REVIEW ARTICLE

Advances in the Application of Ultrasound for Evaluating Placental Function in Fetal Growth Restriction (FGR) Pregnancy

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Received July 19, 2025; revision requested October 14, 2025; accepted November 3, 2025

Abstract: Placenta is a vital organ of a unique circulatory system that allows the exchange of nutrients between maternal and fetal circulations, supporting fetal growth during pregnancy. The placental nutrient transfer capacity is precisely modulated by the signals originating from the fetus, mother, and placenta itself, thereby ensuring appropriate regulation of fetal growth. However, the abnormality of any link in this process may lead to the failure of the regulation, and thus the placenta can no longer meet the fetal demand, causing fetal growth restriction (FGR). This review investigates the morphological and functional alterations in the regulation of placental growth and development, as well as the uteroplacental circulation in human pregnancies complicated by FGR. Additionally, it discusses the ultrasound application in the assessment of placental insufficiency.

Key words: Ultrasonography; Fetal growth restriction; Placenta function; Diagnostic tool assessment

Advanced Ultrasound in Diagnosis and Therapy 2026; 01: 052-060 DOI: 10.26599/AUDT.2026.250064

FGR, affecting up to 5%–10% of pregnancies in developed countries, and approximately 6.39% in China [1], is clinically defined as a birth weight below the tenth centile for gestational age, which means the fetus does not meet its growth potential. This condition is usually associated with a high incidence of perinatal morbidity and mortality, adverse peri-natal outcomes, stillbirth, and neuro developmental delay in the long term [2-5]. Fetal growth is dependent on nutrient supply, which relies on substrate transport and its regulation. Although complex aetiological parameters have been suggested, including maternal, fetal, placental, and other factors, placental insufficiency as a common cause of FGR is not to be overlooked [6]. Ultrasonographic assessment of placental structure and microcirculatory perfusion plays a crucial role in understanding the pathophysiology of FGR [7]. In recent years, with advances in ultrasound technology, various sonographic methods have been widely applied for the non-invasive evaluation of placental function. By detecting key biological features—such as morphological architecture and hemodynamic parameters—these techniques provide valuable insight into placental functional status. As a primary prenatal screening tool, ultrasound combines safety with efficiency, offering essential support for the early identification of placental dysfunction and associated FGR risk. This article reviewed the progress of various ultrasound techniques in evaluating placental function and diagnosing FGR, based on characteristics of placental structure and function in FGR.

The Placenta and Development of Fetal Growth Restriction

Placental adaptations to fetal growth

After implantation, the embryo becomes enveloped by a trophoblast layer that invades the uterine lining.

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Extravillous trophoblast (EVT) cells proliferate to occlude the nearby maternal blood vessels. This creates a low-oxygen environment for the embryo, protecting it from harmful reactive oxygen species and supporting stem cells, while it is nourished by uterine gland secretions [8-10]. Significant maternal blood flow doesn't begin until weeks 10 to 12 of gestation. Before this switch to blood-based nutrition, EVT cells, along with maternal immune cells, invade the decidua and remodel the spiral arteries. They break down the artery walls, turning them into wide, flabby tubes to ensure good blood flow to the placenta [11-13]. Blood vessel development in the placental villi starts around weeks 5 to 6. Until approximately week 24, villi develop through branching angiogenesis. After that, non-branching angiogenesis takes over. Specialized terminal villi form, which are the main sites for efficient gas exchange [14]. If blood flow is insufficient, the fetus may not get enough oxygen and nutrients, leading to FGR [15,16].

