Activation of Leukocytes During the Uteroplacental Passage in Preeclampsia

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Abstract—Endothelial dysfunction and inflammation appear to play a major role in the pathogenesis of preeclampsia. We hypothesize that a chronic inflammation in the decidua and placenta during preeclampsia may lead to a local leukocyte activation in this compartment. Venous blood was sampled simultaneously from antecubital and uterine veins during cesarean sections in 30 women with preeclampsia, 29 with uncomplicated pregnancies, and from 17 nonpregnant women. The expression of adhesion molecules and complement-related markers on neutrophils and monocytes was analyzed by flow cytometry. In patients with preeclampsia, neutrophil expression of the integrins CD11a, CD11b, and CD11c and of the complement related markers CD35 and CD59 was significantly higher in samples from *uterine* than from *antecubital veins*. No differences were found in nonpregnant women. On monocytes the expression of the Sialyl Lewis^x antigen, the integrins CD11a, CD11c, and CD49d, and the complement-related markers CD46 and CD59 was higher in samples from *uterine* than from *antecubital veins* during preeclampsia, but not in uncomplicated pregnancies, whereas in nonpregnant women CD31 was decreased. Our findings suggest activation of neutrophils and monocytes taking place during the uteroplacental passage in preeclamptic, but not in normal pregnancies. Such a local inflammatory response involving enhanced leukocyte/endothelial interaction may contribute to the pathogenesis of this disorder. **(*Hypertension*. 2002;39:155-160.)**

Key Words: preeclampsia ■ leukocytes ■ cell adhesion molecules ■ activation analysis

Preeclampsia is a pregnancy-specific syndrome in a previously healthy woman defined by increased blood pressure and proteinuria presenting after 20 weeks of gestation.[1] Whereas hypertension and proteinuria are regarded as secondary signs, endothelial dysfunction is thought to play a major role in the pathogenesis of preeclampsia.[2] Moreover, preeclampsia appears to be characterized by altered cytokine production[3] and leukocyte activation,[4] and it has been suggested that preeclampsia may represent an excessive maternal inflammatory response to pregnancy.[5]

In preeclampsia there is a reduced invasion of the trophoblast into the uterus and its spiral arteries. Thus, these arteries do not distend properly, and the blood flow through the uteroplacental circulation is reduced by one third and two thirds in mild and severe preeclampsia, respectively, compared with normal pregnancies.[6] This is insufficient to deliver the oxygen and nutrition required, which results in an increased frequency of placental infarcts, intrauterine growth-retarded fetuses, and fetal deaths. Such an ischemic circulation may also be related to an inappropriate inflammatory response during preeclampsia.

We hypothesize that during preeclampsia there is a chronic inflammation in the decidua and placenta contributing to the pathogenesis of this disorder. Then, the degree of leukocyte activation would be higher in blood passing through the uteroplacental circulation compared with mixed venous blood drawn from an antecubital vein. The aim of the present study was to compare the expression of adhesion molecules and complement-related markers as parameters of leukocyte activation on neutrophils and monocytes sampled simultaneously from veins on the uterus and the forearm in women with preeclamptic and normal pregnancies.

Methods

Subjects and Blood Sampling Protocol

Thirty patients who had cesarean sections because of severe preeclampsia were compared with 29 randomly selected healthy women with uncomplicated pregnancies who had elective cesarean sections because of breech presentation, cephalo-pelvic disproportion, or fear of giving vaginal birth. For comparison, a nonpregnant control group of 17 women, who had hysterectomies because of uterine myoma, was included. Severe preeclampsia was defined as (1) blood pressure of ≥160/110 mm Hg measured on 2 occasions 6 hours apart with the

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TABLE 1. Characteristics of Women with Normal and Preeclamptic Pregnancies

