AJRCS GLOBAL RESEARCH NETWORK

Intersections of Faith and Culture: AMERICAN Journal of Religious and Cultural Studies
Volume 4, Issue 01, 2026 ISSN (E): 2993-2599

Determination of Maternal Serum Pro-Inflammatory Cytokine Changes in Intrauterine Growth Restriction

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Abstract: Background: Some fetuses were intrinsically small, registering below 10th percentile in weight for their gestational age, in accordance with their genetic growth potential. They were not growth-restricted & can be precisely characterized as small for gestational age fetuses. Factors leading to fetal growth restriction primarily encompass issues inherent to fetal-placental-maternal unit, fetal undernutrition, & intrauterine spatial constraints that hinder fetal development. Fetal growth restriction was a fetal disorder that could result in significant short-term & long-term challenges, without IUGR adversely impacting quality of life.

Aim: The study was to ascertain alterations in maternal serum pro-inflammatory cytokines in cases with intrauterine growth restriction.

Methods: This case-control study was performed in Department of Obstetrics & Gynaecology affiliated with AlImamain Alkadhimain Medical City. A total of 54 four cases with intrauterine growth restriction (Group A) & 54 controls from labor room or obstetric ward (Group B) were recruited according to study's selection criteria.

Result: No statistically significant differences were seen in age, BMI, gravidity, & parity among analyzed groups based on maternal characteristics. Inflammatory indicators indicated a very significant difference in ESR, Hs CRP, IL-6, & TNF-α across examined groups.

Conclusion: Pro-inflammatory cytokines, ESR, hsCRP, IL-6, & TNF-α levels were elevated in cases with IUGR. Consequently, it was evident that a proinflammatory condition was implicated in pathophysiology of IUGR. Further research will enable identification of particular causes of IUGR & mitigation of this inflammation, so potentially preventing onset of IUGR.

Keywords: Maternal, Cytokine, Intrauterine Growth Restriction.

1. Introduction

Normal fetal development is a tightly controlled complex process, which relies on maternal nutrition availability, placental transport capacity, fetal hormonal regulation and genetic growth potential. The maternal supply of glucose and lipid is central since deficiency and excess of both can have a negative influence on the growth of the fetus. Although long-term severe maternal malnourishment can be linked to fetal growth retardation, maternal hyperglycemia and high levels of free fatty acids are always linked to fetal overgrowth, mediated to a great extent by fetal hyperinsulinemia and placental lipid transport changes (1).

Critical roles in cellular proliferation, differentiation, and neurodevelopment of the fetus is played by placental hormones and growth factors, especially insulin-like growth factor-1 (IGF-1), leptin, and adipokines, with the disruption playing a major role in abnormal growth paths (2). Intrauterine growth restriction (IUGR) is a pathological inability of the fetus to develop to the full extent of genetically pre-determined growth and is related to the higher perinatal morbidity, mortality, and long-term consequences, including metabolic syndrome and cardiovascular disease (3,4).

Symmetric and asymmetric forms of IUGR have been generally categorized, and the major mechanism in the latter is placental insufficiency. Chronic fetal hypoxia and nutrient deprivation are caused by impaired trophoblastic invasion, abnormal spiral artery remodeling, and reduced uteroplacental perfusion (5,6,7). There is growing evidence that inflammation is a central role in the pathogenesis of IUGR. During pregnancy, there is a highly balanced immune condition that is dominated by anti-inflammatory response; however, in IUGR, there is a change in favour of a pro-inflammatory condition (8,9).

Increased serum levels of pro-inflammatory cytokines like tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6), higher erythrocyte sedimentation rate (ESR) and C-reactive protein (hs-CRP) are also consistently observed in the IUGR pregnancies (10,11,12). These mediators inhibit trophoblasts proliferation, augment the apoptotic process, interrupt placental vascular operation, and suppress the transport of amino acids and glucose to the fetus (13,14). Taken together, these results suggest that maternal serum pro-inflammatory cytokines are one of the primary factors that contribute to IUGR and can be used as a biomarker to identify the condition and risk stratify (15). Then, this is to determine changes in maternal serum pro-inflammatory cytokines in intrauterine growth restriction cases.

