Preeclampsia and eclampsia incidence in the eastern anatolia region of Turkey: the effects of high altitude

Türkiye’nin Doğu Anadolu Bölgesinde preklampsi ve eklampsi insidansı: Yüksek rakımın etkileri

Yakup Kurntepe¹, Onur Dündar⁰, Kadir Çetinkaya³, Metin İnegöl⁴
¹Department of Obstetrics and Gynecology, Faculty of Medicine, Atatürk University, Erzurum, Turkey
²Department of Obstetrics and Gynecology, Trabzon Women’s Hospital, Trabzon, Turkey
³Department of Obstetrics and Gynecology, Ankara Oncology Education and Research Hospital, Ankara, Turkey

Abstract

Objective: Hypertensive disorders of pregnancy remain a leading cause of maternal and perinatal mortality and morbidity. The purpose of this study was to determine the distribution map related to pregnancy toxification of provinces in our region and the effects of altitude on hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and eclampsia.

Materials and Methods: Patients who were admitted to Atatürk University, Obstetrics and Gynecology Department with preeclampsia, eclampsia and a diagnosis of HELLP syndrome for the 5 years between 1998-2002 were chosen. The birth rate was obtained from the health directorate of provinces in our area during the same period. Provinces were divided into two groups by altitude: less than and more than 1500 m above sea level.

Results: The rates of HELLP syndrome and eclampsia diagnoses were 1.4 per 10,000 patients living above 1500 m altitude. However, this rate was 0.96 per 10,000 patients living below 1500 m altitude (p < 0.01). The highest rate of eclampsia and HELLP syndrome was seen in the Ardahan province, in 36 patients per 10,000 births, whereas the lowest rate was seen in the Iğdır province, 9.9 patients per 10,000 births.

Conclusion: Altitude contributes to occurrence of HELLP syndrome and eclampsia. Since the rate of pregnancy related hypertension is higher at high altitude, it is vital that these patients should be diagnosed during the early stages of the diseases in order to decrease complications. (J Turkish-German Gynecol Assoc 2011; 12: 26-30)

Key words: Preeclampsia, eclampsia, HELLP syndrome, high altitude

Received: 21 November, 2010 Accepted: 29 January, 2011

Introduction

There is a prominent increase in all arterial flow (consequently, uterine artery blood flow), a decrease in the vasoconstrictor response of the vascular system, and an increase in the vasodilator response during normal pregnancy (1). The results of animal-based studies have shown that there is a decreased response to alpha-adrenergic stimulation of the vascular system and an increase in endothelium-dependent vasodilatation caused by increased basal and stimulated endothelium-derived nitric oxide (2, 3). However, in pregnancies developing preeclampsia at a later stage, there is evidence of vasocostriction, increased vascular tone, platelet aggregation, and an alteration in the thromboxane-to-prostacyclin ratio (4). Maternal and fetal morbidity and mortality rates increase in hypertensive disorders of pregnancy (5).

Preeclampsia is seen in 2-7% of all pregnancies, and its frequency is higher in primigravid than in multigravid women.
It is also more frequently seen in women carrying more than one fetus, older women, women with genetic factors, hyperlipidemia, thrombophilia, obesity, and diabetes mellitus, women experiencing preeclampsia during a previous pregnancy, and those living at high altitudes (8-13).

