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ARTICLE

Internal Quality Network Stress and Inflammation Reaction Indicators in the Expression and Significance of the Serum of Limited Pregnant Women's Serum

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Abstract

Aims/Background Fetal growth restriction (FGR) is a common clinical disorder in pregnant women. Inflammation and endoplasmic reticulum stress play an important role in the occurrence and development of FGR. The purpose of this study was to explore the expression and significance of endoplasmic reticulum stress and inflammatory response indicators in the serum of pregnant women with FGR.

Methods The data of pregnant women admitted to Changzhou Maternal and Child Health Care Hospital from January 2020 to June 2023 were collected and analyzed by propensity score matching (PSM). Pregnant women with FGR were included in the observation group (n = 65), whereas healthy pregnant women admitted to the hospital during the same period were included in the control group (n = 65). Enzyme-linked immunosorbent assay (ELISA) was used to detect the serum levels of inflammatory markers such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) in all the pregnant women recruited in this study. The serum levels of glucose regulatory protein 78 (GRP78) and C/EBP homologous protein (CHOP), which are characteristic indicators of endoplasmic reticulum stress, in the two groups of pregnant women, were also detected and analyzed. A range of parameters concerning fetal growth and development indicators, such as fetal head circumference, abdominal circumference and fetal development index, of the two groups of study subjects were recorded and compared. Analyze the correlation between inflammatory response indicators and endoplasmic reticulum stress factors in pregnant women with FGR and fetal growth and development indicators.

Results The serum levels of TNF-α, IL-1β and IL-6 in the observation group were significantly higher than those in the control group ($p < 0.001$). The serum levels of GRP78 and CHOP in the observation group were significantly higher than those in the control group ($p < 0.001$). The levels of GRP78 and CHOP in pregnant women with FGR were negatively correlated with fetal head circumference, abdominal circumference, and fetal growth and development index ($p < 0.05$).

Conclusion The serum levels of inflammatory markers such as TNF-α, IL-1β and IL-6 in pregnant women with FGR were abnormally elevated, indicating severe inflammatory response. In addition, endoplasmic reticulum stress was observed in pregnant women with FGR, marked by significantly elevated levels of GRP78 and CHOP. The levels of TNF-α, IL-1β, IL-6, GRP78 and CHOP were negatively correlated with fetal head circumference, abdominal circumference and fetal growth and development index, implying their impacts on the occurrence and development of FGR.

Key words: endoplasmic reticulum stress; inflammatory response; fetal growth restriction; serum

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Introduction

Fetal growth restriction (FGR), also known as intrauterine growth restriction, is a common pregnancy disorder. Its main clinical feature is that the fetus is limited by the growth and development of intrauterine environment, fetus, placenta and other factors, and fails to realize the growth potential determined by genetics (Gantenbein and Kanaka-Gantenbein, 2022; Gumina and Su, 2023). The weight or abdominal circumference of the fetus affected by FGR, as estimated by fetal ultrasound, is less than 10% of a healthy fetus during the same gestational age (Gelman et al, 2022). FGR is identified as a risk factor for stillbirth (Page et al, 2021). FGR can cause disruptions in fetal metabolism, body temperature, and circulation disorders, leading to respiratory distress syndrome, necrotizing enteritis, retinopathy of prematurity and other diseases (Dai et al, 2021; Wang et al, 2021).

