Original Article

Total White Blood Cell Count and Its Subtypes in Early Pregnancy and Later Development of Preeclampsia

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Objective: To compare the peripheral white blood cell [WBC] and its differential counts in early pregnancy of women who developed and who did not develop preeclampsia [PE]. Predictive ability of total WBC and differential counts for the risk of PE was also determined.

Materials and Methods: Data from singleton pregnant women who firstly attended the antenatal clinic at gestational age [GA] of ≤16 weeks were collected. WBC and differential counts were categorized into quartiles, and the odds ratio of developing PE comparing each of the upper quartiles with the lowest quartile were analyzed.

Results: The study population consisted of 4,868 gravidas. Of these, 328 (6.7%) developed PE. Total WBCs, absolute neutrophil count, and a ratio of neutrophils to lymphocytes (N/L ratio) were significantly elevated while absolute lymphocyte count was significantly decreased in PE compared to non-preeclamptic gravidas. These four variables were also identified as significant risk factors for PE by multivariable analysis. The most powerful predictor was the WBC count, with the fourth quartile (>8,800/μL) versus the first quartile (≤7,200/μL) increasing the risk by 6.2 folds.

Conclusion: Peripheral total WBC and differential counts in early pregnancy were identified as significant risk factors for PE.

Keywords: Differential count, Preeclampsia, White blood cell

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Preeclampsia [PE] is a major cause of maternal and fetal/neonatal mortality and morbidity worldwide, with reported incidence in 2 to 8% of all pregnancies[1-3]. Aside from being the cause of immediate obstetric complications, PE can predispose a mother and her offspring to long-term health problems including cardiovascular disease, such as stroke, hypertension, etc[4-6]. Recently, it has been proposed that PE is a 2-stage disorder which involves a reduction of placental perfusion followed by placental release of various substances including microparticles, oxidative stress, and angiogenic factors causing maternal leukocyte and endothelial cell activation[7,8]. These activated leukocytes and endothelial cells consequently elicit an inflammatory response as evidenced from several studies which observed an increase of circulating inflammatory mediator levels, such as C-reactive protein [CRP], tumor necrosis factor-α [TNF-α], and interleukin [IL]-6 leading to clinical manifestations with apparent signs or symptoms of PE[9-12].

While normal pregnancy is a mild inflammatory state, PE appears to be an exaggeration of the norm[13]. A few observatory reports found that an increased white blood cell [WBC] count both in the pre-clinical and clinical stages, especially absolute neutrophil count, was associated with PE as well as its severity[14-18]. However, the number of studies regarding this subject is limited. Taking into account that an assessment of complete blood count [CBC] or particularly WBC is easy, simple, and inexpensive, utilizing this test (the WBC count) to screen for PE would then have a great cost benefit, especially in low-resource settings.

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The purpose of the present study was to compare the peripheral WBC count with its differential as well as a ratio of neutrophil to lymphocyte counts (N/L ratio) in early pregnancy of women who developed and who did not develop PE. A further aim was to determine the predictive ability of total and differential WBC counts for the risk of PE.

Materials and Methods

Study population

The present study was conducted after approval of the Bangkok Metropolitan Administration Ethics Committee for Researches Involving Human Subjects (Registered Number 079.52). Data from pregnant women who attended the antenatal clinic of Faculty of Medicine Vajira Hospital between 1 April 2009 and 31 March 2011 were retrospectively reviewed. Eligibility criteria were all singleton pregnancies who started their initial antenatal booking at gestational age [GA] ≤16 weeks in the authors' institution. Exclusion criteria were those who had: known risk factors for PE including chronic hypertension, renal disease, overt diabetes, hyperthyroidism or collagen vascular disease; any conditions that may affect the number of WBC count including immediate past- or current history or signs or symptoms of infection, bone marrow, autoimmune or hematologic diseases; recent (≤ two weeks) intake of steroid or nonsteroidal anti-inflammatory drugs; smoking; incomplete clinical data and elsewhere delivery.

WBC measurement

As a routine practice in the antenatal clinic of the authors' institution, blood sample was drawn from each woman by antecubital venipuncture in the morning of her first antenatal visit. Three millimeters of blood was transferred to disposable plastic test tube containing EDTA as anticoagulant, and it was sent to the laboratory unit to be assessed within one hour after venipuncture. A complete blood profile, including total WBC count with its differential count (neutrophils, lymphocytes, eosinophils, monocytes and basophils), was measured using an automatic counter model LH 750 (Beckman Coulter, Inc., Brea, CA, USA). The intra-assay coefficient of variation for WBC was 2.5%, and the standard errors of neutrophil, lymphocyte, eosinophil, basophil, and monocyte counts were all less than 3%.

