Contents lists available at ScienceDirect

# Heliyon



journal homepage: www.cell.com/heliyon

Research article

5<sup>2</sup>CelPress

# Comprehensive evaluation of fetal renal ultrasound parameters for fetal growth restriction

Qinxiao Wang<sup>a,1</sup>, Liang Wang<sup>b,1</sup>, Mingzi Hu<sup>a</sup>, Sisi Yang<sup>a</sup>, Wen Zhang<sup>a</sup>, Haiying Chen<sup>a</sup>, Yan Jiao<sup>a,\*</sup>

<sup>a</sup> Department of Ultrasound, Wenzhou People's Hospital, Wenzhou, 325000, China
<sup>b</sup> Department of Ultrasound, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, 325027, China

#### ARTICLE INFO

Keywords: Fetal growth restriction Renal ultrasound Diagnostic efficacy Multi-parameter evaluation

#### ABSTRACT

*Objective:* This study aims to investigate variances in renal ultrasound parameters between fetuses experiencing fetal growth restriction (FGR) and those with normal intrauterine development, with the intent to offer actionable insights for clinical management.

*Method:* Forty-five pregnant women diagnosed with FGR between 28 and 36 weeks of gestation, who underwent examination at Wenzhou People's Hospital from September 2021 to June 2023, constituted the FGR group. Concurrently, 65 pregnant women with normal intrauterine development at matching gestational weeks formed the control group. Renal ultrasound parameters, encompassing renal artery peak systolic velocity (PSV), end diastolic velocity (EDV), time averaged maximum velocity (TAMX), resistive indices (S/D, PI, RI), ratios of renal volume to gestational age (RV/WEEK) and estimated fetal weight (RV/EFW), vascular indices (VI, FI, VFI), were compared between the two groups. All parameters represented the mean values of bilateral kidneys.

*Result:* In the FGR group, fetal renal artery PSV (37.71  $\pm$  9.93 cm/s), EDV (6.19  $\pm$  1.50 cm/s), TAMX (15.10  $\pm$  3.83 cm/s), RV/WEEK (0.45  $\pm$  0.12), RV/EFW (7.53  $\pm$  3.24), VI (22.19  $\pm$  15.00), and VFI (5.53  $\pm$  3.63) were significantly lower compared to the control group (PSV: 47.11  $\pm$  11.24 cm/s, EDV: 7.13  $\pm$  2.00 cm/s, TAMX: 17.85  $\pm$  3.85 cm/s, RV/WEEK: 0.66  $\pm$  0.19, RV/ EFW:9.20  $\pm$  3.17, VI: 28.67  $\pm$  14.72, VFI: 7.40  $\pm$  3.68). Conversely, fetal renal artery resistive indices (S/D: 9.09  $\pm$  2.58, PI: 2.71  $\pm$  0.56, RI: 0.92  $\pm$  0.04) in the FGR group were notably higher than those in the control group (S/D: 6.22  $\pm$  1.93, PI: 2.20  $\pm$  0.73, RI: 0.87  $\pm$  0.04), with statistical significance (P < 0.05). No significant difference was found in renal FI between the FGR group (26.78  $\pm$  6.59) and the control group (26.89  $\pm$  5.82) (P > 0.05). Receiver operating characteristic (ROC) curve analysis revealed higher diagnostic efficacy for RV/WEEK and RI among individual indicators, while combined parameter application yielded the highest diagnostic efficiency.

*Conclusion:* Utilizing a comprehensive evaluation of fetal kidney ultrasound parameters with multiple indices facilitates early screening and diagnosis of FGR fetuses, thereby aiding clinical decision-making and enhancing newborn birth outcomes.

https://doi.org/10.1016/j.heliyon.2024.e36687

Received 17 May 2024; Received in revised form 20 August 2024; Accepted 20 August 2024

Available online 28 August 2024

<sup>\*</sup> Corresponding author. Department of Ultrasound, Wenzhou People's Hospital, No.57 Canghou Street, Wenzhou, 325000, Zhejiang, China. *E-mail address:* jiaoyan2001@126.com (Y. Jiao).

<sup>&</sup>lt;sup>1</sup> These authors contributed equally to this work.

<sup>2405-8440/© 2024</sup> The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

#### 1. Introduction

Fetal Growth Restriction (FGR) is defined as a condition where a fetus fails to achieve its genetically determined growth potential, resulting in a birth weight below the 10th percentile for gestational age [1]. FGR is a common and important clinical issue during the perinatal period, affecting approximately 10–15 % of all pregnancies [2,3]. The impact of FGR extends far beyond the immediate perinatal period, making it a critical area of focus in obstetrics and neonatology [4]. The etiology of FGR is multifactorial and complex, involving an intricate interplay of maternal, fetal, and placental factors [5]. Maternal factors contributing to FGR can include hypertensive disorders, malnutrition, smoking, alcohol consumption, and certain medical conditions such as diabetes and autoimmune diseases [6]. Fetal causes may range from chromosomal abnormalities and genetic syndromes to intrauterine infections [7]. Although significant progress has been made in the diagnosis and management of FGR over the past decades, its importance in perinatal maternal and infant mortality remains significant [8]. FGR is not only a major cause of perinatal maternal and infant mortality, but it can also lead to various health problems during the neonatal period and even impact health in adulthood [9]. However, the early diagnosis and management of FGR still pose significant challenges [10].

The occurrence of FGR leads to changes in the fetal blood circulation, which become more pronounced in the middle and late stages of pregnancy [11]. The changes in various blood flow parameters are closely related to the regulatory mechanisms that occur during hypoxia, where the blood supply to vital organs such as the heart and brain is prioritized, while the blood supply to peripheral organs (such as the kidneys) is relatively reduced [12]. It is worth noting that the developmental stage of the fetal renal vasculature is crucial for the fetal renal blood circulation. This redistribution of blood flow, often referred to as the "brain-sparing effect" is a key adaptive mechanism in FGR [13]. While this adaptation may be beneficial in the short term for protecting vital organs, it can have long-term consequences on the development and function of other organs, including the kidneys [14]. The impact on renal development is of particular interest, as it may contribute to the increased risk of hypertension and renal dysfunction observed in individuals who experienced FGR [15]. The fetal kidney plays a crucial role in amniotic fluid production and regulation, which is essential for normal fetal development and lung maturation. Furthermore, proper kidney development during fetal life is critical for long-term renal health. The nephrons, the functional units of the kidney, are formed during fetal development, and their number is largely determined by birth. FGR can potentially lead to a reduced number of nephrons, which may predispose individuals to hypertension and chronic kidney disease later in life [16].