2. Method

This case–control study was conducted in the Department of Obstetrics and Gynaecology at Al-Imamain Al-Kadhimain Medical City. A total of 108 pregnant women were enrolled and divided into two groups: 54 women diagnosed with intrauterine growth restriction (IUGR) constituted the case group (Group A), and 54 pregnant women with normal fetal growth served as the control group (Group B). Participants were recruited from the labor room and obstetric wards according to predefined eligibility criteria.

Some of the cases involved pregnant women whose fetuses were estimated to have a fetal weight that was below the 10 th percentile of gestational age based on ultrasonography. The controls were non pregnant women whose fetuses had not developed growth restriction. The study did not include women who had fetal developmental abnormalities or other maternal diseases like preeclampsia or infectious diseases. The sampling method relied on the use of a simple random sampling technique.

The collection of data was carried out using direct interviews and reviewing medical record during maternal and neonatal discharge. Immediately after delivery, the infants were weighed on a calibrated electronic weighing scale when they were not dressed and neonatal birth weight was recorded.

The history taking of all the participants was done in detail including demographic, obstetric, medical, and surgical history, and general physical examination and calculation of body mass index. Laboratory tests were complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and kidney testing, coagulation, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a). Sample blood taken was the maternal venous blood pre-delivery. The hs-CRP, ESR, IL-6, and TNF-a levels of serum were examined. ESR was assessed by using the method by Westerngren whereas IL-6 and TNF-a were evaluated by using enzyme linked immunosorbent assay (ELISA) per manufacturer instructions. Fetus development was measured by use of third trimester ultrasonography; which began at 32 weeks of gestation and carried out every two weeks. An incidence of standard fetal biometric measurements was taken, which comprise of biparietal diameter, head circumference, abdominal circumference, and femur length, to determine the weight of the fetus and gestational age. After delivery, neonatal outcomes of birth weight and Apgar scores at 1 and 5 minutes were measured.

Ethical approval was obtained from the relevant ethical committee, and written informed consent was secured from all participants. Data were analyzed using SPSS version 26. Quantitative variables were expressed as mean ± standard deviation and compared using Student's t-test, while categorical variables were analyzed using the chi-square test. A p-value ≤ 0.05 was considered statistically significant.

3. Results

Table (1): Distribution of maternal characteristic between studied groups.

	IUGR (N=54)	Control (N=54)	P-value
Age (year) Mean± SD	31.4±3.7	30.8±4.1	0.426
BMI (kg/m2) Mean± SD	23.84±1.47	23.75±1.92	0.785
Gravidity Mean± SD	2.1±0.5	2.2±0.7	0.394
Parity Mean± SD	1±0.5	1.1±0.4	0.253

According to maternal characteristic, there was no statistically significant difference regarding to age, BMI, gravidity & parity between studied groups.

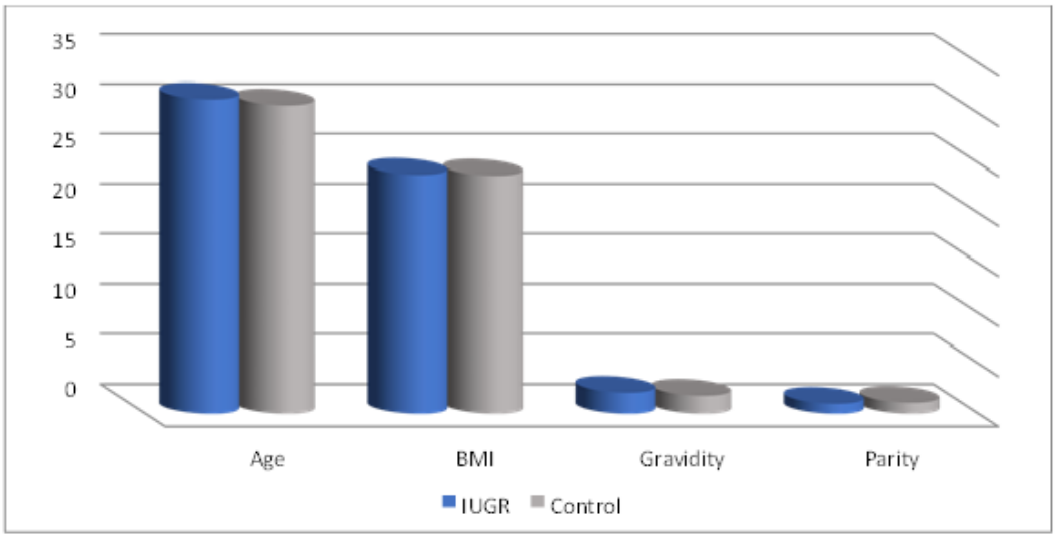

Figure (1): Distribution of maternal characteristic between studied groups.

