Comparative Analysis of Risk Indicators, Pregnancy Outcomes and Neonatal Prognosis between Early-Onset and Late-Onset Fetal Growth Restriction

Junyou Su, Xiaohuan Huang, Lingling Huang, Hongfei Chen, Junru Tong, Yan Huang, Yan Chen*

The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

*Corresponding author: Yan Chen, 543272474@qq.com.

Abstract: This study compares the risk indicators of early-onset and late-onset of fetal growth restriction (FGR) and their impact on pregnancy outcomes. Clinical data of 195 pregnant women (early-onset group, 47 cases; late-onset group, 148 cases) who had singleton pregnancies and experienced FGR were retrospectively analyzed. The comparative analysis assessed the risk indicators, pregnancy outcomes, and neonatal outcomes between the two groups. The overall incidence of hypertensive disorders of pregnancy (HDP) in cases of FGR was 22.05%. The incidence rate of HDP in the early-onset group was relatively higher ($p<0.001$). In the early-onset group, incidence rates of umbilical blood flow abnormalities, premature births, and cesarean section deliveries were comparatively higher (all $p<0.05$). Gestational age at delivery in the early-onset group was significantly lower ($p<0.001$). Moreover, the birth weight of newborns in the early-onset group was significantly lower ($p<0.001$). The early-onset group exhibited relatively high incidence rates of neonatal jaundice, neonatal infection, and intracranial hemorrhage (all $p<0.05$). Duration of hospitalization was also significantly longer than in the early-onset group ($p<0.001$). HDP is a high-risk factor for early-onset FGR. Moreover, early-onset of FGR is associated with a relatively high propensity for adverse pregnancy outcomes and poorer neonatal prognosis.

***Keywords*:** early-onset fetus, late-onset fetus, fetal growth restriction, pregnancy outcome

1. Introduction

Fetal growth restriction (FGR) is a pathological condition in which the fetus has not achieved its expected growth potential during its development within the maternal womb [1,2]. For any gestational age, fetal size less than the third percentile is an isolated criterion for defining FGR [3]. FGR is a serious complication of pregnancy, accounting for approximately 7% to 15% of all pregnancies [4], and it may be related to multiple factors such as maternal condition, placental function, intrauterine infection, and genetics, which can lead to risks such as premature birth, intrauterine hypoxia, neonatal asphyxia, stillbirth, hypoglycemia, and meconium aspiration syndrome (MAS), which increases perinatal mortality and morbidity [5,6]. Approximately, 20% to 50% of stillbirths are related to FGR, and it can also increase the risk of long-term adverse outcomes, such as neurological damage and cognitive impairment, cardiovascular diseases, and endocrine disease in adulthood [7-9].

Currently, there are currently no effective interventions for FGR. The first randomized controlled trial on the delivery timing to determine optimal delivery timing for FGR was the Growth Restriction Intervention Trial (GRIT) [10,11], which was designed to evaluate the efficacy of immediate delivery versus anticipation management. The median delivery time was 4.9 days in the expectant management group and 0.9 days in the immediate delivery group, with no significant difference in neurodevelopmental outcomes at 2 years or school age [12]. In addition, the TRUFFLE study [13] conducted the largest randomized trial of early delivery time of early-onset FGR, and the results showed that the delivery time based on intravenous catheter Doppler examination combined with computerized fetal heart monitoring chart safety standards could improve the long-term (2 years old) neurodevelopmental outcomes of surviving infants. It is important to note that results similar to the TRUFFLE trial can only be replicated by a monitoring protocol and delivery decision criteria using a combination of intravenous catheter Doppler examination and computerized fetal heart charts [14]. In contrast, due to the lack of randomized trials of interventional therapy based on the Doppler index, there is no international consensus on the delivery time of advanced FGR. Studies have shown that women with FGR in the third trimester should deliver based on biophysical assessment or maternal indications [14]. Thus, assessing fetal health before delivery and timely delivery are still key issues.