Preeclampsia is a multisystem disease that affects both mother and fetus. There is a progressive loss of musculoelastic tissue on spiral arteries in normal placental development, because extravillous cytotrophoblasts migrate up the spiral arteries and cause an erosion of the vascular smooth-muscle layer of the maternal spiral arteries, resulting in a loss of vasoactivity, subsequent dilatation, and a decrease in uteroplacental vascular resistance (9). Thus, uterine blood flow increases approximately 25% throughout the first trimester. However, in women living at high altitude, hypoxia inhibits the transition of the trophoblast from a resting, proliferative phenotype to an invasive phenotype and, hence, may inhibit arterial remodeling (10). As a result, maternal arterial oxygen pressure and uterine blood flow decrease at high altitude (11). This physiological dilatation does not occur in patients prone to preeclampsia, because placental trophoblastic cells do not wrap up spiral arteries, therefore spiral arteries are tightened and shortened, and uteroplacental blood flow decreases (14). Because of increased hypoxia, living at high altitude causes important health problems. Studies have revealed that intraterute growth restriction (IUGR), preterm labor, abruptio placenta, and preeclampsia increase with increasing altitude (12, 15). Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome were first diagnosed with preeclampsia had convulsions, once proteinurea was ≥3+ on dipstick in at least two random clean-catch samples at least 4 hours apart, or (3) eclampsia. Preeclampsia was defined in accordance with the criteria of the American College of Obstetrics and Gynecology (20). Mild preeclampsia was diagnosed if systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, and proteinurea was ≥0.3 g/L in a 24-hour urine sample. Severe preeclampsia was diagnosed when one of the following criteria was present: (1) blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least 6 hours apart with the patient on bed rest, (2) proteinurea ≥5 g in a 24-hour urine collection or ≥3+ on dipstick in at least two random clean-catch samples at least 4 hours apart, or (3) eclampsia. Eclampsia was diagnosed if the patient who had previously been diagnosed with preeclampsia had convulsions, once other causes of convulsions had been ruled out. To determine mean hypertension, mean arterial pressure (MAP) was calculated [MAP = (2×diastolic pressure + systolic pressure)/3] after admission and before treatment for each patient. HELLP syndrome was diagnosed according to strict Sibai criteria (17) as follows:

**Material and Methods**

The study was carried out retrospectively by medical record examination, in patients with preeclampsia-eclampsia who had been admitted to Atatürk University, Faculty of Medicine, Department of Obstetrics and Gynecology during the period between 1998-2002. The total number of births that took place in the Eastern Anatolia Region of Turkey during this 5-year period was obtained from the Health Directorate of Provinces. During the same time, the numbers of births and patients with preeclampsia, eclampsia, and HELLP syndrome were recorded. Patients from the city of Erzurum and its provinces and neighboring cities were divided into 2 groups according to altitude (Table 1). Group 1, patients living at over 1500 m, included Karaçoban (1945 m), Köprüköy (1747 m), Tortum (1772 m), Pasinler (1660 m), Aşkale (1700 m), Narman (1830 m), Çat (1920 m), Karayazı (2260 m), and Hınıs (1795 m) provinces and Bayburt (1680 m), Ağrı (1738 m), Kars (1859 m), Ardahan (1929 m), Erzurum (1864 m) city centers. Group 2, patients living at under 1500 m, included Ispir (1222 m), Olur (1300 m), Uzundere (1300 m), and Oltu (1229 m) provinces and Artvin (628 m), İğdır (758 m), Bingöl (1177 m), Erzincan (1058 m), and Muş (1224 m) city centers.

Preeclampsia was defined in accordance with the criteria of the American College of Obstetrics and Gynecology (20). Mild preeclampsia was diagnosed if systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, and proteinurea was ≥0.3 g/L in a 24-hour urine sample. Severe preeclampsia was diagnosed when one of the following criteria was present: (1) blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least 6 hours apart with the patient on bed rest, (2) proteinurea ≥5 g in a 24-hour urine collection or ≥3+ on dipstick in at least two random clean-catch samples at least 4 hours apart, or (3) eclampsia. Eclampsia was diagnosed if the patient who had previously been diagnosed with preeclampsia had convulsions, once other causes of convulsions had been ruled out. To determine mean hypertension, mean arterial pressure (MAP) was calculated [MAP = (2×diastolic pressure + systolic pressure)/3] after admission and before treatment for each patient. HELLP syndrome was diagnosed according to strict Sibai criteria (17) as follows:

