ACH Med J
(2023) 3: 191-195
ISSN:2822-5872
Doi : 10.5505/achmedj.2023.80664

RESEARCH ARTICLE

Evaluation of platelet and inflammatory indices in isolated gestational proteinuria in term pregnancies

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Article Info

Received Date: 10.08.2023
Revision Date: 14.08.2023
Accepted Date: 18.08.2023

Keywords:

Isolated gestational proteinuria, Platelet indices, inflammatory indices, Term pregnancy

Abstract

Introduction: Isolated gestational proteinuria (IGP) is new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs of preeclampsia with no history of hypertension, diabetes, malignancy, autoimmune or kidney disease. IGP can be the first symptom of preeclampsia, however there is no consensus on whether IGP is a mild form of preeclampsia, in which immunologic factors and inflammation take role in pathogenesis. Platelet and inflammatory indices are changed under inflammation as under systemic inflammation neutrophilia, lymphopenia and thrombocytosis and platelet activation occur. Platelet indices are mean platelet volume (MPV) and platelet volume distribution width (PDW). Inflammatory indices include neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio(PLR). This study compared the platelet and inflammatory indices between IGP and healthy pregnancies. **Methods:** Thirty-two IGP and 60 healthy term pregnancies were recruited. Proteinuria was detected in 24-hours urine sample if proteinuria exceeded 300 mg/day. Platelet and inflammatory indices were obtained and calculated from complete blood count test. The groups were compared with respect to participant characteristics, MPV, PDW, NLR and PLR. $p<0.05$ was considered statistically significant. **Results:** : There was no significant difference among the two groups in terms of participant characteristics, pregnancy outcomes. The platelet and inflammatory indices were not significantly different between the groups. **Conclusion:** Mean platelet volume, PDW, NLR and PLR were not significantly different between healthy and IGP pregnancies. The pathophysiology of IGP is still controversial in the literature, but this study showed that inflammatory status was not different in IGP pregnancies than healthy pregnancies.

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Introduction

Gestational proteinuria is diagnosed when the amount of protein excretion in urine exceeds 300 mg in 24 hours during pregnancy.[1] Gestational proteinuria may indicate presence of preeclampsia or renal pathologies.[2] Approximately 30% of gestational proteinuria may be the first sign of preeclampsia.[3,4] Preeclampsia, presents as new onset hypertension with proteinuria or end-organ dysfunction after 20 weeks of gestation with no history of hypertensive disease.[5] There are several pathogenetic pathways under preeclampsia such as immunologic factors, genetic factors and inflammation. In the placental bed natural killer cells are increased and regulatory T cells are decreased.[6] With additional placental hypoxia, trophoblastic necrosis occurs and fetal DNA is released to the maternal circulation. These factors trigger maternal systemic inflammation.[7]

Isolated gestational proteinuria (IGP) is different from preeclampsia and presents as new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs of preeclampsia (low platelet count, elevated liver enzymes, blurred vision etc.). To diagnose IGP there should be no history of hypertension, diabetes, malignancy, autoimmune or kidney diseases.[2]

Inflammatory and platelet indices are obtained from complete blood count tests which are widely performed during pregnancy follow-ups. Platelet indices include mean platelet volume (MPV) and platelet volume distribution width (PDW). These indices reflect platelet activation.[8] Inflammatory indices include neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. The two indices change under inflammation as under systemic inflammation neutrophilia, lymphopenia and thrombocytosis and platelet activation occur. By using aforementioned indices inflammatory status can be revealed.

This study was designed to investigate whether IGP is also associated with inflammation unlike healthy pregnancies. To achieve this, the platelet and inflammatory indices were compared between healthy and IGP pregnancies.