Currently, Doppler ultrasound is primarily used to aid in the diagnosis of FGR, but the ultrasonographic findings are vulnerable to inaccuracies due to the varying fetal position, size, operation technique, instrument resolution and other factors (Lees et al, 2022; Sulas et al, 2021). Due to the lack of effective screening methods in clinical practice, the risk of neonatal FGR is leaked before birth. During pregnancy, the allogeneic fetus may activate the pregnant mother's immune inflammatory response. When immune imbalances occur, highly activated inflammatory cells will release a copious amount of inflammatory factors, which infiltrate the placental tissue and blood vessels under the inflammatory milieu in the long term, ultimately inducing placental vascular endothelial damage (Benagiano et al, 2021). Normal functions of the endovascular network include proper protein folding and glycosylation, fatty acid synthesis, and calcium stability. Hypoxia can lead to misfolded and unfolded proteins aggregation in the endoplasmic reticulum cavity (Brain et al, 2019). Both of them play an important role in the occurrence and development of FGR, and are closely related to their pathogenesis and complex pathogenic factors. The etiological complexity of FGR and the lack of effective treatment measures have made the research concerning the pathogenesis of FGR one of the research hotspots worldwide. On the basis of previous studies, this study examined the level of inflammatory markers and endoplasmic reticulum stress indicators in both healthy and FGR pregnant women, and explored the correlations of these markers with fetal growth and development. In addition, we attempted to pinpoint the influencing factors of FGR in this study, which would provide crucial insights for early diagnosis and prevention of FGR in pregnant women.

Methods

Research Subjects

This single-centre retrospective cohort study included 376 pregnant women who were hospitalized at Changzhou Maternal and Child Health Care Hospital between January 2020 and June 2023.

The pregnant women with FGR were included in the present study if fulfilling these inclusion criteria: (1) natural conception, all of them are single pregnancy; (2) the quality of the fetus or abdomen is below the 10% lyric of the fetal body or below

the corresponding gestational week; (3) from gestational weeks 25 to 35, the file was established in the hospital, with regular production inspection and complete clinical data.

The subjects were excluded from the study if they met the following criteria: (1) individuals with multiple pregnancy; (2) individuals carrying fetuses with abnormal anatomical structure; (3) individuals carrying fetuses with chromosomal abnormalities; (4) pregnant women afflicted with other pregnancy complications, early occurrence of eclampsia, gestational diabetes and hypertension; (5) pregnant women who were long-term smokers, alcoholics or drug abusers; (6) pregnant women with severe infection, immune disease and thyroid disease; and (7) individuals with incomplete clinical data.

Propensity Score Matching (PSM)

The propensity score which is the conditional probability of being treated under the covariate condition, can reduce bias and equalize confounding factors between groups. The propensity score covariates in this study included age, duration of pregnancy, BMI, first birth, cesarean section, gestational diabetes mellitus, gestational hypertension and anemia. The propensity score was calculated by logistic regression analysis using the R software MatchIt package (version 3.6.3, R Foundation, Vienna, Austria) and 1:1 nearest-neighbor matching without a caliper value. After matching, p values for the group samples were all greater than 0.05, indicating a good balance.

Detection of Inflammatory Markers

Five milliliters of peripheral vein blood was drawn from each subject on an empty stomach in the morning and collected in a sterile test tube without containing anticoagulants. After being left at room temperature for 30 min, the test tubes containing the blood samples were centrifuged at 3000 R/min for 20 min. The serum separation was obtained from each test tube and kept in a sterile test tube, which was then stored at –20 °C for future experiments. Double-sandwich enzyme-linked immunosorbent assays (ELISA) were employed to detect the serum levels of tumor necrosis factor alpha (TNF-α; CB11762-Hu, Shanghai Coibo Biotechnology Co., Ltd., Shanghai, China), interleukin-1β (IL-1β; CB10347-Hu, Shanghai Coibo Biotechnology Co., Ltd.) and interleukin-6 (IL-6; CB10373-Hu, Shanghai Coibo Biotechnology Co., Ltd.). The serum levels of these inflammatory markers were measured in accordance with the manufacturers' instructions. The enzyme label used in this study was the Bio-TekELx800 enzyme standard (BioTek, Winooski, VT, USA).

