Comparison of three different international fetal growth restriction definitions in Chinese population

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Abstract

Background Fetal growth restriction (FGR) is defined differently by the American College of Obstetrics and Gynecology (ACOG), Society for Maternal-Fetal Medicine (SMFM), and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). **Objective** The purpose of this study was to investigate the predictive effect of three different diagnostic criteria of FGR on small-for-gestational-age (SGA) and adverse neonatal outcome (ANO), so as to find a better FGR-definition for Chinese population. **Study Design** The clinical data of singleton pregnancy who received regular pregnancy care and gave birth at the Department of Obstetrics and Gynecology of Peking University First Hospital from January 1, 2021, to June 30, 2021 were collected. FGR cases were determined according to three different diagnostic criteria by ACOG, SMFM, or ISUOG. The primary outcome was the prediction of SGA and a composite ANO. SGA was defined as neonatal birth weight less than 10 th percentile. An ANO included one of these adverse outcomes: neonatal umbilical arterial blood pH < 7.1, 5-minute Apgar score<7, acute respiratory distress syndrome (ARDS), intraventricular hemorrhage, and neonatal convulsion, and transfer to the neonatal intensive care unit (NICU). The specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) of the different diagnostic criteria for SGA and ANO were compared. The discriminatory capacities of the three FGR-definitions were compared using the area under receiver-operating-characteristics curves (AUC). **Results** A total of 2340 cases were included in this study, and 115 (4.9%), 63 (2.7%), and 48 (2.1%) cases of FGR were diagnosed using the diagnostic criteria issued by the SMFM, ACOG, and ISUOG respectively. There were 147 (6.28%) cases of SGA neonates. The SMFM criteria had higher sensitivity (40.82% vs 24.49%, 20.41%) for SGA compared to the ACOG and ISUOG criteria. On the contrary, the ISUOG criteria had a higher specificity (99.18% vs 97.49%, 98.77%) than the SMFM and ACOG criteria for predicting SGA. A total of 127 (5.43%) cases were complicated with ANO. All three definitions had low sensitivity for ANO (17.32%, 12.6%, 11.81%) and high specificity of 95.8%, 97.88% and 98.51%. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552). **Conclusion** The predictive value of the SMFM and ISUOG definition for SGA and ANO was better than that of the ACOG criteria. In Chinese population, the discriminatory capacities of SMFM FGR definition were superior compared to the other two definitions.

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Tweetable statement

Fetal growth restriction (FGR) is the leading cause of intrauterine fetal death, neonatal death, and short-term and long-term complications worldwide. It is difficult to evaluate the potential growth of a fetus. Therefore, different countries and associations have developed different guidelines to screen for fetuses with suspected FGR. The purpose of this study was to compare the ability of different FGR definitions to predict small-for-gestational-age (SGA) and adverse neonatal outcomes (ANO), so as to figure out a more suitable definition for Chinese population.

In this respective study, a total of 2340 cases were included. Among them, 115 (4.9%), 63 (2.7%), and 48 (2.1%) cases of FGR were diagnosed using the diagnostic criteria issued by the SMFM, ACOG, and ISUOG respectively. There were 147 (6.28%) cases of SGA neonates. The SMFM criteria had higher sensitivity (40.82% vs 24.49%, 20.41%) for SGA compared to the ACOG and ISUOG criteria. All three definitions had low sensitivity for ANO (17.32%, 12.6%, 11.81%) and high specificity of 95.8%, 97.88% and 98.51%. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552).

Comparison between Fetal Growth Restriction Definitions

AJOG at a Glance

Why was this study conducted

Fetal growth restriction (FGR) is the leading cause of intrauterine fetal death, neonatal death, and short-term and long-term complications worldwide. It is difficult to evaluate the potential growth of a fetus. Therefore, different countries and associations have developed different guidelines to screen for fetuses with suspected FGR. The purpose of this study was to investigate the predictive effect of three different diagnostic criteria of FGR on small-for-gestational-age (SGA) and adverse neonatal outcome (ANO), so as to find a better FGR-definition for Chinese population.