Data collection

Data collection included: maternal age, parity, body mass index [BMI] at first visit, the presence or absence of PE, total and differential WBC counts, GAs at CBC determination and at delivery, route of delivery, and infant birth weight. Maternal age was assigned in the whole number of years at the time of initial booking. PE was diagnosed using the criteria of the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy[19].

Statistical analysis

Statistical analysis was performed using IBM SPSS 22.0 (SPSS Inc., Armonk, NY, USA). Continuous variables were presented as mean with standard deviation [SD], and categorical variables as number with percentage. Student t-test was used for two-group comparisons for continuous variables, and χ^2 test was used for categorical variables. Because WBC and differential counts were non-normally distributed, these variables were categorized into quartiles, and the odds ratio [OR] for each upper quartile was computed with the lowest category as the reference group. The logistic regression model was used to estimate the RRs with 95% confidence intervals for PE. In the regression analysis, some recognized risk factors as well as the significant factors for PE in the present study were included as covariates in the model. The *p*-value <0.05 was considered statistically significant.

Results

The study population consisted of 4,868 pregnant women. Of these, 4,791 (98.4%) were Thai and a few women (1.6%) were other Southeast Asians. Mean age of the subjects was 27.1± 6.4 years and mean BMI was 21.8±4.2 kg/m^2. The prevalence of PE was 6.7%. When PE and non-preeclamptic gravidas were compared for clinical features, the authors observed that women who developed PE were significantly older, had greater mean BMI, systolic, and diastolic blood pressure, rate of cesarean section but lower mean GA at delivery and neonatal birth weight than women who remained normotensive throughout gestation. No significant differences were found between both groups in terms of racial distribution and nullipara rate. The characteristics of all women, preeclamptic, and non-preeclamptic women are summarized in Table 1.

Table 2 compares total WBC and differential counts in early pregnancy of PE and non- preeclamptic women. Mean GAs at WBC determination between the two groups were not significantly different. The analysis demonstrated that total WBC count, number and proportion of neutrophils, and N/L ratio were significantly elevated while lymphocyte number,

Table 1. Baseline characteristics of the study population (n = 4,868)

	Overall (n = 4,868)	No PE (n = 4,540)	PE (n = 328)	*p*-value
Age (years)	27.1 (6.4)	27.0 (6.3)	28.0 (6.8)	0.01*
Race				0.41**
Thai	4,791 (98.4)	4,470 (98.5)	321 (97.9)	
Other Southeast Asians	77 (1.6)	70 (1.5)	7 (2.1)	
Nullipara	2,389 (49.1)	2,221 (48.9)	168 (51.2)	0.42**
BMI at first visit (kg/m^2)	21.8 (4.2)	21.5 (3.9)	25.3 (5.6)	<0.001*
Blood pressure at first visit (mmHg)				
Systolic	113.5 (11.6)	113.4 (11.8)	114.4 (8.6)	0.04*
Diastolic	64.3 (5.8)	64.2 (5.8)	65.9 (4.8)	<0.001*
GA at delivery (weeks)	38.2 (1.6)	38.3 (1.6)	37.8 (2.1)	<0.001*
Route of delivery				<0.001**
Cesarean section	1,784 (36.6)	1,631 (35.9)	153 (46.6)	
Vaginal delivery	3,084 (63.4)	2,909 (64.1)	175 (53.4)	
Neonatal birth weight (g)	3,092.3 (454.3)	3,097.7 (439.9)	3,016.9 (615.7)	0.02*

Data are presented as n (%) or mean (SD) as appropriate
* Student t-test; ** χ^2 test
BMI = body mass index; GA = gestational age; n = number; PE = preeclampsia; SD = standard deviation

Table 2. Total white blood cell and differential counts in early pregnancy of women who developed preeclampsia and those who remained normotensive