Gordijn and colleagues [14,15] achieved consensus through Delphi research. They classified FGR into early-onset

(gestational age <32 weeks, without congenital anomalies) and late-onset (gestational age ≥32 weeks, without congenital anomalies) for antenatal management, after excluding fetal genetic abnormalities. Early-onset and late-onset FGR differ significantly in terms of etiology, pregnancy outcomes and clinical management. Gestational diabetes mellitus, hypertensive disorders of pregnancy, immune system abnormalities in pregnancy (systemic lupus erythematosus, antiphospholipid syndrome, etc.), and thyroid abnormalities in pregnancy, especially hypothyroidism, may be the main causes of both early-onset FGR and late-onset FGR [16]. Fetuses with early-onset FGR are more likely to have severe umbilical blood flow abnormalities, leading to fetal loss. In addition, it has been shown that chromosomal aberrations are strongly associated with early-onset FGR in pregnancy [17]. Early-onset FGR is associated with severe placental vascular insufficiency of the fetus and chronic hypoxia of the fetus, which results in a high degree of umbilical artery Doppler involvement during a short period of gestation, and a higher rate of adverse perinatal outcomes [18]. Late-onset FGR has a lower association with late pulmonary embolism, with less severe placental pathology, and 25% of late-onset FGR may present with late cerebral vasodilatation, suggesting chronic hypoxia [19-21]. Whether early-onset or late-onset, there is a lack of feasible treatment methods, and the only way to remove the fetal intrauterine malnutrition and hypoxia is to terminate the pregnancy. It has been reported that early-onset FGR focuses on management, aiming to achieve the optimal choice between the risk of fetal in utero and the complications of premature delivery; while late-onset FGR focuses on diagnosis, in order to reduce the occurrence of stillbirth in the third trimester [19]. Therefore, understanding the etiology and clinical manifestations of the two types of FGR is of great significance for the early diagnosis, reasonable monitoring, timely delivery, and improvement of the short-term and long-term prognosis of FGR fetuses. Therefore, the purpose of this study was to analyze the risk indicators, pregnancy outcomes and neonatal prognosis of early-onset and late-onset FGR, so as to strengthen the management of FGR, conduct early screening for high-risk pregnant women, formulate the best pregnancy testing program and select appropriate treatment plan to slow down the progression of FGR, and select the right delivery time to reduce the occurrence of adverse perinatal outcomes.

2. Methods

2.1 Subjects

The clinical medical records of 195 pregnant women with singleton pregnancies complicated by FGR who gave birth in the Obstetrics Department of the Second Affiliated Hospital of Guangxi Medical University from August 2018 to March 2022 was retrospectively analyzed. The diagnosis of FGR was based on the whether the newborn's birth weight was lower than the 10th percentile of newborn weight for the same gestational age. According to the gestational age of first diagnosis of FGR, FGR was divided into two groups: early-onset group (the gestational age at which FGR was first diagnosed was <32 weeks, 47 cases, accounting for 24.10%) and late-onset group (gestational age when FGR was first diagnosed ≥32 weeks, 148 cases, accounting for 75.90%). Excluded from this study were individuals with twin or multiple pregnancies, those with postpartum fetal age and weight falling within the normal range, and cases with incomplete clinical data. This study was conducted with approval from the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University [approval number: 2023-KY (0637)], and all participants provided written informed consent.

2.2 Research methods

A retrospective approach was used to statistically analyze the clinical data of the two groups of FGR. This analysis encompassed various aspects, including pregnancy complications and complications, gestational age of onset, umbilical cord abnormalities (circling the neck, twisting, knotting, etc.), and abnormal umbilical artery blood flow [comprising parameters like pulsatility index (PI), resistance index (RI), systolic/diastolic (S/D) ratio, etc.], placental abnormalities (velamentous placenta, racket-shaped placenta, etc.), gestational age, mode of delivery, neonatal birth weight, and neonatal complications.

2.3 Statistical analysis

Data were statistically analyzed using IBM SPSS Statistics 25.0 software. Continuous variables following a normal distribution are presented as mean ± standard deviation (SD), and comparisons between two groups were conducted using the t-test or analysis of variance (ANOVA). Categorical data were represented as frequencies (percentages), and the Chi-square test or Fisher's exact test was employed for analysis. The result of a statistical test is considered as significant for p-value less than 0.05.

3. Results

3.1 Subject information

In the early-onset group, patients ranged in age from 14 to 43 years, with an average age of (31.06±5.75) years. They had an average of (2.26±1.59) pregnancies, (1.15±0.91) parities, and a Body Mass Index (BMI) of (20.38±4.37). In the late-onset group, patients ranged in age from 18 to 42 years, with an average age of (29.58±5.06) years. They had an average of (2.16±1.37) pregnancies, (1.25±0.78) parities, and a BMI of (20.67±3.33). There were no statistically significant differences in terms of age and pregnancy between the two groups. Parity and BMI also showed no statistically significant differences ($p>0.05$).