Key Findings

The criteria by Society for Maternal and Fetal Medicine (SMFM) had higher sensitivity (40.82% vs 24.49%, 20.41%) for small-for gestational age (SGA) compared to the American College of Obstetrics and Gynecology (ACOG) and International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) criteria. On the contrary, the ISUOG criteria had a higher specificity (99.18% vs 97.49%, 98.77%) than the SMFM and ACOG criteria for predicting SGA. All three definitions had low sensitivity for ANO (17.32%, 12.6%, 11.81%) and high specificity of 95.8%, 97.88% and 98.51%. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552).

What does this add to what is known

This is the first study from Chinese population to discuss the discriminatory capacities of different FGR definitions. The predictive value of the SMFM and ISUOG definition for SGA and ANO was better than that of the ACOG criteria. In Chinese population, the discriminatory capacities of SMFM FGR definition were superior compared to the other two definitions.

Abstract

Background Fetal growth restriction (FGR) is defined differently by the American College of Obstetrics and Gynecology (ACOG), Society for Maternal-Fetal Medicine (SMFM), and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).

Objective The purpose of this study was to investigate the predictive effect of three different diagnostic criteria of FGR on small-for-gestational-age (SGA) and adverse neonatal outcome (ANO), so as to find a better FGR-definition for Chinese population.

Study Design The clinical data of singleton pregnancy who received regular pregnancy care and gave birth at the Department of Obstetrics and Gynecology of Peking University First Hospital from January 1, 2021, to June 30, 2021 were collected. FGR cases were determined according to three different diagnostic criteria by ACOG, SMFM, or ISUOG. The primary outcome was the prediction of SGA and a composite ANO. SGA was defined as neonatal birth weight less than 10^{th} percentile. An ANO included one of these adverse outcomes: neonatal umbilical arterial blood pH < 7.1, 5-minute Apgar score<7, acute respiratory distress syndrome (ARDS), intraventricular hemorrhage, and neonatal convulsion, and transfer to the neonatal intensive care unit (NICU). The specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) of the different diagnostic criteria for SGA and ANO were compared. The discriminatory capacities of the three FGR-definitions were compared using the area under receiver-operating-characteristics curves (AUC).

ResultsA total of 2340 cases were included in this study, and 115 (4.9%), 63 (2.7%), and 48 (2.1%) cases of FGR were diagnosed using the diagnostic criteria issued by the SMFM, ACOG, and ISUOG respectively. There were 147 (6.28%) cases of SGA neonates. The SMFM criteria had higher sensitivity (40.82% vs 24.49%, 20.41%) for SGA compared to the ACOG and ISUOG criteria. On the contrary, the ISUOG criteria had a higher specificity (99.18% vs 97.49%, 98.77%) than the SMFM and ACOG criteria for predicting SGA. A total of 127 (5.43%) cases were complicated with ANO. All three definitions had low sensitivity for ANO (17.32%, 12.6%, 11.81%) and high specificity of 95.8%, 97.88% and 98.51%. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552).

ConclusionThe predictive value of the SMFM and ISUOG definition for SGA and ANO was better than that of the ACOG criteria. In Chinese population, the discriminatory capacities of SMFM FGR definition were superior compared to the other two definitions.

Key words : FGR; diagnostic criteria; SGA, ANO, Chinese population

Introduction

Fetal growth restriction (FGR) refers that the fetus has not reached its growth potential due to the influence of certain factors (such as placenta, chromosomes, and infection etc.). It is the leading cause of intrauterine fetal death, neonatal death, and short-term and long-term complications worldwide [1; 2; 3]. In clinical practice, it is difficult to evaluate the growth potential of a fetus, because it is not pragmatic to record the percentile of fetal biometrics and the estimated fetal weight (EFW) at different gestational weeks[4]. In addition, the ability to predict the occurrence of adverse complications in a fetus due to FGR is relatively limited [5].

Therefore, different countries and associations have developed different guidelines to screen for fetuses with suspected FGR. The American College of Obstetrics and Gynecology (ACOG) defines FGR as an EFW less than the 10th percentile.[6]. The Society of Maternal and Fetal Medicine (SMFM)[7] and the Royal College of Obstetrics and Gynecology (ROCG)[8] include abdominal circumference (AC) in the assessment. According

to the Delphi consensus criteria, a consensus on the definition of FGR was established in cooperation with global experts.[9] The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) cited this definition to screen FGR.[10]. The discuss on which definition is more practical has been a hot point in recent years[11; 12; 13; 14].

