

# 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 Kumtepe<sup>1</sup>, Onur Dündar<sup>2</sup>, Kadir Çetinkaya<sup>3</sup>, Metin İngeç<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Atatürk University, Erzurum, Turkey

<sup>2</sup>Department of Obstetrics and Gynecology, Trabzon Women's Hospital, Trabzon, Turkey

<sup>3</sup>Department 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 toxosis 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

## Özet

**Amaç:** Gebeliğin hipertansif hastalıkları maternal ve perinatal mortalite ve morbiditenin önde gelen sebebi olmaya devam etmektedir. Bu çalışmanın amacı, bölgemizdeki illere göre gebelik toksikozu dağılım haritası çıkarmak ve hemoliz, yükselmiş karaciğer enzimleri, düşük platelet (HELLP) sendromu ve eklampsi üzerine yüksek rakımın etkilerini belirlemektir.

**Gereç ve Yöntemler:** Atatürk Üniversitesi, Kadın Hastalıkları ve Doğum bölümüne 1998-2002 yılları arasında 5 yıllık bir dönemde preeklampsi, eklampsi ve HELLP tanısı ile başvuran hastalar seçildi. Aynı dönemde, il sağlık müdürlüklerinden doğum hızları temin edildi. Deniz seviyesine göre 1500 m altında ve üstünde olmak üzere iller iki gruba ayrıldı.

**Bulgular:** HELLP sendromu ve eklampsi tanıları 1500 m üzerinde 10.000 doğumda 1.4 izlenirken, 1500 m altında 0.96 izlenmiştir ( $p < 0.01$ ). En yüksek HELLP sendromu ve eklampsi Ardahan ilinde 10.000 doğumda 36 izlenirken, en düşük Iğdır ilinde 10.000'de 9.9 olarak izlenmiştir.

**Sonuç:** Rakım, HELLP sendromu ve eklampsi oluşumunda rol alır. Yüksek rakımda yaşayanlarda gebelik ile ilişkili hipertansif hastalıkların daha yüksek oranda izlendiği için komplikasyonların azaltılabilmesinde hastalığın erken dönemlerinde tanı alması hayati önem taşımaktadır.

(J Turkish-German Gynecol Assoc 2011; 12: 26-30)

**Anahtar kelimeler:** Preeklampsi, eklampsi, HELLP sendromu, yüksek rakım

**Geliş Tarihi:** 21 Kasım 2010

**Kabul Tarihi:** 29 Ocak 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 vasoconstriction, 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

(6, 7). 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 intrauterine growth restriction (IUGR), preterm labor, abruptio placentae, and preeclampsia increase with increasing altitude (12, 15). Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome were first reported by Weinstein (16) in 1982, and immediate termination of pregnancy was proposed because of high maternal and perinatal mortality rates. However, Weinstein did not announce a cut off value of parameters. The cut off values for HELLP syndrome that are used now were defined by Sibai (17) in 1990. Eclampsia and preeclampsia are serious problems and account for 10% of maternal mortality worldwide (18). HELLP syndrome can be considered a serious variant of preeclampsia, and it occurs in 0.90% of all pregnancies and in 10-20% of cases with severe preeclampsia (19). Associated with liver, kidney, and serious coagulation disorders, HELLP syndrome carries significant maternal and perinatal risk, because disseminated intravascular coagulation (DIC), abruptio placenta, acute renal problems, pulmonary edema, subcapsular liver hematoma, and retinal detachment are frequently seen in HELLP syndrome (4). The purpose of the present study was to determine the rates of HELLP syndrome, preeclampsia, and eclampsia in association with altitude.

## 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), Iğdır (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  $\geq 140$  mmHg, diastolic blood pressure was  $\geq 90$  mmHg, and proteinuria was  $\geq 0.3$  g/L in a 24-hour urine sample. Severe preeclampsia was diagnosed when one of the following criteria was present: (1) blood pressure  $\geq 160$  mmHg systolic or  $\geq 110$  mmHg diastolic on two occasions at least 6 hours apart with the patient on bed rest, (2) proteinuria  $\geq 5$  g in a 24-hour urine collection or  $\geq 3+$  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 [ $MAP = (2 \times \text{diastolic pressure} + \text{systolic pressure})/3$ ] 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**

Group 1 (>1500 m)		Group 2 (<1500 m)	
Province/district	Altitude (m)	Province/district	Altitude (m)
Erzurum (Karaçoban)	1945	Artvin	628
Erzurum (KöprükÖy)	1747	Iğdır	758
Erzurum (Tortum)	1772	Bingöl	1177
Bayburt	1680	Erzincan	1058
Ağrı	1738	Erzurum (İspir)	1222
Erzurum (Aşkale)	1700	Erzurum (Uzundere)	1300
Erzurum (Narman)	1830	Erzurum (Olur)	1300
Erzurum (Hınıs)	1795	Muş	1224
Kars	1859	Erzurum (Oltu)	1229
Ardahan	1929		
Erzurum (Centre)	1864		
Erzurum (Çat)	1920		
Erzurum (Karayazı)	2260		
Mean	1849.2±150.7	Mean	1099.6±243.5

1. Hemolysis: characteristic appearance of peripheral blood smear and serum LDH  $\geq 600$  U/L or serum total bilirubin  $\geq 1.2$  mg/dL.
2. Elevated liver enzymes: AST concentration  $\geq 70$  U/L.
3. Low platelet count:  $< 100,000$  cells/ $\mu$ L.