The diagnosis of FGR typically relies on prenatal ultrasound examination. In recent years, the application of color Doppler ultrasound to fetal blood vessels, including the umbilical artery, middle cerebral artery, and ductus venosus, has enhanced the assessment of fetuses with FGR [17]. However, there is a paucity of research comparing renal characteristics between FGR fetuses and those with normal growth. Renal blood supply is one of the most crucial factors influencing kidney development [18]. Current fetal kidney assessment predominantly employs two-dimensional ultrasonography to measure renal diameters, which are subsequently utilized in volumetric calculations. Some practitioners limit their evaluation to kidney length and thickness measurements, but these parameters alone are insufficient indicators of comprehensive kidney development [19]. Furthermore, the literature on three-dimensional ultrasound technology in fetal kidney evaluation remains limited. The application of traditional single ultrasound parameters is constrained by their suboptimal sensitivity and specificity, which may not accurately reflect the overall condition of the fetus [20]. Therefore, it is necessary to consider multiple factors to improve the accuracy and reliability of the diagnosis. As medical technology has advanced, an increasing number of studies have focused on the role of fetal multi-parameter ultrasound assessment in the diagnosis and management of FGR [21,22]. Fetal renal multi-parameter ultrasound assessment, as an emerging diagnostic tool, has attracted widespread attention in FGR research and clinical practice [23,24]. This method, through the comprehensive evaluation of multiple indicators such as kidney size, morphology, and hemodynamic parameters, can more fully assess the growth and development status of the fetus. Therefore, observing and comparing the differences in renal ultrasound multi-parameters between FGR fetuses and healthy fetuses is of great importance for clinical diagnosis and management of FGR.

This study aimed to explore the potential value of fetal renal multi-parameter ultrasound assessment in the diagnosis and clinical management of FGR, evaluate its guidance for the accuracy of FGR diagnosis and clinical management, and provide new insights and methods to improve the prognosis of FGR patients and enhance the quality of newborn infants.

# 2. Materials and methods

#### 2.1. General information

The Research Ethics Committee of Wenzhou People's Hospital approved this retrospective study (approval no. 2023–283) and waived the need for written informed consent.

This study was conducted from September 2021 to June 2023 at Wenzhou People's Hospital. Forty-five pregnant women with FGR at 28–36 weeks of pregnancy were selected as the FGR group, and 65 pregnant women with normal fetal growth at 28–36 weeks of pregnancy were randomly selected as the control group. All pregnant women were healthy, with mean ages of (29.68  $\pm$  4.35) years and (29.92  $\pm$  3.99) years, and mean gestational weeks of (33.77  $\pm$  2.74) weeks and (33.80  $\pm$  2.68) weeks, respectively. There was no statistically significant difference in age and gestational weeks between the two groups (P > 0.05). Inclusion criteria for fetuses in the FGR group: ① single pregnancy, live fetus, ② fetal body weight lower than the 10th percentile of normal fetuses of the same gestational age, ③ ultrasound examination did not show any structural abnormalities in the fetus. Exclusion criteria: ① Twin or multiple pregnancies, ② previous history of low birth weight, fetal macrosomia, or fetal growth restriction, ③ pregnancy complications such as

gestational diabetes, preeclampsia, etc., ④ other maternal or fetal complications that may affect fetal growth or development, ⑤ pregnant women who cannot fully cooperate with the examination.

# 2.2. Instruments and equipment

Ultrasound examinations were performed using a Voluson E8 color Doppler ultrasound system produced by GE Healthcare. The Voluson E8 is equipped with advanced technologies such as a real-time four-dimensional Doppler color ultrasound diagnostic system, high-resolution blood flow imaging technology, and volume contrast imaging technology. Two specialized probes were employed in this study: the Voluson C1-5-D convex array probe, operating within a frequency range of 3.5–5.0 MHz, and the three-dimensional (3D)/four-dimensional (4D) (RAB6-D) probe, with a frequency range of 2.0–8.0 MHz. These frequency ranges are widely utilized in obstetric and fetal imaging applications, as they offer an optimal balance between penetration depth and resolution, facilitating precise visualization of fetal anatomy and vasculature.

# 2.3. Methods and observation indicators

Firstly, two-dimensional ultrasound examination was performed on the selected two groups of pregnant women to exclude fetal structural abnormalities. The fetal growth parameters, including biparietal diameter, head circumference, abdominal circumference, and femur length, were measured to obtain the estimated fetal body weight (EFW). Then, fetal kidney ultrasound multi-parameter examination was performed, including color Doppler ultrasound examination of renal arteries and three-dimensional power Doppler ultrasound examination of kidneys. Renal artery blood flow detection: Bilateral fetal renal assessment was conducted using color Doppler ultrasound. The angle between the Doppler sound beam and the blood vessel was less than 30°, and the spectrum was recorded for at least 5 stable cycles before freezing the measurement [25]. The parameters measured included peak systolic velocity



Fig. 1. Color Doppler spectrum of the renal artery of a fetus in the FGR group.