Table (2): Distribution of inflammatory markers between studied groups.

	IUGR (N=54)	Control (N=54)	P-value
ESR (mm/hr) Mean± SD	6±1.7	2.7±0.99	<0.001
Hs CRP (mg/L) Mean± SD	1.65±0.67	0.35±0.02	<0.001
IL-6 (pg/mL) Mean± SD	8.6±1.5	1.6±0.4	<0.001
TNF-α (pg/mL) Mean± SD	1.65±0.42	0.9±0.21	<0.001

IUGR: Intra-uterine growth restriction, ESR: Erythrocyte sedimentation rate.

According to inflammatory markers, there was highly statistically significant difference regarding to ESR, Hs CRP, IL-6 & TNF-α between studied groups.

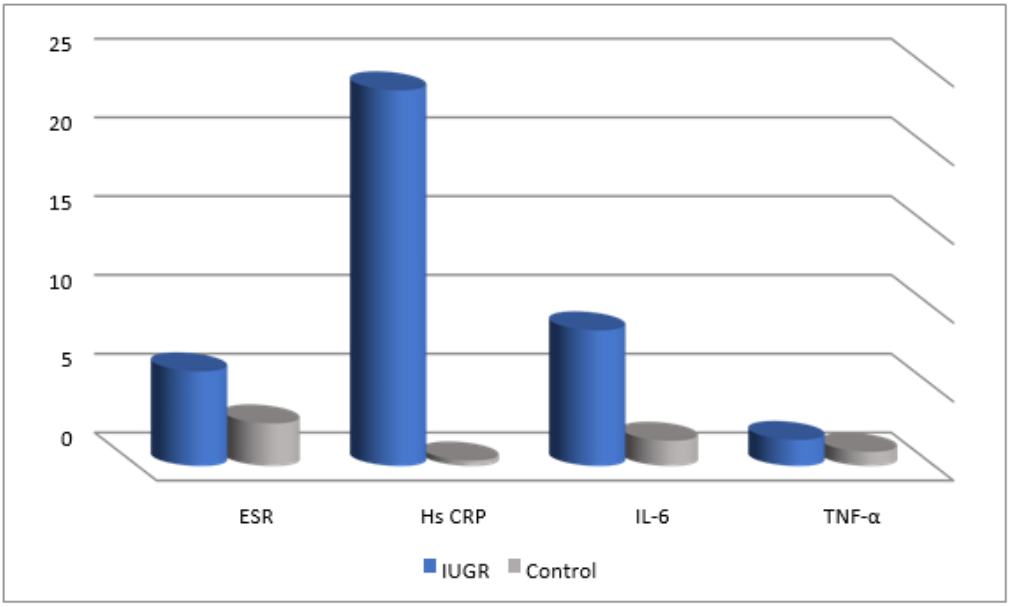

Figure (2): Distribution of inflammatory markers between studied groups.

Table (3): Distribution of neonatal outcome between studied groups.

	IUGR group (N=54)	**Control group (N=54)**	**P-value**
Apgar score (1st min) Mean± SD	7.1±0.85	8.4±0.82	**<0.001**
Apgar score (5th min) Mean± SD	8.5±0.72	9.1±0.68	**<0.001**
Birth weight (g) Mean± SD	1605.4±285.2	3248.5±62.7	**<0.001**

IUGR: Intra-uterine growth restriction

According to neonatal outcome, there was highly statistically significant difference regarding to Apgar score (1st min), Apgar score (5th min) & birth weight between studied groups.

