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Endothelial Activation and Cell Adhesion Molecule Concentrations in Pregnant Women Living at High Altitude

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Abstract

Objectives: Maternal physiology at high altitude could be considered to resemble an intermediate state between preeclampsia and normal pregnancy. The objective of the current study was to determine if cell adhesion molecules, known to be increased in preeclampsia, are increased with chronic maternal and placental hypoxia (due to high-altitude residence) in the absence of preeclampsia.

Methods: Serum was collected from women residing at 3100 m or 1600 m in the three trimesters of pregnancy and postpartum. Vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) were measured by enzyme-linked immunosorbent assay (ELISA).

Results: General linear model (GLM) repeated measures analysis of VCAM-1, E-selectin, and ICAM-1 data showed there were no statistically significant effects of gestation within either the high- or moderate-altitude groups or between the different altitudes.

Conclusion: The increase in cell adhesion molecules reported in preeclampsia is not present in pregnant women at high altitude, suggesting that maternal systemic hypoxia is not responsible for this pathway of endothelial cell activation in preeclampsia.

Keywords

Hypoxia; preeclampsia; endothelium; cell adhesion molecule; erythropoietin receptor; placenta

Preeclampsia is diagnosed by increased blood pressure and proteinuria but is a complex multi-organ syndrome involving reduced organ blood flow, vasoconstriction, and activation of the coagulation cascade.¹ Among the most widely accepted theories about the cause of preeclampsia is a two-stage model in which reduced placental perfusion leads to a second-stage maternal syndrome characterized by endothelial cell dysfunction and/or reduced organ perfusion and tissue damage.² This model emphasized that while the placenta appears to be

a key factor in the causal pathway, there is clearly more to the disorder than simply reduced placental perfusion.

Since the seminal publication of Roberts et al,³ endothelial dysfunction has been pursued as a pathologic/etiologic feature of preeclampsia. Women with preeclampsia show generalized increases in markers of endothelial dysfunction. Blood vessels isolated from the placental and the maternal systemic circulation (eg, omental arteries) show altered endothelial function (increased vascular reactivity) ex vivo in women with pre-eclampsia when compared with healthy controls.⁴ Markers of endothelial activation known to be increased in preeclampsia include pro-inflammatory cytokines such as interleukin (IL)-6⁵ and cell adhesion molecules such as E-selectin and vascular cell adhesion molecule-1 (VCAM-1).^{6,7} The source of the factor(s) causing vascular endothelial cell dysfunction is unknown, but again, a popular theory is that placental hypoxia causes the release of factor(s) damaging to the endothelium.

Most well-described risk factors for preeclampsia are constitutional maternal attributes, such as primiparity, obesity, ethnicity, chronic hypertension, renal disease, etc,^{8–11} or be behavioural attributes such as contraceptive practices or smoking (or the lack thereof).^{11–13} Residence at high altitude (>2700 m) is the only external environmental factor that, to date, has been consistently linked with an increased incidence of preeclampsia.^{14–16} The primary effect of living at high altitude is lowered arterial oxygen tension (pO₂). Thus, of the several competing hypotheses concerning the etiology of preeclampsia, the data from high altitude support the theory that hypoxia of the fetoplacental unit is an underlying cause or at the very least contributes to the development of the disease.

Women residing at high altitude with normal pregnancy outcomes have physiologic changes and remodeling of the uteroplacental arteries intermediate between that observed in normal pregnancy and preeclampsia.^{14,17,18} Uterine blood flow and oxygen flow to the fetoplacental unit are reduced, and pro-inflammatory cytokines and catecholamines are elevated, supporting the idea that placental hypoxia elevates the risk for preeclampsia.^{19,20} Hence, high-altitude pregnancy provides a model to study whether increased markers of endothelial dysfunction in preeclampsia arise as a result of the disease process itself or as a result of chronic placental hypoxia. The aim of the current study was to measure maternal circulating concentrations of the cell adhesion molecules VCAM-1, E-selectin, and intercellular adhesion molecule-1 (ICAM-1) in each trimester of pregnancy and postpartum in healthy pregnant women with normal pregnancy outcomes residing at high altitude. The hypothesis tested was that circulating cell adhesion molecule concentrations would be increased as a result of chronic hypoxia even in the absence of any symptoms of preeclampsia.

MATERIALS AND METHODS

Maternal Serum Collection

Blood samples were obtained from 15 women residing in Denver, CO (moderate-altitude group, 1600 m) and 16 women residing in Leadville, CO (high-altitude group, 3100 m). Informed consent to the study procedures, approved by the University of Colorado Health Sciences Center Institutional Review Board, was obtained from all participants.

