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ORIGINAL ARTICLE

Platelet and White Blood Cell (WBC) Counts in the First Trimester and Pregnancy Outcome: Prospective Controlled Study

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Abstract In pregnancy, there is usually a degree of thrombocytopenia and leukocytosis. Our aim was to find out if raised platelet and white blood cell counts (WBC) in the first trimester above 300 × 10^9/L and 10 × 10^3/mm^3, respectively are related to the pregnancy outcome. This is a prospective controlled trial at Jordan University hospital in the period between June 2017 to September 2018. Pregnant women were enrolled in the study any time less than 14 weeks with platelet count of 300 × 10^9/L or more and white blood cell count of 10.0 × 10^3/mm^3 or more (study group, 100 pregnant women). The control group (84 pregnant women) were recruited at the same time. There was a statistically significant increased risk of miscarriage in the study group, *P* value 0.018, and a statistically significant increased risk of preterm delivery, *P* value 0.001. There was also a higher risk of preterm premature rupture of membranes in the study group than the control, 11.2 versus 3.8%, odds ratio 3.169, but this difference wasn't statistically significant. Pregnancies complicated by preterm premature rupture of membranes had statistically significant higher risk of preterm deliveries, lower birth weight, higher risk of neonatal intensive care unit admission than those without membrane rupture. Elevated platelet and WBC counts in the first trimester are associated with increased risk of miscarriage, increased risk of preterm delivery and relatively increased risk of PPROM. This can serve as an early warning for adverse pregnancy outcome.

Keywords Platelet · White blood cell · Pregnancy · Outcome · Missed miscarriage · Preterm

Abbreviations

WBC	White blood cell
PPROM	Preterm premature rupture of membrane
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
NICU	Neonatal intensive care unit
P value	Probability value

Introduction

In pregnancy, there is usually a degree of thrombocytopenia which is caused by both hemodilution and increased platelet activation and accelerated clearance [1]. Gestational thrombocytopenia is seen in 7–8% of all pregnancies. The increased destruction in pregnancy leads to younger and larger platelets. Most thrombocytopenia in pregnancy is due to increased destruction [2].

White blood cell count in pregnancy is elevated, the lower limit of the reference range being around 6 × 10^9/L. Leucocytosis, occurring during pregnancy is due to the physiologic stress induced by the pregnant state [3]. Pregnancy leukocytosis is primarily related to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and reaches a plateau in the second or third trimester when the white

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blood cell count (WBC) ranges from $9 \times 10^3/mm^3$ to $15 \times 10^3/mm^3$ [4]. Bakrim et al. [5] studied a healthy pregnant population and found that the mean WBC and platelet counts in the first trimester were $7.52 \times 10^3/mm^3$ and $235.85 \times 10^9/L$, respectively.

Early gestational increase in platelet count can be explained by thrombocytosis which is linked to inflammation [6]. The cause of elevated blood leukocyte count in pregnancy is unknown. The increased polymorphonuclear leucocyte count may contribute to oxidative stress in early pregnancy [7]. Previous studies have shown that intrauterine infection triggers a rise of several cytokines in maternal serum as well as amniotic fluid [8, 9]. The aim of the study was to find out if raised platelet count and WBC in the first trimester above $300 \times 10^9/L$ and $10 \times 10^3/mm^3$, respectively are related to the pregnancy outcome.

Materials and Methods

This study was a prospective controlled trial at Jordan University hospital in the period June 2017 to September 2018. Pregnant women were enrolled in the study early in pregnancy (less than 14 weeks) with platelet count of $300 \times 10^9/L$ or more and WBC of $10.0 \times 10^3/mm^3$ or more (study group). The control group were recruited at the same time with platelet count and WBC of less than $300 \times 10^9/L$ and less than $10.0 \times 10^3/mm^3$, respectively. All included patients at the time of complete blood count testing had no evidence of clinical infection (no fever, chills or rigors during the last one week before blood was taken and no evidence of flu, upper respiratory tract infection or urinary symptoms) and normal urinalysis. All were confirmed to have viable pregnancies at the time of blood testing. The booking investigations at Jordan University hospital routinely include a complete blood count (CBC). All patients are booked at Jordan university hospital. Both the study and control groups were counselled regarding all aspects of the study including aim, process, follow up and results. Written informed consents were obtained from the patients including their telephone numbers. Data were obtained from the medical electronic files, antenatal admission notes and delivery registers. Those patients who missed follow up at Jordan university hospital were followed up with phone calls. Pregnant women with previous history of recurrent miscarriages, multiple pregnancies, congenital fetal abnormalities and those who underwent chorionic villus sampling or amniocentesis were excluded. Data including age, weight, height, body mass index (BMI), obstetric history, previous history of preterm premature rupture of membranes (PPROM), previous history of preterm delivery, medical history and underlying current medical diseases and medications were obtained. PPROM was defined as preterm premature rupture of membranes before completing 37 weeks gestation.

