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Analysis of Maternal Risk Factors for Restricted Fetal Growth in Early and Late Onset Fetal Growth Restriction

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Abstract

Purpose: The aim of this study is to analyze the risk factors for early-onset and late-onset fetal growth restriction (FGR) to improve maternal and neonatal outcomes.

Methods: Clinical data from 308 FGR patients were collected and divided into two groups: early-onset group (53 cases) and late-onset group (255 cases). The risk factors of the early-onset and late-onset groups were analyzed by single factor regression analysis and multiple Logistic regression analysis.

Results: By analyzing the risk factors leading to FGR, we found a significantly higher incidence of placental abnormalities and hypothyroidism in the early-onset group, while oligohydramnios was more common in the late-onset group. There were no significant differences between the two groups in terms of pregnancy-induced hypertension, diabetes, hypoalbuminemia, anemia, and fetal factors. Furthermore, we observed that the earlier FGR occurred, the higher the rate of adverse neonatal outcomes and stillbirth.

Conclusion: These findings contribute to the enhanced clinical management of FGR patients, enabling early identification of high-risk pregnant women, and the development of more effective prenatal screening and treatment strategies to mitigate the progression of FGR.

Keywords: Fetal growth restriction; Hypertensive disease of pregnancy; Oligohydramnios; Risk factors; Hypertension

Abbreviations : FGR: Fetal Growth Restriction; IUGR: Intrauterine Growth Restriction; SGA: Small for Gestational Age

Introduction

In recent years, clinical and basic research on fetal growth restriction (FGR) has gained widespread attention. FGR, also known as intrauterine growth restriction (IUGR), refers to compromised fetal growth potential, with the estimated fetal weight below the 10th percentile for the corresponding gestational age, classifying it as small for gestational age (SGA). Even when the estimated weight reaches the 10th percentile, infants with FGR still face an increased risk of adverse perinatal outcomes. Particularly severe FGR is defined as an estimated fetal weight below the 3rd percentile for the corresponding gestational age [1]. Studies indicate that FGR is one of the most common reasons for adverse perinatal outcomes and long-term prognosis. FGR elevates the risk of perinatal fetal death by 1.5 times compared to normal fetuses, and when the fetal weight falls below the 5th percentile for the corresponding gestational age, this risk increases to 2.5% [2]. Based on the gestational week at the time of FGR diagnosis, numerous studies propose that fetal growth restriction identified before 32 weeks of gestation is termed early-onset FGR, while fetal growth restriction identified after 32 weeks of gestation is termed late-onset FGR [3]. Stratifying FGR into early-onset and late-onset categories, determined by the gestational age at the initial diagnosis, enhances our comprehension of the condition and facilitates the development of suitable management and prevention strategies.

Fetal growth restriction (FGR) can lead to various risks, including premature birth, fetal intrauterine hypoxia, neonatal

asphyxia, stillbirth, neonatal polycythemia, hypoglycemia, meconium aspiration syndrome, and other complications. Concerning long-term prognosis, it not only affects the neurobehavioral development of infants but also increases the risk of metabolic syndrome. Currently, there are no effective intervention measures or optimal termination timing. Assessing fetal health before delivery and timely delivery remain crucial issues. The primary goal of clinically managing FGR is to utilize various methods to monitor fetal health, assess the risk of adverse pregnancy outcomes and death, and balance them with the risks of premature birth. This enables the appropriate timing and method for terminating pregnancy.

Study Population and Methods

In this retrospective analysis, we examined clinical data from 308 cases of fetal growth restriction (FGR). Cases were diagnosed based on whether the newborn's weight at birth was below the 10th percentile for the corresponding gestational age. To gain a better understanding of the etiology of FGR, we stratified the cases into two groups: the early-onset FGR group (diagnosed before 32 weeks of gestation, n=53) and the late-onset FGR group (diagnosed at or after 32 weeks of gestation, n=255). We collected data related to high-risk factors, gestational age at onset, delivery methods, and their impact on neonatal outcomes for both groups. Statistical analyses were conducted using SPSS 22.0 software, employing methods such as analysis of variance, t-tests, and χ^2 test. The aim was to provide data support for a comprehensive understanding of the etiology of FGR.

Results

Risk Factors for FGR

Among the risk factors for fetal growth restriction (FGR), pregnancy-induced hypertension accounted for 42.21%. In the early-onset FGR group, the following risk factors were more prevalent: pregnancy-induced hypertension, placental factors, diabetes, and thyroid dysfunction. In the late-onset FGR group, the following risk factors were more prevalent: pregnancy-induced hypertension, oligohydramnios, placental factors, and diabetes. Regardless of early-onset or late-onset FGR, pregnancy-induced hypertension was the predominant risk factor, with a higher proportion than other risk factors. Placental abnormalities and thyroid dysfunction had a larger proportion in the early-onset group, while oligohydramnios had a larger proportion in the late-onset group. These differences were statistically significant (P<0.05). There were no significant differences between the two groups in terms of pregnancy-induced hypertension, diabetes, hypoproteinemia, anemia, and fetal factors (P>0.05). Please refer to Table 1 for details.

