A J M S

Research Article

Online ISSN (2789-3219)

Serum β-hCG Levels in Pregnant Women with Mild and Severe Preeclampsia During the Third Trimester

Maisoon Hanoon Tarish Al-Rubayi[1], Faris Anwar Rasheed[1]*, Alyaa Aziz Ahmed[1]

[1]Al-Elweyia Maternity Teaching Hospital, Baghdad, Iraq

Abstract

Background: Preeclampsia is a prevalent complication that frequently arises during pregnancy. It is a disorder of the trophoblasts. Given that human chorionic gonadotropin is secreted by the trophoblast, this complication may have an impact on its serum concentration. *Objective*: To compare the β-hCG levels of expectant women who are preeclamptic and those who are normotensive. *Methods*: A prospective cross-sectional study design was implemented at Al-Elweyia Maternity Teaching Hospital for this investigation. One hundred fifty expectant women in their third trimester are participating. The study participants were allocated into three cohorts, each consisting of 50 women: normotensive, mild preeclamptic, and severe preeclamptic. β-hCG levels in maternal serum were determined using an enzyme-linked immunosorbent assay (ELISA) in every instance. *Results*: Compared to expectant women with normotensive conditions and patients with mild preeclampsia, the levels of maternal serum β-hCG were significantly elevated in patients with severe preeclampsia. β-hCG levels were not significantly affected by maternal age across all three groups. *Conclusion*: β-hCG concentrations are greater in pregnant women with moderate and severe preeclampsia compared to normotensive women, with severe preeclampsia being more pronounced than mild.
Keywords: β-hCG, Complications, Maternal outcome, Preeclampsia, Pregnancy.

مستويات هرمون موجهة الغدد التناسلية المشيمائية البشرية-بيتا في المصل لدى النساء الحوامل المصابات بتسمم الحمل الخفيف والشديد خلال الثلث الثالث من الحمل

الخلاصة

الخلفية: تسمم الحمل هو أحد المضاعفات السائدة التي تنشأ بشكل متكرر أثناء الحمل. إنه اضطراب في الأرومة الغاذية. بالنظر إلى أن موجهة الغدد التناسلية المشيمية البشرية تفرزها الأرومة الغاذية، فقد يكون لهذه المضاعفات تأثير على تركيزها في المصل. **الهدف**: مقارنة مستويات هرمون موجهة الغدد التناسلية المشيمائية البشرية β لدى النساء الحوامل المصابات بمقدمات الارتعاج والمصابات بضغط الدم الطبيعي. **الطريقة**: تم تنفيذ تصميم دراسة مقطعية مستقبلية في مستشفى العلوية التعليمي للولادة لهذا الغرض. شاركت مائة وخمسون امرأة حامل في الثلث الثالث من الحمل. تم توزيع المشاركين في الدراسة على ثلاث مجموعات، تتكون كل منها من 50 امرأة: ضغط الدم الطبيعي، وتسمم الحمل الخفيف، وتسمم الحمل الشديد. تم تحديد مستويات β-hCG في مصل الأم باستخدام مقايسة الممتز المناعي المرتبط بالإنزيم ELISAفي كل حالة. **النتائج**: بالمقارنة مع النساء الحوامل المصابات بأمراض ضغط الدم والمرضى الذين يعانون من تسمم الحمل الخفيف ، كانت مستويات مصل الأم β-hCG مرتفعة بشكل ملحوظ في المرضى الذين يعانون من تسمم الحمل الشديد. لم تتأثر مستويات هرمون موجهة الغدد التناسلية المشيمائية البشرية β تأثرا كبيرا بعمر الأم في جميع المجموعات الثلاث. **الأستنتاج**: تراكيز هرمون موجهة الغدد التناسلية المشيمائية البشرية β أكبر في النساء الحوامل المصابات بتسمم الحمل المعتدل والشديد مقارنة بالنساء المصابات بضغط الدم الطبيعي، مع كون تسمم الحمل الشديد أكثر وضوحا من الخفيف.