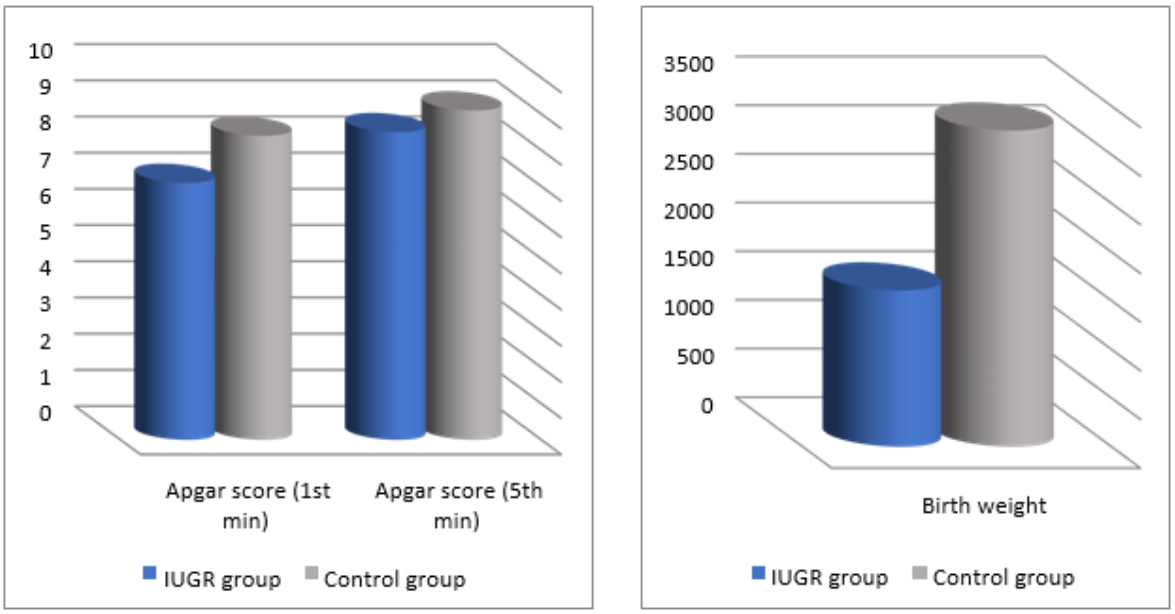

Figure (3): Distribution of neonatal outcome between studied groups.

4. Discussion

IUGR denotes a reduction in growth rate that may transpire in fetuses. precise etiology of IUGR remains unidentified as it impacts over thirty million neonates annually.

It was thought that genetic factors play a role in approximately one-third cases, and maternal, foetal, or placental factors account for the remaining two-thirds. (16)

IUGR foetuses are more vulnerable to perinatal morbidity, such as sepsis, asphyxia and perinatal death. In addition, IUGR was a significant risk factor for development of DM & cardiovascular diseases in childhood & adulthood. For these reasons, it is important to understand the pathogenesis of IUGR and take the necessary precautions. (17, 18)

Immunological balance is of great importance during pregnancy. It is known that some biomarkers and cytokines are responsible for endothelial damage and placental dysfunction in pregnancy. Furthermore, the alteration of the immune balance mediates perinatal complications, such as preterm delivery or abortion. (19,20)

There are few studies in literature investigating relationship between inflammation & IUGR. a study comparing CRP levels in maternal serum & umbilical cord blood during delivery, CRP levels were higher in IUGR group (21,22)**.** There were studies showing that high CRP levels detected in the early weeks of pregnancy can predict which infants will be small for their gestational age at birth. (23)

Recent investigations have examined influence of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, IL-12, IL-18, & IL-23, as well as anti-inflammatory cytokines such as IL-4, IL-10, & IL-13, in aetiology of intrauterine growth restriction (IUGR). these investigations were unable to ascertain which pro- or anti-inflammatory cytokines were significant in development of IUGR, perhaps due to complex & heterogeneous character of condition. (24)

Current study indicated that, based on maternal characteristics, there were no statistically significant differences in age, BMI, gravidity, & parity among analysed groups.

Our findings corroborate those of Kirici et al. (2023) (25), who sought to assess alterations in maternal serum inflammatory markers in pregnancies affected by IUGR . They reported no statistically significant differences between IUGR group control group concerning age, BMI, gravidity, and parity.

Nnamani et al. (2021) (26) aimed to determine whether there was a relationship between prenatal Doppler indices & perinatal outcomes, as well as to assess predictive ability of UA Doppler ultrasonography in distinguishing between normal & growth-restricted pregnancies (27). With control group averaging 1.33 (SD = 1.36) & case group averaging 1.42 (SD = 1.31), they found no discernible difference in mean parity between two groups. Procalcitonin & CRP levels in maternal serum & fetal cord blood samples from cases of idiopathic IUGR were compared to a control group of newborns that were appropriate for gestational age (AGA) by Karlı et al. (2019) (28) .Regarding age, BMI, & gestational period, they found no statistically significant differences between IUGR group & control group.