Table 1: Analysis of risk factors for early-and late-onset FGR.

Risk factors	Early-onset FGR group (53 cases)	Late-onset FGR group (255 cases)	χ^2	P
Hypertensive disorders complicating pregnancy (case %)	24（45.28%）	106（41.57%）	0.248	0.73
Placental factors (case %)	16（30.19%）	28（10.98%）	13.222	0.001
Oligohydramnios (case %)	2（3.78%）	51（20.00%）	8.11	0.004
Hypothyroidism (cases %)	9（16.98）	18（7.06%）	5.402	0.04
Diabetes mellitus (case %)	10（18.87%）	30（11.76%）	1.959	0.24
Hypoproteinemia (case %)	3（5.66%）	22（8.63%）	0.518	0.345
thrombophilia (case %)	7（13.21%）	20（7.84%）	1.579	0.322
Umbilical cord factor (case %)	5（9.43%）	9（3.53%）	3.526	0.13
Anemia (case %)	3（5.66%）	19（7.45%）	0.212	0.867
Fetal factors (case %)	1（1.89%）	17（6.67%）	1.822	0.304

Relationship Between the Onset of FGR and Neonatal Outcomes

In this study, it was observed that in early-onset FGR, the highest percentage of adverse neonatal outcomes occurred between 28 and 28+6 weeks, with the highest proportion of neonatal deaths occurring before 28 weeks. In late-onset FGR, the highest percentage of adverse neonatal outcomes was observed between 32 and 32+6 weeks, and the proportion of neonatal deaths was also the highest in this group. This suggests that the earlier FGR occurs, the higher the rate of adverse neonatal outcomes. Please refer to Figure 1 and Figure 2 for details.

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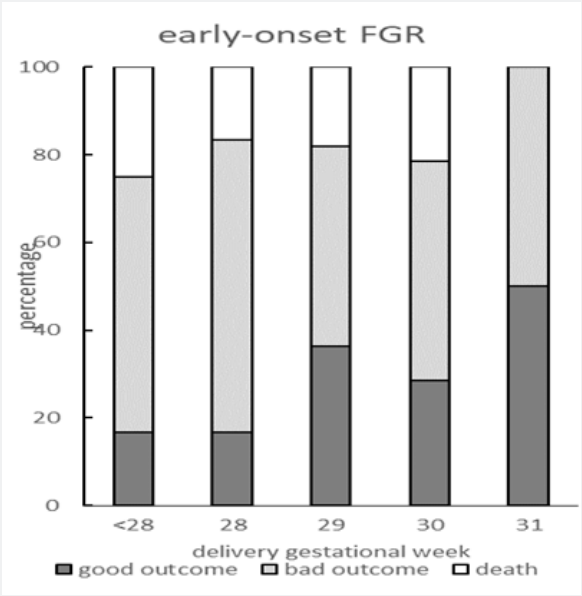

Figure 1: Early-onset FGR.

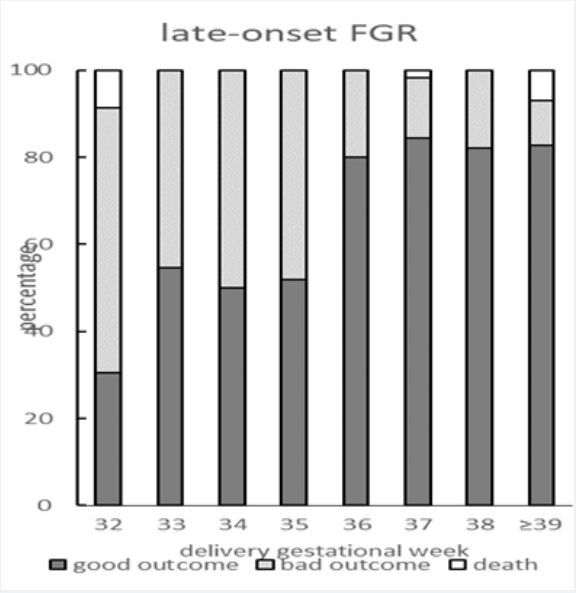

Figure 2: Late-onset FGR.

Relationship between the mode of termination of pregnancy and neonatal outcome in FGR

It was found that the proportion of cesarean deliveries with good neonatal outcome was greater than vaginal deliveries for both early-and late-onset FGR. As shown in Figure 3 and Figure 4.