(PSV), end diastolic velocity (EDV), time averaged maximum velocity (TAMX), systolic maximum velocity/diastolic end velocity (S/D), pulsation index (PI), and resistance index (RI) (Figs. 1–2). Kidney 3D Power Doppler Ultrasound Detection: Using an abdominal volume probe in 3D Power Doppler ultrasound (3D-PDUS) mode, a comprehensive scan of bilateral fetal kidneys was performed. A virtual organ computer-aided analysis (VOCAL imaging) program was used to select a section every 30°, rotate a total of 6 sections, manually draw the envelope line of the observed kidney (Figs. 3A and. 4A), and the computer automatically generated a histogram and calculated the Renal Volume (RV), Vascular Index (VI), Flow Index (FI), and Vascular Flow Index (VFI) of the kidneys (Figs. 3B and. 4B). Bilateral renal measurements were obtained for all indicators, and the mean values of these data were utilized. Data on various parameters from the two groups were collected and analyzed.

#### 2.4. Statistical methods

SPSS 21.0 statistical software was used for data processing and statistical analysis. Quantitative data were represented as mean  $\pm$  standard deviation (mean  $\pm$  SD). Independent-samples t-tests were used to assess inter-group differences. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic efficacy of the parameters. The Intraclass Correlation Coefficient (ICC) was used to evaluate the consistency of measurements between two sonographers. A significance level of P < 0.05 was considered statistically significant for all tests.

# 3. Results

### 3.1. Comparison of indicators between two groups of fetuses

The PSV, EDV, and TAMX of the renal artery in the FGR group were lower than that in the control group, and the S/D, PI, and RI of the renal artery were higher than those in the control group, with statistical significance (P < 0.05), as shown in Table 1.

Fetal kidneys gradually increase in size with gestational weeks. To ensure reliability and stability, the ratio of renal volume to gestational weeks (RV/WEEK) and the ratio of renal volume to estimated fetal weight (RV/EFW) were used as indicators for



Fig. 2. Color Doppler spectrum of the renal artery of a fetus in the control group.

Q. Wang et al.

Heliyon 10 (2024) e36687



Fig. 3. Three-dimensional power Doppler ultrasonography images of the fetal kidney in the FGR group. (A) Manual delineation of the kidney's envelope. (B) Automatic generation of a histogram and computation of parameters.



Fig. 4. Three-dimensional power Doppler ultrasonography images of the fetal kidney in the control group. (A) Manual delineation of the kidney's envelope. (B) Automatic generation of a histogram and computation of parameters.

# Table 1

Comparison of indicators between two groups of fetuses.

| Parameter    | Control group                       | FGR group        | t     | Р       |
|--------------|-------------------------------------|------------------|-------|---------|
| PSV (cm/s)   | $47.11 \pm 11.24$                   | $37.71 \pm 9.93$ | 4.519 | < 0.001 |
| EDV (cm/s)   | $7.13\pm2.00$                       | $6.19 \pm 1.50$  | 2.799 | 0.006   |
| TAMAX (cm/s) | $17.85\pm3.85$                      | $15.10\pm3.83$   | 3.688 | < 0.001 |
| S/D          | $6.22 \pm 1.93$                     | $9.09 \pm 2.58$  | 6.667 | < 0.001 |
| PI           | $2.20\pm0.73$                       | $2.71 \pm 0.56$  | 3.921 | < 0.001 |
| RI           | $0.87\pm0.04$                       | $0.92\pm0.04$    | 7.156 | < 0.001 |
| RV/WEEK      | $0.66\pm0.19$                       | $0.45\pm0.12$    | 7.359 | < 0.001 |
| RV/EFW       | $9.20\pm3.17$                       | $7.53 \pm 3.24$  | 2.691 | 0.008   |
| VI           | $\textbf{28.67} \pm \textbf{14.72}$ | $22.19\pm15.00$  | 2.254 | 0.026   |
| FI           | $26.89 \pm 5.82$                    | $26.78 \pm 6.59$ | 0.088 | 0.930   |
| VFI          | $7.40\pm3.68$                       | $5.53 \pm 3.63$  | 2.644 | 0.009   |

comparison. The FGR group had lower fetal RV/WEEK, RV/EFW, VI, and VFI than the control group, and the difference between the two groups was statistically significant (P < 0.05). There was no statistically significant difference in renal FI between the two groups of fetuses (P > 0.05), as shown in Table 1.

#### 3.2. Diagnostic efficacy of indicators

The diagnostic efficacy of each indicator individually and in combination was calculated using the ROC curve analysis to determine the area under the curve (AUC) for each indicator individually and in combination. The AUC of the above indicators was greater than 0.6, indicating appreciable diagnostic value. Among individual indicators, RV/WEEK and RI exhibited superior diagnostic efficacy when evaluated based on sensitivity, specificity, and Youden index. The combined diagnostic approach, however, yielded the highest AUC, sensitivity, specificity, and Youden index, demonstrating optimal overall diagnostic performance. The ROC curve is shown in Fig. 5, and the specific diagnostic effectiveness is shown in Table 2.

# 3.3. Interobserver agreement test for parameter measurements between two sonographers

Table 3 presents the results of the interobserver agreement test for parameter measurements conducted by two sonographers. The ICC test results for the consistency of measurements across all parameters by the two sonographers showed that the ICC values were greater than 0.8 for all parameters. This indicates a high level of agreement between the two sonographers in their measurements of all parameters.

# 4. Discussion

Compared to fetuses with normal birth weight, FGR fetuses have a 4–8 fold increased risk of perinatal death [26]. Unintervened FGR fetuses may experience various sequelae after birth, including behavioral and cognitive impairments in childhood, which can increase the risk of disease in adulthood and have far-reaching impacts on society and families [27]. With the continuous development of society in recent years, eugenics and fetal eugenics have become increasingly concerned. Given the ongoing societal progress, there is a growing concern regarding eugenics and fetal eugenics. Consequently, early assessment of fetal developmental status, timely diagnosis of FGR, and provision of appropriate interventions have become focal points and challenges for obstetric medical practitioners [28].

