregnant women (HR 0.71; 95% CI 0.52–0.98) and stillbirth rate (HR 0.65; 95 % CI 0.41–1.04) [15, 23, 29, 32].

The assessment of PI in UA has a high predictive value (60%) as its alterations directly correlate with the onset of acute intrauterine hypoxia within 7 days [4]. With early FGR, the deterioration of Doppler parameters occurs sequentially and progressively. The PI in the UA changes first, and subsequently, the indicators in the middle cerebral artery change [32].

Between the first ultrasound findings, indicating the manifestation of an early form of FGR, and terminal damage to the fetal brain (detected by cardiotocographic signs of an obstetric catastrophe), there is a time during which it is possible to detect peripheral vasoconstriction with changes in blood flow in the UA, the disappearance of the end-diastolic component of blood flow or the appearance of reverse blood flow in the UA, the disappearance of a-wave in the venous duct, diastolic and systolic heart failure, and overload of the atrial venous system (negative a-wave in the venous duct) [4, 25].

Diastolic zero blood flow and reverse diastolic blood flow, especially in UA, are associated with poor perinatal outcome in the presence of FGR (with a sensitivity and specificity of 60%), which does not depend on gestational age [4, 6, 15, 27].

Several national guidelines have proposed an algorithm for monitoring the parameters of Doppler measurements in the UA during LF/FGR. If the results of dopplerometry in the PA are normal, then in the case of detection of EFBW less than the 10th percentile. A repeated control study is carried out at least every 2 weeks [3, 15]; in case of slowing down of blood flow in UA more than 95th percentile or EFBW less than 3rd percentile - weekly [4, 6, 9, 15, 27]; with zero diastolic blood flow in the UA - every 2 days [3, 4, 6, 15].

PI in the middle cerebral artery less than the 5th percentile is considered a marker of vasodilation in the brain, even in the case of a normal PI in UA [1, 15, 26, 27]. Pathological results of Doppler examination of the middle cerebral artery in late FGR increase the risk of unfavorable perinatal outcome [4, 5, 21, 23, 25]. Indicators in the middle cerebral artery are especially valuable for identifying and predicting an adverse outcome of late FGR, regardless of the results of a study in PA, which are often within the normal range in these cases [6, 21].

The cerebro-placental ratio can be used to monitor FGR as its low value is considered an independent predictor of stillbirth and perinatal mortality ($p < 0.001$) [20]. A change in the cerebro-placental ratio may occur before the PI in the middle cerebral artery and can go beyond the normal range since this ratio serves as an earlier marker for diagnosing cerebral vasodilation [21, 33]. The altered values of the cerebro-placental ratio increase the likelihood of combined unfavorable perinatal outcomes: severe asphyxia (25%–45%), perinatal mortality (2%–7.4%) [21, 25, 33]. At the same time, a normal cerebro-placental ratio reduces these indicators to 17 and 0.2%, respectively [21, 25, 33].

When predicting stillbirth in the third trimester of pregnancy, the combination of indicators such as percentile values of EFBW, PI in UA, cerebro-placental ratio allows in achieving an accuracy of 88% (95% CI 77–99) with a test sensitivity of 66.7% and a specificity of 92.1% [20]. However, the obstetrician-gynecologist should not rely only on Doppler indicators of fetoplacental blood flow

when calculating the time and method of delivery in the III trimester. In that case, the fetus with late FGR will not be assessed and potential complications will be unpredictable [3, 21, 23, 33].

Monitoring of early FGR should include Doppler sonography in the ductus venosus [8, 15, 25]. The absence or inverted a-wave on the Doppler sonogram of the ductus venosus indicates clear acidemia and the risk of fetal death [8, 15, 25, 29]. Changes in the ductus venosus are not typical for late FGR [6]. Therefore, it is necessary to raise the question of delivery less than 32 weeks of gestation when there is a violation of blood flow in the venous duct [4, 6, 15, 22, 25].

There is a consensus of national guidelines on the indications for Doppler measurements for early termination of pregnancy in patients with LF/FGR [4, 8, 15, 25]:

– the presence of reverse diastolic blood flow in the UA — from 32^{+0} weeks of pregnancy.

– diastolic zero blood flow in the UA — no later than 34^{+0} weeks of pregnancy.

– PI in UA> 95th percentile - no later than 37^{+0} weeks of pregnancy.

– PI in the ductus venosus> 95th percentile — after 26^{+0} weeks of pregnancy.

– diastolic zero blood flow/reverse diastolic blood flow in the ductus venosus — after 26^{+0} weeks of pregnancy.

– in the middle cerebral artery PI <5th percentile — no later than 37^{+0} weeks of pregnancy.

– cerebro-placental ratio <5th percentile — no later than 37^{+0} weeks of pregnancy.

– with isolated LF (normal Doppler results, no additional risk factors) — at 38^{+0} weeks of pregnancy [1, 4–6, 15, 22, 25–27].

All methods to prevent FGR are related to the early form caused by preeclampsia [4, 19, 22, 34]. Prophylaxis with low doses of acetylsalicylic acid (100–150 mg/day) from 13–16 weeks to 36 weeks of gestation is recommended. This provides a 60% reduction in the incidence of preeclampsia [19, 22]. At the beginning of taking acetylsalicylic acid before 16 weeks of pregnancy, there is a significant decrease in the incidence of moderate preeclampsia (HR 0.57; 95% CI 0.43–0.75; $p < 0.001$), severe preeclampsia (HR 0.47; 95% CI 0, 26–0.83; $p = 0.009$) and FGR (HR 0.56; 95% CI 0.44–0.70; $p < 0.001$) [34].

