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Increased Neutrophil Numbers Account for Leukocytosis in Women with Preeclampsia

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Abstract

We evaluated the leukocyte differentials in women with normal pregnancies and in pregnancies complicated by preeclampsia (PE). A retrospective study was performed in 240 women who were delivered at Louisiana State University Health Sciences Center– Shreveport, Louisiana, from January 1, 2002, to July 31, 2003. A total of 80 patients were studied in each group: normal pregnancy, mild PE, or severe PE. Leukocyte total and neutrophil, lymphocyte, monocyte, eosinophil, basophil, hemoglobin, and platelet counts were analyzed by analysis of variance and pairwise comparison. Data are presented as mean ± standard deviation. A p value <0.05 was set as statistically different. The total leukocyte count was significantly increased in women with severe PE compared with women with mild PE and normal pregnant controls: 10.66 ± 3.70 ($p < 0.0001$) versus 9.47 ± 2.59 and 8.55 ± 1.93 (1×10^3/μL), respectively. The increased total leukocyte count was mainly due to the increase in neutrophil numbers: 8.05 ± 4.01 (severe; $p < 0.0001$) versus 6.69 ± 2.23 (mild) and 5.90 ± 1.79 (controls), respectively. The total neutrophil count was further increased 48 hours after delivery in the group with severe PE. No statistical differences for monocyte and lymphocyte counts were observed between normal and PE groups. Increased neutrophil numbers account for the leukocytosis in women with PE.

Keywords

Leukocytes; neutrophils; pregnancy; preeclampsia

Preeclampsia is a hypertensive, multisystem disorder that may occur during human pregnancy. Although the etiology of preeclampsia is unclear, there appears to be several factors including a genetic disposition, abnormal placental invasion, and immunologic or exaggerated inflammatory responses that lead to the development of this pregnancy disorder.[1] In addition, studies have also shown that leukocyte activation plays a significant role during the disease process in preeclampsia. Significant findings of leukocyte activation have been made, including increased superoxide generation and enhanced integrin CD11b and CD64 expressions in monocytes and in neutrophils in women with preeclampsia.[2–6] Activated leukocytes also release a variety of substances such as cytokine interleukin-8 and tumor necrosis factor-α, which are capable of mediating endothelial function. Interactions between activated leukocytes, platelets, and vascular endothelium are believed to contribute to the vascular injury in this pregnancy disorder.[7] Furthermore, neutrophil activation is

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believed to be a major component of exaggerated inflammatory responses in the maternal vascular system during preeclampsia.[6]

Leukocytosis occurs during normal pregnancy.[8] However, reports on leukocyte count and differentials associated with the severity of preeclampsia are scarce. The objective of this study was to determine whether or not there are differences in the white blood count and differentials in women with mild and severe preeclampsia as compared with normal pregnant controls. We hypothesized that increased neutrophil numbers account for the leukocytosis in preeclampsia, and this increase is associated with the severity of preeclampsia.

MATERIALS AND METHODS

A retrospective chart review and analysis was performed in a total of 2763 normal pregnant women and in women with preeclampsia who delivered at the Labor and Delivery Unit of Louisiana State University Health Sciences Center –Shreveport, Louisiana, from January 1, 2002, to July 31, 2003. This study was approved by the Institutional Review Board for Human Research. Normal pregnancy and preeclampsia were defined and classified according to American College of Obstetricians and Gynecologists standards. The diagnosis of mild preeclampsia was defined as maternal blood pressures ≥140/90 mm Hg in two separate readings at least 6 hours apart and the presence of quantitative proteinuria (≥1+ on urine dipstick or >0.3 g in a 24-hour urine). Severe preeclampsia was defined as maternal blood pressures ≥160/110 mm Hg in two separate readings at least 6 hours apart and significant quantitative proteinuria (≥3+ on urine dipstick or >5 g in a 24-hour urine), oliguria, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper-quarter pain, impaired liver function, thrombocytopenia, or fetal growth restriction. The complete blood count with differentials, blood pressures, and proteinuria were recorded at the time of admission to the labor and delivery unit of the hospital. Patients were excluded from this study if any of the followings were present at the time of admission: ruptured membranes, recent or prior administration of corticosteroids, concurrent infections (chorioamnionitis, urinary tract infection, cervicitis, etc.), diabetes, nephropathy, or chronic hypertension. A total of 240 patients were identified using the clinical criteria listed above with 80 patients in the normal pregnant group, 80 patients in the mild preeclampsia group, and 80 patients in the severe preeclampsia group. Patient demographic information, total leukocyte count, leukocyte differentials (neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin levels, and platelet counts were analyzed.