Material and Methods

This study was a retrospective cohort study. The study protocol was appropriate to the Declaration of Helsinki, and ethical approval was obtained from the Ethical Committee of Kocaeli Derince Education and Research Hospital (Approval Date/Number: 08.12.2022/136). A total of 92 pregnant women age between 18 and 45, with a gestational age at least 37 weeks were recruited. This study took place in the Obstetrics and Gynecology Clinics of Kocaeli Derince Education and Research Hospital, between June 2021 and December 2022. The participants of this study were singleton pregnant women without any known comorbidities who were antenatally followed and collected 24-hours urine sample after positive proteinuria (+1 and +2) in spot urine test. The study group involved 32 pregnant women who were diagnosed only with IGP. Isolated gestational proteinuria was defined as new onset gestational proteinuria after 20 weeks of gestation in which the pregnancy is to be completed with normal maternal blood pressure and no signs and symptoms of preeclampsia during pregnancy. These pregnant women had no history of hypertension, diabetes, malignancy, autoimmune or kidney disease.[2] Preeclampsia was diagnosed with respect to ACOG criteria.[9] All participants were evaluated by urine culture. Pregnancies with urinary tract infection, multiple pregnancies, preeclamptic pregnancies, pregnant women with previous history of proteinuria or kidney disease, hypertension, pregestational and gestational diabetes, autoimmune disease and current low glomerular filtration rate, positive urinary sediment, positive nitrite in spot urine test were excluded. The control group consisted of healthy pregnancies without any comorbidities during the same period of participant recruitment. The weight and height of the pregnant women were recorded for body mass index (BMI) calculation. BMI was calculated as weight (kg)/(height ^{2}(m^2). All of the participants were followed up weekly till 6 weeks after the delivery. In the postpartum period, patients were asked to measure arterial hypertension twice a day each week, informed and evaluated for preeclampsia signs and symptoms to exclude postpartum preeclampsia. The patients developing preeclampsia were also excluded from this study.

Maternal venous blood samples obtained for complete blood count analysis, kidney function tests, liver function tests and c-reactive peptide. Blood samples were centrifuged at 3000 RPM for 10 minutes, and serum samples were analyzed for hemoglobin, white blood cell count, platelet count, platelet distribution width, mean platelet volume, neutrophil count, lymphocyte count,

alanine transaminase, aspartate transaminase, creatinine, uric acid, albumin and C-reactive protein.

The statistical analysis of the study was performed using SPSS 20.0 (IBM, USA). Numerical data determined to be normally distributed based on the results of Shapiro-Wilk test are given as mean ± standard deviation (SD) values, while non-normally distributed variables are given as median (25th-75th quartiles, IQR) values. In comparing numerical variables between two groups, the Student's T-test (for those showing a normal distribution) and the Mann Whitney-U test (for those not showing a normal distribution) were used. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

A total of 92 pregnancies were involved in this study. There was no significant difference among the two groups in terms of maternal age, gestational age, BMI, number of gravida, parity, and abortus (Table 1).

Table 1: Maternal characteristics and pregnancy outcomes of the participants.

Maternal Characteristics	Pregnancies with isolated proteinuria n=32	Pregnancies without isolated proteinuria n=60	p
Age, years	26 (23-31)	30 (24-36)	0.084
Gravida	3 (1-4)	3 (1-4)	0.488
Parity	1 (0-2)	1 (0-2)	0.748
Abortus	0 (0-1)	0 (0-0)	0.178
BMI, kg/m^2	23.9 (19.7-27.6)	24.3 (19.5-26.3)	0.407
Pregnancy Outcomes			
Birth weight, g	3000 (2420-3300)	2780 (2550-3245)	0.407
Gestational age at delivery, weeks	38.3 (37.3-39.0)	38.0 (37.0-39.5)	0.935

Data are mean ± standard deviation or median (IQR). Abbreviations: BMI: body mass index.

Pregnancy outcomes did not show a significant difference in birth weight, gestational age at delivery, neonatal intense care unit admission (p=0.463), amniotic fluid index at term (p=0.744), delivery mode (p=0.295), number of fetal growth retardation or appropriate for gestational age fetuses (p=0,473 and p=0,115 respectively).

Table 2: Laboratory results and indices of the participants.

Laboratory Parameters	Pregnancies with Isolated proteinuria n=32	Pregnancies without Isolated proteinuria n=60	p
Hemoglobin, g/dL	11.2 ± 1.3	11.8 ± 1.14	**0.049***
WBC, x10^{-3}/microL	9.752 ± 2.08	10.061 ± 2.44	0.589
PDW, %	17.3 ± 2.79	17.6 ± 2.50	0.612
MPV, fL	9.12 ± 0.88	9.22 ± 0.80	0.595
Neutrophil count, x10^{-3}/microL	6.99 ± 1.8	7.16 ± 2.06	0.726
Lymphocyte count, x10^{-3}/microL	1.93 ± 0.49	1.90 ± 0.52	0.772
Proteinuria, mg/24 hours	632 (407-837)	277 (157-281)	0.097
Platelet count, x10^{-3}/microL	264 (218-313)	226 (201-271)	0.119
MPVxPLT	2.3 (1.96-2.72)	2.1 (1.8-2.44)	0.222
PLR	131 (103-207)	133 (108-158)	0.585
NLR	3.6 (3.0-4.3)	3.7 (3.1-4.5)	0.867
PLT/N	37.0 (32.0-45.4)	35.0 (26.8-42.5))	0.220
ALT, U/L	9 (8-12)	11 (8-14)	0.056
AST, U/L	17 (13-19)	17 (14-22)	0.408
Creatinine, mg/dL	0.59 (0.55-0.65)	0.58 (0.54-0.66)	0.613
Uric acid, mg/dL	4.4 (3.9-5.6)	3.9 (3.3-4.6)	**0.042***
Albumin, g/dL	3.3 (3.1-3.6)	3.3 (3.0-3.6)	0.661
CRP, mg/L	2.0 (2.0-5.0)	2.0 (2.0-3.8)	0.853