Ultrasound is the best examination method for monitoring the fetal development status in the uterus. Due to its advantages of noninvasive and high accuracy, it has become the first choice for clinical imaging examinations of pregnant women [29,30]. In the past, the diagnosis of FGR fetuses mainly relied on regular prenatal examinations and ultrasound monitoring of fetal growth. However, due to various factors such as menstrual cycle disorders in pregnant women and those with unclear last menstrual cycle, errors are prone to occur [31]. In recent years, there has been a tendency to increase the monitoring and diagnosis of fetal color Doppler blood flow in FGR fetuses, including umbilical arteries, middle cerebral arteries, etc [32]. However, the umbilical artery may exhibit false positives or false negatives due to limb compression and the influence of amniotic fluid volume [32]. The middle cerebral artery may exhibit bidirectional spectral changes during hypoxia, and the spectral characteristics in the middle and late stages of hypoxia are similar to those of a normal fetus, which can easily lead to missed diagnosis [33]. So exploring new research methods for diagnosing FGR fetuses with low levels of interference has become a cutting-edge topic and focus in contemporary society. The long-term effects of growth restriction on fetuses will inevitably lead to a redistribution of blood flow, with the aim of ensuring blood supply to important organs and reducing blood supply to peripheral blood vessels [34]. Research suggests that the kidneys are the earliest organs affected by microcirculation damage [35]. There have been few research reports on fetal kidneys in the past, and fetal kidneys, as parenchymal organs, are less disturbed by ultrasound observation in the uterus [36]. So this study mainly compares the differences in multiple kidney parameters between FGR fetuses and normal fetuses, and determines whether real-time ultrasound examination of fetal kidneys can diagnose FGR fetuses early.

The growth and development of various organs in the fetus require blood circulation supply, and the blood supply of normal fetal



Fig. 5. ROC curves of diagnostic efficiency of each parameter for FGR detection.

#### Table 2

Diagnostic efficacy of individual and combined application of parameters.

| Parameter        | AUC   | Sensitivity(%) | Specificity(%) | Youden index | Cutoff value |
|------------------|-------|----------------|----------------|--------------|--------------|
| RV/WEEK          | 0.835 | 84.4           | 70.8           | 0.552        | 0.555        |
| RV/EFW           | 0.701 | 66.7           | 70.8           | 0.375        | 7.260        |
| VI               | 0.633 | 71.1           | 56.9           | 0.280        | 27.770       |
| VFI              | 0.650 | 66.7           | 61.5           | 0.282        | 6.445        |
| PSV              | 0.743 | 57.8           | 80.0           | 0.378        | 38.600       |
| EDV              | 0.634 | 80.0           | 49.2           | 0.292        | 7.150        |
| TAMAX            | 0.715 | 82.2           | 53.8           | 0.360        | 17.470       |
| S/D              | 0.812 | 57.8           | 90.8           | 0.486        | 8.965        |
| PI               | 0.771 | 82.2           | 63.1           | 0.453        | 2.270        |
| RI               | 0.836 | 80.0           | 70.8           | 0.508        | 0.885        |
| Joint prediction | 0.973 | 91.1           | 92.3           | 0.834        | 0.565        |

Table 3

Interobserver agreement test for parameter measurements between two sonographers.

| Parameter    | Sonographer A                     | Sonographer B                      | ICC (95 % CI)      | Р       |
|--------------|-----------------------------------|------------------------------------|--------------------|---------|
| PSV (cm/s)   | $43.27\pm11.64$                   | $42.62\pm11.65$                    | 0.813(0.739-0.868) | < 0.001 |
| EDV (cm/s)   | $6.74 \pm 1.86$                   | $6.86 \pm 1.80$                    | 0.847(0.785-0.893) | < 0.001 |
| TAMAX (cm/s) | $16.72\pm4.06$                    | $16.21\pm4.23$                     | 0.864(0.807-0.904) | < 0.001 |
| S/D          | $7.39 \pm 2.62$                   | $\textbf{7.44} \pm \textbf{2.74}$  | 0.914(0.877-0.940) | < 0.001 |
| PI           | $2.41\pm0.71$                     | $2.43\pm0.71$                      | 0.889(0.843-0.923) | < 0.001 |
| RI           | $0.89\pm0.05$                     | $0.88\pm0.06$                      | 0.831(0.763-0.881) | < 0.001 |
| RV/WEEK      | $0.57\pm0.19$                     | $0.58\pm0.19$                      | 0.913(0.875-0.939) | < 0.001 |
| RV/EFW       | $8.52 \pm 3.29$                   | $8.37\pm3.30$                      | 0.855(0.796-0.899) | < 0.001 |
| VI           | $26.02\pm15.11$                   | $25.98 \pm 15.20$                  | 0.864(0.808-0.905) | < 0.001 |
| FI           | $26.85\pm6.12$                    | $\textbf{27.10} \pm \textbf{6.29}$ | 0.909(0.870-0.937) | < 0.001 |
| VFI          | $\textbf{6.64} \pm \textbf{3.75}$ | $6.97 \pm 3.78$                    | 0.898(0.855–0.929) | < 0.001 |