Our data indicated a very significant difference in ESR, Hs CRP, IL-6, & TNF-α across tested groups.

This was consistent with results of Kirici et al. (2023) (29)**,** that IUGR group & control group differed statistically significantly in terms of ESR, Hs CRP, IL-6, & TNF-α. By comparing groups with & without placental insufficiency, Bartha et al. (2003)(30), aimed to evaluate maternal serum concentrations of two inflammatory cytokines in females with IUGR. They found that TNF-α levels in groups under study differed statistically significantly. (31)

A statistically significant difference in CRP levels between IUGR group & control group was found by Karlı et al. (2019). (28)

In their 2019 study, Kara et al. sought to compare serum levels of interleukin-6 (IL-6), sialic acid (SA), & hs-CRP in pregnancies complicated by IUGR & preeclampsia (PE) to those in healthy pregnancies.

The goal of Al-Azemi et al. (2017) (29) was to quantify the production of cytokines by maternal peripheral blood lymphocytes from pregnant female with IUGR foetus & other female with healthy fetus, as well as to look into connection between cytokine profiles & IUGR. When comparing IUGR group as a whole to normal pregnancy control group, they found no Discernible differences in IL-6 levels. (30)

Our results showed that there was a highly statistically significant difference between study groups in terms of birth weight & Apgar scores at 1st & fifth minutes.

In a similar vein, Kirici et al. (2023) (29) statistically significant difference in birth weight & Apgar scores at 1 & 5 minutes between IUGR group & control group. Karlı et al. (2019) (29) demonstrated that IUGR group & control group differed statistically significantly in terms of birth weight & Apgar score at one-minute mark.

In their 2015 study, Erkenekli et al.(32) aimed to determine if pregnant female with FGR have higher levels of plasma neopterin & CRP than women with normal pregnancies. They found that birth weights of groups under study differed statistically significantly.

5. Conclusion

pro-inflammatory cytokines, ESR, hsCRP, IL-6, & TNF-α levels were elevated in IUGR cases. Consequently, it was evident that a proinflammatory condition was implicated in pathophysiology of IUGR.

References

1. Cunningham FG, Leveno KJ, Dashe JS, Hoffman BL, Spong CY, Casey BM. Williams obstetrics 26e. 26th ed. McGraw-Hill Education/Medical; 2022.
2. Martins JG, Biggio JR, Abuhamad A, Society for Maternal-Fetal Medicine. 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):B2–17.
3. Chew LC, Osuchukwu OO, Reed DJ, Verma RP. Fetal Growth Restriction. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
4. Seal A, Dasgupta A, Sengupta M, Dastider R, Sen S. Analysis of fetal growth restriction in pregnancy in subjects attending in an obstetric clinic of a tertiary care teaching hospital. International Journal of Reproduction, Contraception, Obstetrics and Gynecology.2018;7(3), 973–980.
5. Shrivastava D, Master A. Fetal growth restriction. J Obstet Gynecol India. 2020;70(2):103–10.
6. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: the role of the mother, placenta, and fetus. Endocr Rev. 2006;27(2):141–69.
7. Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. Ultrasound Obstet Gynecol. 2011;37(5):501–14.
8. Kalousova M, Muravska A, Zima T. Pregnancy-associated plasma protein A (PAPPA) and preeclampsia. Adv Clin Chem. 2014;63:169–209.
9. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2):S745–61.
10. Joo EH, Kim YR, Kim N, Jung JE, Han SH, Cho HY. Effect of endogenic and exogenic oxidative stress triggers on adverse pregnancy outcomes: preeclampsia, fetal growth restriction, gestational diabetes mellitus and preterm birth. Int J Mol Sci. 2021;22(18):10122.
11. Marsico C, Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. Ital J Pediatr. 2017;43(1):38.

