Research Article

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An evaluation of serum boron level in pregnancies with severe pre-eclampsia

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Abstract

Objectives: Serum boron level has not been studied in pregnancies with pre-eclampsia. The aim of this study was to compare the levels of serum boron in pregnancies with early onset severe pre-eclampsia and healthy pregnancies.
Methods: The study included 43 pregnant patients with early onset severe pre-eclampsia and a control group of 30 healthy pregnant patients.
Results: The serum boron levels of the patients with severe pre-eclampsia were determined to be significantly higher than those of the control group (28.8 v.s 12.7 μg/L; p<0.05). A statistically significant correlation was determined between the serum boron level and the serum ALT level (r:482, p<0.001), serum AST level (r=554, p<0.001), and platelet count (r=–549, p<0.001). High values of serum boron indicated the presence of pre-eclampsia, with a diagnostic cut-off point of 11.65 μg/L, with 76.7 % sensitivity and 76.7 % specificity (p<0.001, area under curve: 0.832, Confidence interval: 0.736–0.928).
Conclusions: An increase in serum boron levels without reaching clinically toxic levels may contribute to the development of pre-eclampsia, probably by causing impairment in the placentation process. The current study can be considered of value as the first study in literature to show that serum boron levels were increased in pregnancies with early onset severe pre-eclampsia.

Keywords: boron; severe preeclampsia; hepatic funtions; platelet count; pregnancy

Introduction

Boron is a metalloid found in the form of boric acid or borax, depending on oxygen in the bedrock. As boron in soil is water-soluble, boron can be detected in drinking water in amounts varying from region to region [1, 2]. Boron can also be determined in bottled water. The maximum amount of boron in drinking water is recommended as 2.4 mg/L by the World Health Organization (WHO). Boron can also be ingested into the body with the consumption of fruit and vegetables, and it is rapidly absorbed from the gastrointestinal system [2]. The excretion of boron from the body is primarily in the urine, but it may also be eliminated through bile, sweat, and exhaled breath [3].

The first known area of use for boron was for mummification in Ancient Egypt. The first recorded medical use was in the form of borax (Na2B4O710H2O) in Mecca and Medina in the 8th century [4]. In the 1800s, boron was determined in plants and then 50 years later it was detected in humans. Following the determination of boron in humans, research was conducted to investigate what clinical findings and problems could result from the functions, deficiencies and excesses of boron [4].

Controversy continues about whether boron is essential in the human body. Several studies have shown that boron has a role in enzyme activity, in the metabolism of calcium, magnesium and vitamin D, in angiogenesis, and in wound healing [5–7]. However, the role of boron in human metabolism, the level of overdose, toxic effects and the role in existing diseases have still not been fully clarified. Especially in studies conducted after the 1980s, the effects of boron on joint problems, bone remodelling, wound healing, and the immune system have become general research subjects [8, 9].

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Pre-eclampsia (PE) is a disease of multifactorial etiopathogenesis specific to human pregnancy, which causes significant feto-maternal morbidity and mortality, and is a pathology affecting approximately 2–8 % of all pregnancies [10]. The clinical basis of this pathology is hypertension emerging after the 20th week of pregnancy [11]. Although many theories have been proposed about the pathogenesis of PE, the ideas that it is based on the development of the placenta have gathered most interest [12]. Gestational week can be evaluated in the two main PE categories of potential morbidity and mortality, and pathogenesis. It has been suggested that in early onset pre-eclampsia (EOPE) diagnosed between 24 and 33 $^{6/7}$ weeks, the spiral artery remodelling is impaired because of insufficient trophoblast invasion. Late-onset pre-eclampsia (LOPE), diagnosed in the 34th week of pregnancy and later, has been suggested to be caused by maternal cardiovascular or metabolic incompatibility. Due to generalised vazospasm, pre-eclampsia may involve and impair several organs and systems in the body. For example, severe forms of pre-eclampsia are associated with impairment in hepatic and renal functions, decreased platelet count and microangiopathic hemolysisis [13]. Regardless of the etiology and classification, the definitive and curative treatment for PE is delivery of the fetus [11].