organs needs to operate in the best proportion according to the needs of various systems. The kidney is one of the most abundant organs for fetal blood flow perfusion, with 3 %–7 % of fetal cardiac output flowing to the kidney [37]. One of the most important factors affecting fetal kidney development is the blood supply to the kidney. The changes in renal artery blood flow spectrum can comprehensively evaluate changes in renal function, reflect fetal intrauterine conditions more comprehensively, and help guide early clinical treatment and improve adverse fetal prognosis [38]. The main representative of peripheral blood vessels is the renal artery, which reflects the blood flow status of the lower part of the fetal body. Insufficient blood supply to FGR fetuses can easily lead to intrauterine fetal distress. The generation of neuroprotective effects leads to a decrease in renal perfusion blood flow, with renal blood vessels in a contracted state, and an increase in RI, PI, and S/D values. At the same time, the indicators increase with the severity of intrauterine distress [39]. Our results showed that FGR fetuses had lower renal artery PSV, EDV, and TAMX, and higher S/D, PI, and RI compared to the control group. When comparing our findings to the normal reference values presented in Table 4, we observe notable deviations in the FGR group. For instance, our FGR group showed a mean PSV of  $37.71 \pm 9.93$  cm/s, which is considerably lower than the normal ranges reported by Afsari et al. [40] and Laag et al. [41]. This reduction in PSV aligns with the findings of Stigter et al. who observed significantly lower PSV values in the renal arteries of fetuses with severe FGR [42]. The increased S/D, PI, and RI values in our FGR group also deviate from the normal ranges. Our FGR group showed mean values of S/D: 9.09  $\pm$  2.58, PI: 2.71  $\pm$  0.56, and RI: 0.92  $\pm$ 0.04. These are notably higher than the normal ranges reported by Afsari et al. [40] and significantly higher than those reported by Wu et al. [43]. These results suggest that in the normal fetal group, renal blood flow increases with gestational age, accompanied by gradual renal vascular development, increased vessel diameter, decreased blood flow resistance index, and continuous blood flow enhancement to meet fetal growth and developmental requirements. However, in fetuses with FGR, renal artery indicators change as hypoxia intensifies, with the impact increasing proportionally to gestational age and hypoxic severity. Consequently, renal vascular development is compromised, resulting in reduced vessel diameter, vasoconstriction, increased blood flow resistance index, and gradually diminished blood flow perfusion, which fails to meet fetal growth and developmental needs. Therefore, it is necessary to strengthen timely monitoring of renal artery blood flow parameters during pregnancy for such fetuses.

Pathological changes in the fetal kidney often occur in the second half of pregnancy, and changes in the size and morphology of the fetal kidney can provide useful prognostic information [44]. In the past, measurements of kidney size were only made through two-dimensional three-way measurements, which may have errors due to factors such as fetal position. 3D-PDUS can be combined with virtual organ computer-aided analysis software to obtain parameter values of internal blood flow in the area of interest, including RV, VI, FI, and VFI. The kidneys are also substantial organs, and the examination of fetal kidneys using 3D-PDUS provides us with direction. Our 3D-PDUS analysis revealed lower RV/WEEK, RV/EFW, VI, and VFI in the FGR group. These results align with the findings of Chang et al. who confirmed the impact of fetal growth restriction on renal volume [45]. The normal fetal kidney volume increases with gestational age, and the fetal body weight also increases accordingly. Therefore, comparing RV/WEEK and RV/EFW between two groups is more reliable and accurate. The ratio of these two items in the FGR group is significantly lower than that in the

#### Table 4

Normal reference values for fetal renal artery Doppler parameters.

| Author        | Parameters                         | Parameters                         |                                   |               |                                   |  |
|---------------|------------------------------------|------------------------------------|-----------------------------------|---------------|-----------------------------------|--|
|               | PSV ( cm/s )                       | EDV ( cm/s )                       | S/D                               | PI            | RI                                |  |
| Afsari et al. | $53.43 \pm 12.66$                  | N/A                                | $\textbf{7.58} \pm \textbf{3.80}$ | $2.35\pm0.63$ | $\textbf{0.86} \pm \textbf{0.05}$ |  |
| Laag et al.   | $54.88 \pm 15.17$                  | $12.41\pm3.38$                     | $4.44\pm0.71$                     | $1.47\pm0.16$ | $0.77\pm0.03$                     |  |
| Wu et al.     | $\textbf{45.13} \pm \textbf{7.45}$ | $\textbf{24.17} \pm \textbf{6.05}$ | $1.87\pm0.44$                     | $1.14\pm0.09$ | $0.56\pm0.09$                     |  |

normal fetal group, indicating that the fetal kidney of FGR has insufficient energy supply, delayed development. Moreover, the degree of renal impairment caused by FGR is more pronounced compared to the changes in fetal body weight, suggesting that FGR has a substantial impact on fetal kidney development. The VI and VFI of the FGR group were lower than those of the control group, indicating a decrease in the number and diameter of blood vessels in the kidneys, leading to insufficient blood perfusion and affecting the growth and development of the kidneys. These findings demonstrate a correlation between the quantitative analysis parameters of three-dimensional power Doppler ultrasound and renal blood flow in FGR fetuses. This technology can be utilized to evaluate fetal kidney risk and predict FGR, making it an effective tool for early diagnosis of FGR and playing a crucial role in assessing fetal growth and development. There was no significant difference between the two groups of FI, possibly because it only reflects blood flow intensity rather than perfusion degree, and insufficient perfusion directly leads to renal development obstruction. Therefore, the application of three-dimensional power Doppler ultrasound in fetal kidneys can effectively reduce misdiagnosis and missed diagnosis rates, improve diagnostic accuracy, and contribute to the prevention and reduction of clinical mortality in newborns.

Through the research of the FGR group and control group mentioned above, it was found that multiple indicators of the kidneys can assist in diagnosing the renal development status of the two groups of fetuses. The diagnostic value of each indicator is assisted by the ROC curve. Among the individual indicators, RV/WEEK and RI demonstrated superior diagnostic efficiency, with values of 0.835 and 0.836, respectively. These findings suggest that as gestational age advances, the growth rate of kidney volume in fetuses with FGR decelerates, indicating progressively compromised renal blood and energy supply, coupled with an increasing renal artery resistance index. The impact on renal blood supply becomes more pronounced over time, implying that earlier onset of FGR-induced fetal hypoxia correlates with greater developmental impact and poorer prognosis. Consequently, early screening for FGR fetuses is crucial, as delayed intervention may lead to serious consequences. However, the combined application of all indicators has the highest diagnostic efficiency, reaching 0.973, with a sensitivity of 91.1 %, a specificity of 92.3 %, and a Youden index of 0.834. All these indicators are optimal when applied in combination, providing the best approach for early diagnosis of FGR fetuses. Therefore, the combined application of various effective indicators can increase the diagnostic value, provide timely feedback on the condition of the fetus in the uterus, detect abnormal phenomena early, and provide protection for the healthy pregnancy of the fetus.