* *Corresponding author*: Faris A. Rasheed, Al-Elweyia Maternity Teaching Hospital, Baghdad, Iraq; Email: Faris54@yahoo.com

INTRODUCTION

Preeclampsia (PE), an enigmatic condition that may manifest during pregnancy, has the potential to inflict damage upon a multitude of organs. This multisystemic disorder, which is associated with insufficient early placentation, manifests as proteinuria and increased blood pressure beyond the 20th week of gestation. Numerous organ systems are profoundly affected, encompassing neurological disorders, hematological complications, renal and hepatic impairments, and indicators of uteroplacental dysfunction [1–4]. Pregnancy-related hospitalizations are primarily attributed to PE, which is ranked as the second most prevalent cause of maternal mortality on a global scale. The prevalence of PE varies considerably between 2% and 10% worldwide but is substantially higher in developing nations, where it ranges from 4% to 18% [5,6]. Prenatal control for pregnant women and active termination of pregnancy for patients with severe PE are the only effective methods of reducing morbidity and mortality among pregnant women and their infants at this time. A lot of research suggests that the main cause of PE may be inadequate trophoblast invasion into the mother's spiral arteries, which leads to decreased placental blood flow, trophoblast apoptosis, and the release of pro-inflammatory cytokines [7]. However, the exact causes of PE are still unknown. Recent research utilizing placentas and maternal blood from patients with PE provides additional support for the notion that the placenta may be the pathophysiological origin of PE. So, being able to accurately predict placental failure by finding early proteomic biomarkers of dysfunction would be very helpful for being able to take action quickly to lower the risk of PE. Several biochemical indicators of placental dysfunction have been utilized thus far to evaluate prognostic factors for PE before clinical symptoms manifest. Preeclampsia (PE) may be influenced by β-human chorionic gonadotropin (β-hCG), according to some studies [8,9]. β-hCG has also been proposed as a serum marker for PE screening during the 8–14 weeks of the gestational period. β-hCG, a glycoprotein hormone generated by trophoblasts, is commonly utilized in the diagnostic processes of hydatidiform mole, pregnancy, and ectopic pregnancy. Trophoblasts are places of placental vascularization, placental implantation, and blastocyst attachment [10]. Trophoblasts are specialized placental cells. Their function is to enable the transfer of nutrients and gases from the placenta to the neonate. In a normal pregnancy, the peak concentration of β-hCG is observed during the 10th and 12th weeks of gestation, after which it gradually decreases. hCG levels in the serum may fluctuate in response to abnormal placental development or function [11]. Several studies have established a correlation between reduced β-hCG levels in the first trimester and the development of preeclampsia [12]. However, some findings are inconsistent with one another [13,14]. Certain studies have indicated that patients who were diagnosed with severe PE had substantially elevated β-hCG levels, while those with moderate PE did not demonstrate any noticeable alteration

[13]. To investigate the predictive value of serum-hCG levels, specific researchers conducted a meta-analysis. The findings revealed that pregnant women with PE had substantially elevated β-hCG levels compared to healthy women. However, this study did not investigate the temporal aspect of serum β-hCG detection [9]. After this, numerous studies investigated the correlation between blood β-hCG levels and PE. Nevertheless, a number of articles reached the conclusion that the relationship lacked statistical significance [15–18].

METHODS

Study design and sample selection

This prospective cross-sectional investigation was carried out at the Baghdad-based Al-Elweyia Maternity Teaching Hospital. The Hospital Administration and the Obstetrics and Gynecology Committee of the Arabic Board for Medical Specialization both granted sanction for the study protocol. In this investigation, a sample of 150 pregnant women was evaluated. Specifically, they were all between the 28th and 40th weeks of gestation during their third trimester. The duration of pregnancy was ascertained by utilizing the first day of the preceding menstrual cycle or an early pregnancy based on ultrasonography examination in cases where the woman had irregular periods or was uncertain of her last menstrual period (LMP). Pregnant women with mild preeclampsia, pregnant women with severe preeclampsia, and normotensive pregnant women (the control group) comprised the study cohort.

Inclusion criteria

The study included patients who were 18–40 years old, singleton pregnant in the third trimester, and had no prior history of diabetes mellitus, hypertension, or any other chronic illness.

Exclusion criteria

Excluded from the study were women who had previously experienced chronic hypertension, diabetes mellitus, or any other chronic disease, as well as those who were older than 40 or had a history of multiple pregnancies.