To date, the relationship between the blood levels of several trace elements including copper, zinc, iron, magnesium, selenium, and calcium in pregnancy and PE has been evaluated. A decrease in blood levels of calcium, selenium, magnesium and zinc, and an increase in iron have often been associated with the development of PE [14, 15]. However, to the best of our knowledge, there is no study in literature that has examined the serum boron level in pregnant patients with severe pre-eclampsia. Boron has been found to play a role in cellular migration, proliferation and angiogenesis [16, 17]. Since pre-eclampsia is associated with impaired trophoblastic cell migration and and with placental hypoxia, the hypothesis of this study was that the serum boron level may be altered in patients with pre-eclampsia. To be able to examine similar patients in terms of the etiopathogenesis, the study group was formed of pregnant patients with early-onset severe pre-eclampsia.

The aim of this study was to compare the maternal serum boron levels in patients with early-onset severe PE and a control group of healthy pregnant women.

Materials and methods

This cross-sectional case control study was conducted in the obstetrics clinic of a tertiary level reference university hospital, The study was planned to include women with singleton pregnancies at 24–33 $^{6/7}$ gestational weeks. Group 1 comprised 43 pregnant patients with early onset severe pre-eclampsia who were diagnosed according to the ACOG criteria [13]. Although it had been planned to include an equal number of participants in the study and control groups, only 30 healthy pregnant woman of the appropriate gestational age presented at the clinic during the study period. Therefore, the control group was formed of 30 healthy pregnant women matched in respect of age, body mass index and gestational week. Approval for the study was granted by the Ethics Committee of Kahramanmaraş Sütcü İmam University School of Medicine. All patients provided informed consent.

In the ACOG guidelines, a diagnosis of pre-eclampsia can be made from new-onset hypertension (systolic blood pressure≥140 mm Hg or diastolic blood pressure≥90 mmHg on 2 occasions at least 4 h apart) after the 20th gestational week with or without proteinuria (≥300 mg per 24-h urine collection, protein/creatinine ratio≥0.3, or dipstick reading of 1+) [13].

Where there is no proteinuria, a diagnosis of severe pre-eclampsia can be made with any one of the following conditions: 1) severe hypertension (systolic blood pressure≥160 mmHg or diastolic blood pressure≥110 mmHg or higher in 2 different measurements after resting without antihypertensive medication; 2) thrombocytopenia (platelet count<100,000/μL); 3) impaired liver function [2-fold increment of liver transaminases; alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]; 4) new development of renal insufficiency (elevated serum creatinine>1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease); 5) pulmonary edema; or 6) new-onset cerebral or visual disturbances. When hemolysis, impaired liver function, and thrombocytopenia are determined, HELLP syndrome is diagnosed. Eclampsia is also diagnosed with the occurrence of grandmal seizure in a patient with pre-eclampsia and no history of seizure [13].

The study exclusion criteria were as follows: Patients with chronic diseases (e.g., diagnosed chronic hypertension), or metabolic or endocrine disorders, those who smoked or drank alcohol, patients with a multiple pregnancy, with an eating disorder, gastrointestinal, hematological, hepatic or renal disease, BMI>30 kg/m^2, if there was suspicion or determination of chromosomal anomaly or fetal morphological anomaly on the fetal ultrasonography, or if there was maternal heart disease.

Blood sampling

Before the application of any medical or surgical intervention, or administration of any drugs, a blood sample was

taken from each patient in the study and control groups. Blood was taken from the antecubital vein and collected into vacutainer tubes with no additives (Becton-Dickinson, Franklin Lakes, NJ) in accordance with the standard hospital guidelines. After clotting of the specimens, the serum was separated with centrifugation at 4,000 *g* for 10 mins. The separated plasma was stored at −80 °C until the assays to determine the serum boron levels. Measurements were taken after thawing of the serum samples.