Statistical analysis was performed with analysis of variance using the computer software program StatView (SAS Institute Inc, Cary, NC). Data are presented as mean ± standard deviation. Fisher protected least significant difference (PLSD) and Student-Newman-Keuls tests were used as post hoc tests. Pairwise comparison was also made using the *t* test. A p level <0.05 was set as statistically different. Power analysis was performed with statistical software, Power and Precision (Biostat, Englewood, NJ). A sample size of 80 in each group based upon the total leukocyte count has a power >80% to detect a difference in neutrophil counts between groups (type I error = 0.05, power = 0.80, with 2 standard deviations).

RESULTS

Table 1 shows the demographic data for the study patients including maternal age, racial status, gestational age, blood pressure, proteinuria, mode of delivery, and parity. There is no difference for maternal age or gravidity between the three groups. Significant differences were noticed in the severe preeclampsia group with increased systolic and diastolic blood

pressures, proteinuria, and earlier gestational age between mild and severe preeclamptic patients.

Table 2 shows leukocyte counts with differentials, hemoglobin, and platelet counts in normal pregnant controls and in women with mild and severe preeclampsia. The total leukocyte count is significantly increased in mild preeclamptic patients ($p < 0.05$) and further increased in severe preeclamptic patients ($p < 0.0001$). Neutrophil count was slightly increased in women with mild preeclampsia, but significantly increased in women with severe preeclampsia compared with normal pregnant controls. There was no significant difference between the three groups in absolute lymphocyte, monocyte, eosinophil, and basophil counts. Increased hemoglobin levels and decreased platelet counts were also observed in the severe preeclamptic patients compared with normal pregnant controls and mild preeclamptic patients. In addition, we also observed that neutrophil numbers were further increased 48 hours after delivery in severe preeclamptic patients: 8.048 ± 4.011 at admission compared with 12.907 ± 5.087 at 8 hours postpartum, 11.112 ± 4.423 at 24 hours postpartum, and 11.298 ± 3.809 at 48 hours postpartum($p < 0.001$), respectively.

DISCUSSION

In this study, we analyzed maternal leukocyte count and differential profiles in normal pregnant women and in women with preeclampsia. Our results showed that the leukocyte count is elevated in mild preeclampsia and significantly increased in severe preeclampsia compared with normal pregnant controls. Differential analyses further demonstrated that the increased neutrophil, not monocyte or lymphocyte, numbers account for the total leukocyte increase in preeclampsia. The significant increases in neutrophil numbers occur only in women with severe preeclampsia compared with normal pregnant controls and women with mild preeclampsia, whereas no significant increases were observed in neutrophil numbers between mild preeclampsia patients and normal pregnant patients. These findings implicated that the increased neutrophil count is associated with the severity of the disease. Our data are consistent with the observations made by Lurie et al, in which an increase in neutrophil count in severe preeclamptic patients was noticed, but with only 16 cases in the severe group in their study.[9] In our study, we recruited 80 patients in each group. Power analysis revealed that the *p* level reached 0.997 in neutrophil count between severe preeclampsia and mild preeclampsia groups. Pitkin and Witte reported increased monocyte numbers during normal pregnancy.[8] Our data showed that monocyte, lymphocyte, eosinophil, and basophil numbers were slightly increased in mild and severe preeclamptic patients compared with normal controls; however, no statistical differences were found. Therefore, our data suggest that leukocytosis in severe preeclampsia is mainly due to increased neutrophil numbers in the maternal circulation. Leukocytosis occurs during normal pregnancy. The increased neutrophil count in severe preeclampsia indicates leukocytosis is pronounced especially in severe cases in preeclampsia.

Leukocytosis is considered to be evidence of an increased inflammatory response during normal pregnancy and in preeclampsia. This also occurs in patients who have been administered steroids. An increased leukocyte count was observed in antenatal dexamethasone administration in pregnant women10 and in premature infants.[11] Terrone et al also found the total leukocyte count was even higher in preeclamptic patients with hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP syndrome) than those without HELLP syndrome, suggesting an association between increased leukocytes and worsening thrombocytopenia in those patients.[12] In the present study, to eliminate those variables that may influence the leukocyte count, patients with HELLP syndrome, patients who were administered steroids, and patients with preterm rupture of membranes or who had symptoms of infection were excluded. Therefore, we believe that our data of increased

neutrophil count in severe preeclampsia may represent the severity of inflammatory response during the disease process.