Data are mean ± standard deviation or median (IQR). *p<0.05 indicates statistical significance. Abbreviations: WBC: White blood cell, PDW: platelet distribution width, MPV: mean platelet volume, PLT: platelet, PLR: platelet leukocyte ratio (platelet count/leukocyte count), NLR: neutrophil leukocyte ratio (neutrophil count/leukocyte count), N: neutrophil, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, IQR: interquartile range, SD:standard deviation

There was no significant difference between laboratory parameters of two groups except hemoglobin and uric acid levels. Platelet indices were not significantly different between the groups.

Discussion

This study was designed to compare inflammatory status by using platelet and inflammatory indices between healthy pregnancies and pregnancies with isolated gestational proteinuria. To

our knowledge, this was the first study designed to evaluate platelet and inflammatory indices in IGP.

The study and the control groups did not differ by means of gestational and maternal age. The blood draw period was limited to term pregnancy in order to exclude preeclamptic pregnancies. Platelet indices which are mean platelet volume (MPV) and platelet volume distribution width (PDW) and inflammatory indices which include neutrophil-lymphocyte ratio; and platelet-lymphocyte ratio were not significantly different between the groups. By this result, we showed that inflammatory status was not altered in isolated gestational proteinuria with respect to healthy pregnancies.

Previous studies by Thalor et al. and Bawore et al. showed that the platelet indices, especially the MPV and PDW were significantly increased in preeclampsia.[10,11] NLR was found to be significantly higher in preeclampsia whereas PLR was lower in preeclamptic pregnancies.[12] Systemic inflammatory response takes place in the pathophysiology of preeclampsia and inflammatory and platelet indeces were altered.[2] Maynard et al. showed that increased placental soluble fms-like tyrosine kinase 1 decreased VEGF and PIGF which created endothelial dysfunction, oxidative stress and inflammation leading to proteinuria and preeclampsia.[13] In the prospective study of Holston et al. these angiogenic factors were studied in IGP. They have concluded that IGP could be defined as mild version of preeclampsia.[14] They showed IGP was associated with lower levels of PIGF and transiently elevated soluble fms-like tyrosine kinase and soluble endoglin concentrations before the onset of proteinuria.[14] Besides, it is known that 30% of isolated gestational proteinuria progresses to preeclampsia.[3,4] However, we think that isolated gestational proteinuria pregnancies who will have future preeclampsia and will not have, are not the same and might have pathophysiological differences underneath. Because in this study, IGP pregnant women without preeclampsia progression, did not have altered inflammatory and platelet indices from healthy pregnancies. In addition to this, Kattah et al. also hypothesized that IGP should not be taken into account as mild preeclampsia because they found no association of nulliparity with IGP but it is known that preeclampsia is associated with nulliparity.[14] Another limitation of the study of Holston was, the follow up of pregnant women ended after only 24 hours after delivery. It was shown that postpartum preeclampsia could occur in pregnancies with IGP and pregnant women should be followed at least 48 hours to 6 weeks after pregnancy for preeclampsia.[15,16]

Hemoglobin and uric acid levels between the groups were statistically significant but these had no clinical significance. Mean hemoglobin and median uric acid levels of both groups were in normal ranges.

The limitations of this study were, the two clinical situations, transient or orthostatic proteinuria could not be ruled out as 24-hour urine sample was evaluated only once before delivery. Secondly, this study was performed with a small sample size and was a single center study. Proteinuria status of women with IGP after delivery and preeclamptic pregnancies were not in the scope of this study. A future study might be performed to compare inflammatory and platelet indices of preeclamptic, healthy and IGP pregnancies together and follow proteinuria status after the delivery.

Conclusion

Mean platelet volume, platelet volume distribution width, neutrophil-lymphocyte ratio; and platelet-lymphocyte ratio were not significantly different between healthy and IGP pregnancies. The pathophysiology of IGP is still controversial in the literature, but this study showed that inflammatory status was not different in IGP pregnancies than healthy pregnancies.

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