3.2 Comparative analysis of risk indicators for early-onset and late-onset FGR

The overall incidence rate of hypertensive disorders of pregnancy (HDP) in FGR was 22.05% (43/195). Notably, the incidence rate of HDP in the early-onset group was significantly higher than that in the late-onset group (46.81% vs.14.19%, $p<0.001$). However, there was no statistically significant difference in the incidence rates of gestational diabetes mellitus (GDM), immune system diseases, thyroid disease, heart disease, anemia, placental structural abnormalities, umbilical cord abnormalities between the two groups (all $p>0.05$) (Table 1).

Table 1. Comparison of risk indicators between early-onset and late-onset FGR.

Risk Indicators	Early-Onset Group (n=47)	Late-Onset Group (n=148)	p
HDP (n, %)	22 (46.81)	21 (14.19)	<0.001
GDM (n, %)	8 (17.02)	23 (15.54)	0.809
Immune System Disorders (n, %)	3 (6.38)	2 (1.35)	0.170
Thyroid Disorders (n, %)	4 (8.51)	6 (4.05)	0.228
Heart Disease (n, %)	1 (2.13)	2 (1.35)	0.706
Anemia (n, %)	7 (14.89)	24 (16.22)	0.829
Placental Structural Abnormalities (n, %)	5 (10.64)	7 (4.73)	0.142
Umbilical Cord Abnormalities (n, %)	23 (48.94)	67 (45.27)	0.871

HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus.

3.3 Comparative analysis of pregnancy outcomes between early-onset and late-onset FGR

The incidence rates of abnormal umbilical blood flow, premature delivery, and cesarean section in the early-onset group (12.77%, 46.81%, 68.08%, respectively) were significantly higher than those in the late-onset group (3.38%, 8.78%, 48.65%, respectively). Additionally, the gestational age of delivery was significantly smaller than the late-onset group (35.81±3.15 weeks vs. 37.97±1.36 weeks, $p<0.001$) (Table 2).

Table 2. Comparative analysis of pregnancy outcomes between early-onset and late-onset FGR.

Complications	Early-Onset Group (n=47)	Late-Onset Group (n=148)	p
Turbid Amniotic Fluid (n, %)	11 (23.40)	23 (15.54)	0.216
Fetal Distress (n, %)	8 (17.02)	23 (15.54)	0.809
Abnormal Umbilical Blood Flow (n, %)	6 (12.77)	5 (3.38)	0.015
Gestational Age of Delivery (weeks)	35.81±3.15	37.97±1.36	<0.001
Premature Birth (n, %)	22 (46.81)	13 (8.78)	<0.001
Cesarean Section (n, %)	32 (68.08)	72 (48.65)	0.020

3.4 Comparative analysis of neonatal prognosis between early-onset and late-onset FGR

The neonatal birth weight in the early-onset group was significantly lower than that in the late-onset group (1961.81±551.48 g vs. 2384.22±246.46 g, $p<0.001$). Additionally, the early-onset group exhibited significantly higher incidence rates of neonatal jaundice, neonatal infection, and brain hemorrhage (70.12%, 36.17%, 8.51%, respectively) compared to the late-onset group (40.54%, 12.16%, 1.35%, respectively). Moreover, the neonatal hospitalization days in the early-onset group was significantly longer than the late-onset group (14.04±16.74 days vs. 5.83±5.18 days, $p<0.001$) (Table 3).

Table 3. Comparative analysis of neonatal outcomes in early-onset and late-onset FGR.

Neonatal Prognosis	Early-Onset Group (n=47)	Late-Onset Group (n=148)	p
Neonatal Birth Weight (g)	1961.81±551.48	2384.22±246.46	<0.001
Neonatal Asphyxia (n, %)	4 (8.51)	6 (4.05)	0.458
Neonatal Jaundice (n, %)	33 (70.21)	60 (40.54)	<0.001
Neonatal Infection (n, %)	17 (36.17)	18 (12.16)	<0.001
Neonatal Brain Hemorrhage (n, %)	4 (8.51)	2 (1.35)	0.046
Neonatal Hospitalization Days (days)	14.04±16.74	5.83±5.18	<0.001