12. Pay A, Frøen JF, Staff AC, Jacobsson B, Gjessing HK. Prediction of small-for-gestational-age status by symphysis-fundus height: a registry-based population cohort study. BJOG. 2016 Jun;123(7):1167-73.
13. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane database Syst Rev. 2015;(6):CD00145.
14. Lainé F, Angeli A, Ropert M, Jezequel C, Bardou-Jacquet E, Deugnier Y, Gissot V, Lacut K, Sacher-Huvelin S, Lavenu A, Laviolle B, Comets E. Variations of hepcidin and iron-status parameters during the menstrual cycle in healthy women. Br J Haematol. 2016 175(5):980-982.
15. Raghupathy R, Al-Azemi M, Azizieh F. Intrauterine growth restriction: cytokine profiles of trophoblast antigen-stimulated maternal lymphocytes. Clin Dev Immunol. 2012; 2012:734865.
16. Kamphof HD, Posthuma S, Gordijn SJ, Ganzevoort W. Fetal growth restriction: mechanisms, epidemiology, and management. Maternal-Fetal Medicine.2022; 4(3), 186-196.
17. Damhuis SE, Ganzevoort W, Gordijn, SJ. Abnormal fetal growth: small for gestational age, fetal growth restriction, large for gestational age: definitions and epidemiology. Obstetrics and Gynaecology Clinics. 2021; 48(2), 267-279.
18. Gallego EM, Pujol AT, Bartra AJC, & Roig MDG. Fetal growth restriction. In: Ahmed RG, Uçar A, editors. Growth Disorders and Acromegaly. IntechOpen; 2020.
19. Orefice R. Immunology and the immunological response in pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology. 2021;76(6):3-12.
20. Green ES, Arck PC. Pathogenesis of preterm birth: bidirectional inflammation in mother and foetus. Seminars in Immunopathology. 2020;42(4):413-429.
21. Sadiq AM, Hussein CM, Yousif M, Mohammed R. Correlation Between Highly Sensitive C-Reactive Protein Level in Cases of Preeclampsia with or without Intrauterine-Growth Restriction. Indian Journal of Forensic Medicine & Toxicology. 2020;14(4).
22. Nikbakht R, Moghadam EK, Nasirkhani Z. Maternal serum levels of C-reactive protein at early pregnancy to predict fetal growth restriction and preterm delivery: A prospective cohort study. International Journal of Reproductive Biomedicine. 2020;18(3):157-164.
23. Armengaud JB, Yzydorczyk C, Siddeek B, Peyter A C, Simeoni U. Intrauterine growth restriction: Clinical consequences on health and disease at adulthood. Reproductive Toxicology. 2020; 99:168-176.
24. Karlı P, Özdemir AZ, Ayan D. Maternal serum and fetal cord blood C-reactive protein levels but not procalcitonin levels are increased in idiopathic intrauterine growth restriction. Med Sci Monit Int Med J Exp Clin Res. 2019; 25:6512.
25. Kirici P, Yildirim G, Togrul C, et al. Maternal serum inflammatory markers in pregnancies complicated by intrauterine growth restriction. Journal of Obstetrics and Gynaecology Research. 2023;49(4):1294–1302.
26. Nnamani CD, Ugwu EO, Dim CC, et al. Umbilical artery Doppler indices and perinatal outcomes in growth-restricted fetuses. BMC Pregnancy and Childbirth. 2021;21:372.
27. Alfirevic Z, Stampalija T, Gyte GML. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database of Systematic Reviews. 2017;6:CD007529.
28. Karlı P, Yavuzcan A, Çağlar GS, et al. Procalcitonin and C-reactive protein levels in idiopathic intrauterine growth restriction. Journal of Obstetrics and Gynaecology Research. 2019;45(3):621–628.

29. Al-Azemi M, Refaat B, Abo El-Matty DM, et al. Cytokine production by maternal lymphocytes in pregnancies complicated by intrauterine growth restriction. Journal of Reproductive Immunology. 2017;123:52–58.
30. Bartha JL, Romero-Carmona R, Comino-Delgado R. Inflammatory cytokines in intrauterine growth retardation. Acta Obstetricia et Gynecologica Scandinavica. 2003;82(12):1099–1102.
31. Hung TH, Charnock-Jones DS, Burton GJ. Hypoxia-induced TNF-α expression and placental dysfunction. International Journal of Molecular Sciences. 2020;21(3):848.
32. Erkenekli K, Sanhal CY, Yucel A, et al. Plasma neopterin and C-reactive protein levels in fetal growth restriction. Journal of Perinatal Medicine. 2015;43(5):579–585.