Attempts have been made to prevent preeclampsia and IGR with low molecular weight heparins [35, 36]. However, it was found that the use of acetylsalicylic acid in combination with low molecular weight heparins does not reduce the incidence of placenta-mediated complications (including preeclampsia and FGR) compared with acetylsalicylic acid monotherapy (HR 1.19; 95% CI 0.53–2.64) [35].

With diagnosed FGR, no convincing data are indicating effective methods of correction [3, 4]. The effectiveness of hospitalization with adherence to bed rest, dietary changes, taking food supplements, prescribing progesterone, vasodilators has not been established [3, 6, 9, 28]. The effectiveness of the appointment of oxygen therapy in FGR is questionable [9]. The effectiveness of smoking cessation has been established, with an increased risk of preeclampsia — the appointment of acetylsalicylic acid [3, 4, 6, 9, 25, 28, 37].

Measures that improve neonatal outcomes include prophylaxis of respiratory distress syndrome with glucocorticoids at 24^{+0} to 34^{+0} weeks of gestation with expected delivery within 7 days. In addition, theuse of neuroprotection with magnesium sulfate facilitates expected delivery within 1 day in the period from 24^{+0} to 34^{+0} weeks of pregnancy [3, 4, 6, 28].

Certain agreements have been reached regarding delivery timing with LF/FGR depending on the ultrasound parameters [4]. With LF, the incidence of stillbirths increases from the 38th week of pregnancy. Therefore, pre-induction and delivery at 37^{+0} to 39^{+0} weeks of gestation under the control of computerized cardiotocography are recommended [3, 4, 6]. This tactic reduces perinatal mortality with MP without increasing the frequency of operative delivery [4, 5, 27, 38, 39].

In the case of late FGR, delivery times vary depending on the severity of changes in Doppler and computerized cardiotocography. National agreements recommend delivery at 36^{+0} to 37^{+0} weeks of gestation in case of PI in UA more than 95th percentile; with diastolic zero blood flow in the UA — at 33^{+0} to 37^{+0} weeks; with reverse diastolic blood flow in the UA — at 30^{+0} to 32^{+0} weeks of pregnancy [3, 4, 6]. If PI <5th percentile is detected in the middle cerebral artery — no later than 37^{+0} to 38^{+0} weeks of pregnancy, if the cerebro-placental ratio is less than 5th percentile — no later than 37^{+0} weeks of pregnancy is recommended[4].

The combination of fetal body weight less than the 10th percentile with oligohydramnios, preeclampsia, chronic arterial hypertension indicates delivery from 34^{+0} to 37^{+6} weeks of pregnancy [4, 6].

In the case of early FGR, the following tactics have been adopted: gestational periods of 22^{+0}–23^{+6} weeks of pregnancy are not considered as possible for termination of pregnancy in the interests of the fetus; at 24^{+0}–25^{+6} weeks of pregnancy, the approach is individual; in 26^{+0}–31^{+6}, early operative delivery is shown in case of detection of diastolic zero blood flow / reverse diastolic blood flow in the ductus venosus [4, 40].

The data of computerized cardiotocography in early FGR can be indications for operative delivery with repeated decelerations, STV <2.6 ms at 26^{+0} –28^{+6} weeks of gestation and STV <3.0 ms at 29^{+0} –31^{+6} weeks of gestation [4, 40]. With critical STV indices of less than 2.6 ms at 26–29 weeks and less than 3.0 ms at 29–32 weeks of gestation, the prognosis significantly worsens [4, 40].

Considering the presence of severe placental insufficiency, elective cesarean section is indicated in most cases of early FGR [4, 40]. This tactic allows you to minimize the negative impact of prematurity on the newborn and improve the health indicators of children under 2 years of age [4, 40]. In addition, surgical delivery is indicated in diastolic zero blood flow / reverse diastolic blood flow in the UA with preliminary, if necessary, prophylaxis of fetal distress syndrome [3, 4].

Conclusion. LF/FGR remain complex obstetric problems with low detection rates, limited prevention options, and a lack of proven effective treatment. The positions of the scientific communities have reached a certain agreement on the diagnostic criteria for LF/FGR, a clinically justified classification of FGR has been recommended, and basic monitoring strategies have been developed for both high-risk groups and pregnant women with LF/FGR [41].

Many researchers consider LF to be constitutionally healthy [42–44]. However, there is no single standard for the median not only for EFBW/abdominal circumference but also for Doppler measurements and their normative range [4, 6, 25, 42, 45–49]. In addition, the issues of pregnancy management with EFBW/fetal abdominal circumference of more than the 10th percentile, but with a decrease in fetal body weight gain, remain unresolved [50].

It is important to consider that in every second case, a child with FGR is born in the absence of any risk factors [23, 26], there is a need to search for new tests. Unfortunately, to date, there is not a single test with high sensitivity and specificity for early diagnosis or detection of the risk of FGR [4, 6, 8, 18, 23].

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