This multi-parameter approach to renal assessment in FGR is particularly relevant given the potential long-term implications for kidney function. By evaluating multiple renal parameters, clinicians may gain a more nuanced understanding of how FGR affects kidney development and function. This comprehensive assessment may include evaluation of renal size and volume, which can be indicators of overall fetal growth and development. Doppler studies of renal arteries can offer valuable information about renal perfusion and vascular resistance, which may be altered in FGR. The integration of these multiple parameters could potentially improve the accuracy of FGR diagnosis, help differentiate between constitutionally small fetuses and those with true growth restriction, and provide prognostic information. Moreover, this comprehensive assessment may guide clinical management decisions, such as the timing of delivery or the need for more intensive fetal monitoring.

The current study has some limitations. Firstly, the retrospective design of the study may introduce inherent biases and limit the generalizability of the findings. Additionally, the relatively small sample size may not adequately represent the broader population, necessitating cautious interpretation of the results. Moreover, the study predominantly focuses on fetal renal parameters, thereby potentially overlooking the multifaceted nature of FGR pathology. Future research endeavors should strive for larger, prospective cohorts and encompass a broader spectrum of fetal parameters to enhance the robustness and applicability of the findings.

#### 5. Conclusions

In summary, the observation of fetal renal artery by color Doppler ultrasound and the quantitative analysis of renal volume and blood flow perfusion by 3D-PDUS parameters can predict and evaluate FGR fetuses. Single indicators may have deviations due to various factors, and the combination of multiple parameters is the most valuable. It is recommended to use multiple effective indicators in combination to improve diagnostic accuracy and reliability. Early screening and diagnosis of FGR can provide clinical assistance and guide early intervention, reduce or delay the occurrence of adverse prognosis in FGR fetuses, effectively reduce the incidence and mortality rate of perinatal infants, and give birth to more healthy newborns. These two technologies are worthy of active promotion and application.

# Funding statement

This research was supported by the Wenzhou Science & Technology Bureau (Project No. Y20211034), and the Huadong Medicine Joint Funds of the Zhejiang Provincial Natural Science Foundation of China (Grant No. LHDMY24H280003).

#### Data availability statement

Data will be made available on request.

#### Additional information

No additional information is available for this paper.

# CRediT authorship contribution statement

**Qinxiao Wang:** Writing – original draft, Investigation, Data curation. **Liang Wang:** Writing – original draft, Supervision, Conceptualization. **Mingzi Hu:** Writing – review & editing, Methodology, Data curation. **Sisi Yang:** Writing – review & editing, Methodology, Data curation. **Wen Zhang:** Writing – review & editing, Supervision, Software. **Haiying Chen:** Writing – review & editing, Supervision, Software. **Haiying Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

We would like to thank our colleagues in the Department of Ultrasound for their cooperations.