A previous report showed that average total leukocyte numbers and neutrophil numbers during pregnancy were reduced 6 weeks postpartum in normal pregnant patients.[8] In our study, we found that neutrophil numbers were even increased within 48 hours after delivery in severe preeclamptic patients. The increased neutrophil count in severe preeclamptic patients could be explained by a stress-induced response during and after labor, or by diuresis that occurs after labor. Unfortunately, we were unable to obtain neutrophil information at 6 weeks after delivery for a comparison. However, our data indicate that leukocytosis continues, at least, within 48 hours after delivery in preeclamptic patients.

A delayed neutrophil apoptosis due to an increased inflammatory response is believed to contribute to leukocytosis or neutrophilia during pregnancy and preeclampsia. Von Dadelszen et al investigated the relationship of inflammatory response and neutrophil apoptosis after 18 hours of incubation with endotoxin.[13] Using an apoptosis marker of propidium iodide neutrophil nuclei staining accessed by flow cytometry, they found that iodide-stained neutrophils were significantly reduced in neutrophils from normal pregnancies and further reduced in neutrophils from preeclampsia compared with nonpregnant controls.[14] In contrast, CD16-positive neutrophils were increased in preeclampsia. These findings demonstrated a delayed apoptosis process occurring in preeclampsia, which explains the persistence of neutrophilia after delivery.

Our data also show increased neutrophil count accompanied by augmented hemoglobin levels and decreased platelet numbers in women with severe preeclampsia compared with mild preeclampsia. Whether or not this phenomenon is a compensatory reaction or exaggerated response to the severity of the disease is unknown. However, it is clear that the increased absolute neutrophil count is a significant integral modification of leukocytosis during severe preeclampsia. Further studies are needed to learn the regulation of neutrophil function, especially neutrophil function at cellular and molecular levels during pregnancy and their role in preeclampsia. Also, further studies are needed to determine the degree of delayed neutrophil apoptosis and its contribution to endothelial activation or dysfunction in preeclampsia.

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Table 1

Demographic Characteristics for Normal and Preeclamptic Pregnancies

Variable	Normal (*n* = 80)	Mild PE (*n* = 80)	Severe PE (*n* = 80)	*p* Value
Maternal age (y)	23.5 ± 6.0	23.3 ± 5.4	23.1 ± 5.6	0.904
Racial status				
White	12	18	26	—
African-American	68	60	51	—
Other	0	2	3	—
Gestational age (wk)	38 ± 2	37 ± 4	34 ± 1	<0.001*
Blood pressure				
Systolic (mm Hg)	123 ± 10	148 ± 7	162 ± 15	<0.001*
Diastolic (mm Hg)	72 ± 8	88 ± 9	98 ± 11	<0.001*
Proteinuria	—	1–2+	3–4+	<0.001*
Mode of delivery				
Vaginal	56	57	42	—
Cesarean section	24	23	38	—
Nulliparous (%)	34%	38	49	—

*Severe PE versus normal control and mild PE.

Data are presented as mean ± standard deviation. PE, preeclampsia.

Table 2

Complete Blood Count with Differentials in Normal and Preeclamptic Pregnancies

Variable	Normal (*n* = 80)	Mild PE (*n* = 80)	Severe PE (*n* = 80)	*p* Value*	Power
Total leukocyte count ($1 \times 10^3/\mu L$)	8.547 ± 1.934	9.474 ± 2.589†	10.662 ± 3.699‡	<0.0001	0.996
Differential ($1 \times 10^3/\mu L$)					
Neutrophils	5.902 ± 1.787	6.688 ± 2.299	8.048 ± 4.011‡	<0.0001	0.997
Monocytes	0.685 ± 0.204	0.729 ± 0.315	0.699 ± 0.361	0.394	0.236
Lymphocytes	1.872 ± 0.577	1.896 ± 0.580	2.013 ± 0.835	0.185	0.216
Eosinophils	0.090 ± 0.071	0.096 ± 0.056	0.119 ± 0.120	0.038	0.462
Basophils	0.042 ± 0.037	0.054 ± 0.047	0.059 ± 0.059	0.040	0.445
Hemoglobin (g/dL)	11.047 ± 1.396	10.931 ± 1.539	11.764 ± 1.580‡	0.003	0.994
Platelets ($1 \times 10^3/\mu L$)	225.0 ± 69.4	234.7 ± 63.3	195.7 ± 80.7‡	0.011	0.911

*Severe PE versus normal control.

†$p < 0.05$: mild PE versus normal controls.

‡$p < 0.01$: severe PE versus mild PE.

Data are presented as mean ± standard deviation. PE, preeclampsia.