In the chemical analysis, 2 mL of pure water, 2 mL H2O2 (30 %) (Merck, Darmastadt, Germany) and 4 mL HNO3 (65 %) (Merck, Darmastadt, Germany) were added to 0.3 mL of the sample. After placing the samples in a microwave oven (HP-500 CEM MARS 5 crop. Mathews NC, USA) for 5 min at 200 °C, they were cooled to room temperature, filtered through Whatman 541 filter paper, and then diluted with deionized water up to 25 mL.

The analysis of the standards and samples was performed using an Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) (Perkin Elmer Optima 2100 DV, Eugene, OR, USA) in the main laboratory of Kahramanmaras Sutcu Imam University Research and Application Centre (ÜSKİM). The calibration range was defined according to the commercially available certified reference kit, Sucelpo, Merck ilaç ecza ve kimya, Istanbul, Türkiye and the samples were studied by making comparisons according to the kit.

Correlation coefficient and calibration range were 0.999774 and 0.1–2 µg/L respectively in calibration display for linearity.

The intra assay and inter assay coefficients of variation are 3.48 and 5.84 %, respectively. The limit of detection (LOD) and the limit of quantification (LOQ) for boron were 3.4 µg/L and 9.5 µg/L respectively in serum. All of the samples were above LOQ.

The serum creatinine clearance values were calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation [18, 19].

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 software (SPSS IBM Inc., Armonk, NY, USA). Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. The Student's t-test was applied in the comparisons of hemoglobin and creatinine values showing normal distribution and the Mann Whitney U-test in comparisons of data not showing normal distribution. Descriptive variables were stated as mean ± standard deviation (SD) or median, minumum and maximum values depending on the conformity to normal distribution and categorical data as number (n) and percentage (%). A value of $p<0.05$ was accepted as statistically significant.

Correlations between variables were examined with Pearson correlation analysis for data with normal distribution and with Spearman correlation analysis when data did not show normal distribution.

Receiver operating characteristic (ROC) curve analyses were applied to determine cut-off points at which serum boron levels had optimum sensitivity and specificity for the diagnosis of pre-eclampsia.

Post hoc analysis was applied as a retrospective power analysis. It was determined that a cohort size of 73 cases (43 in Group 1, and 30 in Group 2) had 97.1 % power to detect differences at the 0.05 significance level.

Results

No statistically significant difference was determined between Groups 1 and 2 in respect of mean age, number of pregnancies, parity, body mass index, and gestational week (Table 1). The mean serum ALT and AST levels were determined to be statistically significantly higher in Group 1 than Group 2 (ALT:143.1 ± 64.8 vs. 20.0 ± 3.4 U/L; AST:147.9 ± 61 vs. 22.2 ± 4.8 U/L) and platelet count was determined to be significantly lower (84.7 ± 40.8 vs. 208.0 ± 30.1 $x10^3$/µL; $p<0.05$ for all) (Table 2). The mean serum boron levels of Group 1 were determined to be significantly higher than those of Group 2 (28.8 ± 24.5 µg/L vs. 12.7 ± 4.6 µg/L; $p<0.05$) (Figure 1).

High values of serum boron indicated the presence of pre-eclampsia, with a diagnostic cut-off point of 11.65 µg/L, 76.7 % sensitivity and 76.7 % specificity ($p<0.001$, area under curve: 0.832, 95 % Confidence Interval: 0.736–0.928) (Figure 2).

A statistically significant correlation was determined between the serum boron level and the serum ALT level

Table 1: Demographic and clinical characteristics of participants.

Study group (n=43)		Control group (n=30)	p-Value
Maternal age, years	28.6 ± 5.9	27.1 ± 4.7	0.243
Gravida	3.2 ± 1.6	4.0 ± 3.9	0.678
Parity	1.6 ± 1.1	1.6 ± 1.0	0.942
Body mass index, kg/m^2	27.6 ± 1.9	27.9 ± 2.3	0.620
Gestational age at sampling, weeks	31.3 ± 2.4	30.3 ± 2.5	0.082

Values were expressed as mean ± standard deviation. $p<0.05$ was statistically significant.