The purpose of this study was to compare the ability of different FGR definitions to predict small-for-gestational-age (SGA) and adverse neonatal outcomes (ANO), so as to figure out a more suitable definition for Chinese population.

Materials and Methods

Study design and participants

This study retrospectively collected the clinical data of pregnant woman who received routine pregnancy care and gave birth at the Department of Obstetrics and Gynecology of Peking University First Hospital from January 1, 2021, to June 30, 2021. We included all singleton pregnancies during the period. The exclusion criteria were as follows: fetal major structural abnormalities, chromosomal abnormalities and missing data (Figure 1). This study was approved by the Ethics Committee of Peking University First Hospital (2013-572). Informed consent was obtained from all participants involved in the study.

Protocols and definitions

In this study, demographic data and clinical characteristics of all enrolled subjects were collected, including maternal age, height, weight, body mass index (BMI), gravida, parity, pregnancy method (spontaneous / in vitro fertilization and embryo transfer (IVF-ET)), maternal complications during pregnancy (pregestational diabetes mellitus, gestational diabetes mellitus, gestational hypertension, preeclampsia, chronic hypertension, chronic hypertension with preeclampsia, nephropathy, autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, and Sjogren's syndrome, thyroid diseases, and placental umbilical cord abnormalities such as single umbilical artery and velamentous placenta), gestational age at delivery, delivery method, and results of ultrasound examinations during pregnancy. Neonatal outcome included neonatal 1-minute and 5-minute Apgar scores, umbilical arterial blood pH value, admission (or not) to the neonatal intensive care unit (NICU) and hospital stays, admission (or not) to the pediatric ward and hospital stays, need for mechanical ventilation and phototherapy, neonatal hypoglycemia, acute respiratory distress syndrome (ARDS), intraventricular hemorrhage (IVH), anemia, necrotizing enterocolitis, retinopathy, sepsis, convulsions, and pneumonia.

The gestational age was dated by the last menstrual period (LMP) or assisted reproduction technology dating. If LMP was unknown or the period was irregular, the first trimester ultrasound would be used. The Hadlock formula III was used to calculate the EFW[15]. Three guidelines were used to define FGR: (1) the ACOG criteria for FGR: EFW less than the 10th percentile; (2) The SMFM criteria for FGR: EFW or AC less than the 10th percentile; (3) The ISUOG criteria for FGR: EFW or AC $< 3^{\text{rd}}$percentile, or EFW or AC $< 10^{\text{th}}$ percentile with abnormal blood flow. Doppler blood flow abnormalities in the ISUOG guideline included abnormal uterine artery pulsation index (PI) $> 95^{\text{th}}$ percentile, abnormal umbilical artery PI $> 95^{\text{th}}$ percentile, and abnormal brain-placental ratio $< 5^{\text{th}}$ percentile. The definition of SGA newborn was birth weight lower than the 10^{th} percentile of neonatal growth standards.

A composite ANO included one of these adverse outcomes: neonatal umbilical arterial blood pH<7.1, 5-minute Apgar score<7, acute respiratory distress syndrome (ARDS), intraventricular hemorrhage, neonatal seizures, and admission to the neonatal intensive care unit (NICU).

Statistical analysis

We used SAS 9.4 for the statistical analysis. Kolmogorov-Smimov normality test checks the continuous data for normal distribution. If the data complied with the normal distribution, measurement data are expressed as the mean (standard deviation). Comparisons between groups were performed using the variance analysis. If the data was not consistent with the normal distribution, measurement data were expressed as the

median (quartile). Comparisons between groups were performed using the Kruskal-Wallis H test. Categorical data are expressed as the number (percentage). The chi-square test (or Fisher's exact test) was used for comparisons between groups. $P < 0.05$ was considered statistically significant.

The sensitivity, specificity, positive predictive value and negative predictive value of ACOG, SMFM and ISUOG for neonatal SGA and ANO were calculated using the fourfold (2X2) contingency table. The discriminatory capacities of three FGR definitions to predict outcome SGA and ANO was compared using the area under receiver-operating-characteristics curves (AUC). Risk ratio (RR) and 95% confidence interval (CI) to predict SGA and ANO were also compared.