Determination of the Levels of Endoplasmic Reticulum Stress Indicators

Five milliliters of peripheral vein blood was drawn from each subject on an empty stomach in the morning and collected in a sterile test tube without anticoagulants. After being left at room temperature for 30 min, the test tubes were centrifuged at 3000 R/min for 20 min. The serum separated was obtained from each test tube and collected in a sterile test tube, prior to storage in a –20 °C. Double-

sandwich ELISA were employed to detect the serum levels of glucose regulatory protein 78 (GRP78; ABS2103, Sigma-Aldrich, St Louis, MO, USA) and C/EBP homologous protein (CHOP; ABC955, Sigma-Aldrich, St Louis, MO, USA). The absorbance was read at the wavelength of 450 nm. A standard curve was plotted using the standard concentration data, and based on this, the serum level of the measured marker was determined. The enzyme label used was the American BIO-TekelX-8000 enzyme standard.

Determination of Fetal Growth and Development Indicators

The color Doppler ultrasound was used to measure the fetal head circumference, abdominal circumference, and fetal development index.

Statistical Analysis

Statistical analysis of the data obtained was performed using Statistical Product and Service Solutions (SPSS) software (version: 18.0, IBM Corporation, Armonk, NY, USA). Quantitative data were tested for conformance to normality. Normally distributed data are expressed as mean ± standard deviation, and were analyzed using independent samples *t* test for inter-group comparison. Categorical data are expressed as count and percentage, and Chi-square test was used for data comparison. Pearson's correlation analysis was used to analyze the correlations of serum inflammatory markers and endoplasmic reticulum stress indicators with fetal growth and development index. $p < 0.05$ indicated that the difference is statistically significant.

Results

Baseline Characteristics of Patients before and after PSM

A total of 227 patients were considered eligible for this study: 65 (28.63%) in the observation group (diagnosed with FGR) and 162 (71.37%) in the control group. After PSM, 130 patients were enrolled in the study, 65 in the observation group and 65 in the control group (Fig. 1). Before PSM, there were no significant differences in cesarean section between the two groups ($p > 0.05$), but there were significant differences in age, duration of pregnancy, body mass index (BMI), first birth, gestational diabetes mellitus, gestational hypertension and anemia ($p < 0.05$). After matching, there were no significant differences in age, duration of pregnancy, BMI, first birth, cesarean section, gestational diabetes mellitus, gestational hypertension and anemia among all groups ($p > 0.05$; Table 1), which was comparable.

Comparison of Serum Levels of Inflammatory Markers between the Observation and Control Groups

The serum levels of inflammatory markers such as TNF-α, IL-1β and IL-6 in the observation group were significantly higher than those in the control group ($p < 0.001$; Table 2).

Table 1. Comparison of baseline characteristics between the observation and control groups before and after PSM.

Parameter	Before PSM				After PSM			
	Control group (n = 162)	Observation group (n = 65)	t/χ^2	p-value	Control group (n = 65)	Observation group (n = 65)	t/χ^2	p-value
Age (years)	31.29 ± 3.46	27.96 ± 2.81	6.897	<0.001	28.24 ± 2.55	27.96 ± 2.81	0.595	0.553
Duration of pregnancy (weeks)	31.41 ± 3.77	30.12 ± 3.62	2.357	0.019	30.69 ± 3.54	30.12 ± 3.62	0.908	0.366
BMI (kg/m^2)	25.94 ± 2.97	24.12 ± 2.36	4.411	<0.001	23.85 ± 2.68	24.12 ± 2.36	0.610	0.543
First birth (Yes/No)	69/93	46/19	14.734	<0.001	41/24	46/19	0.869	0.351
Cesarean section (Yes/No)	137/25	59/6	1.513	0.219	58/7	59/6	0.085	0.770
Gestational diabetes mellitus (Yes/No)	39/123	3/62	11.648	0.001	2/63	3/62	0.000	1.000
Gestational hypertension (Yes/No)	41/121	2/63	14.932	<0.001	5/60	2/63	0.604	0.437
Anemia (Yes/No)	23/139	3/62	4.200	0.040	6/59	3/62	0.478	0.490