# References

- [1] D. Shrivastava, A. Master, Fetal growth restriction, J. Obstet. Gynaecol. India 70 (2) (2020) 103–110, https://doi.org/10.1007/s13224-019-01278-4.
- [2] A.R. Clark, K. Yoshida, M.L. Oyen, Computational modeling in pregnancy biomechanics research, J. Mech. Behav. Biomed. Mater. 128 (2022) 105099, https:// doi.org/10.1016/j.jmbbm.2022.105099.
- [3] J.B. Armengaud, C. Yzydorczyk, B. Siddeek, A.C. Peyter, U. Simeoni, Intrauterine growth restriction: clinical consequences on health and disease at adulthood, Reprod Toxicol 99 (2021) 168–176, https://doi.org/10.1016/j.reprotox.2020.10.005.
- [4] D. Sharma, S. Shastri, P. Sharma, Intrauterine growth restriction: antenatal and postnatal aspects, Clin. Med. Insights Pediatr. 10 (2016) 67–83, https://doi.org/ 10.4137/CMPed.S40070.
- [5] A. Malhotra, B.J. Allison, M. Castillo-Melendez, G. Jenkin, G.R. Polglase, S.L. Miller, Neonatal morbidities of fetal growth restriction: pathophysiology and impact, Front. Endocrinol. 10 (2019) 55, https://doi.org/10.3389/fendo.2019.00055.
- [6] F. Figueras, E. Gratacos, An integrated approach to fetal growth restriction, Best Pract. Res. Clin. Obstet. Gynaecol. 38 (2017) 48–58, https://doi.org/10.1016/j. bpobgyn.2016.10.006.
- [7] L.M. Nardozza, A.C. Caetano, A.C. Zamarian, J.B. Mazzola, C.P. Silva, V.M. Marcal, T.F. Lobo, A.B. Peixoto, E. Araujo Junior, Fetal growth restriction: current knowledge, Arch. Gynecol. Obstet. 295 (5) (2017) 1061–1077, https://doi.org/10.1007/s00404-017-4341-9.
- [8] M. Mascherpa, C. Pegoire, A. Meroni, M. Minopoli, B. Thilaganathan, A. Frick, A. Bhide, Prenatal prediction of adverse outcome using different charts and definitions of fetal growth restriction, Ultrasound Obstet. Gynecol. 63 (5) (2024) 605–612, https://doi.org/10.1002/uog.27568.
- [9] D. Pan, M. Lin, C. Mu, C. Yu, B. Ye, J. Liang, Y. Sheng, D. Huang, S. Liu, X. Zeng, H.J. Jennifer Tan, V. Chongsuvivatwong, X. Qiu, Maternal exposure to neonicotinoid insecticides and fetal growth restriction: a nested case-control study in the guangxi Zhuang birth cohort, Chemosphere 336 (2023) 139217, https://doi.org/10.1016/j.chemosphere.2023.139217.
- [10] N.H.M. van Oostrum, K. Derks, D.A.A. van der Woude, S.A. Clur, S.G. Oei, J. van Laar, Two-dimensional speckle tracking echocardiography in fetal growth restriction: a systematic review, Eur. J. Obstet. Gynecol. Reprod. Biol. 254 (2020) 87–94, https://doi.org/10.1016/j.ejogrb.2020.08.052.
- [11] S. Xu, W. Wang, Q. Li, L. Huang, X. Chen, X. Zhang, X. Wang, W. Han, X. Hu, X. Yang, L. Hao, G. Xiong, N. Yang, Association of maternal longitudinal hemoglobin with small for gestational age during pregnancy: a prospective cohort study, Nutrients 14 (7) (2022), https://doi.org/10.3390/nu14071403.
- [12] P. Montaldo, S. Puzone, E. Caredda, U. Pugliese, E. Inserra, G. Cirillo, F. Gicchino, G. Campana, D. Ursi, F. Galdo, M. Internicola, F. Spagnuolo, M. Carpentieri, C. Capristo, P. Marzuillo, E.M. Del Giudice, Impact of intrauterine growth restriction on cerebral and renal oxygenation and perfusion during the first 3 days after birth. Sci. Rep. 12 (1) (2022) 5067. https://doi.org/10.1038/s41598-022-09199-5.
- [13] E. Cohen, W. Baerts, F. van Bel, Brains, napring in intrauterine growth restriction: considerations for the neonatologist, Neonatology 108 (4) (2015) 269–276, https://doi.org/10.1159/000438451.
- [14] H.G. Richter, E.J. Camm, B.N. Modi, F. Naeem, C.M. Cross, T. Cindrova-Davies, O. Spasic-Boskovic, C. Dunster, I.S. Mudway, F.J. Kelly, G.J. Burton, L. Poston, D.A. Giussani, Ascorbate prevents placental oxidative stress and enhances birth weight in hypoxic pregnancy in rats, J. Physiol. 590 (6) (2012) 1377–1387, https://doi.org/10.1113/jphysiol.2011.226340.
- [15] V.A. Luyckx, J.F. Bertram, B.M. Brenner, C. Fall, W.E. Hoy, S.E. Ozanne, B.E. Vikse, Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease, Lancet 382 (9888) (2013) 273–283, https://doi.org/10.1016/S0140-6736(13)60311-6.
- [16] V.A. Luyckx, R.L. Chevalier, Impact of early life development on later onset chronic kidney disease and hypertension and the role of evolutionary trade-offs, Exp. Physiol. 107 (5) (2022) 410–414, https://doi.org/10.1113/EP089918.
- [17] F. Gaccioli, I. Aye, U. Sovio, D.S. Charnock-Jones, G.C.S. Smith, Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers, Am. J. Obstet. Gynecol. 218 (2S) (2018) S725–S737, https://doi.org/10.1016/j.ajog.2017.12.002.
- [18] J. Liefke, C. Heijl, K. Steding-Ehrenborg, E. Morsing, H. Arheden, D. Ley, E. Hedstrom, Fetal growth restriction followed by very preterm birth is associated with smaller kidneys but preserved kidney function in adolescence, Pediatr. Nephrol. 38 (6) (2023) 1855–1866, https://doi.org/10.1007/s00467-022-05785-x.
- [19] T. Kiserud, G. Piaggio, G. Carroli, M. Widmer, J. Carvalho, L. Neerup Jensen, D. Giordano, J.G. Cecatti, H. Abdel Aleem, S.A. Talegawkar, A. Benachi, A. Diemert, A. Tshefu Kitoto, J. Thinkhamrop, P. Lumbiganon, A. Tabor, A. Kriplani, R. Gonzalez Perez, K. Hecher, M.A. Hanson, A.M. Gulmezoglu, L.D. Platt, The world health organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight, PLoS Med. 14 (1) (2017) e1002220, https://doi.org/10.1371/journal.pmed.1002220.
- [20] S. Xiao, J. Zhang, Y. Zhu, Z. Zhang, H. Cao, M. Xie, L. Zhang, Application and progress of artificial intelligence in fetal ultrasound, J. Clin. Med. 12 (9) (2023), https://doi.org/10.3390/jcm12093298.