Results

After excluding data that met exclusive criteria, a total of 2340 cases were included for final analysis. Among whom, the number of FGR cases defined by SMFM definition, ACOG definition and ISUOG definition were 115 (4.9%), 63 (2.7%) and 48 (2.1%) separately. Due to the overlapping of these three definitions, those FGR cases identified by ACOG and ISUOG were included in the cases defined by SMFM (Figure 2). Therefore, there were 2225 cases in the non-FGR group.

As shown in Table 1, the incidences of preeclampsia in the FGR groups according to different definitions were significantly higher than those in the non-FGR group (13.91%, 17.46%, 29.17% vs 1.39%), so was the preterm birth rate (26.96%, 36.51%, 50% vs 6.2%) .

Regarding the neonatal outcomes, there were 147 cases (6.28%) of SGA newborns. The incidence of SGA in the different FGR groups was significantly higher than that in the non-FGR group (52.17%, 57.14%, 62.5% vs 3.91%). There were 127 foetus (5.43%) who were complicated with ANO. The incidence of ANO in the FGR group was higher compared to the non-FGR group (19.13%, 25.4%, 31.25% vs 4.72%). Likewise, the incidence of each neonatal complications in the different FGR group were also higher than that in the non-FGR group (Table 2).

When comparing the discriminatory capacities of the three different definitions for predicting SGA (Table 3), the SMFM criteria had the highest sensitivity (40.82% vs 24.49%, 20.41%), while the ISUOG criteria had the highest specificity (99.18% vs 97.49%, 98.77. As for the predictive value for a composite ANO, it was displayed that all three definitions had low sensitivity (17.32%, 12.6%, 11.81%) and high specificity of 95.8%, 97.88% and 98.51%. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552)

Comment

Main findings

The number of FGR cases defined by SMFM definition, ACOG definition and ISUOG definition were 115 (4.9%), 63 (2.7%) and 48 (2.1%) separately. There were 147 (6.28%) cases of SGA neonates and 127 (5.43%) cases complicated with ANO. As for predicting SGA or a composite ANO, the SMFM criteria had the highest sensitivity and NPV, while the ISUOG criteria had the highest specificity and positive predictive value. The AUCs of SMFM for predicting SGA (0.692) and ANO (0.566) were slightly higher than those of ACOG (0.616, 0.552) and ISUOG (0.598, 0.552).

Strengths and limitations

This was a cross-sectional study that collected the clinical data of pregnant women who had given birth at our center. All singleton pregnancies were included during the period except those with fetal structural or chromosomal abnormalities or missing data. Compared to the other studies analyzed in the population high-risk for FGR, our data tended to summarize and analyze the data in a general population. It was because third-trimester growth ultrasound was part of routine prenatal care late pregnancy ultrasound in China. Besides, this study compared the three most common FGR definitions in one paper in order to make a more comprehensive and convictive conclusion, thereby providing evidenct on choosing the most suitable FGR definition for Chiense population.

However, this study has limitations. The primary and secondary outcomes of this study only focused on the neonatal period, but not the long-term complications. Therefore, we should continue to follow up on long-term neurological development disorders and the incidence of cardiovascular and metabolic diseases in the children with suspected FGR. Because the number of early FGR cases in this study was relatively small, we did not distinguish early FGR and late FGR in this study. In the future, we hope to perform prospective studies and increase the sample size. Additionally, this study mainly used the last ultrasound biometrics as indexes to assess growth potential. However, obviously, according to the core meaning of FGR, it would make more sense if the fetal growth curve could be tracked during the whole pregnancy. Therefore, the next step was to improve the FGR detection rate by studying longitudinal changes in FGR.