Both groups were followed up. Pregnancy outcomes were recorded in both groups and compared. The primary outcomes were missed miscarriage, preterm delivery and PPROM. Missed miscarriage was defined as an unrecognized intrauterine death of the embryo or fetus without expulsion of the products of conception where there was an arrest of embryonic or fetal development with ultrasound findings of an empty gestational sac or an embryo/fetus without cardiac activity.

Data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA). Frequency and percentage were calculated for the categorical data, an independent samples t test to compare means, odds ratios are used to compare the relative odds of the occurrence of the outcome, Pearson's Chi squared test. Fisher exact test was used when the cell is less than 5.0. Significance was set at $P < 0.05$. The study is powered for the three primary outcomes; missed miscarriage, preterm delivery and preterm premature rupture of membranes (the power is 0.8).

The study was approved by the Ethics Committee for Medical Research at the Jordan University Hospital and—the University of Jordan, Decision Number 173/2017. All methods were performed in accordance with the relevant guidelines and regulations.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

A total of 184 pregnant women were recruited. There were 100 pregnant women in the study group and 84 in the control group. The mean platelet counts in the study and control group were $351.8 \times 10^9/L$ and $229 \times 10^9/L$, respectively. The mean WBC in the study and control group was $11.5 \times 10^3/mm^3$ and $7.9 \times 10^3/mm^3$, respectively (Table 1).

There were no statistically significant differences between both groups in age, BMI, parity, history of preterm deliveries, history of PPROM, history of ectopic pregnancies and history of miscarriages (Table 2). Moreover, there were no differences in medical and surgical histories between both groups.

There were 20 missed miscarriages in the study group (20%) and only 6 cases in the control group (7.1%). This was a statistically significant difference, P value 0.018, odds ratio (OR) 3.25 [confidence interval (CI) 1.24–8.52]. All cases in the study group were less than 16 weeks gestation (Table 3).

Table 1 Platelet and WBC counts in the study and control groups

Variable	Study group (n = 100) 54.3% Mean ± SD	Control group (n = 84) 45.7% Mean ± SD	Total (n = 184) 100%
Platelets ($\times 10^9$/L)	351.8 ± 45.9	229.0 ± 43.4	295.73 ± 75.9
WBC ($\times 10^3$/mm^3)	11.5 ± 1.5	7.9 ± 1.4	9.9 ± 2.3

n number, *WBC* white blood cell, *SD* standard deviation

Table 2 Demographic characteristics of patients

	Study group No. = 100 (54.3%)	Control group No. = 84 (45.7%)	Total No. = 184 (100%)	*P* value	OR (95% CI)
Age (years)	30.7 ± 6.1	30.9 ± 5.3	30.8 ± 5.7	0.890	0.116 (− 1.532, 1.763)
BMI (kg/m^2)	28.0 ± 3.7	27.8 ± 3.8	27.9 ± 3.1	0.981	0.015 (− 1.202, 1.123)
Parity (number)	1.57 ± 1.7	1.40 ± 1.5	1.5 ± 1.6	0.483	0.165 (− .303, 0.629)
Gravidity (number)	3.16 ± 2.3	3.23 ± 2.7	3.19 ± 2.5	0.860	− 0.066 (− .805, 0.673)
Hx of preterm delivery	12 (12.0%)	8 (9.5%)	20 (10.9%)	0.591	1.295 (0.503, 3.336)
Hx of PPROM	2 (2.0%)	1 (1.2%)	3 (1.6%)	1.000	1.694 (0.151, 19.015)
Hx of ectopic pregnancies	0 (0.0%)	2 (2.3%)	2 (1.1%)	0.207	0.976 (0.944, 1.009)
Hx of miscarriage	44 (44%)	29 (34.5%)	73 (39.7%)	0.191	1.45 (0.819, 2.711)
GA at the previous PPROM (weeks)	30.0 ± 8.5	23.0 ± 0.0	27.7 ± 7.2	0.623	–