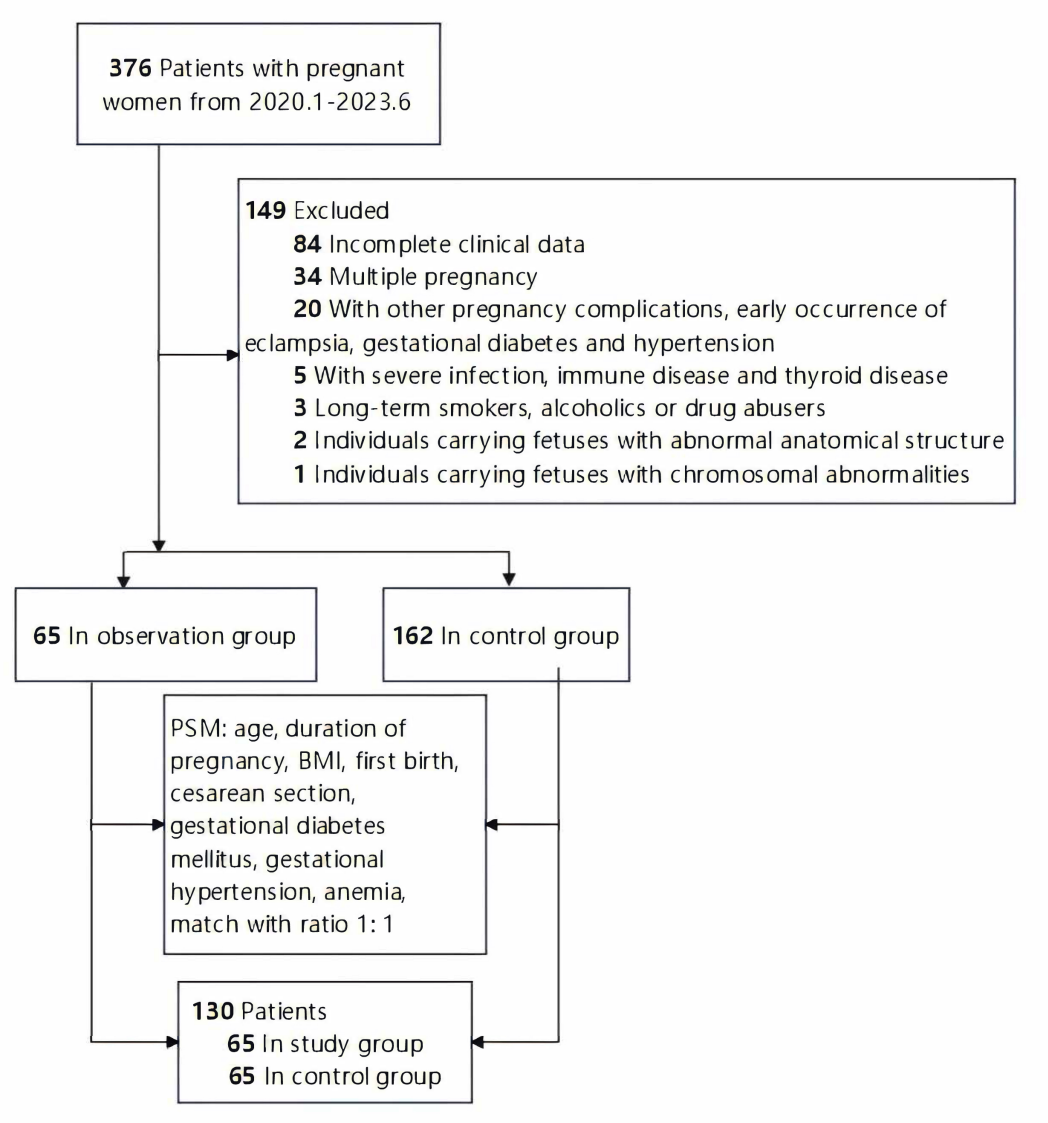

Fig. 1. Flow diagram of participant selection. Note: PSM, propensity score matching; BMI, body mass index.

Comparison of Serum Levels of Endoplasmic Reticulum Stress Indicators between the Observation and Control Groups

The comparison analysis revealed that the serum levels of endoplasmic reticulum stress indicators such as GRP78 and CHOP in the observation group significantly surpassed those in the control group ($p < 0.001$; Table 3).