Evaluation and outcomes measurements

Prior to being included in the study, written agreement was obtained from each participant. The patients were split up into three groups of fifty each, according to the following categories: Group 1 consists of expectant mothers who have visited the hospital's antenatal clinic and have normal blood pressure. Group 2 consists of pregnant women with mild preeclampsia whose blood pressure is within 140/110 mmHg to 140/110 mmHg, who have proteinuria (defined as urine dipstick samples with less than 2+ albumin) and no other significant problems

that could harm the mother or the fetus. Severe preeclamptic pregnant women in Group 3 have a systolic blood pressure of at least 160 mmHg, a diastolic blood pressure of at least 110 mmHg, and a proteinuria defined as a urine dipstick sample with a protein content of >2+ albumin. These patients may also exhibit complications that impact the mother or the fetus, such as cerebral or visual impairment, epigastric pain, pulmonary edema, a platelet count below 100,000/ml, abnormal liver function, oliguria (urine output of less than 30 ml/hr) or urine output of 400 ml/24 hr. Every patient gave a thorough medical history that covered things like age, parity, employment, history of hypertension, other medical disorders, headache, vertigo, vision disturbance, and heartburn symptoms.

An evaluation was performed to detect any abnormalities related to edema, soreness in the epigastrium, or abnormalities in awareness and reflexes. Systolic and diastolic pressures were measured on a regular basis. A thorough biochemical test was carried out to measure blood urea, albuminuria, serum creatinine, uric acid, liver enzymes, and platelet count in order to rule out any possible abnormalities in the vital organs. The ELISA method was used to measure the amounts of β-hCG in serum.

Statistical analysis

Data were analyzed using MINI TAB software version 14. One-way analysis of variance (ANOVA) was used to estimate the differences in means of maternal serum β-hCG hormone among the three groups. Also Student *t*-test was used to assess the difference between two groups. Values with *p*-value < 0.05 were considered statistically different.

RESULTS

Figure 1 shows that the average level of β-hCG in the blood of pregnant women who did not have high blood pressure (the control group) was 9.7±2.47 IU/mL. It was 18.4±2.7 IU/mL in women with mild preeclampsia and 24.13±4.63 IU/mL in women with severe preeclampsia. Based on the ANOVA analysis, there was a significant difference among the groups (*p*-value= 0.0001).

Based on the *post hoc* analysis, Figure 1 revealed significant differences between the three groups when compared with each other (*p*<0.001). In Figure 2A, the results demonstrate no significant difference among the three groups (*p*=0.221) regarding the gestational age; the mean gestational age in the normotensive group was 37.7±1.9 weeks, 37.5±2.1 weeks in the mild preeclampsia group, and 36.9±3.0 weeks in the severe preeclampsia group. Meanwhile, Figure 2B showed non-significant differences (*p*=0.331) among the three groups regarding maternal age. In normotensive women, the mean age was 26.0±6.2 years, 24.3±6.1 years in the mild preeclampsia

group, and 25.2±7.4 years in the severe preeclampsia group.

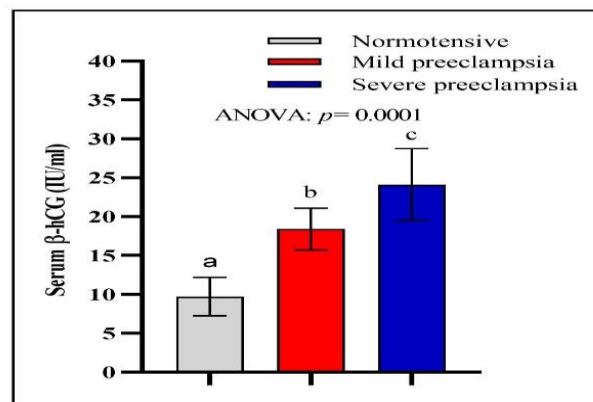**Figure 1**: Serum β-hCG levels in Normotensive and preeclamptic women. Values are expressed as mean±SD; values with different letters (a,b,c) among groups are significantly different (*p*<0.05).