**Table 1. Altitudes of provinces and districts**

<table>
<thead>
<tr>
<th>Group 1 (&gt;1500 m)</th>
<th>Group 2 (&lt;1500 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Province/district</td>
<td>Altitude (m)</td>
</tr>
<tr>
<td>Erzurum (Karaçoban)</td>
<td>1945</td>
</tr>
<tr>
<td>Erzurum (Köprüköy)</td>
<td>1747</td>
</tr>
<tr>
<td>Erzurum (Tortum)</td>
<td>1772</td>
</tr>
<tr>
<td>Bayburt</td>
<td>1680</td>
</tr>
<tr>
<td>Ağrı</td>
<td>1738</td>
</tr>
<tr>
<td>Erzurum (Aşkale)</td>
<td>1700</td>
</tr>
<tr>
<td>Erzurum (Narman)</td>
<td>1830</td>
</tr>
<tr>
<td>Erzurum (Hınıs)</td>
<td>1795</td>
</tr>
<tr>
<td>Kars</td>
<td>1859</td>
</tr>
<tr>
<td>Ardahan</td>
<td>1929</td>
</tr>
<tr>
<td>Erzurum (Centre)</td>
<td>1864</td>
</tr>
<tr>
<td>Erzurum (Çat)</td>
<td>1920</td>
</tr>
<tr>
<td>Erzurum (Karıyaz)</td>
<td>2260</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>1849.2±150.7</strong></td>
</tr>
</tbody>
</table>
1. Hemolysis: characteristic appearance of peripheral blood smear and serum LDH ≥ 600 U/L or serum total bilirubin ≥ 1.2 mg/dL.
2. Elevated liver enzymes: AST concentration ≥ 70 U/L.
3. Low platelet count: < 100,000/μL.

The patients who had all these 3 indications and those who had 1 and/or 2 of these indications were categorized as complete and partial HELLP syndrome.

Our database included only the patients with HELLP syndrome and eclampsia. Maternal age, gravidity, parity, and gestational age were recorded in patients with HELLP syndrome and eclampsia in both groups. Numbers of Cesarean births were obtained for an evaluation of birth position for both groups. Fetal or live birth numbers and birth weights were recorded to evaluate the incidence rate of HELLP syndrome.

Statistical analyses were performed using the Minitab Packed program, and differences between groups were determined by the Mann Whitney U test. Data are given as mean ± standard deviation.

**Results**

The total number of births was 114,819 in group 1 and 81,454 births in group 2 over the 5-year period (1998-2002) (Table 2).

In group 1, there was a total of 164 diagnosed patients (HELLP+eclampsia) and 75 of these had eclampsia (54 patients accompanied by HELLP syndrome and 21 patients accompanied by preeclampsia). In group 2, there was a total of 78 diagnosed patients (HELLP+eclampsia) and 45 had eclampsia (33 patients accompanied by HELLP syndrome and 12 patients accompanied by preeclampsia) (Table 3).

There were no differences in the two groups for age, gravidity, parity, gestational age, normal birth rate, and fetal weight. Cesarean births in groups 1 and 2 were 94 (57%) and 44 (56%), respectively. Platelet count and concentrations of AST and LDH were 87.648±109.970/μl, 172±237 IU/L, and 1208±755 IU/L, respectively in patients in group 1 (>1500 m altitude) and 96.347±109.970/μl, 146±109 IU/L, and 1208±755 IU/L, respectively in patients in group 2 (<1500 m altitude) (Table 4).

During this study, 8100 births occurred in our clinic, and in 582 cases preeclampsia and eclampsia were diagnosed (7.2%). A total of 242 patients were evaluated for HELLP syndrome and eclampsia, and 10 patients were excluded from the study because of a high level of liver enzymes suggestive of viral hepatitis in 4 patients, DIC owing to an intrauterine dead fetus in 3 patients, and hepatotoxic medicine usage in 3 patients. In group 1, of 144 patients who were suspected of having HELLP syndrome, there were 69 (48%) with complete and 75 (52%) with partial HELLP syndrome. Of 75 patients with partial HELLP syndrome, AST level was > 70 IU/L in 38 patients, AST level and platelet count were > 70 IU/L and < 100,000/μL in 19 patients, and the platelet count was < 100,000/μL in 17 patients. When parity and maternal age in patients with complete and partial HELLP syndrome were considered in group 1, maternal age and parity in patients with complete and partial HELLP syndrome were 32.6±5.6 and 3.6±3.8 and 27.0±4.3 and 3.4±3.2, respectively.