Table 2: Comparison of serum levels of laboratory parameters between healthy pregnancies and pregnancies with severe pre-eclampsia.

	Study group (n=43)	Control group (n=30)	p-Value
Hemogram value [a] (g/dL), mean ± SD	10.6 ± 1.7	10.6 ± 0.6	0.978
Platelet count [b] (10^3/μL), mean ± SD (median; min-max)	84.7 ± 40.8 (69; 45–176)	208.0 ± 30.1 (212;130–250)	<0.001[c]
ALT [b] (U/L), mean ± SD (median; min-max)	143.1 ± 64.8 (160; 23–260)	20.0 ± 3.4(20; 11–25)	<0.001[c]
AST [b] (U/L), mean ± SD (median; min-max)	147.9 ± 61.41(155;18–260)	22.2 ± 4.8 (21; 15–34)	<0.001[c]
Creatinine [a] (mg/dL), mean ± SD	0.81 ± 0.34	0.66 ± 0.40	0.083
Serum boron level [b](μg/L), mean ± SD (median; min-max)	28.8 ± 24.5 (11.9; 10.7–69.8)	12.7 ± 4.6 (10.8; 10.5–21.8.)	0.001[c]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; [a]Student's t-test, [b] Mann–Whitney U test. [c]p<0.05 was statistically significant.

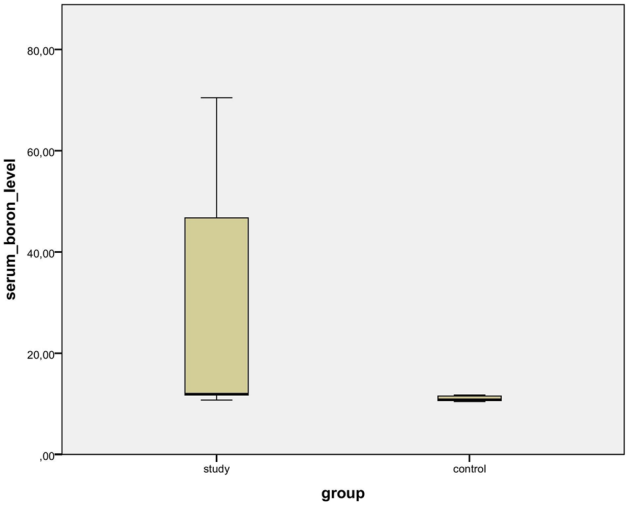

Figure 1: Box plot analysis of serum boron level for study and control groups.

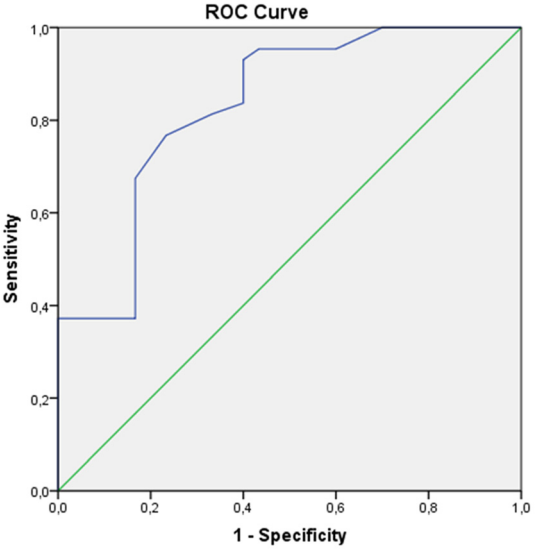

Figure 2: ROC curve analysis of the serum boron level in determining pre-eclampsia (area under curve: 0.832, 95 % confidence interval: 0.736–0.928).