Deficient placental development in FGR

In early pregnancy, risk factors of maternal vascular malperfusion (MVM), such as the adverse maternal environment, maternal advanced age, gestational hyperglycemia, and gestational hypertension, can result in placental insufficiency, a condition characterized by impaired delivery of essential nutrients and oxygen to the developing fetus [17,18]. MVM is considered the most common placental pathology underlying fetal growth restriction [19]. Its primary mechanism involves abnormal spiral artery remodeling, with multiple consequences, analyzed as follows. First, MVM adversely affects the velocity of the maternal blood entering the placental intervillous space: the persistence of high-velocity, pulsatile inflow causes mechanical damage to placental villi, thereby compromising maternal perfusion. This results in villous hypoplasia, manifested as reduced placental weight, increased syncytial knots, fibrin deposition in the intervillous space, and distal villous hypoplasia [19,20]. Second, Defective maternal vascular transformation in FGR pregnancies is likely to cause greater intermittent perfusion of the placenta, exposing the placenta to recurrent ischemia-reperfusion-type insults. The pulsatile flow causes fluctuations in placental perfusion, leading to intermittent hypoxia and reoxygenation that induce oxidative stress and excessive production of ROS and RNS. These reactive species damage DNA, lipids, and proteins; impair mitochondria and other subcellular components; activate cell death pathways; and disrupt cellular respiration and ATP synthesis. Collectively, these alterations disrupt placental nutrient transport, increased apoptosis, and accelerate replicative senescence, ultimately compromising placental function and fetal growth [20,21]. Third, deficient remodeling predisposes spiral arteries to acute atherosis, characterized by accumulation of foam cells and fibrous tissue in vessel walls, leading to wall thickening and luminal narrowing. Microscopic plaques may obstruct blood flow, severely restricting placental perfusion and promoting the development of MVM-related diseases such as FGR and preeclampsia. Villous vascular lesions associated with maternal hypoperfusion are more frequent in early-onset than late-onset FGR.

Other placental lesions associated with FGR include fetal vascular malperfusion (FVM) and villitis of unknown etiology (VUE) [22]. FVM is mostly caused by the obstruction of fetal blood flow due to thrombosis or other pathological changes. Persistent abnormal hypercoagulability can lead to a thrombotic tendency in placental tissue, resulting in placental thrombosis, reduced uteroplacental blood flow, and consequent placental dysfunction, which induces FGR [23], with placental thrombosis and infarction the most common pathological changes in pregnancy complicated by FGR with or without preeclampsia. hese manifestations appear as large hypoechoic areas or diffuse hyperechoic regions within the placenta on ultrasound examination, with the extent of diffuse hyperechoic areas increasing as gestational age advances [16].

As other placental inflammatory diseases, the prevalence of various metabolic diseases or immune diseases could be raised in women, which develop VUE, an inflammation limited to the interstitial lymphoid tissue of the terminal villi. This inflammation can be associated with vascular lesions, such as stem vessel obliteration and thrombosis, and avascular villi. Enhanced local inflammatory responses—including immune cell infiltration, dysregulated T-cell activity, and activation of nuclear factor kappa B (NF-kB) and interleukin-17 (IL-17) signaling pathways—may exacerbate placental inflammation [24-28]. VUE is associated with vascular pathology such as thrombosis, primary vascular occlusion, and the development of avascular villi [29]. It typically presents with late onset of FGR, and earlier detection of villitis should raise suspicion for an infectious origin [29].

Angiogenic and vasculogenic processes are vital for tplacental vasculature development. Placentas from pregnancies complicated by severe early-onset FGR exhibit diminished vascular development mediated by impaired angiogenesis. Studies support the hypothesis that the villous stromal extracellular matrix (ECM) regulates fetoplacental vascular development [30-32]. Impaired endothelial cell (EC) motility—a critical process for both angiogenesis and vasculogenesis—is observed in severe FGR. Within the placental villous

stroma, the extracellular matrix (ECM) plays a key regulatory role in fetoplacental vascular development. Fibronectin, one of the most abundant ECM components, interacts with endothelial integrins to modulate placental angiogenesis. Dysregulation of two major fibronectin-binding integrins, αvβ3 and α5β1, expressed on ECs represents a potential mechanism contributing to FGR [33]. In addition, Lower quantities of aryl hydrocarbon receptor nuclear translocator (ARNT) resulting in impaired EC migration [34]. Other mediators—including vascular endothelial growth factor (VEGF), Placental Growth Factor (PGF), Hepatocyte Growth Factor (HGF), Endothelial Cell-Specific Molecule-1 (ESM1) and Tissue Inhibitor of Metalloproteinase 3 (TIMP3)—are also contribute to cell growth, motility, and angiogenesis [24]. In FGR pregnancies, impaired placental angiogenesis results in an inadequate, poorly branched vascular tree, which can be detected clinically using ultrasound.