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *Hx* history, *PPROM* preterm premature rupture of membranes, *GA* gestational age

Table 3 Missed miscarriage in the study and control groups

Missed miscarriage	Study group	Control group	Total	*P* value	OR (CI 95%)
Yes	20 (20.0%)	6 (7.1%)	26 (14.1%)	**0.018**	3.250 (1.239, 8.523)
No	80 (80.0%)	78 (92.9%)	158 (85.1%)		

OR odds ratio, *CI* confidence interval

Bold indicate statistically significant

In a further analysis of the total cases of missed miscarriages compared with those who continued their pregnancy, maternal age, parity and gravidity were significantly higher in the patients with missed miscarriage, *P* values were 0.009, 0.042 and 0.019, respectively. The BMI had no influence on the risk of missed miscarriage, *P* value 0.770 (Table 4).

The pregnancies which continued into viability were evaluated. There were no statistically significant differences between the study and control group with regards to maternal age, BMI, parity, gestational age at delivery and mode of delivery. Caesarean delivery accounted for 41.1% of the overall patients. However, there were 22 preterm deliveries (27.5%) in the study group and 5 preterm deliveries (6.4%) in the control group. This difference was statistically significant, *P* value 0.001, OR 5.538 (CI 1.98–15.52). There was also a higher risk of PPROM in the study group than the control, 11.2 versus

Table 4 Patients' characteristics between missed miscarriages and continuing pregnancies

	Pregnancies with Missed miscarriage No. = 26 (14.1%)	Pregnancies continued into viablility No. = 158 (85.1%)	Total No. = 184 (100%)	*P* value	OR (95% CI)
Age (years)	33.5 ± 5.6	30.26 ± 5.6	30.8 ± 5.7	**0.009**	3.279 (0.864–5.694)
BMI (kg/m^2)	27.8 ± 3.2	28.0 ± 3.8	27.9 ± 3.1	0.770	0.698 (− 1.620–1.209)
Parity (number)	2.15 ± 1.74	1.39 ± 1.56	1.5 ± 1.6	**0.042**	0.768 (0.030–1.506)
Gravidity (number)	4.4 ± 2.6	3.0 ± 2.4	3.19 ± 2.5	**0.019**	1.346 (0.544–0.239)

OR odds ratio, *CI* confidence interval, *BMI* body mass index

Bold indicates statistically significant

Table 5 Patients' characteristics and different pregnancy outcomes between study and control groups

	Study group No. = 80 (50.6%)	Control group No. = 78 (49.4%)	Total No. = 158 (100%)	*P* value	OR (95% CI)
Age (years)	29.7 ± 5.9	30.7 ± 5.2	30.3 ± 5.6	0.185	1.184 (− 0.571, 2.939)
BMI (kg/m^2)	28.2 ± 3.8	27.8 ± 3.9	28.0 ± 3.8	0.512	0.399 (− 0.798, 1.596)
Parity (number)	1.4 ± 1.6	1.37 ± 1.5	1.4 ± 1.6	0.910	0.028 (− 0.463, 0.520)
Gravidity (number)	2.90 ± 2.2	3.1 ± 2.6	3.0 ± 2.4	0.602	0.203 (− 0.563, 0.969)
PPROM (number)	9 (11.2%)	3 (3.8%)	12 (7.6%)	0.131	3.169 (0.825, 12.180)
GA at PPROM	33.4 ± 2.7	29.0 ± 7.5	32.3 ± 4.5	0.141	4.444 (− 1.756, 10.645)
Preterm deliveries	22 (27.5%)	5 (6.4%)	27 (17.1%)	**0.001**	5.538 (1.976, 15.519)
Mode of delivery					
Normal delivery	48 (60.0%)	45 (57.7%)	93 (58.9%)	0.768	0.909 (0.482, 1.714)
Cesarean section	32 (40.0%)	33 (42.3%)	65 (41.1%)		