Variable	Normal (n=29)	Preeclampsia (n=30)	*P* value
Maternal age, y	31.5 (29.5–33)	30.5 (29–33)	NS
Initial blood pressure, mm Hg	110/68 (108/63–113/70)	120/75 (115/70–123/78)	0.005
Delivery blood pressure, mm Hg	115/70 (108/68–120/75)	175/115 (170/110–180/115)	<0.001
Proteinuria, g/L	0+	6.83 (5.35–10.35)	<0.001
Hemoglobin, g/dL	11.3 (10.9–11.8)	12.6 (12.2–13.0)	<0.001
Platelet count, $\times 10^9$/L	208 (183–236)	195 (170–225)	NS
Uric acid, mmol/L	289 (208–391)	388 (361–416)	<0.001
Primigravid/parous ratio	16/13	22/8	<0.001
Gestational age, wk+d	38.3 (38.2–38.4)	30.6 (29.2–32.4)	<0.001
Birth weight, kg	3,500 (3280–3710)	1,154 (885–1468)	<0.001
Initial maternal weight, kg	61 (57.5–66.5)	66.5 (61.5–73.5)	NS
Maternal weight at term, kg	78 (73.5–83)	80 (74.5–87)	NS

Data are given as median and 95% confidence interval. NS, not significant.

patient at bed rest and (2) ≥5 g/24 hours urinary protein excretion, or ≥3 + on urinary dip sticks, in (3) a previous healthy women with an uncomplicated pregnancy up to 20 weeks. These women were all admitted for observation because of preeclampsia. The day a fetal or maternal indication for terminating the pregnancy occurred, the operation was performed 3 to 24 hours later, with a median of 10 hours. Only women who were delivered by a cesarean section were included in the study because labor in itself may induce acidosis[7] and neutrophil activation in the fetal circulation.[4] None had ruptured membranes or were failed inductions. Because few patients with mild preeclampsia are delivered by a cesarean section, a group of severe preeclampsia patients was chosen.

To draw blood samples from a uterine vein in the operation field, EDTA vacutainers, a holder, and a 0.8 mm needle had been packed together and surface sterilized by 32 kGy gamma irradiation. Simultaneously sampling of blood from uterine and antecubital veins was performed when the uterus was visible in the operation field, but before the uterotomy and delivery of the fetus, ie, with an intact uteroplacental circulation. The arm from which the blood was drawn had no infusion lines, and no stasis was applied.

The study was approved by the Regional Committee of Ethics, written informed consent was obtained from all women, and the procedures followed were in accordance with the institutional guidelines.

Staining and Flow Cytometry Analysis

Most of this section has been previously published in *Hypertension*.[8] In addition, mouse monoclonal antibodies to human CD35 (complement receptor, CR 1), CD55 (decay accelerating factor, DAF), and CD59 (complement protectin) were purchased from Pharmingen, and CD46 (membrane cofactor protein, MCP) and CD88 (C5a receptor) from Serotec.

Statistical Analyses

Because some variables were not normally distributed, nonparametric statistics were used (MINITAB statistical software). The results

TABLE 2. Expression of Adhesion Molecules and Complement-Related Markers on Neutrophils and Monocytes Sampled from Antecubital or Uterine Veins during Cesarean Sections in Uncomplicated (n=29) and Preeclamptic (n=30) Pregnancies

	Mean Fluorescence Intensity					
	Antecubital Veins			Uterine Veins		
Antigens	Uncomplicated	Preeclampsia	*P* value	Uncomplicated	Preeclampsia	*P* value
Neutrophils						
Selectins						
L-selectin	26.9 (21.4–34.6)	18.2 (14.9–20.9)	**0.003**	14.7 (11.5–17.2)	10.7 (8.3–12.6)	0.02
Integrins						
CD11b	201 (111–280)	173 (123–228)	0.43	107 (74–169)	228 (170–308)	**0.006**
CD11c	20.7 (18.3–33.5)	22.5 (16.4–36.8)	0.97	16.3 (14.4–24.3)	36.4 (28.3–44.8)	**0.001**
CD49d	1.9 (1.1–2.1)	1.0 (0.5–1.2)	**0.01**	1.4 (1.1–1.8)	1.0 (0.8–1.6)	**0.21**
Complement receptors						
CD35	9.5 (6.8–16.6)	10.2 (6.9–13.6)	0.83	5.4 (4.4–12.6)	15.5 (11.8–19.3)	**0.004**
CD55	11.1 (10.3–15.4)	14.7 (13.4–18.8)	**0.01**	10.1 (9.0–13.4)	16.0 (13.7–16.9)	**0.004**
CD88	105 (51–165)	47 (36–69)	**0.01**	103 (9–153)	66 (36–102)	0.07
Monocytes						
Integrins						
CD49d	84 (66–112)	56 (48–70)	**<0.001**	92 (83–109)	70 (52–87)	**0.006**

Mean fluorescence intensity is expressed as median and 95% CI. Boldface numbers indicate significant differences.