Placental abnormalities are classified into MVM, FVM, placental microvasculopathy, and cord abnormalities (single umbilical artery, marginal or velamentous or furcate insertion, true knots, hyper- or hypo-coiling) [14,35]. Placental villous dysfunction and reduced perfusion are the mechanistic origins of FGR, primarily characterized by the maldevelopment of placental villi and fetal vasculature [36-38]. Based on the pathological mechanisms of placental dysfunction in FGR, the methods currently employed in clinical practice to assess placental function include maternal blood biomarkers, ultrasound, and magnetic resonance imaging (MRI). Extensive studies have explored potential biomarkers for FGR, including placental hormones, inflammatory cytokines, and metabolites. However, current existing biomarkers often lack adequate sensitivity and specificity for broad clinical use. Furthermore, the multifactorial nature of FGR, involving maternal, fetal, and placental components, comprehensive assessment through a single biomarker remains challenging [24]. Studies have explored prenatal MRI as a valuable tool for placental functional assessment [39-41]. Its widespread clinical application remains limited because it is costly and time-consuming. In contrast, ultrasound is widely used in clinical practice due to its convenience, non-invasive nature. Clinically, this early abnormal development of the definitive placenta may be detected sonographically as abnormal Doppler waveforms, and/or by other ultrasound techniques (Fig. 1).

Ultrasound Evaluation of Placental Function

Doppler evaluation of placental

Uteroplacental insufficiency is associated with altered blood flow resistance in the uterine, placental and fetal vasculature. Increased vascular resistance in MVM and FVM can be detected, and it can be assessed throughout the pregnancy by measuring the blood flow pattern of maternal and fetal arteries, including the uterine artery (UtA), umbilical artery (UA), middle cerebral artery (MCA), cerebroplacentall ratio (CPR) and cerebral-placental-uterine ratio (CPUR) [35,42]. The Doppler parameter most strongly associated with placental insufficiency was a newly developed one, the cerebral-placental-uterine ratio (CPUR), which is calculated as the cerebroplacental ratio (CPR) (middle cerebral artery pulsatility index(PI) /umbilical artery PI) divided by the mean uterine artery PI [43].

The blood flow pattern of uterine artery, as an indirect measure of spiral artery resistance, reflects the maternal perfusion to the placental bed. In early pregnancy, it shows a transition from high to low resistance, that does not fully occur in defective trophoblast invasion, leading to an increased pulsatility index (PI). In the uterine artery during mid-pregnancy, the retained high resistance, associated with placental dysfunction, will increase the risk of FGR [16,44,45].

The blood flow parameters of umbilical artery reflect placental circulation resistance to the fetal and blood perfusion volume. In cases of placental insufficiency, capillary arterioles may exhibit pathological changes such as spasm and edema, leading to increased umbilical artery resistance index (RI). For high-risk pregnancies, umbilical artery Doppler ultrasound is recommended as the preferred fetal monitoring method. During normal pregnancy, umbilical artery PI and systolic and diastolic blood flow velocity ratio (S/D) decrease with gestational age; at ≥ 28 weeks, S/D > 3.0 or RI > 0.6 is the optimal threshold for the identification of high-risk pregnant women with adverse outcomes [46]. Umbilical artery blood flow monitoring is of great clinical significance in FGR populations, with UtA-PI the optimal predictor of mid-pregnancy placental disease [47]. Early-onset FGR is characterized by abnormal UA velocity wave forms and elevated UA-PI, whereas in late-onset FGR, mild placental dysfunction often results in normal UA-PI. Umbilical artery blood flow changes typically occur when about two-thirds of the placenta becomes necrotic, so unless there is an increase, absence, or reversal of diastolic end-diastolic flow, placental insufficiency in late-onset FGR is usually not detectable through UA Doppler scanning. The absence and reversal of diastolic end-diastolic flow represent the final stage of histological and functional damage to the placenta [47,48].

The early response to placental insufficiency is the "brain retention effect": when fetal chronic hypoxia occurs, fetal cerebral arteries dilate, manifesting as a