In group 2, of 66 patients suspected as having HELLP syndrome, patients with complete and partial HELLP syndrome were 27 (40.9%) and 39 (59.1%), respectively. Of 39 patients with partial HELLP syndrome, the AST level was > 70 IU/L in 12 patients, and AST and platelet count were > 70 IU/L and < 100,000/μL in 19 patients, respectively. The platelet count was < 100,000/μL in 5 patients. Parity and maternal age in patients with complete and partial HELLP syndrome were 2.9±1.6 and 26.7±5.3 and 2.4±1.6 and 25.5±5.2, respectively. The rates of HELLP syndrome and eclampsia per 10,000 births in provinces are shown in Figure 1. The incidence rate of HELLP syndrome and eclampsia were evaluated, the highest rate was seen in the Ardahan province (36 per 10,000 births). With 28 per 10,000 births, Artvin had the second-highest rate, and Erzurum, Kars, Ağrı, Bayburt, Muş, Bingöl, Erzincan, and Iğdır followed these provinces.
Table 4. Comparison of parameters in subject populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n:164) (altitude &gt;1500 m)</th>
<th>Group 2 (n:78) (altitude &lt;1500 m)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.6±7.3</td>
<td>26.0±6.0</td>
<td>ns</td>
</tr>
<tr>
<td>Gestational age (year)</td>
<td>35.2±5.4</td>
<td>34.0±5.1</td>
<td>ns</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>124.4±9.2</td>
<td>118.4±8.6</td>
<td>ns</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.9±2.2</td>
<td>11.7±2.2</td>
<td>ns</td>
</tr>
<tr>
<td>Thrombocyte (μl)</td>
<td>87,648±1099</td>
<td>96,347.0±107.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>172.0±237.0</td>
<td>130.5±150.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>286.0±91.0</td>
<td>111.7±208.0</td>
<td>0.01</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>1208.0±755.0</td>
<td>1366.0±1293.0</td>
<td>ns</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.2±2.4</td>
<td>6.7±2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2031±964</td>
<td>2197±893</td>
<td>ns</td>
</tr>
<tr>
<td>Cesarean rate (%)</td>
<td>57</td>
<td>56</td>
<td>ns</td>
</tr>
<tr>
<td>Fetal death (%)</td>
<td>38</td>
<td>17</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ns = not significant

Discussion

Women living at high altitude have low uterine blood flow (21) and a high rate of IUGR (22). The maternal arterial system is normally insensitive to pressor agents in the circulation (23). However, in the case of a deterioration of insensitivity due to uteroplacental ischemia resulting from extreme vasoconstriction, hypoxia develops and this causes IUGR, maternal hypertension, and endothelial cell damage. Indeed, hypoxia deteriorates the arterial structure causing decreased sensitivity against vasoconstriction in pregnancy (24). These suggest that, because of increasing hypoxia, a higher rate of damaged placenta is the reason for increasing rates of preeclampsia at high altitudes. Barometric pressure decreases with increasing altitude; pressure at sea level is 760 mmHg and this decreases to 490 mmHg at 4000 m altitude (25). Besides, arterial PO2 and hemoglobin O2 saturation, which are 95 mmHg and 87% at sea level, decline to 50 mmHg and 80%, respectively, at high altitude (25). Hypoxia causes venous damages which is associated with low birth weight, thrombosis, and preeclampsia (25, 26). Kametas et al. (27) observed a 15% decrease in plasma volume in pregnancy as altitude increased. The increased erythrocyte mass and decreased plasma volume cause hemococoncentration and hyperviscosity, and consequently a decrease in fetoplacental blood flow which could lead to IUGR and preeclampsia (28). Sibai et al. (29) reported that mean maternal age was 27.4±6.7 in their study. In the present study, in patients with HELLP syndrome, maternal ages were 28.6±7.3 in group 1 and 26.0±6.0 in group 2. In this study, maternal age, gravidity, parity, and gestational age were insignificant, but hemoglobin levels increased with altitude (12.9 vs. 11.7 g/L in Group 1 and 2; p<0.01). Palmer et al. (12) revealed that the incidence of preeclampsia at 3100 m and 1260 m was 16% and 3%, respectively, and it increased with increasing altitude. In the present study, overall preeclampsia and eclampsia incidence rate was 7.2% (n=582) during the last 5 years, which is in agreement with the literature (6, 7). Taking patients with HELLP syndrome and eclampsia into consideration, we aimed to determine the present situation in the Eastern Anatolian region. With 209 cases in the past 5 years, HELLP syndrome occurred in 2.6% of total births and 36% of preeclamptic patients in our clinic. It was reported that HELLP syndrome progressed in 4-12% of preeclamptic patients (30). In the present study, the rates of HELLP syndrome are 3-9 times higher than literature findings. This could be due to the fact that preeclamptic patients seek health care only when their health status is complicated by conditions such as HELLP syndrome and eclampsia. Total birth number and the number of cases of HELLP syndrome and eclampsia in the last 5 years were 114,899 and 164, respectively, in places higher than 1500 m altitude. The rate of HELLP syndrome and eclampsia was 0.14%, in places lower than 500 m altitude, the total birth number was 81,374, and the rate of cases of HELLP syndrome and eclampsia was 0.096% (p<0.01). When the rate for HELLP syndrome and eclampsia is combined, the rate in places higher than 1500 m altitude was much higher than in places below 1500 m altitude. The highest rate was seen in Ardahan (36 cases per 10,000 births), and the lowest rate was seen in Iğdır (9.8 cases per 10,000 births).