Comparison of Fetal Growth and Development Indexes between the Observation and Control Groups

The current set of results also unveiled that the fetuses in the observation group had significantly lower head circumference, abdominal circumference and growth and development indexes compared with those in the control group ($p < 0.001$; Table 4).

Table 2. Comparison of serum levels of inflammatory markers between the observation and control groups.

Group	Number of patients	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)
Control group	65	53.30 ± 4.81	36.55 ± 3.71	24.59 ± 2.37
Observation group	65	77.43 ± 6.12	67.38 ± 6.67	45.67 ± 4.48
t-value		24.993	32.566	33.533
p-value		<0.001	<0.001	<0.001

Abbreviations: TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1β; IL-6, interleukin-6.

Table 3. Comparison of serum levels of endoplasmic reticulum stress indicators between the observation and control groups.

Group	Number of patients	GRP78 (pg/mL)	CHOP (ng/mL)
Control group	65	58.72 ± 4.19	66.42 ± 6.82
Observation group	65	85.45 ± 7.84	128.35 ± 10.14
t-value		24.243	40.858
p-value		<0.001	<0.001

Abbreviations: GRP78, glucose regulatory protein 78; CHOP, C/EBP homologous protein.

Correlations of Inflammatory Markers and Endoplasmic Reticulum Stress Indicators with Fetal Growth and Development Parameters in Pregnant Women with FGR

The Pearson's correlation test showed that the serum levels of TNF-α, IL-1β and IL-6 in pregnant women with FGR were negatively correlated with fetal head circumference, abdominal circumference and fetal growth and development index ($p < 0.05$). The serum levels of GRP78 and CHOP in FGR presented negative correlations with fetal head circumference, abdominal circumference, and fetal growth and development index ($p < 0.05$; Table 5).

Discussion

FGR is a common obstetric complication of pregnancy and one of the major fetal factors leading to poor perinatal and long-term prognosis (D'Agostin et al, 2023). The pathogenesis of FGR is complex and unclear, and many influencing factors may lead to the occurrence and development of FGR. Factors such as poor placental perfusion, multiple pregnancy, maternal malnutrition, severe maternal inflammation, fetal chromosomal defects, and congenital inheritance may increase the risk of FGR (Kochhar et al, 2022; Ramirez Zegarra et al, 2022; Sławek-Szmyt et al, 2022). Although ultrasound is the most widely used screening method, clinical screening and diagnosis of FGR remains significantly challenging, while exploration of other screening indicators for FGR are still in the clinical research stage. In addition, the pathological mechanism of FGR remains largely obscure, and there are still no effective prevention and treatment measures at present. Therefore, it is

Table 4. Comparison of fetal growth and development parameters between the observation and control groups.

Group	Number of patients	Head circumference (cm)	Abdominal circumference (cm)	Fetal growth and development index
Control group	65	30.64 ± 3.32	30.78 ± 3.27	0.44 ± 0.25
Observation group	65	24.67 ± 2.71	23.82 ± 2.62	–4.12 ± 1.32
t-value		11.231	13.392	27.365
p-value		<0.001	<0.001	<0.001

Table 5. Correlations of inflammatory markers and endoplasmic reticulum stress indicators with fetal growth and development parameters in pregnant women with FGR.

Items	Head circumference	Abdominal circumference	Fetal growth and development index
TNF-α	–0.373*	–0.334*	–0.567*
IL-1β	–0.415*	–0.382*	–0.534*
IL-6	–0.355*	–0.329*	–0.521*
GRP78	–0.318*	–0.347*	–0.533*
CHOP	–0.401*	–0.338*	–0.539*

Note: *$p < 0.05$.

of great significance to explore the mechanism underlying the occurrence and development of FGR and identify key molecular markers that are potent enough for early clinical diagnosis and treatment of FGR.