TABLE 3. Expression of Adhesion Molecules and Complement-Related Markers on Neutrophils and Monocytes Sampled from Antecubital and Uterine Veins during Cesarean Sections in Preeclamptic Pregnancies (n=30)

	Mean Fluorescence Intensity					
	Neutrophils			Monocytes		
Antigens	Antecubital Vein	Uterine Vein	*P* value	Antecubital Vein	Uterine Vein	*P* value
Selectins						
L-selectin	18.2 (14.9–20.9)	18.7 (14.6–23.3)	0.78	10.7 (8.3–12.6)	10.6 (8.0–14.2)	0.25
P-selectin	1.3 (0.3–2.3)	1.0 (0.1–1.8)	0.65	1.8 (0.5–7.3)	2.3 (1.2–11.8)	0.05
Mucins						
Sialyl Lewis^x	215 (139–339)	251 (153–394)	0.46	50 (42–103)	75 (44–170)	**0.01**
PSGL-1	170 (144–202)	180 (138–193)	0.13	331 (294–437)	332 (282–435)	0.47
Integrins						
CD11a	8.6 (5.1–10.1)	10.1 (6.1–11.9)	**0.009**	41 (34–55)	52 (39–60)	**0.006**
CD11b	173 (123–228)	228 (170–308)	**0.008**	367 (271–473)	332 (262–617)	0.09
CD11c	22.5 (16.4–36.8)	36.4 (28.3–44.8)	**0.002**	111 (93–140)	137 (113–187)	**<0.001**
CD49d	1.0 (0.5–1.2)	1.0 (0.8–1.6)	0.91	56 (48–70)	70 (52–87)	**0.008**
CD29	14.1 (12.0–17.8)	13.8 (11.3–16.2)	0.67	100 (81–114)	94 (83–125)	0.61
Immunoglobulin-like superfamily						
ICAM-1	9.5 (8.6–11.8)	11.6 (8.4–15.1)	0.08	76.4 (65–81)	84 (69–98)	0.03
ICAM-3	345 (218–396)	351 (202–452)	0.44	267 (212–374)	293 (197–464)	0.08
CD31	13.0 (10.9–14.4)	14.3 (11.3–16.8)	0.03	40 (36–47)	46 (42–50)	0.07
Complement-related markers						
CD35	10.2 (6.9–13.6)	15.5 (11.8–19.3)	**0.003**	22.3 (15.5–27.7)	20.6 (16.2–28.7)	0.30
CD46	23.2 (16.1–52)	27.3 (14.0–62)	0.02	32 (13–82)	33 (16–87)	**0.01**
CD55	14.7 (13.4–18.8)	16.0 (13.7–16.9)	0.33	33.6 (28.1–39.2)	31.4 (25.4–36.7)	0.63
CD59	14.8 (14.0–18.8)	18.2 (16.0–22.0)	**0.01**	11.3 (8.7–13.9)	12.8 (11.5–14.2)	**0.01**
CD88	47.4 (36.0–69)	66.4 (36.0–102)	0.06	38 (21–65)	47 (19–71)	0.61

Mean fluorescence intensity is expressed as median and 95% CI. Boldface numbers indicate significant differences.

are presented as medians with 95% confidence intervals. Statistical analyses within groups were made by the Wilcoxon signed-rank test and between groups with the Mann-Whitney *U* test. Because of the many parameters studied, only differences ≤0.01 were considered statistically significant.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results

There were no significant differences between the mothers in terms of age, but the mean gestational length was shorter ($P<0.001$) and mean birth weight lower ($P<0.001$) in the preeclamptic group. In addition, both the initial and final blood pressures were significantly higher in women with preeclampsia (Table 1).