Moreover, *post hoc* analysis did not show significant differences among groups when compared with each other in both gestational and maternal ages (*p*>0.05).
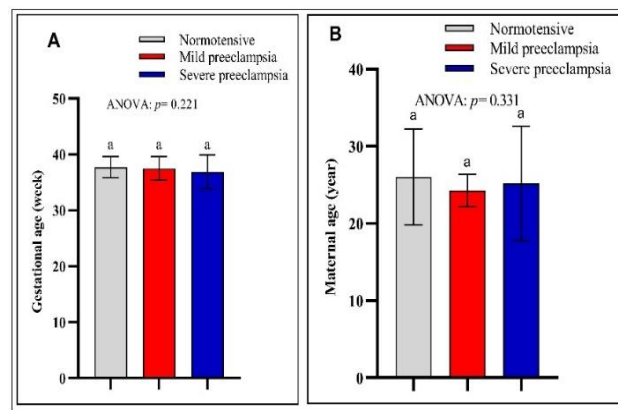

Figure 2: Gestational age (A) and maternal age (B) of normotensive and preeclamptic women. Values are expressed as mean±SD; values with different letters (a,b,c) among groups are significantly different (*p*<0.05).

The systolic blood pressure results in Figure 3A show a big difference between the three groups (*p*<0.001): the normotensive group had a mean value of 114.8±7.4 mmHg, the mild preeclampsia group had 149.6±4.9 mmHg, and the severe preeclampsia group had 174.9±11.5 mmHg. Meanwhile, Figure 2B showed significant differences (*p*<0.0.001) among the three groups regarding the diastolic pressure. In normotensive women, the diastolic pressure was 72.2±6.9 mmHg, 94.2±4.2 mmHg in the mild preeclampsia group, and 118.9±7.4 mmHg in the severe preeclampsia group. Moreover, *post hoc* analysis revealed significant differences among groups when compared with each other in both the systolic and diastolic pressures (*p*<0.05).
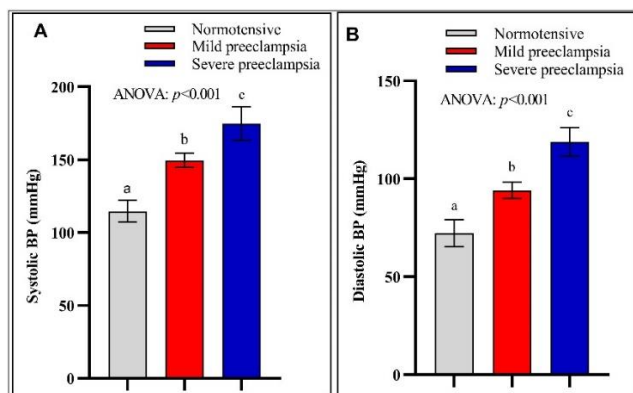
Figure 3: Differences in systolic BP (A) and diastolic BP (B) of normotensive and preeclamptic women. Values are expressed as mean±SD; values with different letters (a,b,c) among groups are significantly different (*p*<0.05).

When the studied groups were adjusted according to the maternal age range into <30 years and >30 years, Figure 4 shows that the levels of serum β-hCG in all patients aged less than 30 years in the three groups were 9.59±2.7 IU/ml in normotensive patients (*n*=34), 18.4±3.0 IU/ml in the mild preeclampsia group (*n*=37), and 24.5±3.6 IU/ml in the severe preeclampsia group (*n*=32). These results were statistically significant according to the ANOVA outcome (*p*=0.001). Moreover, Figure 4 shows that the levels of serum β-hCG in all patients older than 30 years in the three groups were 9.97±2.1 IU/ml in normotensive patients (*n*=16), 18.6±1.11 IU/ml in the mild preeclampsia group (*n*=13), and 23.6±6.2 IU/ml in the severe preeclampsia group (*n*=18), and these results were statistically significant according to the ANOVA outcome (*p*=0.001). Based on the *post hoc* analysis, there are no significant differences between the values of β-hCG levels between the different age groups within the same degree of disease severity (*p*>0.05).
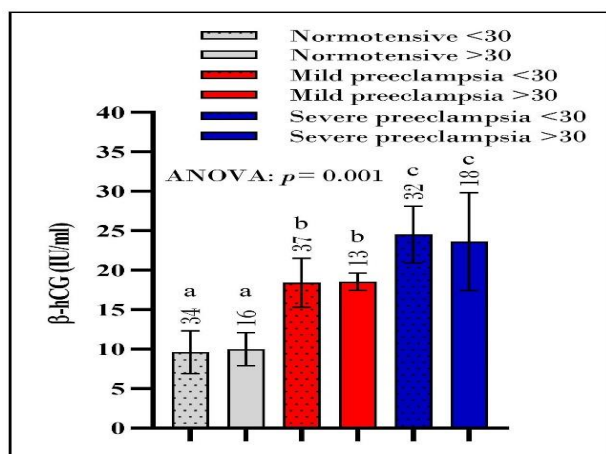