4. Discussion

4.1 Risk indicators for early-onset and late-onset FGR

FGR is a prevalent and serious complication in obstetrics. The 32nd week of gestation is considered a crucial milestone, distinguishing between early-onset and late-onset FGR, and marks a turning point in pregnancy outcomes. These two forms of FGR present distinct pathological and clinical characteristics, significantly impacting the perinatal period. Early-onset FGR, which constitutes approximately 30% of FGR cases, often progresses to severe FGR, resulting in adverse pregnancy outcomes [14]. Identifying the risk indicators for FGR is of paramount importance in enhancing pregnancy outcomes. FGR is associated with various factors, such as maternal, fetal, umbilical cord, and placental factors, with maternal factors playing a prominent role. Maternal complications during pregnancy can lead to physiological changes that contribute to the development of FGR. HDP, particularly preeclampsia, are closely linked to poor fetal growth, growth restriction, and low birth weight [22]. In our study, early-onset FGR accounted for 24.10% of FGR cases, which was slightly lower than previously reported in the literature. The overall incidence of HDP in FGR cases was 22.05%, surpassing other factors like gestational diabetes, thyroid disease, and immune system disorders. Notably, the incidence of HDP in early-onset FGR (46.81%) was significantly higher than in late-onset FGR (14.19%). This suggests that HDP stands as the primary risk factor for FGR, particularly early-onset FGR. This relationship can be attributed to the pathophysiological changes induced by HDP, including small vessel injury and vascular endothelial damage within the maternal system. HDP affects the uterine spiral arterioles, leading to inadequate remodeling, excessive activation of inflammatory immunity, and loss of vascular endothelium [23]. These processes result in placental hypoxia and insufficient fetal blood flow reperfusion, culminating in the occurrence of FGR, primarily in early-onset FGR. However, the correlation between late-onset FGR and HDP is less pronounced, and it may be associated with milder placental function impairment, hypoxia, and abnormal trophoblast cell invasion, possibly due to inflammatory damage and placental calcification [19]. One study [24] found that the earlier the gestational week of hypertension, the more severe the condition, the more likely the fetus is to suffer from hypoxia in utero, the greater the risk of FGR, and the worse the perinatal outcome and prognosis. Therefore, it is crucial to closely monitor maternal blood pressure and fetal growth and development throughout pregnancy. For pregnant women diagnosed with HDP before the 32nd week of pregnancy, appropriate measures should be taken to manage and mitigate the risks associated with these conditions and to reduce the incidence of FGR.

4.2 Pregnancy outcomes of early-onset and late-onset FGR

Doppler ultrasonography plays a vital role in monitoring FGR during pregnancy, as it enables the assessment of fetal blood flow, reflecting pathological changes in both the placenta and the mother [25]. In the course of a normal pregnancy, vascular resistance decreases, resulting in decreased values for parameters like PI, RI, and S/D ratio. However, when placental function is compromised, resistance increases, leading to elevated values for PI, RI, and S/D, and in some cases, even the disappearance or reversal of end-diastolic blood flow. In our study, 5.64% (11/195) of the FGR cases exhibited abnormal umbilical blood flow. Among these cases, early-onset FGR had a significantly higher incidence of abnormal umbilical blood flow at 12.77%, in contrast to late-onset FGR at 3.38%. This suggests that early-onset FGR is more prone to abnormal umbilical blood flow, which is consistent with Xiao et al. (2020) [16]. The etiology of early-onset FGR is multifaceted, and abnormal fetal blood flow is influenced by numerous factors. Studies have demonstrated that HDP can lead to impaired placental function, prolonged severe hypoxia, reduced fetal weight, and systemic vascular adaptive changes (compensatory response), resulting in abnormal Doppler blood flow patterns [23]. As mentioned earlier, the incidence of HDP is higher in early-onset FGR. Therefore, this study posits that the increased incidence of abnormal umbilical blood flow in early-onset FGR is linked to HDP. Furthermore, our study found that early-onset FGR had a lower gestational age and a higher rate of premature delivery compared to late-onset FGR. The timing of delivery in FGR is influenced by multiple factors, including

gestational age, underlying cause, FGR type, parental expectations, and neonatal care capabilities. Clinical management of early-onset FGR aims to safely extend gestational age. Nevertheless, fetuses with early-onset FGR often have limited tolerance, and abnormal umbilical artery blood flow serves as a warning sign, indicating a high risk of fetal distress or even intrauterine demise. Consequently, early termination of pregnancy is often necessitated to safeguard the fetus, resulting in lower gestational ages at delivery and a higher incidence of adverse pregnancy outcomes, particularly premature births. In our study, the cesarean section rate for FGR was 53.33% (104/195). Notably, the cesarean section rate for early-onset FGR was even higher at 68.08%. FGR itself does not mandate a cesarean section, but when FGR is coupled with the loss or reversal of end-diastolic blood flow in the umbilical artery, both the American Society of Maternal-Fetal Medicine and China's FGR guidelines recommend cesarean section to terminate the pregnancy [1,2]. Thus, early-onset FGR is more prone to adverse pregnancy outcomes, including abnormal umbilical blood flow, lower gestational age, and higher rates of premature birth and cesarean section.