Expression of Adhesion Molecules and Complement-Related Markers on Leukocytes from Antecubital Veins

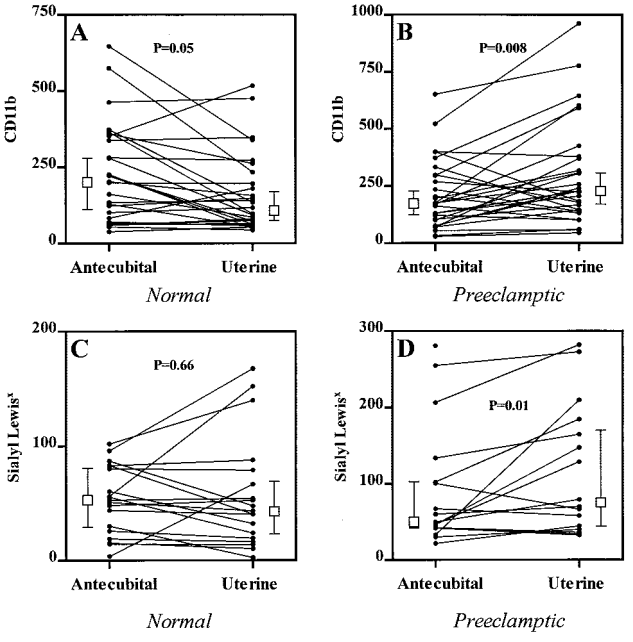
On neutrophils there was a decreased expression of L-selectin, CD49d, and CD88 and increased CD55 in preeclampsia. On monocytes CD49d was decreased (Table 2).

Expression of Adhesion Molecules and Complement-Related Markers in Leukocytes from Uterine Veins

Neutrophils isolated from uterine venous blood of preeclamptic women displayed increased expression of the integrins CD11b and CD11c, as well as the complement receptors CD35 and CD55, when compared with normotensive controls. On monocytes CD49d was decreased (Table 2).

Expression of Adhesion Molecules and Complement-Related Markers on Leukocytes During the Uteroplacental Passage

The differences between the expression of these molecules isolated from systemic and uterine compartments reflect changes taking place during the uteroplacental passage. In patients with preeclampsia, the expression of the integrins CD11a, CD11b, CD11c, as well as the complement-related markers CD35 and CD59, was significantly higher on neutrophils sampled from *uterine* than from *antecubital veins* (Table 3). In contrast, in uncomplicated pregnancies there were no differences between samples from these two compartments (data not shown, n=29). The CD11b values on neutrophils are shown in the Figure.



Change in the expression (mean fluorescence intensity) of CD11b on neutrophils (A and B) and Sialyl Lewis^x (C and D) on monocytes, isolated simultaneously from antecubital and uterine veins during cesarean sections in preeclamptic (n=30; right panels) and normal (n=29; left panels) pregnancies. Sialyl Lewis^x was analyzed in only 19 normal and 17 preeclamptic pregnancies. Median and 95% confidence interval are also shown. The mean fluorescence intensity is given in arbitrary units.

Monocytes also showed enhanced expression of several surface molecules during the uterine passage in preeclampsia, with increased expression of the Sialyl Lewis^x antigen, the integrins CD11a, CD11c, and CD49d, and the complement-related markers CD46 and CD59, in samples from *uterine* compared with those from *antecubital veins* (Table 3). These changes were not observed in uncomplicated pregnancies (data not shown, n=29). The Sialyl Lewis^x values on monocytes are shown in the Figure.

Expression of Adhesion Molecules and Complement-Related Markers in Primigravidas

Primigravidas may be protected by greater immune activation than women in later pregnancies,[9] and the possibility exists that the differences between normal and preeclamptic pregnancies reported above may reflect, at least partly, an increased proportion of primigravidas in the latter group (Table 1). However, a similar pattern of differences between these two groups of pregnancies were found also when including only primigravidas from each group, with increased leukocyte activation during uterine passage in preeclamptic, but not in normal pregnancies (data not shown).

Expression of Adhesion Molecules and Complement-Related Markers in Nonpregnant Women

For comparison, we also examined the expression of adhesion molecules and complement-related markers on neutrophils and monocytes in 17 nonpregnant women. On monocytes the expression of CD31 was lower in samples from *uterine* than from *antecubital veins*, (Table 4). Otherwise, and comparably to uncomplicated pregnancies, there were no differences between the two compartments (Table 4).