(r=482, p<0.001), serum AST level (r=554, p<0.001), and platelet count

(r=–549, p<0.001). No correlation was determined between the serum boron level and body mass index, gestational week, age, gravida, parity, or serum creatinine level (Table 3). When the parameters which had been found as statistically meaningful in the correlation analysis were analysed in the linear regression analysis, no significant effect was detected between the serum boron level as independent variable and ALT and platelet count as dependent variables. When serum boron level and AST were evaluated in the linear regression analysis, the beta value was found to be 0.324, t=2.06 (p=0.047).

Discussion

The results of this study demonstrated that the serum boron level was statistically significantly higher in pre-eclamptic pregnancies than in healthy pregnancies. Several studies have shown that the serum levels of trace elements including zinc, copper, calcium, selenium, and magnesium were different in pregnancies with pre-eclampsia compared to healthy pregnacies [14]. Of these trace elements, one of the relatively less well known is boron. As there are differences in the amount of boron in drinking water and the soil, and thus the amount ingested per day throughout the world and even within the same country, it is difficult to fully understand the level and role in pregnancy.

The effects of boron in the body are dose-dependent and can show differences from cell to cell [20]. It has been suggested that boron stimulates wound healing by increasing angiogenesis and stimulating the expression of mediators such as VEGF. In a study by Park et al., it was shown that boron at a concentration of 0.1–0.5 nM stimulated cell growth and proliferation but at concentrations over 1 nM, cell growth and proliferation were inhibited [16]. Boron supplementation at physiological and pharmacological

Table 3: Correlation of serum boron level with clinical and laboratory parameters.

	r-Value	p-Value[a]
Age, years	−0.052	0.662
Body mass index, kg/m^2	−0.067	0.571
Gravida	−0.020	0.869
Parity	0.025	0.835
Gestational age, weeks	0.215	0.067
Serum ALT level	0.482	<0.001[a]
Serum AST level	0.554	<0.001[a]
Serum creatinine level	−0.012	0.921
Platelet count	−0.549	<0.001[a]

Spearman correlation test was used. [a]p-Value of <0.05 was accepted as statistically significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

doses prevents the excessive accumulation of oxygen radicals by supporting antioxidant enzymes in the body. This may play an important role in neovascularisation and the associated development of the placenta bed [21]. In evaluations made with boron-doped bioactive glass as a supplement, it has been determined that proliferation and migration are increased in the human umbilical vein endothelial cells [17]. Boron is known to pass from the placenta to the fetus [22]. In an experimental rat study, it was shown that increased maternal boron exposure caused fetal skeletal malformation and impaired fetal growth [23]. In a community-based study in the Marmara region of Turkey, no relationship was found between obstetric and fetal complications, including spontaneous abortion (miscarriage), stillbirth, infant death, neonatal death, early neonatal death, preterm birth, congenital anomalies, and the high levels of boron ingested routinely from drinking water and food due to the regional characteristics [24]. In contrast, a recent study by Igra et al. showed a correlation between high serum boron levels and impaired human fetal development [1].

In human embryo placentation, proliferation of the trophoblastic cell mass, spiral artery remodelling and formation of neoangiogenesis in chorionic villi are among the major processes. Migration of invasive trophoblastic cells into spiral arteries transforms those high resistance arteries into dilated, low-resistance arteries in order to provide sufficient blood flow to the placenta [25]. It has been suggested that inadequate remodelling of spiral arteries during the placentation leads to a complex ischemia-reperfusion process in the placental cells resulting in increased oxidative stress, which plays a major role in early-onset type pre-eclampsia [26]. The current study can be considered of value as the first study in literature to show that serum boron levels in pregnancies with severe pre-eclampsia are significantly higher than those of healthy pregnancies [16]. Therefore, in the light of information that boron has effects on cellular proliferation, angiogenesis and oxidative stress, it can be suggested that boron over a certain level may play a role in the development of pre-eclampsia by causing impairment in the placentation process.