4.3 Neonatal outcomes of early-onset and late-onset FGR

This study conducted a comparative analysis of neonatal outcomes in early-onset FGR and late-onset FGR, revealing that neonates with early-onset FGR exhibited significantly lower birth weights and higher incidence rates of complications such as neonatal jaundice, infections, and cerebral hemorrhages. They also had longer hospitalization durations. These findings suggest that neonatal outcomes for early-onset FGR are less favorable than those for late-onset FGR. The reasons behind these differences can be attributed to the fact that early-onset FGR patients experience the condition's onset and delivery at earlier gestational ages, making them more susceptible to complications like HDP and abnormal umbilical blood flow. Fetuses affected by early-onset FGR endure adverse conditions in utero for more extended periods, experiencing insufficient placental perfusion and failing to achieve their expected growth potential. Consequently, they have a higher likelihood of premature birth, low birth weight, reduced resistance, and tolerance, and an increased susceptibility to neonatal complications. FGR is an independent risk factor for low-grade fetal inflammatory response [26]. Preterm birth and low birth weight are recognized as high-risk factors for neonatal jaundice and infections, particularly among neonates with very low birth weights (less than 1500 grams), who face a heightened risk of infection and even sepsis [27,28]. Prolonged placental hypoperfusion and abnormal umbilical blood flow can result in fetal middle cerebral artery hypoperfusion, impacting fetal brain growth and development. Premature infants often experience inadequate brain development, increasing their vulnerability to neonatal intracranial hemorrhages associated with premature birth[29]. Consequently, high-risk groups for FGR should undergo comprehensive monitoring during pregnancy to enable the early detection of FGR. This includes promoting balanced nutrition during pregnancy to enhance fetal growth. Both domestic and international guidelines recommend the use of magnesium sulfate to protect the fetus and the neonatal central nervous system when FGR fetuses are delivered before 32 weeks of gestation. Additionally, glucocorticoids should be administered before delivery, before 34 weeks of gestation, to enhance perinatal outcomes for premature infants and reduce the risk of respiratory distress syndrome and fetal and neonatal mortality [1,2,4,30]. Furthermore, while late-onset FGR is generally less severe than early-onset FGR, it still adversely impacts neonatal prognosis. Therefore, monitoring of late-onset FGR during pregnancy should also be prioritized.

There are several limitations in our study. First, retrospective and single-center studies may result in a lack of generality. The limited number of patients is a second limitation of this study. Therefore, a future multi-center study with more sample sizes is very necessary.

5. Conclusion

In summary, HDP has been determined as a significant risk factor for FGR, particularly regarding early-onset FGR. Early-onset FGR carries a higher risk of adverse pregnancy outcomes, including abnormal umbilical blood flow, shorter gestational age delivery, increased rates of premature birth and cesarean section deliveries. Furthermore, in neonatal outcomes, it can lead to lower birth weights for newborns, and increased occurrence of complications like neonatal jaundice, infections, and cerebral hemorrhages. These outcomes can result in longer neonatal hospital stays and poorer prognosis. Enhanced monitoring of FGR, especially early-onset cases, is essential. Early diagnosis, proper monitoring, active intervention, and timely delivery are critical in improving the pregnancy outcomes and neonatal prognosis for FGR.

Acknowledgments

This research was supported by the Self-financed scientific research of Guangxi Zhuang Autonomous Region Health Commission in 2022 (grant number: Z-A20220569 and Z-A20220631).

References

[1] Society for Maternal-Fetal Medicine (SMFM), Martins JG, Biggio JR, et al. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol. 2020;223(4):B2-B17.

[2] Wu J, Lu AD, Zhang LP, et al. Study of clinical outcome and prognosis in pediatric core binding factor-acute myeloid leukemia. Chin J Hematol. 2019;40(1):52-57.

[3] Damhuis SE, Ganzevoort W, Gordijn SJ. Abnormal Fetal Growth: Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology. Obstet Gynecol Clin North Am. 2021;48(2):267-279.