Discussion

The present study indicates that activation of neutrophils and monocytes takes place during the passage through the uteroplacental circulation in preeclampsia. The expression of these activation markers was enhanced on cells from uterine, compared with peripheral, veins in preeclamptic pregnancies. This local leukocyte activation during uteroplacental circulation in preeclampsia may possibly contribute to the pathogenesis of this disorder.

The decreased expression of L-selectin on neutrophils from the peripheral circulation in preeclampsia may be an early marker of leukocyte activation.[10] The lower expression of the integrin α_4 (CD49d) and CD88 in the preeclamptic group may reflect the masking of receptors because of enhanced ligand binding, e.g., enhanced C5a binding to CD88 because of complement activation. It may also reflect that there is no extensive leukocyte activation in the peripheral circulation in preeclamptic, compared with normal, pregnancies[11] or that the most activated leukocytes have been trapped in the microcirculation in different organs.[12]

On leukocytes the integrin α_4 supports rolling on the endothelium and the β_2 integrins (CD11a, CD11b, CD11c) reduce rolling velocity besides being responsible for firm leukocyte-endothelial adhesion.[13] In addition, CD11a and CD11b are critically important for transendothelial migration by interacting with intercellular adhesion molecule 1 (ICAM-1) on the surface of the endothelium.[14] Notably, treatment of cultured trophoblasts with the pro-inflammatory cytokines, interleukin-1 and tumor necrosis factor-α, known to be increased in preeclamptic[15] and hypoxic[16] placentas, may lead to upregulation of ICAM-1 on the trophoblast, with enhanced adhesion of maternal monocytes expressing CD11a.[17] Enhanced ICAM-1 expression in uteroplacental arteries has been shown during preeclampsia.[18] Thus, the findings in the present study of increased expression of the β_2 integrins CD11a, CD11b, and CD11c on neutrophils, as well as Sialyl Lewis^x, CD11a, CD11c, and the α_4 subunit on monocytes, taking place during the uteroplacental passage, indicate a potential for enhanced leukocyte-endothelial interactions in preeclampsia. In fact, the findings suggest an enhanced capacity for all the steps in leukocyte/endothelial interaction, including capture, rolling, firm adhesion, and transmigration in preeclampsia. This may be the mechanism behind the increased infiltrate of neutrophils[19] and mononuclear perivascular cells[20] found in the decidua in preeclampsia.

Migration of activated leukocytes to the peripheral circulation may lead to microcirculatory entrapment of leukocytes as, eg, in the kidneys, affecting the whole organ perfusion pressure, leading to organ damage and increased blood pressure.[12] Thus, therapeutic intervention blocking integrin-endothelial cell interaction might be of interest to investigate in this disorder.

In a study measuring the mean transit time for plasma through the intervillous space, the median time was 46

TABLE 4. Expression of Adhesion Molecules and Complement-Related Markers on Neutrophils and Monocytes Sampled from Antecubital and Uterine Veins during Laparatomy in Nonpregnant Women (n=17)