No study could be found in literature which evaluated boron levels in pre-eclampsia and there are very few that have evaluated the serum boron level in healthy pregnancies. Serum boron levels were determined as 15.5 ± 4.2 μg/L in 15 healthy pregnancies at 24–28 gestational weeks in a study conducted in the central Anatolian region of Turkey, and as 23 ± 13 μg/L in 16 healthy pregnancies in the 2nd trimester in California, USA [27, 28]. In the current study, the serum boron level in healthy pregnancies was determined as 12.7 μg/L. However, it is interesting that in studies conducted in Argentina and Israel, much higher serum boron levels were determined in pregnant patients than the values in the above-mentioned studies. In a study by Igra et al. of 196 healthy pregnant patients living in northern Argentina, the serum boron level was determined as 133 μg/L in the 2nd trimester and 205 μg/L in the 3rd trimester [1]. Silberstein et al. measured the trace element levels in the plasma and amniotic fluid at gestational week 17 in 40 healthy pregnant patients living in Beersheba in southern Israel. In that study, the plasma boron level was reported as 122 ± 39 μg/L [29].

Even if patients are living within the same national borders, for individuals living in different regions there may be differences in the amount of boron exposure due to different amounts of boron in the bedrock, and thus different amounts in the drinking water [24, 28]. The hospital where the current study was conducted is a tertiary level reference hospital in the south of Turkey, serving a region approximately 200 km in area diameter. There could be differences in the type and source of drinking water consumed, for example in the form of tap water, natural spring water or bottled water. In addition, the amount of food consumed containing boron, such as fruit, vegetables and dried fruits and nuts varies from person to person. Therefore, there are differences in the daily boron intake of participants. A limitation of the current study was that the boron level in drinking water and consumed food was not analysed. Based on findings of the current study, it may be proposed that a determination and the standardisation of boron levels in drinking water in all regions of a country may be helpful to prevent overconsumption of boron and thereby to prevent potential hazards due to that overconsumption.

In a study conducted by creating liver damage in rats, boron was seen to have a hepatoprotective effect [30, 31]. In addition, a positive correlation was determined in the current study between an increasing boron level and serum ALT and AST levels. Türkez et al. showed that antioxidant

enzyme activity in peripheral cell cultures was supported with exposure to a low dose of boron, but at high doses, there could be tissue damage through an increase in oxidative stress [32]. Therefore, an increased level of serum boron could be considered to contribute to the high serum level of transaminases in severe pre-eclampsia, probably through the mechanism of hepatocyte injury due to increased oxidative stress.

In a study by Nielsen et al., when subjects on a boron-deficient diet were given boron supplementation, there was seen to be a reduction in platelet count [33]. Keklik et al. added boron to the drinking water of rats and reported a decrease in white blood cells, platelets and erythrocyte count [34]. Similarly in the current study, a significant negative correlation was determined between serum boron level and platelet count. The effects of boron on platelet count may be explained by the fact that boron reacts with glycolipids of cell membranes and has a role in cell membrane function and stability [33].

Conclusions

The results of this study showed that the serum boron level was statistically significantly higher in pregnant patients with severe pre-eclampsia than in healthy pregnant women and high values of serum boron indicated the presence of pre-eclampsia, with a diagnostic cut-off point of 11.65 μg/L. This study is of value as the first study to investigate the relationship between boron and early onset severe pre-eclampsia. Moreover, a significant and positive correlation was determined between serum boron level and serum ALT and AST levels, and a negative correlation was determined with platelet count. Based on the findings of the present study, it may be prudent to follow-up serum boron level especially in pregnant women at risk of pre-eclampsia. The findings of this study can be considered to contribute to the literature and be of guidance for new research to investigate boron levels in placental tissue and the relationship between oxidative stress markers and boron in cases of pre-eclampsia.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).approval no:#2018/16.
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: The raw data can be obtained on request from the corresponding author.

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