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Maternal Serum Surfactant Protein-D (SP-D) levels in pregnancies complicated with mild and severe preeclampsia: A case control study

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Abstract

Considering that preeclampsia is a systemic disease that affects nearly all systems and end organs, it is likely that the maternal pul- monary arteries and maternal alveoli are also affected by this condition. Therefore, in the present study we aimed to evaluate maternal serum surfactant protein D (SP-D) levels in pregnancies complicated by mild and severe preeclampsia. In this cross-sectional study, we engaged 90 pregnant women between 18 and 40 years old who were divided into the following two groups: control (n: 30) and mild preeclampsia (n: 30) and severe preeclampsia (n: 30).Maternal serum SP-D level was the main outcome of the study. Maternal serum SP-D levels were determined using enzyme-linked immunosorbent assay kit. Maternal characteristics of the groups were statistically similar between the groups. The maternal serum SP-D level was 39.16 ± 31.6 ng/mL in the control group, 21.28 ± 14.07 ng/mL in the mild preeclampsia group and 19.83 ± 19.59 ng/mL in severe preeclampsia group. The maternal serum SP-D levels were statistically decreased in mild and severe preeclampsia group compared to control group (p: 0.002). The maternal serum SP-D level was statistically similar between mild preeclampsia group to severe preeclampsia group (p: 0.967). This results indicated that maternal type II cells and Clara cells in the alveoli were adversely affected by mild and severe pre- eclampsia. In further studies that evaluate types I-II alveolar and Clara cell damage will show the clinical significance of the present findings more clearly.

Keywords: Severe preeclampsia, Surfactant protein D, SP-D, type II alveoli cells, Clara cells

Introduction

Preeclampsia in pregnancy is a severe condition of endothelial dysfunction that results in hypertension and proteinuria following 20 gestational weeks. Because there are few therapeutic options while remaining pregnant, this condition is a major factor in fetal and maternal morbidities and mortalities throughout the world, especially in developing countries. [1, 2] the cause of preeclampsia has not been determined, and the effects vary from minor lack of organ function to severe organ deterioration [3], which are believed to be caused by vasospasms, endothelial dysfunction, and ischemia with clear signs of edema [3]; therefore, several organs can be affected and various symptoms can manifest depending on which organ is involved. Maternal lungs can be affected by this condition; however, this has not been fully studied. Collagen-containing C-type lectins (collectins) are a type of soluble pattern recognition proteins of the innate immune system that play a major role in the host's defense and immunomodulation. Members of this family include surfactant protein-D (SP-D), a 42-kDa protein that is encoded by a single SP-D gene, SFTPD, on human chromosome 10. [4] Collectins work within the airways to opsonize bacteria and increase local immune defenses. By interacting with toll-like receptors, colletins use pulmonary macrophages to help rid the body of unwanted organisms and produce inflammatory media- tors [5]. As part of these immunity mechanisms, type II and Clara cells in the alveoli synthesize SP-D. This protein is not found in exogenous surfactant supplements [6] and is detectable in only minute quantities within the systemic circulation system in healthy women. Any acute lung in- jury and acute respiratory distress syndrome (ALI/ARDS) will damage the alveolar epithelial barrier, and SP-D may then cross this damaged endothelium to enter the circulation

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system, which has been detected in adults with ALI/ ARDS. This condition is believed to be the result of both capillary leakage and the increased release of SP-D caused by inflammation. During ALI/ARDS, any elevated levels of serum SP-D could be associated with a negative clinical outcome [7].

Considering that especially severe preeclampsia is a systemic disease that affects nearly all systems and end organs, it is likely that maternal pulmonary arteries and maternal alveoli would be also affected by this condition. It can be hypothesized that in the presence of preeclampsia, type II cells and Clara cells in the alveoli, in which SP-D is synthesized, will be affected; therefore, the aim of the present study was to evaluate maternal serum SP-D levels in pregnancies complicated with mild and severe preeclampsia.

Methods

This cross-sectional study was conducted at Erciyes University Faculty of Medicine, Department of Obstetrics, Turkey, in accordance with the Declaration of Helsinki and approved by the Erciyes University Ethics Commit- tee (decision number: 2020/512). All participants gave their informed consent to participate in the study.