Approximately 10 mL of blood was withdrawn from the antecubital vein once per month beginning as early in pregnancy as possible and at 3 months postpartum. Blood was allowed to clot for 1 hour. Serum was separated by centrifugation, flash-frozen in liquid nitrogen, and then stored in a -80C freezer. The week of pregnancy reported here for the time of the blood draw was back-calculated from the clinically assessed gestational age evaluated at birth. For the present study, blood samples were matched insofar as possible between altitudes for week of pregnancy. One sample each from the first, second, and third trimester, as well as approximately 3 months post-partum were analyzed.

ENZYME-LINKED IMMUNOSORBENT ASSAY.—Concentrations of the cell adhesion molecules VCAM-1, ICAM-1 and E-selectin were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Abingdon, UK). Assays were performed according to the manufacturer's instructions. The number of serum samples available for assay was slightly different for each cell adhesion molecule measured and also for each trimester studied; thus, the number of samples analyzed for each altitude is shown in the results section as appropriate. For all assays, samples were diluted to the manufacturer's recommendations using the kit-provided sample diluent (1:50 VCAM-I, 1:20 for both ICAM-I and E-selectin). The standard curves supplied with the kits were run in duplicate with each assay. All samples measured yielded values within the range of the standard curve for the specific assay. The interassay coefficient of variation (CV) was 8.5% to 10.2% for VCAM-I, 6.0% to 10.1% for ICAM-I, and 5.7% to 8.8% for E-selectin. The intra-assay CV was 4.3% to 5.9% for VCAM-I, 3.3% to 4.8% for ICAM-I, and 3.3% to 4.8% for E-selectin.

STATISTICS.—Maternal demographic attributes and clinical data (birth weight, gestational age, etc) were compared using Student *t* tests or Chi-square test as appropriate.

Analysis of VCAM, ICAM, and E-Selectin data was performed using the general linear model (GLM) for repeated measures. A full factorial model was fitted with altitude (moderate and high) as a between-subjects factor and trimester (first, second, third, and postpartum) as a within-subjects factor. Correlation between gestation at sampling and altitude was investigated by Pearson correlation analysis. Significance was set at $P < .05$.

RESULTS

The comparisons of demographic characteristics and pregnancy outcome for the moderate- and high-altitude women are shown in Table 1. Women at 1600 m had more years of education, larger babies, and smaller placentas than women at high altitude but were otherwise similar. None of the women had any chronic conditions predisposing to preeclampsia such as renal disease, diabetes, or obesity. The women were healthy nonsmoking and primiparous and were also matched for race. The majority of serum samples were assayed for all three adhesion molecules at the same time in pregnancy for each subject, but in some cases, due to small sample volume, a slightly different subset of samples was used. The numbers for each assay are shown in Table 2.

The median gestation and range for each trimester are listed in Table 3. There was no difference in the gestational age at which samples were obtained for analysis in the first, second, or third trimesters at moderate versus high altitude for any of the assays.

The data for VCAM-1 are shown as a scattergram in Figure 1. The mean $\pm$ SE values (ng/mL) were as follows: first trimester, 563.82 ± 108.18 at moderate altitude and 468.3 ± 27.87 at high altitude; second trimester, 529.3 ± 40.1 at moderate altitude and 456.3 ± 24.4 at high altitude; third trimester, 639.39 ± 62.0 at moderate altitude and 545.21 ± 38.5 at high altitude; and postpartum, 585.77 ± 61.05 at moderate altitude and 450.5 ± 30.35 at high altitude.

The data for E-selectin are shown as a scattergram in Figure 2. The mean $\pm$ SE (ng/mL) values were as follows: first trimester, 32.49 ± 5.32 at moderate altitude and 38.87 ± 4.77 at high altitude; second trimester, 39.8 ± 2.95 at moderate altitude and 37.05 ± 2.92 at high altitude; third trimester, 36.6 ± 4.63 at moderate altitude and 37.09 ± 4.27 at high altitude; and postpartum, 37.1 ± 4.03 at moderate altitude and 43.3 ± 5.88 at high altitude.

The data for ICAM-1 are shown as a scattergram in Figure 3. The mean ICAM-1 concentrations (ng/mL) were as follows: first trimester, 270.65 ± 31.8 at moderate altitude versus 255.29 ± 20.09 at high altitude; second trimester, 279.16 ± 13.79 at moderate altitude versus 246.7 ± 14.29 at high altitude; third trimester, 279.89 ± 28.15 at moderate altitude versus 272.87 ± 24.0 at high altitude; and for post-partum, 331.7 ± 39.3 at moderate altitude versus 316.02 ± 24.88 at high altitude.