Leukocyte (/µL)	Overall (n = 4,868)	No PE (n = 4,540)	PE (n = 328)	*p*-value*
GA at testing (weeks)	12.8 (2.0)	12.8 (2.0)	13.0 (1.9)	0.22
Total WBC count	8,007.9 (1,210.7)	7,944.0 (1,180.9)	8,891.5 (1,272.7)	<0.001
Neutrophil				
Absolute count	5,543.7 (1,166.0)	5,463.4 (1,095.4)	6,655.2 (1,500.2)	<0.001
Proportion (%)	68.5 (6.0)	68.2 (5.9)	72.5 (6.7)	<0.001
Lymphocyte				
Absolute count	1,921.4 (429.9)	1,925.9 (423.9)	1,859.1 (503.3)	0.02
Proportion (%)	24.1 (5.2)	24.4 (5.1)	20.8 (5.8)	<0.001
Eosinophil				
Absolute count	138.5 (152.0)	138.3 (151.2)	141.1 (163.3)	0.75
Proportion (%)	1.7 (1.9)	1.7 (1.9)	1.5 (1.7)	0.06
Monocyte				
Absolute count	415.6 (160.4)	414.8 (159.7)	425.6 (169.2)	0.27
Proportion (%)	5.2 (1.9)	5.2 (1.9)	4.7 (1.8)	<0.001
Basophil				
Absolute count	19.9 (25.2)	20.1 (25.7)	17.6 (17.5)	0.08
Proportion (%)	0.2 (0.3)	0.3 (0.3)	0.2 (0.2)	<0.001
Neutrophil to lymphocyte ratio	3.0 (1.0)	3.0 (0.9)	3.9 (1.7)	<0.001

Data are presented as mean (SD)
* Student t-test
GA = gestational age; PE = preeclampsia; SD = standard deviation; WBC = white blood cell

proportions of lymphocytes, monocytes, and basophils were significantly decreased in women who had PE compared to non-preeclamptic gravidas.

The authors selected the four significant

Table 3. Crude and adjusted odds ratios of preeclampsia according to quartiles of white blood cell or differential counts, with the lowest quartile serving as the reference group

Leukocyte (/μL)	No PE	PE	Crude OR (95% CI)	Adjusted OR* (95% CI)
Total white blood cell count				
Q1 (≤7,200), n = 1,253	1,224 (97.7)	29 (2.3)	1.0	1.0
Q2 (7,201 to 7,900), n = 1,264	1,212 (95.9)	52 (4.1)	1.8 (1.1 to 2.9)	1.7 (1.1 to 2.8)
Q3 (7,901 to 8,800), n = 1,200	1,114 (92.8)	86 (7.2)	3.3 (2.1 to 5.0)	3.4 (2.1 to 5.2)
Q4 (>8,800), n = 1,151	990 (86.0)	161 (14.0)	6.9 (4.6 to 10.3)	6.2 (4.1 to 9.4)
Absolute neutrophil count				
Q1 (≤4,800), n = 1,238	1,207 (97.5)	31 (2.5)	1.0	1.0
Q2 (4,801 to 5,450), n = 1,202	1,166 (97.0)	36 (3.0)	1.2 (0.7 to 2.0)	1.2 (0.7 to 2.0)
Q3 (5,451 to 6,150), n = 1,189	1,110 (93.4)	79 (6.6)	2.8 (1.8 to 4.2)	2.7 (1.7 to 4.1)
Q4 (>6,150), n = 1,239	1,057 (85.3)	182 (14.7)	6.7 (4.5 to 9.9)	5.9 (3.9 to 8.8)
Absolute lymphocyte count				
Q1 (≤1,650), n = 1,313	1,200 (91.4)	113 (8.6)	1.0	1.0
Q2 (1,651 to 1,900), n = 1,190	1,115 (93.7)	75 (6.3)	0.7 (0.5 to 0.9)	0.7 (0.5 to 0.9)
Q3 (1,901 to 2,150), n = 1,104	1,038 (94.0)	66 (6.0)	0.7 (0.5 to 0.9)	0.7 (0.5 to 0.9)
Q4 (>2,150), n = 1,261	1,187 (94.1)	74 (5.9)	0.6 (0.5 to 0.8)	0.7 (0.5 to 0.9)
Neutrophil to lymphocyte ratio				
Q1 (≤2.40), n = 1,206	1,172 (97.2)	34 (2.8)	1.0	1.0
Q2 (2.41 to 2.90), n = 1,256	1,202 (95.7)	54 (4.3)	1.5 (1.0 to 2.4)	1.4 (0.9 to 2.3)
Q3 (2.91 to 3.50), n = 1,249	1,169 (93.6)	80 (6.4)	2.4 (1.6 to 3.6)	2.0 (1.3 to 3.1)
Q4 (>3.50), n = 1,157	997 (86.2)	160 (13.8)	5.5 (3.8 to 8.1)	4.7 (3.2 to 7.0)