Our study comprised 90 pregnant women, who were divided into the following three groups: control (n = 30), mild preeclampsia (n=30), and severe preeclampsia (n= 30). The exclusion criteria were as follows: 1) multiple pregnancies, 2) preterm premature rupture of membranes, 3) chromosomal or fetal anomaly, 4) type 2 diabetes mellitus or gestational diabetes mellitus, 5) chronic hyper- tension, 6) collagen vascular disease, or 7) chronic systemic diseases. Since the effect of preeclampsia on the lungs was evaluated in the current study, these pregnant women were excluded from the study in the presence of smoking, which may cause alveolar damage, active or prior SARS- CoV-2 infection, maternal asthma and allergic reactions, chronic obstructive pulmonary diseases, and known chronic or acute lung disease. Preeclampsia diagnosis was made according to the following criteria: systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg, measured at least twice within a 6-hour period after 20 gestational weeks, and a proteinuria level >0.3 g/24 h or a spot urine protein/creatinine ratio >300 mg/mmol [3]. Severe preeclampsia was diagnosed if the women had one or more of the following: blood pressure ≥160/110 mmHg, thrombocytopenia <100,000/ μL, impaired liver function, visual or cerebral disturbance, progressive renal insufficiency, or pulmonary edema [3]. Fetal growth restriction in the absence of congenital anomalies was diagnosed using the Delphi consensus criteria [8].

Venous blood samples were obtained from the pregnant women with severe preeclampsia just before delivery for biochemical analyses and to evaluate maternal serum SP-D levels. Because gestational age at blood draw, maternal age, and body mass index would influence maternal serum SP-D levels, serum samples were obtained from the mild preeclampsia and control groups at similar gestational ages during their clinical visits, to homogenize these parameters; these patients were also followed up. To analyze the maternal serum SP-D levels, 4 mL venous blood was collected, placed in biochemistry tubes, and centrifuged at 1000 rpm at 4°C for 10 minutes. The supernatant from each sample was transferred into a cle- ar 2-mL Eppendorf tube and kept frozen at −80°C until use in the enzyme-linked immunosorbent assay (ELI- SA). SP-D levels were assayed using the SP-D ELISA kit (CUSABIO-E11166h, Wuhan, China), which contained a microtiter plate precoated with an antibody specific to SP-D. Standards or specimens were added to each plate well using a biotin-conjugated SP-D antibody and avidin conjugated to horseradish peroxidase. A 3,3′,5,5′-tetramethylbenzidine substrate solution was then placed into each well. A color change was observed in only those wells that contained SP-D, biotin-conjugated antibody, and enzyme-conjugated avidin. Sulfuric acid solution was ad- ded to stop the enzyme–substrate reaction. Any change in color was quantified using a spectrophotometer at a wavelength of 450 ± 2 nm. The SP-D concentration was subsequently calculated by comparing the optical density of the specimens with those of a standard

Statistical analyses were performed using the Statistical Package for the Social Sciences version 18 (IBM Inc., Armonk, NY, USA). The Kruskal Wallis H test was used to assess the normality of the data. The Levene test was used to evaluate the assumption of variance homogeneity. Values are expressed as mean

± standard deviation, median (25th–75th percentile), or n (%). A p-value <0.05 was considered statistically significant. One-way analysis of variance was performed to compare multiple groups. (Tukey's post hoc test) after assessing normality. Categorical variables between paired groups were compared using the chi-square test, while non-categorical variables were compared using the Mann–Whitney U test.

Results

The characteristics of the women in all the groups were compared and are presented in Table 1. Maternal age, nulliparity, body mass index (BMI) (kg/m^2) at blood sampling, ethnicity, and history of caesarean section were statistically similar between the groups.

Table 1. Comparision of maternal characteristics of the groups.