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 fetal situation. Platelet count as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), bilirubin, and uric acid levels in blood were analyzed 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  $\pm$  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  $87.648 \pm 109.970/\mu$ L,  $172 \pm 237$  IU/L, and  $1366 \pm 1293$  IU/L, respectively in patients in group 1 ( $> 1500$  m altitude) and  $96.347 \pm 109.970/\mu$ L,  $146 \pm 109$  IU/L, and  $1208 \pm 755$  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 suggesting 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  $< 100,000/\mu$ L in 19 patients, and the platelet count was  $< 100,000/\mu$ L in 17 patients. When parity and maternal age in patients with complete and partial HELLP

**Table 2. Birth numbers in subject populations**

Groups	Year					
	1998	1999	2000	2001	2002	Total
<b>Group 1 (altitude &gt; 1500 m)</b>						
Ağrı	5746	7984	7885	7853	7950	37418
Ardahan	210	1082	1532	974	1071	4869
Bayburt	1215	1563	1308	1197	1092	6375
Erzurum <sup>+</sup>	15200	13813	14689	12969	7517	50108
Kars	3028	2896	2600	3208	4317	16049
Grand Total						114819
<b>Group 2 (altitude &lt; 1500 m)</b>						
Artvin	1816	1749	1775	1339	1377	8056
Bingöl	2634	2508	2550	2561	1921	12174
Erzincan	4363	5658	6009	5039	3521	24590
Iğdır	2118	1739	1093	1369	1547	7866
Muş	2234	3050	3309	3479	2616	14688
Erzurum <sup>++</sup>	2852	2951	2742	2789	2746	14080
Grand Total						81454
*Erzurum centre and Aşkale, Hınıs, Çat, Karayazı, Karaçoban, Horasan, Pasinler, Köprüköy, Tortum, and Şenkaya districts.						
**Oltu, Olur, İspir, and Uzundere districts						

**Table 3. Patients with HELLP syndrome and eclampsia**

Diagnosis	Group 1 (altitude > 1500 m)	Group 2 (altitude < 1500 m)
Total patients	164	78
Total HELLP	143	66
Eclampsia	75	45
Eclampsia accompanied by HELLP	54	33

syndrome were considered in group 1, maternal age and parity in patients with complete and partial HELLP syndrome were  $32.6 \pm 5.6$  and  $3.6 \pm 3.8$  and  $27.0 \pm 4.3$  and  $3.4 \pm 3.2$ , 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  $< 100,000/\mu$ L in 19 patients, respectively. The platelet count was  $< 100,000/\mu$ L in 5 patients. Parity and maternal age in patients with complete and partial HELLP syndrome were  $2.9 \pm 1.6$  and  $26.7 \pm 5.3$  and  $2.4 \pm 1.6$  and  $25.5 \pm 5.2$ , respectively.

The rates of HELLP syndrome and eclampsia per 10,000 births in provinces are shown in Figure 1. When 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**

Parameter	Group 1 (n:164) (altitude >1500 m)	Group 2 (n:78) (altitude <1500 m)	p
Altitude (m)	1040±287	1736±122	<0.01
Age (years)	28.6±7.3	26.0±6.0	ns
Gravidity (n)	2.8±2.6	2.7±2.6	ns
Parity (n)	1.6±2.0	1.4±2.1	ns
Gestational age (year)	35.2±5.4	34.0±5.1	ns
MAP (mmHg)	124.4±9.2	118.4±8.6	ns
Hb (g/dl)	12.9±2.2	11.7±2.2	ns
Thrombocyte ( $\mu$ l)	87,648±109.9	96,347.0±107.0	<0.05
AST (IU/L)	172.0±237.0	130.5±150.9	<0.01
ALT (IU/L)	286.0±91.0	111.7±208.0	0.01
LDH (IU/L)	1208.0±755.0	1366.0±1293.0	ns
Uric acid (mg/dl)	7.2±2.4	6.7±2.7	ns
Birth weight (g)	2031±964	2197±893	ns
Cesarean rate (%)	57	56	ns
Fetal death (%)	38	17	<0.01
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 PO<sub>2</sub> and hemoglobin O<sub>2</sub> 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 hemoconcentration 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 ges-

tational 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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