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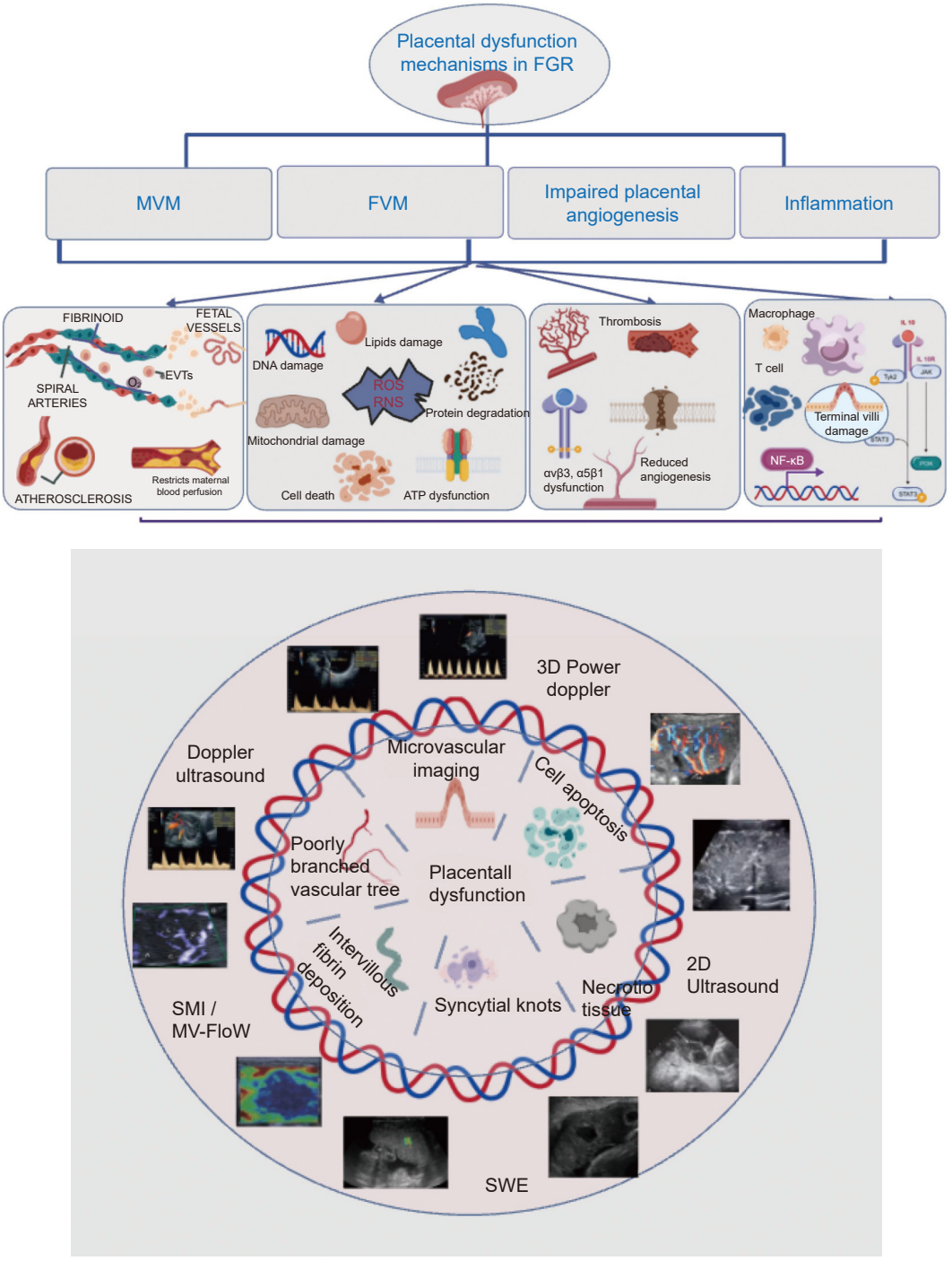

Figure 1 Correlation between ultrasound indicators and etiological mechanisms in placental dysfunction.

decrease in MCA-PI. However, this reaction can't provide long-term neural protection. Abnormal MCA-PI is associated with poor neurological outcomes and is an essential indicator of adverse outcomes in late-onset FGR pregnancies. However, it is of low sensitivity for the prediction of FGR. CPR and CPUR are particularly critical indicators of small for gestational age (SGA) fetuses at higher risk of adverse perinatal outcomes, especially for detecting late-onset FGR. Fetuses with abnormal CPR demonstrate higher incidences of MVM and FVM lesions [49]. A prospective cohort study found that CPUR showed the strongest correlations with the important indicators of placental insufficiency, including third-trimester fetal growth velocity and neonatal fat measures, which reflect in-utero substrate supply [43]. Pathologically, in late-onset FGR with CPUR abnormalities, there are signs of poor placental vascular perfusion, which is more strongly correlated with late mild placental insufficiency compared to CPR and/or mean UtA-PI [45].