*Adjusted for maternal age, race, parity, body mass index, blood pressure, and gestational age at white blood cell determination
CI = confidence interval; OR = odds ratio; PE = preeclampsia; Q = quartile

leukocyte parameters in Table 2 which included total WBC count, absolute neutrophil and lymphocyte counts, and N/L ratio and divided subjects into quartiles according to the distributions of these parameters. Table 3 shows ORs of PE in relation to quartiles of these four variables, with the first quartile serving as the reference group. By univariable analysis, an increased risk of PE was associated with the second, third, and fourth (vs. first) quartiles of total WBC count (ORs = 1.8, 3.3, and 6.9, respectively; $p<0.05$ for all). Similarly, the third and fourth (vs. first) quartiles of absolute neutrophil count (ORs = 2.8 and 6.7, respectively; $p<0.001$ for both) and the third and fourth (vs. first) quartiles of N/L ratio (ORs = 2.4 and 5.5, respectively; $p<0.01$ for both) were significantly associated with an increased risk of PE. In the reverse direction, the second, third, and fourth (vs. first) quartiles of absolute lymphocyte count were significantly associated with a reduced risk of PE (ORs = 0.7, 0.7, and 0.6, respectively; $p<0.5$ for all). After adjustment for potential confounding factors for PE or leukocyte number including age, race, first-visit BMI and blood pressure, GDM status, and GA at WBC determination using multivariable analysis, these four parameters were retained as significant risk factors for PE. The greatest risk predictor was the total WBC count, with the fourth quartile (>8,800/μL) versus the first quartile (≤7,200/μL) increasing the risk by 6.2 folds.

Discussion

Despite extensive research in this field, the true cause of PE is still unknown[19]. Nevertheless, increasing evidence suggests that an exaggerated maternal inflammatory response is involved in the pathogenesis of the disease[9-13]. The physiological immune response to systemic inflammation has been described as a remarkable up-regulation in number and activation of neutrophils along with a decline in lymphocyte number[20,21]. Hence, the authors looked at the impact of WBC count and its subtypes, particularly neutrophils, lymphocytes, and N/L ratio on the development of PE.

The findings of the present study demonstrated that an increase in peripheral total WBC count, or absolute neutrophil count, or N/L ratio, or a low lymphocyte count in early pregnancy were

associated with the risk of PE in late pregnancy. These associations persisted even after controlling for PE risk factors including age, race, BMI, blood pressure, and GDM status. Moreover, the authors also found a gradual increase in PE rates with increasing quartiles of total WBCs, or absolute neutrophil count, or N/L ratio. These data suggested a dose-related association between inflammation and the risk of developing this complex disease.

So far, there has been one study which reported WBC indices in early pregnancy as prognostic values for PE. From a report of Matsuo et al on 3,350 Japanese gravidas who had a CBC test in the period of placentation (5 to 16 weeks of gestation), there was a significant increase in circulating total WBCs and absolute neutrophil count in women who developed PE as compared to those who remained normotensive throughout gestation[18]. Besides, Matsuo et al found that total WBC count was the best predictor of PE, i.e. women with WBC count above 8,500/μL had a 2.4-fold greater risk of PE than women whose WBC count was below 8500/μL. Although the present study was conducted in a different racial group with dissimilar prevalence rate of PE and used different cutoff levels of WBCs to determine PE risk (i.e. the authors compared the second, third, and fourth quartiles of leukocytes with the first quartile), the total WBC count was also identified as the most powerful predictor of PE among various leukocyte indices.

Apart from an assessment of WBCs in early pregnancy, few other studies observed an elevation of total WBC count, number and proportion of neutrophils, but a drop in number and proportion of lymphocytes in women who already had the clinical syndrome of PE[14-17]. A combination of results from the present study, Matsuo et al[18], and these studies[14-17] lend support to the hypothesis that a generalized inflammatory response, representing as relative neutrophilia along with lymphocytopenia, starts in early pregnancy and continue through the third trimester in women who later develop PE. Furthermore, some of these studies also identified the correlation of PE severity (severe PE, eclampsia, or HELLP syndrome) with these WBC alterations[14,16,17]. Unfortunately, the present study did not assess the hematologic features of women who already developed PE because the clinical manifestations were already apparent for clinical management.