- [21] A. Dall'Asta, T. Stampalija, F. Mecacci, M. Minopoli, G.B.L. Schera, G. Cagninelli, C. Ottaviani, I. Fantasia, M. Barbieri, F. Lisi, S. Simeone, T. Ghi, T. Frusca, Ultrasound prediction of adverse perinatal outcome at diagnosis of late-onset fetal growth restriction, Ultrasound Obstet. Gynecol. 59 (3) (2022) 342–349, https://doi.org/10.1002/uog.23714.
- [22] Y. Wang, A. Zhang, T. Stock, E. Lopriore, D. Oepkes, Q. Wang, The accuracy of prenatal diagnosis of selective fetal growth restriction with second trimester Doppler ultrasound in monochorionic diamniotic twin pregnancies, PLoS One 16 (8) (2021) e0255897, https://doi.org/10.1371/journal.pone.0255897.
- [23] D. Adiyaman, M. Kuyucu, B. Konuralp Atakul, H. Golbasi, H.G. Pala, Assessment of renal volume by 3D VOCAL Ultrasonography method in late-onset growthrestricted fetuses with normal amniotic fluid index, Ginekol. Pol. 91 (11) (2020) 679–684, https://doi.org/10.5603/GP.2020.0113.
- [24] A. Sadat Jamal, M. Modarresi, Renal artery Doppler in fetal sonography: a narrative review, Int J Reprod Biomed 21 (10) (2023) 789–800, https://doi.org/ 10.18502/ijrm.v21i10.14534.
- [25] L. Oltra, V. Reverte, A. Tapia, J.M. Moreno, F.J. Salazar, M.T. Llinas, Cardiac, renal and uterine hemodynamics changes throughout pregnancy in rats with a prolonged high fat diet from an early age, PLoS One 15 (6) (2020) e0234861, https://doi.org/10.1371/journal.pone.0234861.
- [26] L. Hiersch, N. Melamed, Fetal growth velocity and body proportion in the assessment of growth, Am. J. Obstet. Gynecol. 218 (2S) (2018) S700–S711 e1, https:// doi.org/10.1016/j.ajog.2017.12.014.
- [27] N. Yakoub, T. Reinelt, G. Natalucci, Behavioural outcomes of children born with intrauterine growth restriction: protocol for a systematic review and metaanalysis, BMJ Open 13 (11) (2023) e074417, https://doi.org/10.1136/bmjopen-2023-074417.
- [28] M. Meng, Y.K.Y. Cheng, L. Wu, P. Chaemsaithong, M.B.W. Leung, S.S.C. Chim, D.S. Sahota, W. Li, L.C.Y. Poon, C.C. Wang, T.Y. Leung, Whole genome miRNA profiling revealed miR-199a as potential placental pathogenesis of selective fetal growth restriction in monochorionic twin pregnancies, Placenta 92 (2020) 44–53, https://doi.org/10.1016/j.placenta.2020.02.002.
- [29] S.J. Davidson, S.J. de Jersey, F.L. Britten, P. Wolski, R. Sekar, L.K. Callaway, Fetal ultrasound scans to guide management of gestational diabetes: improved neonatal outcomes in routine clinical practice, Diabetes Res. Clin. Pract. 173 (2021) 108696, https://doi.org/10.1016/j.diabres.2021.108696.
- [30] R.M. Kale, R.G. Tirupathi, S.R. Sheela, Role of ultrasonography and color Doppler in the assessment of high-risk pregnancies and their accuracy in predicting fetal outcome, Cureus 15 (5) (2023) e39017, https://doi.org/10.7759/cureus.39017.
- [31] J. Gardosi, S.M. Kady, P. McGeown, A. Francis, A. Tonks, Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study, BMJ 331 (7525) (2005) 1113–1117, https://doi.org/10.1136/bmj.38629.587639.7C.
- [32] Z. Alfirevic, T. Stampalija, T. Dowswell, Fetal and umbilical Doppler ultrasound in high-risk pregnancies, Cochrane Database Syst. Rev. 6 (6) (2017) CD007529, https://doi.org/10.1002/14651858.CD007529.pub4.
- [33] G. Mari, Middle cerebral artery peak systolic velocity for the diagnosis of fetal anemia: the untold story, Ultrasound Obstet. Gynecol. 25 (4) (2005) 323–330, https://doi.org/10.1002/uog.1882.
- [34] A.A. Baschat, U. Gembruch, I. Reiss, L. Gortner, C.P. Weiner, C.R. Harman, Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction, Ultrasound Obstet. Gynecol. 16 (5) (2000) 407–413, https://doi.org/10.1046/j.1469-0705.2000.00284.x.
- [35] O. Beharier, I. Shoham-Vardi, G. Pariente, R. Sergienko, R. Kessous, Y. Baumfeld, I. Szaingurten-Solodkin, E. Sheiner, Gestational diabetes mellitus is a
- significant risk factor for long-term maternal renal disease, J. Clin. Endocrinol. Metab. 100 (4) (2015) 1412-1416, https://doi.org/10.1210/jc.2014-4474.
- [36] S. Brennan, Y. Kandasamy, D. Rudd, M. Schneider, D. Watson, Fetal kidney charts of a novel measurement of the renal parenchymal thickness to evaluate fetal kidney growth and potential function, Prenat. Diagn. 40 (7) (2020) 860–869, https://doi.org/10.1002/pd.5701.
- [37] M.C. De Smedt, G.H. Visser, E.J. Meijboom, Fetal cardiac output estimated by Doppler echocardiography during mid- and late gestation, Am. J. Cardiol. 60 (4) (1987) 338–342, https://doi.org/10.1016/0002-9149(87)90238-4.
- [38] S. Magawa, H. Tanaka, M. Nii, S. Maki, Y. Kamimoto, T. Ikeda, In utero spontaneous bladder rupture in a fetus with posterior urethral valve: a case report of prenatal diagnosis and management, J. Obstet. Gynaecol. Res. 44 (7) (2018) 1318–1321, https://doi.org/10.1111/jog.13646.
- [39] A.S. Souza, M.M. Amorim, M.J. Vasconcelos-Neto, J.R. Oliveira-Filho, F.A. Sousa-Junior, [Factors associated with fetal brain-sparing effect in patients with hypertension in pregnancy], Rev. Bras. Ginecol. Obstet. 35 (7) (2013) 309–316, https://doi.org/10.1590/s0100-72032013000700005.
- [40] E. Afsari, F. Abbasalizadeh, Z. Fardiazar, S. Shahali, Y. Soltan Ahmadi, Is there a relationship between the severity of preeclampsia and fetal renal Doppler indices? Int J Women Heal Rep 9 (4) (2021) 263–267, https://doi.org/10.15296/ijwhr.2021.48.
- [41] A.I. Laag, N.M. Elhamamy, A.M.T. Elbadry, A.H. Teama, Relation between fetal renal artery Doppler indices and non-PROM oligohydramnios in third trimester of pregnancy, J Adv Med Med Res 33 (23) (2021) 1–8, https://doi.org/10.9734/JAMMR/2021/v33i2331179.
- [42] R.H. Stigter, E.J. Mulder, H.W. Bruinse, G.H. Visser, Doppler studies on the fetal renal artery in the severely growth-restricted fetus, Ultrasound Obstet. Gynecol. 18 (2) (2001) 141–145, https://doi.org/10.1046/j.1469-0705.2001.00493.x.
- [43] M. Wu, Y. Lin, F. Lei, Y. Yang, L. Yu, X. Liu, Diagnostic value of prenatal ultrasound for detecting abnormal fetal blood flow, Am J Transl Res 13 (5) (2021) 5094–5100.
- [44] G. Faa, C. Gerosa, D. Fanni, G. Monga, M. Zaffanello, P. Van Eyken, V. Fanos, Morphogenesis and molecular mechanisms involved in human kidney development, J. Cell. Physiol. 227 (3) (2012) 1257–1268, https://doi.org/10.1002/jcp.22985.
- [45] C.H. Chang, P.Y. Tsai, C.H. Yu, H.C. Ko, F.M. Chang, Predicting fetal growth restriction with renal volume using 3-D ultrasound: efficacy evaluation, Ultrasound Med. Biol. 34 (4) (2008) 533–537, https://doi.org/10.1016/j.ultrasmedbio.2007.10.006.