Two-dimensional ultrasound evaluation of placenta

With advancing gestation, accumulation of fibrin under the chorionic plate and increased calcification on the maternal side of the placenta can be observed. Abnormally accelerated, premature placental senescence plays a crucial role in the genesis of gestational pathologies and obstetric complications, such as abnormal fetal growth. The premature aging of placental villi are crucial in the pathological diagnosis of MVM and help clinicians understand the underlying causes of placental dysfunction. On ultrasound, these diffuse hyperechogenic lesions show increase in size. Disorders of villous maturation were more frequent in the research group than in the control group. Among these disorders, delayed villous maturation was the most common, followed by accelerated villous maturation [14]. The maturity of the placenta, according to the Grannum grading system, is classified into 0-III grades. The premature aging of placental villi is crucial in the pathological diagnosis of MVM, helping clinicians figure out the underlying causes of placental dysfunction. However, this classification, mainly relying on the subjective judgment of doctors, lacks objective standards. Lei et al. proposed a method for placental maturity grading, which employs a dense Fisher vector, and achieved an area under the receiver operating characteristic curve (AUC) of 96.77%, as well as the sensitivity and specificity values of 98.04% and 93.75%, respectively [50]. However, isolated placental grading, calcification, and aging are insufficient to represent placental function, and thus cannot serve as independent indicators for the prediction of pregnancy outcomes.

The morphology, size, and position of the placenta, as well as abnormalities of the umbilical cord insertion are all associated with poor obstetric outcomes, in particular poor fetal growth [16]. Placental thickening is a compensatory marker of poor uterine-placental perfusion. In FGR pregnancies, the placenta may be smaller or more localized compared to normal ones, with spiral arterioles showing lesions leading to FGR. The abnormalities of the umbilical cord insertion are often correlated with abnormalities of the placental shape, but no data support a direct link between the location of the umbilical cord insertion and poor fetal growth. Currently, the application of ultrasound imaging and color doppler imaging makes the diagnosis of these anomalies in early pregnancy possible.

Placental thromboses, resulted from focal coagulation of maternal blood inside the intervillous space, are found mainly in areas of lower villous density, such as under the fetal or chorionic plate, in the placental marginal areas, and in the center of cotyledons. They are often described as echogenic cystic lesions or hypoechoic areas on ultrasound. Massive subchorial thromboses have been reported in pregnancies complicated by FGR and stillbirth [51,52]. Placental volume serves as an independent predictive indicator of FGR, with its predictive power improving as Doppler waveforms become abnormal. Since the emergence of 3D ultrasound, the assessment of placental volume becomes operable. The placental volume analysis tools, such as Virtual Organ Computer-aided analysis (VOCAL), can quickly and repeatedly calculate placental volume [53]. However, in mid to late pregnancy, the placental volume is too large to be accurately assessed for the current placental volume analysis tools.

Three-dimensional doppler ultrasound (3D-PD) evaluation of placenta

As a result of continuous technical refinement, previous studies have drawn attention to the visualization of microvascular flow in the placenta. 3D-PD can quantitatively analyze the intensity of blood flow and vascular density within the placenta, using vascularization index (VI), blood flow index (FI), and vascularized blood flow index (VFI) as the main indicators. In FGR, it shows a reduction in the volume and uniformity of the umbilical vessels and first to second-order chorionic villi. In pregnancy with hypertensive disorders, it reveals uneven diameters and irregular surfaces of the umbilical vessels and first to second-order chorionic villi, accompanied by nodules and indentations [54]. VI and FI are positively correlated with newborn birth weight. It was found that 3D-PD can assess the blood perfusion status of the fetus and placenta in early pregnancy, and predict pregnancy outcomes, with significant potential in the early diagnosis of FGR [55]. Studies report that all the three vascular indicators (VI, FI, and VFI) in the FGR group are significantly lower than those in the normal group. In terms of the correlation between parameters and perinatal outcomes, a study found that VI in the FGR group was significantly associated with the Apgar score at 5 minutes ($r = 0.416$, $P = 0.022$) [56]. Due to the influence of machine parameters such as pulse repetition frequency, smoothness, filtering, the gain, the occlusion by the fetal trunk and limbs, and fetal movement, 3D-PD is limited in clinical applicability: it is effective in the study of fetal placental microvascular structure in early pregnancy, but less effective for exploring the posterior wall of the placenta in late pregnancy.

SWE evaluation of placenta

Shear wave elastography (SWE) can detect the propagation speed of shear waves in the tissue and calculate Young's modulus, thus quantitatively investigating the