GLM repeated measures analysis of VCAM-1, E-selectin, and ICAM-1 data showed there were no statistically significant effects of gestation within either the high- or moderate-altitude groups or between the different altitudes.

There was no correlation between VCAM and gestation in either the high-altitude or moderate-altitude groups individually, but when the groups were combined there was a positive correlation of VCAM with gestation ($P < .05$, $R = 0.22$). There was no correlation between ICAM and gestation or between E-selectin and gestation.

Finally, in this set of analyses, VCAM-1, ICAM-1, and E-selectin concentrations were analysed with a Pearson's correlation to determine if there was any correlation between the concentrations of each at either or both altitudes. When high altitude was analyzed alone, there was a positive correlation between ICAM-1 and VCAM-1 concentrations ($P < .01$; $r = 0.4$), ie, when a woman had high concentrations of ICAM-1 she also tended to have high concentrations of VCAM-1. There were no correlations between circulating cell adhesion molecule concentrations at moderate altitude. When both altitudes were included in the analysis, there was a positive correlation between ICAM-1 and E-selectin concentrations ($P < .01$, $r = 0.33$), ie, when a woman had high concentrations of ICAM-1 she also tended to have high concentrations of E-selectin.

In a previous study we found that placental microvillous membrane erythropoietin receptor protein levels were elevated in high-altitude placentae, consistent with hypoxia.²¹ Since these placentae were obtained from a subset of the women in the present study ($n = 12$ at

1600 m and $n = 10$ at 3100 m), we tested whether any of the cell adhesion markers obtained late in pregnancy correlated with the expression of placental erythropoietin receptor, a classic marker of hypoxia. They did not. The r^2 values ranged from 0.01 to 0.09 at 1600 m and from 0.00 to 0.25 at 3100 m.

DISCUSSION

This study has shown that VCAM-1, E-selectin, and ICAM-1 concentrations did not change throughout pregnancy at 1600 m or at 3100 m.

In this study we did not have direct measurements of maternal hypoxia, eg, arterial blood gases or oxygen saturations, nor was there a prospective study of similar design conducted at the same time at sea level (there are no sea level sites in Colorado). Nonetheless, there is no evidence that an altitude of 1600 m is associated with reduced birth weight or increased complications of pregnancy; the oxygen dissociation curve is shaped such that oxygen saturation does not decline much until one is over 2700 m altitude.²² The incidence of preeclampsia is 12% at Leadville and 3% at Denver (ie, similar to sea level). That the women living at 3100 m were subjected to hypoxic stress is supported by a study of the placentas obtained from the women measured in this study. We found a 40% increase in the density of microvillous syncytial membrane erythropoietin receptor, a classic marker of hypoxia.²¹ In our previous studies, arterial oxygen saturation in women residing at 3100 m ranged from 86% to 94%; the mean of $90\% \pm 1\%$ was significantly lower than the $95\% \pm 1\%$ measured at 1600 m.¹⁷ That there was not a relationship between the placental erythropoietin receptor density and any of the cell adhesion molecules also suggests that maternal and/or placental hypoxia are not responsible for the elevation in circulating concentrations of cell adhesion molecules observed in preeclampsia at sea level.

Preeclampsia remains an important cause of maternal and fetal morbidity.²³ A number of maternal circulating factors have been associated with the maternal syndrome.^{5–7,24–31} The model of chronic hypoxia in pregnancy offered by high-altitude residence is unique in allowing investigators the opportunity to distinguish between specific circulating and molecular markers of preeclampsia from those which may be due to hypoxia alone, without pathologic consequences.^{32–35} The rate of preeclampsia is increased (12%) in Leadville (3100 m) versus (3%) Denver (1600 m). In the present study, all women had normal outcomes.³⁶ The data presented here suggest that chronic maternal systemic hypoxia per se is not responsible for increased cell adhesion molecules in preeclampsia. We therefore suggest that an increase in circulating cell adhesion molecules in preeclampsia cannot be directly linked to hypoxia and is likely to be a secondary response to other events.

We have previously reported concentrations of VCAM-1, E-selectin, and ICAM-1 in women living at sea level (Glasgow).^{6,7} The values we reported for VCAM-1 in the third trimester for the sea level group (560.2 ± 47.0) are in the range of the values found for moderate altitude (639.39 ± 62.0) and high altitude (545.21 ± 38.5). In contrast, the value for women with preeclampsia at sea level was significantly higher (841.9 ± 49.7). For E-selectin, we reported concentrations for normal third trimester pregnancies of 45.8 ± 4.6 at sea level compared to 36.6 ± 4.63 at moderate altitude and 37.09 ± 4.27 at high altitude. Finally, for

ICAM-1 we reported sea level values of 187.3 ± 15.8 compared with values of 279.89 ± 28.15 at moderate altitude versus 272.87 ± 24.0 at high altitude. It is difficult to make direct comparisons between the third trimester results between the two different studies, since the sea level group constitute a different population of women. Only VCAM-1 was reduced overall at high altitude compared with moderate altitude, yet VCAM-1 shows the biggest increase in preeclampsia, further suggesting that the effects of maternal hypoxia have different effects on VCAM-1 to the effects of the maternal endothelium in preeclampsia.

