Editorial

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# Evidence-Based Screening, Diagnosis and Management of Fetal Growth Restriction: Challenges and Confusions

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Fetal growth restriction (FGR) describes a pathological condition in which the fetus fails to fulfill its growth potential. FGR is associated with higher perinatal mortality and morbidity rates as well as a variety of long-term adverse outcomes.[1–4] Unfortunately, consensus is still lacking regarding the definition and diagnostic criteria of FGR, despite the recent publication of guidelines from the American College of Obstetricians and Gynecologists Committee,[5] International Society of Ultrasound in Obstetrics and Gynecology,[6] Society for Maternal-Fetal Medicine,[7] and the International Federation of Gynecology and Obstetrics.[8] Further well-designed and prospective clinical studies are needed to fill in knowledge gaps in the areas of screening, prevention, surveillance, diagnosis, and clinical management for FGR fetuses. In this issue, we introduce a Chinese expert consensus on FGR (*Matern Fetal Med* 2022;4(3):162-168) based on three-round Delphi procedures among multidisciplinary experts and organized by the Society of Chinese Perinatal Medicine, and five reviews related to several hot topics of FGR, including "Establishing Chinese fetal growth standards: why and how," "Genetics etiology associated with fetal growth restriction," "The update of fetal growth restriction associated with biomarkers," "Fetal growth restriction: mechanisms, epidemiology and management," and "Preventing stillbirth: a review of screening and prevention strategies."

Although the definition of FGR varies between guidelines from different countries, there is a consensus that it should be based on fetal size percentiles. Growth charts, either reference or standard ones, are used to identify fetuses with an abnormal size or growth velocity, which is associated with an increased risk of perinatal or long-term adverse outcomes. There have been numerous fetal growth standards established since the 1980s. The most widely used growth chart to date was established by Hadlock in 1985 in white women.[9] More recently, however, the following three well-known multi-center longitudinal growth charts were developed from healthy, low-risk pregnancies in different populations: the International Fetal and Newborn Growth Consortium for the 21st Century Fetal Growth Standard (INTERGROWTH-21st), the World Health Organization Fetal Growth Charts (standards), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Standards.[10–12] The INTERGROWTH-21st project established an overall growth chart despite considerate variations among different populations. The World Health Organization standard revealed variations among countries and suggested adjusting the overall chart by adapting cutoffs (eg, from the 10th to 5th percentile or others) to fit diverse populations. The NICHD standards addressed ethnic variations and established separate curves according to different ethnicities (White, Black, Hispanic, and Asian). However, whether a fetal growth standard should fit all populations or whether different standards should be constructed for diverse populations remains controversial. As for Chinese clinicians, there are three main unanswered questions in this context as follows: (1) which standards should be used; (2) is it necessary to establish Chinese fetal growth standards; and (3) if it is necessary, how should the standard be built? In this special issue on FGR, we invited Prof. Zhang and colleagues (*Matern Fetal Med* 2022;4(3):197-205) to comment on why and how to establish Chinese fetal growth standards. In the Chinese expert consensus for FGR published in 2019, a customized growth chart was recommended; however, in the absence of such a chart designed specifically for China, the Asian growth chart from the NICHD was recommended, and use of the chart generated from Hong Kong, China, was recommended for pregnant women from southern China.[13,14]

The etiologies of FGR can be broadly categorized into maternal complications, fetal diseases, and placental

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abnormalities. Cases of FGR related to maternal and placental diseases can experience relatively good outcomes through appropriate intrauterine surveillance and timely treatments. However, there has been no effective prenatal intervention for FGR caused by genetic problems. With the application of chromosomal microarray analysis and next-generation sequencing, more and more FGR cases secondary to genetic diseases can be diagnosed prenatally.[15] In this issue, Shi *et al.* (*Matern Fetal Med* 2022;4(3):206-209) provide an overview on genetic abnormalities related to FGR, including fetal chromosomal abnormalities, copy number variants, monogenic disorders, uniparental disomy, confined placental mosaicism, and epigenetic changes. The authors recommend that prenatal genetic testing should be offered in cases of early-onset and severe FGR or FGR accompanied by structural abnormalities. More studies describing how to choose appropriate genetic testing for different types of FGR at different gestation ages are expected.

Besides etiologies from fetal origin, the majority of FGR cases are associated with placental insufficiency due to different underlying causes, such as maternal vascular malperfusion, fetal vascular malperfusion, and villitis. Recently, the use of angiogenic biomarkers, metabolites, and epigenetic markers for screening of early and severe FGR mediated by placental insufficiency has been investigated.[4,16–19] In this issue, Sun (*Matern Fetal Med* 2022;4(3):210-217) provides an update on the potential value of promising biomarkers in the prediction of severe FGR and demonstrates the specific mechanisms of impaired fetal growth on diseases later in life.

Kamphof *et al.* (*Matern Fetal Med* 2022;4(3):186-196) review the contemporary diagnosis and management issues in FGR and discuss the value of different diagnostic markers, like Doppler measurements, estimated fetal growth, interval growth, fetal movements, biomarkers, and placental markers.

Among the short- and long-term adverse outcomes associated with FGR, stillbirth is the most devastating complication.[8] Due to the absence of an effective individualized screening model, identifying women at increased risk for stillbirth remains a challenge. Placental insufficiency is associated with a 60% rate of intrauterine fetal demise according to the most recent studies. Noël *et al.* (*Matern Fetal Med* 2022;4(3):218-228) suggest in this issue that preeclampsia, FGR, and stillbirth are caused by the same disorder—namely, placental insufficiency. The authors comment that a first-trimester combined screening algorithm built by the Fetal Medicine Foundation for predicting preeclampsia also shows good performance for screening for other placental diseases, like FGR and stillbirth. Although there are no ideal or equivalent prediction models for the second trimester, the review still summarizes some second-trimester screening tools for pregnancies at high risk of placental insufficiency.

These articles presented in this special issue aim to provide insightful updates on various topics of FGR. However, to date, adequate diagnostic approaches, as well as prophylactic and therapeutic interventions, are still lacking in number. Efforts should be directed in the near future toward developing early prediction and effective preventive strategies, timely and accurate diagnosis, and management with a standardized protocol to improve perinatal outcomes in pregnancies complicated by FGR.

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