When HELLP syndrome and eclampsia rates were considered, it could be clearly seen that provinces with similar altitudes have similar rates; for example, 22.9 in Erzurum (1864 m.), 18.8 in Kars (1875 m.) and Ağrı (1732 m.), and 18.0 in Bayburt (1684 m.). Although the Ardahan province has a similar altitude (1929 m.), the rate in this province was 36. Likewise, Artvin is located at low altitude, the rate, 28 per 10,000 births, was much higher than the group mean (11.5). This could be related to other nutritional and environmental factors that could contribute to preeclampsia. On the other hand, with 9.9 and 10 cases per 10,000 births, Iğdır and Erzincan in group 2 (<1500 m altitude) had the lowest rates among the other provinces.

Liver impairment could result in serious problems in HELLP syndrome and plays a vital role in mortality; it is the cause of 1 out of 6 maternal mortalities (4). Elevations in enzyme levels, especially AST, indicate liver impairment. Leakage of enzymes from cell membranes to the blood is the reason for high enzyme levels in HELLP syndrome. With 172.0±237.0 IU/L (72-1061), AST levels in group 1 were significantly higher (p<0.01) than those in group 2, 130.5±150.9 IU/L (82-1064). It could be inferred that, with increasing altitude, a higher rate of HELLP syndrome was seen. With 166 g difference, fetal weight was found to be lower in group 1 than group 2 (2031±964 g in group 1 and 2197±893 in group 2). Palmer et al. (12) reported that with 285 g difference, people living at 3100 m altitude had a lower fetal weight than those at 1260 m altitude. At 38%, (62 cases), the fetal death rate in group 1 was higher than that in group 2 with 18% (14
cases), but no studies of high fetal death rates at high altitude could be found in the literature. However, it is clear that, in our study, death rate of preeclamptic babies at high altitude is about twice that at lower altitude. The eclampsia rate is about 1 in 2000 pregnancies in developed countries (31), whereas this rate was determined to be 1 in 100-1700 pregnancies in developing countries, and eclampsia is still the reason for 10% of maternal mortalities (18). Chen et al. (32) reported that this rate in Singapore is 6.7 per 10,000 pregnancies. With 45 cases, our eclampsia rate is similar to rates found in that study. The etiological relation of HELLP syndrome and eclampsia to preeclampsia is not well known. Moreover, it was previously thought that abnormal trophoblast invasion of uterine arteries, immunological intolerance between fetoplacental and maternal tissue, maladaptation to cardiovascular changes of pregnancy, dietary deficiency, and genetic abnormalities could affect these illnesses (33).

Our study demonstrated a greater incidence of eclampsia accompanied by complete and/or incomplete HELLP syndrome among women living at high altitude (>1500 m). However, our results have certain limitations that probably contribute to this illness, such as economical and nutritional status, diagnosis time relative to disease onset, and interactions among these and other unmentioned causes.

**Conflict of interest**
None declared.

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