The source of an increase in circulating leukocytes in preeclamptic women is a matter of speculation. Some authors have suggested that this condition is an inflammatory consequence of placental hypoxia/ischemia secondary to shallow trophoblast invasion of spiral arteries during the placentation phase[7,8], while others have proposed that delayed neutrophil apoptosis in consequence of endothelial cell activation could result in high peripheral blood leukocytes[12,22]. Aside from both potential sites, subclinical infection of other organs such as chronic periodontal disease and urogenital infection have been linked with risk of PE and also high circulating WBCs[23-25]. Genetic factor is another possible cause since genetic variants have been shown to influence the number of peripheral blood leukocytes[26].

It is widely recognized that WBCs have a role in the pathogenesis of atherosclerosis, which is a pathological process leading to CVD[27]. The biological mechanism of this event is that leukocytes are recruited to the site of endothelium; they adhere to the vessel wall, enter it, and eventually cause endothelial damage[28]. Recently, PE has been considered a precursor of CVD[4,6], and several authors also observed a considerable increase in leukocyte-endothelial interaction in women who were complicated by PE[28,29]. Cadden and Walsh immunohistochemically stained subcutaneous fat tissues of PE, non-PE pregnant, and non-pregnant women for neutrophil, lymphocyte, and monocyte/macrophage antigens, and found a significantly higher number of neutrophils adhering to endothelium and infiltrating into the intima layer of systemic vasculature of preeclamptic gravidas than that of the other two groups of women[30]. Their results have suggested that neutrophils are the WBC subtype that is involved in vascular dysfunction of preeclamptic women[30]. Besides the mechanisms of recruitment, aggregation, and adherence to the endothelium that lead to vascular plugging, activated neutrophils could also release toxic substances, such as reactive oxygen species, TNF-α, myeloperoxidase, and matrix metalloproteinase-8, all of which can also cause vascular dysfunction[31,32].

At present, the automated hematology analyzers are used in most laboratories. Determinations of circulating WBC and differential counts are available in daily practices including routine antenatal care services. Hence, using these blood profiles to detect women at risk for PE is more practicable with no extra cost than the measurement of other inflammatory markers, such as CRP or pro-inflammatory cytokines which are more expensive and cumbersome. An identification of women at risk for PE or early detection when the clinical signs or symptoms of the disease

are not evident may improve antenatal care and consequent pregnancy outcomes. Data of the present study may be clinically useful for a physician to apply this basic hematologic laboratory test for general pregnant women. In any event when an individual has elevated WBCs in an absence of signs or symptoms of infection or even subclinical infection, such as periodontal disease or asymptomatic bacteriuria, this pregnant woman should be informed about the possibility for PE development and be closely monitored by a physician.

The strength of the present study was that it included only pregnant women who had blood test early in their pregnancies and had a clinical follow-up until delivery. Nevertheless, it was limited by being an observational study in which pathological mechanism of WBC elevation in PE could not be explored. Another possible limitation was an influence of diurnal variation on WBC levels. However, blood samples of all women in this study were drawn only in the morning. There were only few cases of severe PE (n = 62) and eclampsia (n = 3) in this study, so the sample size had inadequate power to determine the association of PE severity with WBC levels.

Conclusion

Peripheral total WBCs, absolute neutrophil and lymphocyte counts, and N/L ratio in early pregnancy were identified as significant risk factors for PE. The most powerful risk prediction was the total WBC count. It is interesting to determine if giving anti-inflammatory drugs women without clinical or subclinical infection but having high WBC levels in early pregnancy (during the placentation phase) could prevent or minimize the risk of PE.

What is already known on this topic?

Evidence suggests that an exaggerated maternal inflammatory response is involved in the pathogenesis of preeclampsia. Several observatory studies found that an increase in WBCs in the clinical stage was associated with PE as well as its severity. However, data about an association of WBC and differential counts in early pregnancy with the development of preeclampsia in late gestation are still limited.

What this study adds?

The present study confirmed the association of total WBCs, absolute neutrophil and lymphocyte counts, and N/L ratio in early pregnancy with the risk of preeclampsia. This study also found a dose-related association between inflammation and the risk of developing preeclampsia.

Potential conflicts of interest

The authors declare no conflict of interest.

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