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mechanism of how tissue elasticity is affected by pathological changes [57]. Studies show that SWE has promising diagnostic efficacy in the evaluation of placental function in cases of preeclampsia and gestational diabetes [58,59]. CHEN et al. [60] reported that the elasticity of a normal placenta, from hard to soft, is sequentially the edge (the area within 2 cm of the placental margin), the middle (the area with a diameter less than 1cm from the umbilical cord entry), and the center (the area equidistant from the placental center to the edge), with significant differences between the edge and middle regions. However, there remains controversy concerning the variations in Young's modulus values across different regions of the placenta [59,61], which requires further research. Placental stiffness is significantly increased in pregnancies with intrauterine growth restriction, possibly due to increased syncytial knots, fibrosis of the villous stroma, and deposition of vascular fibrin, which can all lead to placental hardening. Additionally, the elastic value of the infarcted area in placenta was higher than that of normal area in vitro test [62]. Studies show that the placental SWE value is weakly negatively correlated with CPUR value, negatively correlated with fetal weight, and slightly positively correlated with NICU admission [58,63]. Therefore, SWE can be used to assess placental function and serve as an effective indicator for diagnosing and predicting FGR. However, it should be noted that pre-pregnancy BMI, weight gain during pregnancy, and depth all have influence on the measurement of placental stiffness.

Evaluation of placental microcirculation

Superfine blood flow imaging (SMI) can minimize motion artifacts to improve the visualization of small vessels by eliminating signals based on tissue movement analysis. Compared to traditional color doppler imaging methods, SMI can evaluate placental microcirculation in pregnancy, identify placental branch vessels and chorion trees, and detect pathological manifestations such as placental infarction and avascular chorions, thereby predicting placental function [64-66]. Hasegawa et al. found that SMI imaging in normal placenta clearly visualizes structures ranging from branching vessels to peripheral villous trees in the cotyledons, which are not visible in cases of fetal growth restriction [67]. Studies have shown that the VI value is positively correlated with gestational age (r = 0.962, $P < 0.05$), with the VI value of the placenta increasing as gestational age increases. They also provided a 95% reference range for normal placental VI values at different gestational ages, which serves as a basis for evaluating placental blood perfusion during pregnancy. A multicenter prospective study [2] used SMI technology to detect spiral arteries (SA) and fetal-side chorionic villi arteries (IVA) in the placenta to predict FGR. It was found that the average SA-RI and IVA-RI values in the FGR group at late gestation were significantly higher than those in pregnancies without FGR. Specifically, when using SA-RI screening for FGR, the areas under the receiver operating characteristic curves (AUC) for pre-, mid-, and late-gestational patients were 0.68, 0.73, and 0.73, respectively, and the AUCs for IVA-RI at each gestational period were 0.72, 0.72, and 0.73, respectively. Besides, a prospective study suggested that SMI can be used to assess suspected late-onset fetal restriction by measuring the pulsatility index (PI) of the villous template [68]. In another study, the placental vascular index (VI^{MV}) was obtained utilizing the MV-Flow region of interest, and it was found that the VI^{MV} values in the FGR group were lower compared to the control group in the upper, middle, and lower parts of the placenta [69]. Maternal microvascular lesions are associated with the early onset of preeclampsia, while fetal villous lesions are more closely related to FGR [69], with the blood flow index of FGR being lower than that of the control group. Therefore, detailed localization of structural abnormalities within the placenta can contribute to the differential diagnosis. MV-Flow and SMI can differentiate maternal vascular lakes from fetal villous vascular trees [70], demonstrating their feasibility and clinical significance in the evaluation of placental function. However, large-scale studies are warranted for further validation.

Conclusions

Through improving the understanding of placental development and the specific mechanisms behind placental dysfunction, the fetus in need of management can be identified. Ultrasound imaging, in particular color Doppler imaging, is postulated to provide insight into the state of the placenta. However, Doppler parameters offer the overall resistive indicators calculated from variables of the flow velocity upstream of vascular beds on the fetal and maternal sides of the placenta instead of images specifically of the placental microvascular circulation itself.

More recently, 3-dimensional Doppler imaging and the SWE technique have been applied to investigate the development of the placental and fetal circulations. However, their application in clinical practice remains limited.

The evaluation of placental microcirculation may increase the sensitivity of Doppler measurements and improve the efficiency. It seems that this technique is effective in the assessment of placental function and may strengthen the utility of Doppler parameters for the

prediction of adverse perinatal outcomes in high-risk pregnancies.

A comprehensive assessment of placental function cannot be based on a single ultrasonographic parameter. It requires the integrated analysis of multimodal ultrasound imaging, placental morphology, fetal growth parameters, Doppler hemodynamic indices, and relevant maternal biomarkers.

Acknowledgment

Not applicable.

Authors' Contributions

Ming-Li Shi drafted the manuscript; Guo-Hui Liu performed review, editing, and overall supervision; Fu-Xing Bao performed the English language review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Data Availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Conflict of interest

The authors have no conflict of interest to declare.

Consent for publication

Not applicable.

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