It is known that during pregnancy, the allogeneic fetus may activate the maternal immune inflammatory response, without exacerbating the inflammatory state. During immune imbalance, highly activated inflammatory cells release copious amounts of inflammatory factors, resulting in long-term massive infiltration of placental tissues and blood vessels into the inflammatory environment, and finally triggering FGR (Ortega et al, 2022). The TNF-α, IL-1β, and IL-6 are classical indicators of inflammation, which can be utilized to capture a snapshot of the inflammatory extent in the body (Kokot et al, 2021). In this study, 65 pregnant women with FGR were selected as research objects, and the serum levels of TNF-α, IL-1β and IL-6, as well as GRP78 and CHOP levels between pregnant women with FGR and healthy pregnant women, were compared. Furthermore, the correlations of these markers with fetal growth and development indicators were analyzed to establish an understanding of their clinical significance. The results showed that in this study, the serum levels of TNF-α, IL-1β and IL-6 in the observation group were significantly higher than those in the control group. Compared with healthy pregnant women, pregnant women with FGR had abnormally high levels of inflammatory factors, which indicates a severe inflammatory response in pregnant women with FGR. It is speculated that when placental tissues and blood vessels infiltrate the inflammatory environment for a long time, endothelial function will be damaged to a certain extent, and vascular tension and homeostasis will be destroyed (San Juan-Reyes et al, 2020). This will reduce trophoblast invasion, lead

to incomplete remodeling of placental blood vessels, and increase uterine spiral artery wall thickness. Adding to the burden is the uteroplacental circulation suffering from high resistance to circulation and reduced blood flow (Gyselaers and Lees, 2022; Moore et al, 2022). While the pregnancy persists, the placental vascular function would suffer from a dramatic decline, accompanied by reduced uterine and placental blood perfusion, as well as the occurrence of local microthrombosis and hypercoagulability, leading to FGR (Odukoya et al, 2021). Abnormally elevated levels of pro-inflammatory factors can impair placental circulation and affect nutrient exchange between mother and fetus (Benagiano et al, 2021). At the same time, free radicals and other substances are generated, further aggravating inflammatory lesions, inhibiting the metabolic function of trophoblasts, causing placental ischemia and hypoxia, and suppressing fetal growth (Liu et al, 2022a). In addition, this study further found that the serum levels of TNF-α, IL-1β and IL-6 in pregnant women with FGR were negatively correlated with fetal head circumference, abdominal circumference and fetal growth and development index. A study has shown that there is a significant correlation between the level of inflammatory markers and FGR. Inflammatory cytokines released as a result of stimulation by biological factors and some abiotic factors could trigger the release of neuroinflammatory mediators, which impact the homeostasis of maternal inflammation and aggravate the inflammation-induced damage to cells and placenta (Yap and Perlman, 2020).

The endoplasmic reticulum is an important cellular organelle, which functions to facilitate protein folding and glycosylation, fatty acid synthesis, and calcium homeostasis (Lemmer et al, 2021). The endoplasmic reticulum senses, coordinates, and regulates stress responses. The endoplasmic reticulum is extremely sensitive to various stimuli. When the organelle is in a state of hypoxia, ischemia, starvation, and calcium imbalance, misfolded and unfolded proteins will start accumulating in its cavity, resulting in endoplasmic reticulum stress (Liu et al, 2022b). Cells exposed to endoplasmic reticulum stress regulate the expression or activation of endoplasmic reticulum stress-related pro-apoptotic and pro-survival molecules, ultimately determining the fate of the cell—adapts or dies. A study has found that alterations in endoplasmic reticulum self-homeostasis play an important role in the pathogenesis of numerous chronic diseases, such as type 1 and type 2 diabetes, myocardial ischemic infarction, stroke, neurodegeneration, etc. (Chen and Zhang, 2023). In recent years, it has been found that elevated endoplasmic reticulum stress can be detected in the placenta in the case of FGR and preeclampsia + FGR, associated with decreased cell proliferation and increased apoptosis, and it is considered the prime reason that the placenta can recognize these growth phenotypes (Du et al, 2022).