Interpretation

In our study, the SMFM definition identified 115 cases (4.91%) of FGR, the ACOG definition identified 63 cases (2.7%) of FGR, while the ISUOG definition identified 48 cases (2.05%) of FGR. However, when Molina et al.[12] and Roeckner et al.[13]analyzed the data of the Redefining Fetal Growth Restriction (RFGR) project, the ACOG definition identified 8.63% (91/1055) of FGR cases, the SMFM definition identified 13.0% (137/1054) of FGR cases, and the ISUOG definition identified 5.2.% (55/1055, 55/1054) of FGR cases, with percentages that were higher than the incidence observed in this study. The reason of the higher incidence was that the population enrolled in the RFGR program was at high risk of developing FGR. High risk factors included uterine height inconsistent with gestational age, hypertension, diabetes, and other chronic kidneys, blood vessel, and hemoglobin diseases. In their study, pregnant women with chronic hypertension and pre-pregnancy diabetes accounted for 14% and 8% of the sample, respectively. Nevertheless, the samples in our study were from the general population. The percentages of chronic hypertension and pregestational diabetes mellitus in this study were 1.1% and 1.3%, respectively Furthermore, our institution offered third trimester ultrasound as a routine protocol, which provided sufficient ultrasound biometric information for the calculation of EFW in the late pregnancy.

The reason why SGA was selected as a primary outcome is that SGA is associated with ANO and adult cardiovascular diseases and metabolic diseases [16; 17]. In addition, it has a clear definition (birth weight less than the 10th percentile). Therefore, many studies have used SGA as one of the indicators of the accuracy of FGR predictions.[11; 12; 13]. The results from this study indicate that the performance of the SMFM-FGR definition to predict SGA was higher than those of the ACOG-FGR and ISUOG-FGR criteria (AUC: 0.69 vs. 0.62 and 0.60), mainly because the sensitivity of the SMFM-FGR criteria to detect SGA was significantly higher than those of the ACOG-FGR and ISUOG-FGR criteria (40.8% vs. 24.5%, 20%). In 2018, Blue et al. compared the ability of RCOG (same as SMFM-FGR) and ACOG criteria for FGR to predict SGA and found that the SMFM-FGR criteria were slightly better than those of the ACOG-FGR criteria (AUC: 0.78 vs. 0.76)[11]. When comparing the SMFM-FGR and ISUOG-FGR criteria, Roeckner et al. also found that the sensitivity of the SMFM-FGR criteria to predict SGA was significantly higher than that of the ISUOG-FGR criteria (54.7% vs. 28.8%), while the specificity was slightly lower than that of the ISUOG-FGR criteria (93.3% vs. 98.4%)[13].

As is known that not all SGA cases are pathological. Most of SGAs are constitutional. Using the SGA alone to assess compare the predictive ability of different FGR definition was comprehensive. Considering that FGR fetuses were at an increased risk of fetal and neonatal mortality and complications due to their reduced growth potential, there were also a few studies which used neonatal complications and mortality as primary outcome, thereby the concept of composite ANO being proposed[12; 13]. When Molina et al. compared the ability of the ACOG-FGR and ISUOG-FGR criteria to predict ANO, the performance of the ISUOG-FGR criteria was superior to that of the ACOG-FGR criteria (sensitivity: 10.1% vs. 9.3%; specificity: 95.5% > 91.5%) [12]. In our study, the sensitivity of the ACOG-FGR criteria for predicting ANO was slightly higher than that of the ISUOG-FGR criteria, but the specificity was slightly lower, and the AUC of the two groups was similar (0.552). When Roeckner et al. compared the SMFM-FGR and ISUOG-FGR criteria, they found that, although the sensitivity of the SMSM-FGR criteria was higher than that of the ISUOG criteria, the specificity was lower than that of the ISUOG criteria, and the AUC of the two groups was 0.51 vs. 0.53.

In this study, the sensitivity of the SMFM-FGR criteria for predicting ANO was higher than that of the ISUOG criteria, but the specificity was slightly lower, and the final AUC for the SMFM-FGR criteria was slightly higher. However, the differences in the medical resources and capabilities of different institutions to deal with neonatal complications also led to differences in ANO between studies.