[4] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins — Obstetrics and the Society forMaternal-FetalMedicin. ACOG Practice Bulletin No. 204: Fetal Growth Restriction. Obstet Gynecol. 2019;133(2):e97-e109.

[5] Pels A, Beune IM, van Wassenaer-Leemhuis AG, et al. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. Acta Obstet Gynecol Scand. 2020;99(2):153-166.

[6] Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. Aust N Z J Obstet Gynaecol. 2014;54(4):354-359.

[7] Freedman AA, Silver RM, Gibbins KJ, et al. The association of stillbirth with placental abnormalities in growth-restricted and normally grown fetuses. Paediatr Perinat Epidemiol. 2019;33(4):274-383.

[8] Gerosa C, Faa G, Fanni D, et al. Fetal programming of atherosclerosis: may the barker hypothesis explain the susceptibility of a subset of patients to develop stroke or cardiac infarct? Eur Rev Med Pharmacol Sci. 2021;25(21):6633-6641.

[9] Meher S, Hernandez-Andrade E, Basheer SN, et al. Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review. Ultrasound Obstet Gynecol. 2015;46(4):398-404.

[10] GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG. 2003;110(1):27-32.

[11] Thornton JG, Hornbuckle J, Vail A, et al. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet. 2004;364(9433):513-520.

[12] Walker DM, Marlow N, Upstone L, et al. The Growth Restriction Intervention Trial: long-term outcomes in a randomized trial of timing of delivery in fetal growth restriction. Am J Obstet Gynecol. 2011;204(1):34.e1-34.e9.

[13] Lees CC, Marlow N, van Wassenaer-Leemhuis A, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet. 2015;385(9983):2162-2172.

[14] Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298-312.

[15] Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333-339.

[16] Xiao WL, Pan SL, Cai W, et al. Comparison of the etiology and pregnancy outcome of fetal growth restriction in early-onset and late-onset singletons. Shandong Med J. 2020;60(18):75-77.

[17] Borrell A, Grande M, Meler E, et al. Genomic Microarray in Fetuses with Early Growth Restriction: A Multicenter Study. Fetal Diagn Ther. 2017;42(3):174-180.

[18] Malhotra A, Allison BJ, Castillo-Melendez M, et al. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. Front Endocrinol (Lausanne). 2019;10:55.

[19] Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014;36(2):86-98.

[20] Muniz CS, Dias BF, Motoyama PVP, et al. Doppler abnormalities and perinatal outcomes in pregnant women with early-onset fetal growth restriction. J Matern Fetal Neonatal Med. 2022;35(257276-7279.

[21] Mureșan D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. Med Ultrason. 2016;18(1):103-109.

[22] Ashraf UM, Hall DL, Rawls AZ, et al. Epigenetic processes during preeclampsia and effects on fetal development and chronic health. Clin Sci (Lond). 2021;135(19):2307-2327.

[23] Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2S):S745-S761.

[24] Xiao J, Zhu FF. Analysis the Correlative Factors of 140 FGR With Different Gestation Ages. J Pract Obstet Gynaecol. 2011;27:539-541.

[25] Rubin JM, Fowlkes JB, Pinter SZ, et al. Umbilical Vein Pulse Wave Spectral Analysis: A Possible Method for Placental Assessment Through Evaluation of Maternal and Fetal Flow Components. J Ultrasound Med. 2022;41(10):2445-2457.

[26] Moon KC, Park CW, Park JS, et al. Fetal Growth Restriction and Subsequent Low Grade Fetal Inflammatory Response Are Associated with Early-Onset Neonatal Sepsis in the Context of Early Preterm Sterile Intrauterine Environment. J Clin Med. 2021;10(9):2018.
[27] Yadav P, Yadav SK. Progress in Diagnosis and Treatment of Neonatal Sepsis: A Review Article. J Nepal Med Assoc. 2022;60(247):318-324.
[28] Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017;78(12):699-704.
[29] Tan AP, Svrckova P, Cowan F, et al. Intracranial hemorrhage in neonates: A review of etiologies, patterns and predicted clinical outcomes. Eur J Paediatr Neurol. 2018;22(4):690-717.
[30] Daskalakis G, Pergialiotis V, Domellöf M, et al. European guidelines on perinatal care: corticosteroids for women at risk of preterm birth. J Matern Fetal Neonatal Med. 2023;36(1):2160628.