Characteristic	Control group (n = 30)	Mild PE group (n= 30)	Severe-PE group (n = 30)	P-value
Maternal age (years)	30.4 ± 1.9	30.6 ± 2.1	29.2 ± 2.1	0.620
Nuliparity	11 (36.6)	10 (33.3)	9 (30)	0.510
BMI at blood sampling (kg/m^2)	30.1 ± 3.9	29.6 ± 3.2	29.2 ± 3.4	0.730
Ethnicity (Caucasian)	28 (93.3)	29 (96.6)	28 (93.3)	0.830
Previous CS history	7 (23.3)	10 (33.3)	8 (26.6)	0.710

Notes: PE, preeclampsia; BMI, body mass index; CS, caesarian section; values were presented as the mean ± standard deviation or n (%).

The perinatal outcomes and biochemical results of the women in all the groups were compared and are presented in Table 2. Systolic blood pressure (SBP) at the time of diagnosis, diastolic blood pres- sure (DBP) at the time of diagnosis, 24-hour protein excretion, and fetal growth restriction rates were siginificantly higher in the mild and severe preeclampsia groups than in the control group. Gestational age at delivery and mean birth weight were significantly lower in the severe preeclampsia group than in the mild preeclampsia and control groups. Gestational age at blood sampling was similar among the groups.

Table 2. Comparison of perinatal outcomes and maternal biochemical results between the groups.

Characteristic	Control group (n = 30)	Mild PE group (30)	Severe PE group (n =30)	P-value
Gestational age at delivery (weeks)	39.8 ± 1.8	37.2 ± 2.1	32.9 ± 1.7	<0.001
SBP at the time of diagnosis (mm/Hg)	110 (90–120)	140 (140-150)	160 (150–170)	<0.001
DBP at the time of diagnosis (mm/Hg)	75 (70–80)	95 (90-100)	115 (110–120)	<0.001
Mean birth weight percentile	88.3 ± 18.7	58.2 ± 16.4	14.3 ± 5.1	<0.001
Biochemical parameters				
Gestational age at blood sampling (weeks)	32.2±1.6	33.2 ± 1.5	32.8 ± 1.4	0.920
Maternal serum SP-D (ng/mL)	39.16 ± 31.6	21.28 ± 14.07	19.83 ± 19.59	0.002*
Serum Na (mmol/L)	136.9 ± 2.4	136.8 ± 2.8	137.8 ± 3.1	0.480
Serum K(mmol/L)	4.4 ± 0.4	4.1 ± 0.3	4.3 ± 0.3	0.780
Serum BUN (mg/dl)	7.6 ± 2.1	8.2 ± 3.6	15.4 ± 9.6	<0.001

Serum Creatinine (mg/dl)	0.59 ± 0.15	0.67 ±0.25	1.12± 0.67	<0.001
Serum AST (u/L)	16.4 ± 6.1	18.2 ± 7.2	52.1 ± 25.8	<0.001
Serum ALT (u/L)	16.1 ± 11.4	16.5 ± 10.7	51.5 ± 26.7	<0.001
Serum LDH (u/L)	207.3 ± 42.0	120.2 ± 53.2	391.4 ± 175.3	<0.001

Notes: PE= preeclampsia; SBP= systolic blood pressure; DBP= diastolic blood pressure; SP-D= surfactant protein D; Na= sodium; K= potassium; BUN= blood urea nitrogen; AST= aspartate aminot- ransferase; ALT= alanine transaminase; LDH= lactate dehydrogenase. Values were presented as the mean ± standard deviation or n (%). Comparisons was calculated by ANOVA test. *For Maternal serum SP-D; control vs mild preeclampsia p= 0.009, control vs severe preeclampsia p= 0.005 mild preeclampsia vs severe preeclampsia p = 0.967

The mean serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels were significantly increased in the severe preeclampsia group compared to the mild preeclampsia and control groups.

The maternal serum SP-D level was 39.16 ± 31.6 ng/mL in the control group, 21.28 ± 14.07 ng/mL in the mild preeclampsia group, and 19.83 ± 19.59 ng/mL in the severe preeclampsia group. Maternal serum SP-D levels were statistically decreased in the mild and severe preeclampsia groups compared to the control group. However, maternal serum SP-D levels were statistically similar between the mild and severe preeclampsia groups.