Many studies have shown that different growth curves produce different percentiles, thereby affecting the rates of detection of SGA and LGA.[18; 19]. In addition, different ethnic groups have different growth potentials. For example, the average birth weight of newborns in India is 2.9 kg, and the average birth weight of newborns in the UK is 3.5 kg, with a difference of 600 g.[20]. Therefore, the National Institute of Child Health and Human Development (NICHD) developed different growth curves for Caucasian, Black, Hispanic, and Asian fetuses.[21] Because there is no authoritative local growth curve in China, the EFW percentile in this study was determined based on the growth curve of Asian women developed by the NIICHD[21; 22]. The percentiles for newborns are based on newly released data of newborns in nine cities in southern and northern China in 2020.[23].

Conclusion

The predictive value of the SMFM and ISUOG definition for SGA and ANO was better than that of the ACOG criteria. In China, the discriminatory capacities of SMFM FGR definition were superior compared to the other two definitions.

Declaration section

Author contributions

HJZ and YBG designed the research and drafted the manuscript. MXS competed data analysis. WWZ, CLF and HYZ performed data collection and literature search. YS and HXY were chief director of maternal and foetal unit, and participated in its design and coordination. HXY provided substantial edits and additions to the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Ethical approval and informed consent

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Peking University First Hospital (protocol code 2013[572]). Informed consent was obtained from all participants involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Figure and table legends

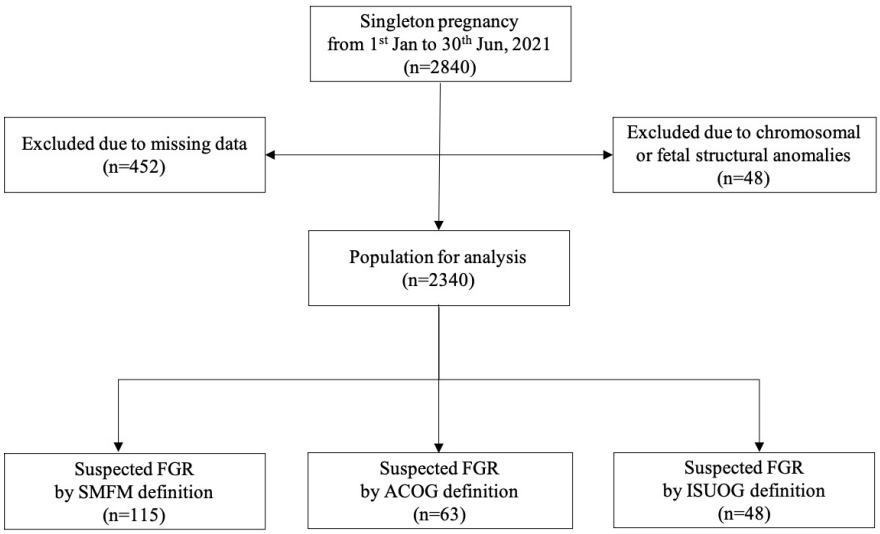
Figure 1 Overview of participants and FGR cases.

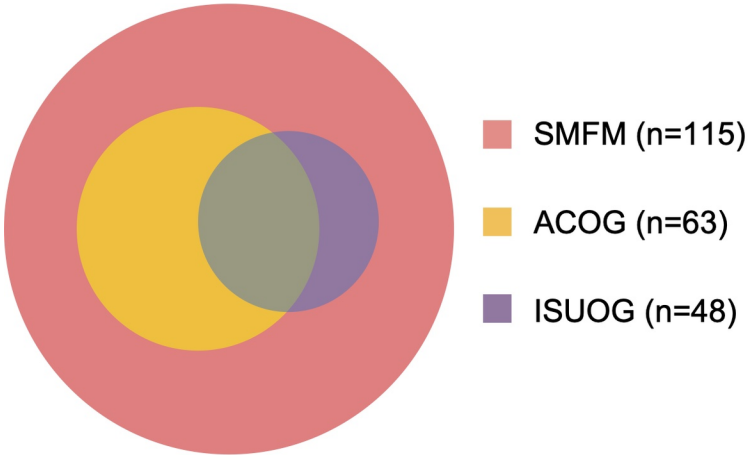
Figure 2 Composition of FGR group

Table 1 Demographic characteristics of the study population

Table 2 Neonatal outcomes

Table 3 The discriminatory capacities of the three different definitions





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Tables.docx available at https://authorea.com/users/628882/articles/649344-comparison-of-three-different-international-fetal-growth-restriction-definitions-in-chinese-population