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *PPROM* preterm premature rupture of membranes

Bold indicate statistically significant

Table 6 Patients' characteristics and different pregnancy outcomes in the study and control groups with regards to PPROM

	PPROM No. = 12 (7.6%)	No PPROM No. = 146 (92.4%)	Total No. = 158 (100%)	*P* value	OR (95% CI)
Age (years)	33.2 ± 6.2	30.0 ± 5.5	30.3 ± 5.6	0.112	3.146 (− 0.847, 7.139)
BMI (kg/m^2)	28.2 ± 2.5	28.0 ± 3.9	28.0 ± 3.8	0.755	0.249 (− 1.415, 1.912)
Parity (number)	1.9 ± 1.9	1.3 ± 1.5	1.4 ± 1.6	0.334	0.574 (0.668, 1.816)
Gravidity (number)	3.7 ± 2.8	3.0 ± 2.4	3.0 ± 2.4	0.399	0.721 (− 1.070, 2.513)
GA at delivery (weeks)	34.6 ± 5.2	38.1 ± 2.0	37.9 ± 2.6	**0.038**	3.540 (− 0.239, 6.841)
Preterm	10 (88.4%)	17 (11.6%)	27 (17.1%)	**0.000**	37.941 (7.659, 187.960)
Mode of delivery					
Normal delivery	7 (58.3%)	86 (58.9%)	93 (58.9%)	0.969	1.024 (0.310, 3.379)
Cesarean section	5 (41.7%)	60 (41.1%)	65 (41.1%)		
Birth weight (g)	2350.0 ± 806.7	3028.5 ± 471.0	2976.7 ± 532.0	**0.014**	678.199 (− 161.872, 1194.525)
NICU admission	5 (41.7%)	16 (11.0%)	21 (13.3%)	**0.011**	0.172 (0.049, 0.607)

PPROM preterm premature rupture of membranes, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *NICU* neonatal intensive care unit

Bold indicates statistically significant

3.8%, *P* value 0.131, OR 3.169, but this difference wasn't statistically significant. The gestational age at delivery in those with PPROM was 33.4 ± 2.7 weeks in the study group and 29 ± 7.5 weeks in the control group. This difference was not statistically significant, *P* value 0.141(Table 5).

Pregnancies complicated by PPROM, compared with non-PPROM pregnancies, had significantly higher risk of preterm deliveries (88.4 vs 11.6%, *P* value 0.000, OR 37.941, CI 7.66–187.96), significantly lower birth weight (median birth weight 2350 vs 3028.5 g, *P* value 0.014), higher risk of neonatal intensive care unit (NICU) admission (41.7 vs 11%, *P* value 0.01) and statistically significant earlier gestational age at delivery (34.6 vs 38.1 weeks, *P* value 0.038) (Table 6).

Discussion

This study indicated statistically significant increased risk of adverse early pregnancy outcome in the form of missed miscarriages in the study group. This finding can be explained by both immunological and inflammatory mechanisms which are associated with increased fetal loss. The increased PMNL count is probably a compensatory response to PMNL priming. The increased rate of superoxide release from primed PMNL may contribute to oxidative stress in early pregnancy [7]. Increased peripheral lymphocytes are found in women with recurrent pregnancy loss and in infertile women with multiple failed in vitro fertilization cycles [10]. Park et al. found that peripheral Natural Killer (pNK) cell level is a clinically

useful marker to predict pregnancy outcome [11]. It can also be associated with infertility [10, 12]. The increased WBC in the peripheral blood can be associated with inflammatory environment that leads to poor pregnancy outcome in the form of preeclampsia [13, 14]. It was also found that elevated WBC above 15×10^9/L in the peripheral blood of women with ovarian hyperstimulation syndrome is associated with increased risk of miscarriage [15]. Platelet count in early pregnancy was also found to be associated with adverse pregnancy outcome [16], while platelet activation early in pregnancy remains at low level in normal pregnancies [17]. The elevated platelet count was used in the present study to predict pregnancy outcome as thrombocytosis is linked to inflammation [6]. Platelet-to-lymphatic ratio was found by Toprak et al. [18] to be a cost effective, easy and practical marker for the early diagnosis of PPROM.