An emerging study suggested that FGR may represent the severe stage of the clinical manifestations of a damaged placenta (Mecacci et al, 2021). Recently, molecular findings of protein synthesis inhibited by endoplasmic reticulum stress offered evidence that small placenta can be considered a disease. In this study, serum GRP78 and CHOP levels in the observation group were significantly higher than those in the control group. Compared with healthy pregnant women, pregnant women with FGR had abnormally high levels of endoplasmic reticulum stress-

related factors, suggesting that pregnant women with FGR have serious endoplasmic reticulum stress responses. GRP78 and CHOP are members of the C/EBP transcription factor family involved in the regulation of apoptosis, which are basically undetectable under normal physiological conditions, but become significantly induced and abnormally elevated in the presence of endoplasmic reticulum stress (Ghemrawi and Khair, 2020). When severe endoplasmic reticulum stress occurs in pregnant women, pro-inflammatory factors, antiangiogenic factors, and trophoblastic apoptotic fragments enter the maternal blood circulation, causing circulatory syndrome (Mehta et al, 2020). The major maternal and fetal factors may alter the response of the placenta to maternal vascular injury and the effects of placental factor released by the pregnant mother. However, for both maternal and fetal factors, the placental spiral artery remodeling is the major factor correlating with the severity of endoplasmic reticulum stress and oxidative stress. This study further discovered that GRP78 and CHOP levels in pregnant women with FGR were negatively correlated with fetal head circumference, abdominal circumference, and fetal growth and development index, indicating that the endoplasmic reticulum stress pathway is related to the mechanism of FGR development. Upon adverse stimulation, endoplasmic reticulum stress starts to develop in the body, and the long-term stress could lead to apoptosis, which seriously affects the exchange of substances and nutrients between the mother and the fetus, ultimately leading to FGR.

However, in this retrospective study, only single-center case data were collected and the sample size of included cases was small. Besides, there was no analysis of an extended range of neonatal outcomes, and no histopathological examination of placenta was performed, so the inclusion of healthy children in the FGR group could not be ruled out, and the study results were biased to some extent. In future studies, multi-center, large-sample prospective studies can be carried out to further explore the relationship between changes in peripheral blood inflammatory markers and the occurrence and development of FGR, so as to provide meaningful data for the formulation of early intervention measures to improve pregnancy outcomes and neonatal prognosis.

Conclusion

In summary, the levels of serum inflammatory markers such as TNF-α, IL-1β and IL-6 in pregnant women with FGR are abnormally elevated, indicating severe inflammatory response. In addition, heightened endoplasmic reticulum stress, marked by significantly elevated levels of GRP78 and CHOP, is prevalent among pregnant women with FGR. The current study also demonstrated that the levels of TNF-α, IL-1β, IL-6, GRP78 and CHOP are negatively correlated with fetal head circumference, abdominal circumference and fetal growth and development index, indicating their association with the occurrence and development of FGR.

Key Points

- Endoplasmic reticulum stress and inflammation play an important role in the occurrence and development of fetal growth restriction (FGR).
- Serum levels of inflammatory markers (TNF-α, IL-1β and IL-6) and endoplasmic reticulum stress indicators (GRP78 and CHOP) were significantly increased in pregnant women with FGR.
- Serum inflammatory response and endoplasmic reticulum stress indexes are related to the occurrence and development of FGR.
- Endoplasmic reticulum stress and inflammatory response indicators are expected to provide guidance for the prevention and treatment of FGR patients.

Availability of Data and Materials

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

Author Contributions

QS and LTY were responsible for the concept and study design, provided critical review of the manuscript; LTY and HZ were responsible for laboratory experiments, data collection, data analysis; QS was responsible for drafting the manuscript and all authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Changzhou Maternal and Child Health Care Hospital Ethics Commission (Ethics approval number: 202408), and the informed consent of the patients or their family members was obtained and signed prior to the study. The study was carried out in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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