Discussion

It is well known that severe preeclampsia affects nearly all systems and end organs, and it is likely that maternal pulmonary arteries and alveoli are also affected by this condition. In the present study, we aimed to evaluate maternal serum SP-D levels in pregnancies complicated by preeclampsia to assess potential alveolar damage. The key findings of the study were: (1) maternal serum SP-D levels were significantly decreased in the mild and severe preeclampsia groups compared to the control group, and (2) maternal type II alveolar cells and Clara cells appeared to be adversely affected by both mild and severe preec lampsia.

Various studies evaluating the inflammatory and immunomodulatory roles of collectins during pregnancy can be found in the literature. It has been shown that SP-D modulates lipopolysaccharide-induced intrauterine inflammation related to preterm birth and the key inflammatory events leading to parturition [9, 10]. Collectins have been associated with various inflammation-related pregnancy complications. It has been reported that intrauterine growth-restricted cases exhibit increased maternal serum and umbilical cord blood SP-D levels [11]. Women who experienced spontaneous abortion demonstrated altered expression levels of SP-A and SP-D in placental tissues during the first trimester [12]. Kale et al. [13] observed decreased serum levels of SP-A and SP-D in women who subsequently developed severe early-onset preeclampsia, along with significantly increased collectin levels in both serum and placental tissues. Although these studies demonstrate the extrapulmonary inflammatory and immunomodulatory roles of SP-D particularly in placental tissues its major function in the lungs remains as a reulator of pulmonary surfactant and is secreted by type II alveolar cells and Clara cells [14].

In the present study, although we hypothesized that severe preeclampsia would result in maternal lung damage, we unexpectedly found that even mild preeclampsia may also be associated with such injury. We observed that maternal serum SP-D levels were significantly decreased in both mild and severe preeclampsia groups compared to the control group. These results suggest that preeclampsia affects the pulmonary system and likely involves maternal pulmonary arteries and alveoli. The condition may impair type II alveolar and Clara cells. Although SP-D is primarily involved in surfactant homeostasis, it also appears to contribute to the regulation of lung inflammation. In ALI/ARDS, SP-D synthesis and secretion are affected, with the protein entering the systemic circulation due to epithelial barrier damage [14].

Several studies support our findings. One study showed that administration of the steroid dexamethasone to cultured fetal lung explants

increased SP-D mRNA and protein levels [15], and that maternal steroid treatment increased fetal serum SP-D concentrations [16]. Both in vitro and in vivo studies have confirmed that SP-D expression significantly increases following glucocorticoid administration prior to delivery. [17, 18]

We acknowledge several limitations in our study. The small sample size and cross-sectional design are the most significant. Nevertheless, we believe our findings may encourage future investigations and contribute to the emerging research on maternal lung injury in preeclampsia. First, we biochemically evaluated maternal serum SP-D levels. Future studies including histopathological evaluations demonstrating alveolar injury, and immuno-histochemical studies in rat models assessing damage to type I and II alveolar cells and Clara cells, would be ide- al for confirming alveolar involvement. Second, studies combining clinical parameters with other specific lung injury markers—such as receptors for advanced glycation end products (type I alveolar cells), SP-A and SP-B (type II alveolar cells), club cell secretory protein (bronchiolar club cells), laminin and desmosine (lung matrix), and mini-BALF protein (pulmonary vascular permeability)—could open new perspectives for understanding the pulmonary effects of severe preeclampsia [19].

Third, fluid management during the antenatal and postpartum periods is critical in patients with preeclampsia to prevent pulmonary edema. Although pulmonary edema is a known life-threatening complication [20], maternal serum SP-D levels might serve as an early marker of pulmonary edema risk, especially in pregnant women without overt edema. Thus, monitoring SP-D levels could aid in predicting pulmonary edema in future studies. Fluid management strategies may be particularly important for patients with low SP-D levels [21].

Finally, lung ultrasound is a useful diagnostic and prognostic tool for assessing pulmonary conditions, par- ticularly lung congestion. It can detect pulmonary edema in parturients with severe preeclampsia [22]. In patients with low SP-D levels, lung ultrasound evaluation and follow-up during pregnancy may help prevent the development of pulmonary edema.

Conclusion

This results indicated that maternal type II cells and Clara cells in the alveoli were adversely affected by mild and severe preeclampsia. In further studies that evaluate types I-II alveolar and Clara cell damage will show the clinical significance of the present findings more clearly.

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