Discussion

Analysis of risk factors

The development of the fetus within the maternal uterine cavity is influenced by a multitude of factors that can be summarized into four main categories: maternal factors, fetal factors, umbilical cord and placental factors. This group's case study revealed that Fetal Growth Restriction (FGR) is the result of the combined influence of various factors, many of which intersect. Notably, maternal factors account for the majority of FGR cases. The effects of these diverse factors result in inadequate placental perfusion, subsequently leading to a deficiency in fetal blood, oxygen, and nutrients, thereby constraining fetal growth and development. Previous research has shown that hypertension

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during pregnancy significantly increases the incidence of FGR, particularly when accompanied by pre-eclampsia, with rates ranging from 21.7% to 61.9% [4]. In our study on risk factors for FGR in our hospital, we observed that in the early-onset FGR group, prominent risk factors include pregnancy-induced hypertension, placental factors, diabetes, and hypothyroidism. Conversely, in the late-onset FGR group, significant risk factors include pregnancy-induced hypertension, oligohydramnios, placental factors, and diabetes. This study highlights that regardless of whether FGR is early or late-onset, pregnancy-induced hypertension remains a primary risk factor, accounting for a higher proportion than other risk factors. Some research suggests that early-onset preeclampsia has a more pronounced impact on early-onset FGR, likely due to the association between early-onset FGR and early-onset preeclampsia, both linked to uterine spiral artery damage-induced placental hypoxia-reperfusion injury [5].

During neonatal delivery, the compression of the birth canal leads to a further reduction in fetal blood flow, increasing the incidence of fetal distress. Preeclampsia is considered a clinical syndrome, with Fetal Growth Restriction (FGR) recognized as one of the symptoms associated with impaired uteroplacental blood flow [6]. Multiple placental infarctions are common in both pre-eclampsia and FGR [7], suggesting a potentially close connection between these two clinical conditions. Pregnant women who have experienced fetal growth restriction coupled with preeclampsia are at a higher risk of developing preeclampsia in subsequent pregnancies [8]. The earlier preeclampsia occurs, the more severe the disease, the higher the incidence of fetal growth restriction, and the worse the fetal outcome. Sarrafia et al. [9] described how placental factors causing maternal under perfusion during preeclampsia increase the incidence of FGR, with 75-80% occurring in early-onset preeclampsia [10,11]. In contrast, late-onset FGR has a weaker correlation with preeclampsia, featuring milder placental pathology, primarily characterized by non-specific inflammatory damage and placental calcification [12]. Therefore, rigorous monitoring of maternal blood pressure during pregnancy, early detection of pregnancy-induced hypertension, and the implementation of appropriate interventions are essential for reducing the incidence of FGR.

Additionally, early-onset FGR is associated with placental factors such as sail-like placenta, low-lying placenta, chorionic vascular tumors, placental insufficiency, and placental infarction. These factors reduce placental blood and oxygen supply, affecting fetal growth and development. Maternal complications, including diabetes, thrombophilia, and hypothyroidism, have a higher incidence in the early-onset group compared to the late-onset group. These poorly controlled conditions have a prolonged adverse effect on fetal growth during pregnancy [13], leading to FGR occurring before 32 weeks of gestation and explaining the higher incidence in early-onset FGR. Oligohydramnios is more prevalent in the late-onset group. In late pregnancy, amniotic fluid primarily originates from fetal urine, fetal lung, and fetal swallowing. If fetal growth is restricted, ischemia and hypoxia reduce renal blood supply to the fetus, leading to decreased urine production and, subsequently, reduced amniotic fluid. Therefore, monitoring amniotic fluid is a primary concern in diagnosing late-onset FGR. Intrauterine fetal infections, such as rubella virus, cytomegalovirus, varicella-zoster virus, and toxoplasmosis, can directly interfere with cell proliferation, resulting in chromosomal rupture and cell dissolution, ultimately leading to FGR.

Some studies [14,15] have suggested that certain chromosomal abnormalities, particularly involving chromosomes 13, 18, and 21, may be associated with FGR, emphasizing the need to screen for chromosomal abnormalities in FGR cases. Other factors, such as maternal malnutrition and smoking, can also impact fetal growth and development. Therefore, a comprehensive analysis of factors related to FGR is essential for improved prevention, diagnosis, and treatment of FGR. In conclusion, this discussion provides a comprehensive understanding of the multifactorial nature of FGR, with a particular focus on the significance of pregnancy-induced hypertension, preeclampsia, placental factors, and diabetes. This knowledge is invaluable for healthcare providers and researchers seeking to enhance their understanding of FGR's pathogenesis and take appropriate measures to reduce risks for patients and improve neonatal outcomes.