	Mean Fluorescence Intensity					
	Neutrophils			Monocytes		
Antigens	Antecubital Vein	Uterine Vein	*P* value	Antecubital Vein	Uterine Vein	*P* value
Selectins						
L-selectin	27.8 (22.4–38.7)	29.7 (23.3–37.0)	0.71	15.6 (11.6–17.7)	12.8 (9.7–16.9)	0.08
P-selectin	0.4 (0.0–1.7)	1.0 (0.1–2.8)	0.66	1.1 (0.0–12.0)	1.4 (0.0–7.0)	0.33
Mucins						
Sialyl Lewis^x	248 (122–461)	179 (112–312)	0.73	84 (41–307)	73 (42–124)	0.31
PSGL	161 (145–221)	157 (129–221)	0.59	337 (291–554)	368 (279–496)	0.79
Integrins						
CD11a	4.9 (3.1–11.9)	6.4 (4.9–9.6)	0.51	34 (30–53)	44 (26–55)	0.67
CD11b	178 (64–271)	188 (103–297)	0.39	338 (183–415)	375 (292–438)	0.50
CD11c	18.0 (12.9–26.0)	19.1 (13.3–26.5)	0.16	119 (104–149)	129 (98–178)	0.91
CD49d	1.8 (0.6–2.6)	1.9 (1.4–3.7)	0.55	100 (78–141)	109 (87–137)	0.17
CD29	16.9 (13.4–18.9)	15.3 (12.9–22.6)	0.61	131 (87–163)	111 (86–151)	0.46
Immunoglobulin gene superfamily						
ICAM-1	9.2 (7.3–10.7)	10.2 (8.4–12.7)	0.32	82 (74–95)	82 (72–94)	0.71
ICAM-3	334 (227–549)	290 (218–453)	1.00	355 (223–485)	316 (218–462)	0.46
CD31	18.0 (11.5–21.7)	13.4 (10.8–18.1)	0.61	51 (38–55)	45 (35–54)	**0.008**
Complement receptors						
CD35	5.7 (2.3–11.3)	7.3 (5.1–12.7)	0.16	20.1 (16.1–29.8)	15.6 (12.6–26.4)	0.31
CD46	65 (19–82)	49 (34–89)	0.78	64 (19–103)	52 (32–104)	0.53
CD55	10.3 (8.9–12.1)	9.9 (8.2–12.1)	0.73	21.4 (17.8–26.3)	20.1 (18.0–25.6)	0.81
CD59	10.6 (8.9–14.1)	12.3 (8.1–17.0)	0.16	7.4 (5.6–9.7)	7.9 (6.2–9.5)	0.31
CD88	84 (43–117)	71 (45–109)	0.81	47 (23–95)	40 (25–56)	0.48

Mean fluorescence intensity is expressed as median and 95% CI. Boldface numbers indicate significant differences.

seconds for passing 1/5 of the placental area.[21] The total passage time is therefore substantially longer. Moreover, the passage time may also be delayed during preeclampsia characterized by enhanced leukocyte/endothelial adhesion in this circulation. In experimental models, avidity change of CD11b can be seen within 10 seconds after stimulation,[22] and increased expression leading to adhesion may peak within 30 seconds.[22] Thus, the passage through the uteroplacental circulation may allow sufficient time for the integrin adhesion molecules to be upregulated.

As complement deposits are found in the placenta during preeclampsia,[23] complement activation may take place in the uteroplacental compartment in this disorder. CD35 (CR-1) inhibits the complement system by inactivating the C3 convertase[24] and is an early marker of neutrophil activation. CD46 (MCP) supports conversion of the activation products C3b and C4b into smaller fragments, inhibiting further activation of the complement cascade.[25] CD59 (protectin) blocks the assembly of the membrane attack complex by binding to C8 and C9.[25] The expression of molecules with complement inhibitory activity, ie, CD35 and CD59 on neutrophils and CD46 and CD59 on monocytes, increased during the uteroplacental passage, and this supports a local leukocyte activation taking place in preeclampsia. However, the biological consequence of this upregulation may represent a principle for protection against complement attack.

When comparing differences in adhesion molecules and complement receptors between uterine and antecubital veins, the findings are compatible with a marked leukocyte activation induced during the uteroplacental passage in preeclamptic pregnancies. Interestingly, a similar finding of leukocyte activation has been reported in the coronary circulation during myocardial ischemia.[26] Thus, this phenomenon may represent a pattern of leukocyte activation taking place in the passage of an organ subjected to ischemia. However, other factors may also be involved in this process, such as increased shear stress and enhanced cytokine production from endothelial cells and trophoblasts, as well as platelet activation with release of mediators such as chemokines, leukotrienes, and CD40 ligand.[3,27,28] Whatever the mechanisms, and although not necessarily the primary event or the cause of preeclampsia, leukocyte activation may contribute to the progression of this disorder. In fact, whereas endothelial activation may exist prior to and induce leukocyte activation, leukocyte activation may in turn further promote endothelial cell activation, possibly representing a vicious circle in preeclampsia. Such a local inflammatory response involving enhanced leukocyte-endothelial cell interaction may contribute to the pathogenesis of, and may potentially also represent new targets for therapeutic intervention in, this disorder.

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