The maternal age in years in the study and control groups was almost similar (30.7 ± 6.1 and 30.9 ± 5.3, respectively). Therefore, the increased missed miscarriage in the study group could not be contributed to by maternal age. However, in a subgroup analysis of the study women, the maternal age in missed-miscarriage pregnancies was 33.5 ± 5.6 years which was significantly older than those who continued to viability (30.26 ± 5.6 years), *P* value 0.009. This difference was within the study group only. Elise et al. [19] found that the risk of miscarriage is higher if the maternal and paternal age is 35 years or older and 40 years or older, respectively. In the present study, we did not include the paternal age. A study from Israel in 2017 [20] found that miscarriage rates rose with increasing maternal age, increasing parity and with pre-pregnancy BMI of 30 or more. This study showed that those with miscarriages have significantly higher gravidity and parity but the risk of miscarriage was not related to maternal BMI. The finding in the present study that BMI had no influence on the risk of miscarriage could possibly be explained by the small number of cases and, in this study, all cases were missed miscarriages. But, overall, in our study group the BMI was elevated (28.0).

Other important findings were the statistically significant increased risk of preterm delivery in the study group (*P* value 0.001, OR 5.538, CI 1.98–15.52) and the relative increased risk of PPROM in the study group (OR 3.169) although it does not reach a statistical significance. The non-significant increased risk of PPROM is explained statistically by the small number of cases caused by the small size of the study. Ekin et al. [21] found that pregnancies complicated by PPROM had significantly increased levels of platelet count in the first trimester. Gomez et al. [22] provided evidence that infection is an essential factor in both preterm labour and PPROM and both conditions can be considered an expression of the same basic phenomenon. We did not find studies combining both the WBC and platelet count early in pregnancy to predict adverse pregnancy outcome. Cho et al. [23] found that delta neutrophil index is a predictor marker for histological chorioamnionitis in patients who already had PPROM. Also Dhaifalah et al. [24], used azurocidin levels in maternal serum early in pregnancy to predict PPROM.

Zhan et al. [25] found that blood routine test using WBC can be used to predict the risk of premature rupture of membranes, the cut off value of WBC was 9.63×10^3/mm^3. They also stated that combining multiple parameters can improve the sensitivity and specificity. The cut-off value of WBC in this study was 10×10^3/mm^3 and was combined with platelet count. There wasn't a statistically significant difference in the gestational age at which PPROM occurred in the study and control group (33.4 ± 2.7 weeks and 29.0 ± 7.5 weeks, respectively, *P* value 0.141). This could be explained by the wide standard deviation in the control group (29.0 ± 7.5 weeks). Moreover, the etiology of PPROM is multifactorial [26]. In addition, there was no significant difference in the mode of delivery between the study and control groups as the mode of delivery was dictated by obstetric indications.

The adverse pregnancy outcome in pregnancies complicated by PPROM (higher risk of preterm deliveries, lower fetal birth weight, higher risk of neonatal intensive care unit (NICU) admission earlier gestational age at delivery are all statistically significant. The findings from the present study are similar to other studies investigating the outcome after PPROM [27–29]. We did not study maternal and other perinatal outcomes after PPROM. In fact, Dundar et al. [30] found that platelet indices had a predictive value for respiratory distress syndrome (RDS) in PPROM cases. Further large multicentre studies are recommended to investigate the effect of raised platelet and WBC counts in the first trimester on pregnancy outcome.

Conclusion

Elevated platelet and WBC counts in the first trimester are associated with increased risk of missed miscarriage, increased risk of preterm delivery and relatively increased risk of PPROM. This can serve as an early warning for adverse pregnancy outcome.

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Authors Contribution The first three co-authors have equal roles in some data collection. The last co-author (Muna Alhusban) has a role in revising the manuscript.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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