Figure 4: The differences in serum β-hCG levels of normotensive and preeclamptic women after adjustment of participants according to age groups (<30 and >30 years). Values are expressed as mean±SD; values with different letters (a,b,c) among groups are significantly different (*p*<0.05).

DISCUSSION

The precise etiology of preeclampsia remains unknown. One of the most significant factors, however, is vasospasm, which induces local hypoxia and vascular injury [19]. Many of the changes seen in the ultrastructure of placental tissue from women who are preeclamptic are similar to changes seen in placental tissue that was cultured in an environment with low oxygen [20]. The findings of the current investigation demonstrated a noteworthy correlation between heightened levels of β-hCG in the maternal serum and the degree of preeclampsia. Specifically, severe preeclamptic pregnancies exhibited a substantially higher concentration of β-hCG than normotensive and mildly preeclamptic pregnancies. This finding is consistent with the majority of prior research [21], albeit divergent from a few additional studies [22,23]. A potential correlation has been identified between the level of β-hCG and the severity of preeclampsia [24]. Other authors have found that the β-hCG level may show if someone has preeclampsia [25] and may also show if the placental trophoblast isn't working properly in cases of pregnancy-induced high blood pressure. In a study conducted in Istanbul (2004), Gurbuz *et al*. compared the mean levels of β-hCG in pregnant women with mild preeclampsia, severe preeclampsia, superimposed hypertension, and chronic hypertension to those of normotensive pregnant women. The researchers discovered that the mean levels of β-hCG were significantly elevated in the severe cases [26]. Also, different research has found that pregnant women who are preeclamptic have significantly higher levels of gonadotropin in their urine compared to women who are not preeclamptic [27]. Urine gonadotropin is the urinary metabolite of β-hCG. According to these findings [28], placental hypoperfusion may be a contributing factor in preeclampsia. An additional investigation found that β-hCG concentrations were notably greater in expectant women afflicted with severe preeclampsia in the third trimester as opposed to those with mild cases or those with normal blood pressure [29]. Hence, while the quantification of β-hCG levels might not serve as an early diagnostic tool [30], it could potentially provide insight into the disease's severity [31]. Using serum β-hCG as a marker of cytotrophoblast differentiation, researchers found that pregnant women with intrauterine growth restriction (IUGR) and preeclampsia had higher levels of serum β-hCG [32]. The current investigation reveals that significantly increased β-hCG levels may indicate intrauterine growth restriction and adverse neonatal outcomes.

Conclusion

Serum levels of β-hCG are higher in preeclamptic women (both moderate and severe) than in normotensive pregnant women, and this difference could serve as a predictor of bad outcomes for both the mother and the fetus.

Conflict of interests

No conflict of interest was declared by the authors.

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Lim R, Barker G, Lappas M. TREM-1 expression is increased in human placentas from severe early-onset preeclamptic pregnancies where it may be involved in syncytialization. *Reprod Sci (Thousand Oaks Calif.).* 2014;21:562–572. doi: 10.1177/1933719113503406.

2. Nikolic A, Cabarkapa V, Novakov Mikic A, Jakovljević A, Stosic Z. Ceruloplasmin and antioxidative enzymes in pre-Eclampsia. *J Maternal-Fetal Neonatal Med*. 2016;29:2987–2993. doi: 10.3109/14767058.2015.1111333.