Analysis of the relationship between gestational week of onset of FGR and neonatal outcome

This study identified that in early-onset Fetal Growth Restriction (FGR), the percentage of adverse neonatal outcomes was highest when onset occurred between 28 and 28+6 weeks, with the highest proportion of neonatal deaths occurring when FGR developed before 28 weeks. Conversely, late-onset FGR showed the highest percentage of adverse neonatal outcomes when onset was between 32 and 32+6 weeks, with the highest mortality rate. This suggests that the earlier FGR occurs during gestation, the higher the incidence of adverse neonatal outcomes. Prolonged exposure of the fetus to an unfavorable intrauterine environment, leading to inadequate blood and oxygen supply, results in an increased proportion of poor neonatal prognosis. Therefore, once Fetal Growth Restriction (FGR) is diagnosed, close monitoring should be initiated promptly, enabling early intervention to reduce the occurrence of adverse fetal outcomes.

Termination of pregnancy by FGR

This study revealed that both early-onset and late-onset fetal growth restriction (FGR) had a higher proportion of adverse neonatal outcomes in the group delivered through vaginal delivery compared to those delivered via cesarean section. This may be attributed to the very low tolerance of early-onset FGR to hypoxia. During the process of labor, the fetal blood flow is further reduced due to the compression of the birth canal, leading to an increased incidence of fetal distress and a higher proportion of adverse outcomes in newborns. Additionally, cases of FGR diagnosed with severe blood flow abnormalities and complications at the time of consultation predict a higher likelihood of adverse neonatal

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outcomes, leading some to choose vaginal delivery to avoid potential harm to pregnant women from cesarean section.

Cesarean section delivery can reduce the impact of uterine contractions on the fetus, allowing the fetus to quickly escape from the unfavorable intrauterine environment and thus reducing the incidence of fetal distress. While most experts both domestically and internationally [16] believe that isolated FGR is not an indication for cesarean section, and if fetal Doppler blood flow monitoring and fetal heart monitoring show no abnormalities, vaginal delivery can be chosen under close monitoring. However, if the fetus exhibits significant hypoxemia and acidosis, and the mother has serious medical conditions, the risks of vaginal delivery may be high, justifying a more flexible approach to the indications for cesarean section [17,18]. Nevertheless, there is still controversy regarding the timing and method of terminating pregnancy for FGR. Therefore, when dealing with FGR, it is crucial to strengthen fetal heart monitoring, optimize the timing of delivery, and be well-prepared for neonatal resuscitation. When terminating pregnancy in cases of Fetal Growth Restriction (FGR), a careful consideration of clinical circumstances, especially gestational age, is essential. This involves balancing the risks of preterm delivery against the risks of stillbirth and continued pregnancy leading to long-term neurodevelopmental damage.

Some infants with fetal growth restriction (FGR) may reach normal weight or slightly below normal weight in adulthood. Overseas studies have shown that if fetal head growth retardation occurs before the 26th week of pregnancy, infants will exhibit significant developmental delay at the age of 4 and may also experience some cognitive impairments in adulthood. Research indicates that compared to normal newborns, infants born at full term with a birth weight below 2500g have a threefold higher risk of developing coronary heart disease in later life [19].

Conclusion

In conclusion, both early-onset and late-onset fetal growth restriction (FGR) are primarily associated with hypertensive disorders during pregnancy. Although there is no significant difference between the two groups, they exhibit a higher proportion compared to other risk factors. Placental factors and hypothyroidism are closely related to early-onset fetal growth restriction, while oligohydramnios is one of the main clinical manifestations of late-onset fetal growth restriction. However, it is important to note that FGR, regardless of its type, is the result of the combined action of multiple factors.

Limitations and Future Research Directions

This study has several limitations. Firstly, it is a retrospective analysis of clinical data, which might introduce selection and information bias. Further prospective studies with larger sample sizes are needed to validate these findings. Secondly, the study focused on FGR without considering other potential maternal and neonatal factors that might affect pregnancy outcomes, such as maternal age, socioeconomic status, and neonatal interventions. Future research should consider these additional variables. Thirdly, the study was conducted at a single medical center, which could limit the generalizability of the results. Multicenter studies would be valuable to assess the broader population. Fourthly, the study primarily examined pregnancy outcomes and neonatal characteristics, while the long-term effects on the health and development of FGR infants were not fully explored. Future research could investigate the long-term health outcomes and developmental trajectories of FGR infants to gain a more comprehensive understanding of their well-being.

Author Contributions

Tingting Cheng: Data collection and management; Data analysis; Manuscript writing.

Xiujuan Wang, Xiaoli Zhao and Xiaomei Zhao: Data collection.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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