Acute high-altitude exposure leads to an increase in IL-6 and other indicators of an immune system inflammatory response.^{36–39} We found that maternal circulating concentrations of the pro-inflammatory cytokines IL-6, tumor necrosis factor-alpha, and IL-8 were all elevated late in pregnancy in women residing at high altitude, but did not differ even marginally between high and moderate altitude in the non-pregnant state. The same subjects failed to increase their levels of anti-inflammatory (Th-2) IL-10 during pregnancy, causing a marked reduction in circulating concentrations relative to moderate-altitude control subjects that was, again, most pronounced in the third trimester when pregnancy complications develop.²⁰ The complexity of the systems involved can support a number of different explanations.²⁰

In a previous study we also showed that IL-6 can increase the expression of VCAM-1 and E-selectin in vitro.⁴⁰ Since we have shown all three were increased in preeclampsia, we speculated that IL-6 may be responsible, at least in part, for increased circulating cell adhesion molecules in preeclampsia. Yet, despite the increase in IL-6 at high altitude, cell adhesion molecules were not increased overall. Hence, IL-6 may not be the factor increasing VCAM-1 or other factors, yet to identified, may be limiting VCAM-1 release at high altitude.

In summary, because there is unquestionable lowered maternal arterial pO₂ at high altitude, and evidence of placental hypoxia in the pregnancies considered in this report, the data support that maternal and/or placental hypoxia are not responsible for the elevation in circulating concentrations of cell adhesion molecules observed in preeclampsia at sea level.

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Figure 1. VCAM-1 concentrations throughout pregnancy at moderate altitude (*open circles*) and high altitude (*shaded circles*).

Figure 2. E-Selectin concentrations throughout pregnancy at moderate altitude (*open circles*) and high altitude (*shaded circles*).

Figure 3.
ICAM-1 concentrations throughout pregnancy at moderate altitude (*open circles*) and high altitude (*shaded circles*).

Table 1.

Demographic Details of Patients Studied

	Maximum no. of cases studied	
	1600 m (n = 15)	3100 m (n = 21)
Age (y)	28 ± 4	27 ± 7
Height (cm)	167 ± 6	165 ± 8
Pre-pregnant weight (kg)	62 ± 6	61 ± 6
BMI (kg/m ²)	22 ± 2	22 ± 2
Weight gain with pregnancy (kg)	14 ± 4	16 ± 5
Maternal education (y)	17 ± 3	14 ± 3 [†]
Paternal education (y)	16 ± 3	16 ± 3
Birth weight (g)	3332 ± 346	3076 ± 390 [*]
Gestational age (wk)	39.2 ± 1.2	39.8 ± 1.7
Baby length (cm)	50.2 ± 2.6	50.3 ± 3.1
Placental weight (g)	517 ± 109	596 ± 85 [†]

Maternal characteristics, mean ± SD. BMI = body mass index.

^{*} $P < .05$.

[†] $P < .05$.

Table 2.

Number of Cases Studied at Each Trimester at Moderate and High Altitude

	First trimester	Second trimester	Third trimester	Postpartum
VCAM-1 MA	5	21	15	13
VCAM-1 HA	5	17	19	11
E-Selectin MA	5	15	11	7
E-Selectin HA	5	17	16	11
ICAM-1 MA	5	21	15	13
ICAM-1 HA	5	16	18	11

MA = moderate altitude; HA = high altitude.

Table 3.
Gestations at the Time of Blood Sampling From Women Residing at High and Moderate Altitudes

	MA			HA			<i>P</i>
	VCAM-1 Median (range)	E-selectin Median (range)	ICAM-1 Median (range)	VCAM-1 Median (range)	E-selectin Median (range)	ICAM-1 Median (range)	
First trimester (wk)	12 (12–14)	12 (12–14)	12 (12–14)	12 (11–14)	12 (11–14)	12 (11–14)	NS
Second trimester (wk)	25 (15–27)	26 (15–27)	25 (15–27)	25 (15–28)	25 (15–28)	25 (15–28)	NS
Third trimester (wk)	37 (32–39)	37 (32–39)	37 (32–39)	37 (31–40)	37 (32–39)	37 (31–40)	NS

MA = moderate altitude; HA = high altitude; NS = not significant ($P > .05$).