3. Novakov Mikic A, Cabarkapa V, Nikolic A, Maric D, Brkic S, Mitic G, et al. Cystatin C in pre-eclampsia. *J Maternal-Fetal Neonatal Med*. 2012;25:961–965. doi: 10.3109/14767058.2011.601366.

4. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertension*. 2014;4:97–104. doi: 10.1016/j.preghy.2014.02.001.

5. Al-Jameil N, Tabassum H, Ali MN, Qadeer MA, Khan FA, Al-Rashed M. Correlation between serum trace elements and risk of preeclampsia: A case controlled study in Riyadh, Saudi Arabia. *Saudi J Biol Sci*. 2017;24:1142–118.doi: 10.1016/j.sjbs.2015.02.009.

6. Ugwuja EI, Famurewa AC, Ikaraoha CI. Comparison of serum calcium and magnesium between preeclamptic and normotensive pregnant nigerian women in Abakaliki, Nigeria. *Ann Med Health Sci Res*. 2016;6:33–37.doi: 10.4103/2141-9248.180269.

7. Rolfo A, Giuffrida D, Nuzzo AM, Pierobon D, Cardaropoli S, Piccoli E, et al. Pro-inflammatory profile of preeclamptic placental mesenchymal stromal cells: New insights into the etiopathogenesis of preeclampsia. *PloS One*. 2013;8:e59403.doi: 10.1371/journal.pone.0059403.

8. Wortelboer EJ, Koster MP, Kuc S, Eijkemans MJ, Bilardo CM, Schielen PC, et al. Longitudinal trends in fetoplacental biochemical markers, uterine artery pulsatility index and maternal blood pressure during the first trimester of pregnancy. *Ultrasound Obstetrics Gynecol*. 2011;38:383–388. doi: 10.1002/uog.9029.

9. Liu HQ, Wang YH, Wang LL, Hao M. Predictive value of free β-hCG multiple of the median for women with preeclampsia. *Gynecologic Obstetric Invest*. 2015;81:137–47.doi: 10.1159/000433434.

10. Ding X, Yang KL. Antibody-Free Detection of Human Chorionic Gonadotropin by Use of Liquid Crystals. *Analytical Chem*. 2013;85:10710–10716.doi: 10.1021/ac400732n.

11. El-Baradie SM, Mahmoud M, Makhlouf HH. Elevated serum levels of interleukin-15, interleukin-16, and human chorionic gonadotropin in women with preeclampsia. *J Obstetrics Gynaecol Can*. 2009;31:142–148.doi: 10.1016/s1701-2163(16)34098-1.

12. Karahasanovic A, Sørensen S, Nilas L. First trimester pregnancy-associated plasma protein A and human chorionic gonadotropin-beta in early and late pre-eclampsia. *Clin Chem Lab Med*. 2014;52:521–525.doi: 10.1515/cclm-2013-0338.

13. Zheng Q, Deng Y, Zhong S, Shi Y. Human chorionic gonadotropin, fetal sex and risk of Hhypertensive disorders of pregnancy: A nested case-control study. *Pregnancy Hypertension*. 2016;6:17–21. doi: 10.1016/j.preghy.2016.01.006.

14. Lee LC, Sheu BC, Shau WY, Liu DM, Lai TJ, Lee YH, et al. Mid-trimester beta-hCG levels incorporated in a multifactorial model for the prediction of severe pre-eclampsia. *Prenatal Diagnosis*. 2000;20:738–743. doi: 10.1002/1097-0223(200009)20:9<738::aid-pd917>3.0.co;2-r.

15. Long W, Zhou Q, Wang H, Lu B, Chen Y, Zhang B, et al. Second-trimester maternal serum screening biomarkers in the risk assessment for preeclampsia. *Ann Clin Lab Sci*. 2018;48:308–313. PMID: 29970433.

16. Papastefanou I, Chrelias C, Siristatidis C, Kappou D, Eleftheriades M, Kassanos D. Placental volume at 11 to 14 gestational weeks in pregnancies complicated with fetal growth restriction and preeclampsia. *Prenatal Diagnosis*. 2018;38:928–935.doi: 10.1002/pd.5356.

17. Yu N, Cui H, Chen X, Chang Y. First trimester maternal serum analytes and second trimester uterine artery doppler in the prediction of preeclampsia and fetal growth restriction. *Taiwanese J Obstetrics Gynecol*. 2017;56:358–361.doi: 10.1016/j.tjog.2017.01.009.

18. Kim SY, Kim HJ, Park SY, Han YJ, Choi JS, Ryu HM. Early prediction of hypertensive disorders of pregnancy using cell-free fetal DNA, cell-free total DNA, and biochemical markers. *Fetal Diagnosis Ther*. 2016;40:255–262.doi: 10.1159/000444524.

19. Opichka MA, Rappelt MW, Gutterman DD, Grobe JL, McIntosh JJ. Vascular dysfunction in preeclampsia. *Cells*. 2021;10(11):3055. doi: 10.3390/cells10113055.

20. Fisher SJ. Why is placentation abnormal in preeclampsia? *Am J Obstet Gynecol*. 2015;213(4 Suppl):S115-22. doi: 10.1016/j.ajog.2015.08.042.

21. Zahra Basirat Z, Barat S. Serum beta-human chorionic gonadotropin levels and preeclampsia. *Saudi Med J*. 2006;27(7):1001-1004.

22. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). *Am J Obstet Gynecol*. 2004;191(4):1446-1451. doi: 10.1016/j.ajog.2004.06.052.

23. Khanam Z, Mittal P, Suri J. Does the addition of serum PAPP-A and *β*-hCG improve the predictive value of uterine artery pulsatility index for preeclampsia at 11–14 weeks of gestation? A prospective observational study. *J Obstet Gynecol India* 2021;71:226–234. doi: 10.1007/s13224-020-01420-7.

24. Erez O, Romero R, Maymon E, Chaemsaithong P, Done B, Pacora P, et al. The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study. *PLoS One*. 2017;12(7):e0181468. doi: 10.1371/journal.pone.0181468.

25. Yadav K, Aggarwal S, Verma K. Serum βhCG and lipid profile in early second trimester as predictors of pregnancy-induced hypertension. *J Obstet Gynaecol India*. 2014;64(3):169-174. doi: 10.1007/s13224-013-0490-3.

26. Gurbuz A, Karateke A, Mengulluoglu M, Gedikbasi A, Ozturkmen M, Kabaca C, et al. Can serum HCG values be used in the differential diagnosis of pregnancy complicated by hypertension? *Hypertens Pregnancy*. 2004;23(1):1-12. doi: 10.1081/PRG-120028276.

27. Danielli M, Thomas RC, Gillies CL, Hu J, Khunti K, Tan BK. Blood biomarkers to predict the onset of pre-eclampsia: A systematic review and meta-analysis. *Heliyon*. 2022;8(11):e11226. doi: 10.1016/j.heliyon.2022.e11226.

28. Chang KJ, Seow KM, Chen KH. Preeclampsia: Recent advances in predicting, preventing, and managing the maternal and fetal life-threatening condition. *Int J Environ Res Public Health*. 2023;20(4):2994. doi: 10.3390/ijerph20042994.

29. Rybak-Krzyszkowska M, Staniczek J, Kondracka A, Bogusławska J, Kwiatkowski S, Góra T, et al. From biomarkers to the molecular mechanism of preeclampsia-A comprehensive literature review. *Int J Mol Sci*. 2023;24(17):13252. doi: 10.3390/ijms241713252.

30. Kasraeian M, Asadi N, Vafaei H, Zamanpour T, Shahraki HR, Bazrafshan K. Evaluation of serum biomarkers for detection of preeclampsia severity in pregnant women. *Pak J Med Sci*. 2018;34(4):869-873. doi: 10.12669/pjms.344.14393.

31. Han L, Holland OJ, Da Silva Costa F, Perkins AV. Potential biomarkers for late-onset and term preeclampsia: A scoping review. *Front Physiol*. 2023;14:1143543. doi: 10.3389/fphys.2023.1143543.

32. Eskild A, Strøm-Roum EM, Haavaldsen C. Does the biological response to fetal hypoxia involve angiogenesis, placental enlargement and preeclampsia? *Paediatr Perinat Epidemiol*. 2016;30(3):305-309. doi: 10.1111/ppe.12283.