The importance of second-trimester AFP and preconception TSH levels for predicting the severity of proteinuria in patients with preeclampsia

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ABSTRACT

Objectives: This study aimed to investigate the relationships between preconception thyroid stimulating hormone (TSH) and thyroxine (T4) levels, as well as second-trimester alpha-fetoprotein (AFP) levels, and the severity of proteinuria in 24-hour urine samples from patients with preeclampsia.

Method: This retrospective analysis focused on preeclampsia patients categorized by proteinuria in 24-hour urine. Inclusion criteria involved patients aged 20-44 with singleton pregnancies diagnosed with preeclampsia and delivery after 20 weeks of gestation. Patients were divided into mild (0.3 to <2 g, n = 94), severe (2 to <5 g, n = 38), and massive (≥5 g, n = 11) proteinuria groups. Comparison included second-trimester AFP levels, preconception TSH, and maternal/neonatal outcomes.

Results: Second-trimester AFP levels increased with proteinuria severity (mild: 47.97 ng/ml; severe: 60.52 ng/ml; massive: 65.50 ng/ml [p<0.001]). AFP emerged as a significant independent predictor of severe proteinuria (odds ratio=1.041), while TSH was not predictive (odds ratio=1.098; p=0.463).

Conclusion: AFP proved to be a valuable marker for predicting proteinuria severity in 24-hour urine samples from preeclampsia patients, whereas preconception TSH was a less compelling predictor.

Keyword: AFP, TSH, preeclampsia, proteinuria, pregnancy

Preeclampsia poses significant challenges in obstetrics, contributing to maternal and neonatal mortality and morbidity [1]. Effective treatment involves the removal of the placenta through delivery, particularly in severe cases requiring urgent action. Accurately assessing preeclampsia severity is crucial for identifying high-risk

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pregnant women [2]. Therefore, the accurate determination of the severity of preeclampsia is important for identifying pregnant women at greater risk of complications. Recent publications have shown that severe proteinuria is valuable in the prediction of poor obstetric outcomes in women with preeclampsia [3, 4]. In the past, the amount of proteinuria was important to assess the severity of preeclampsia [5]. However, in 2013, the American College of Obstetricians and Gynecologists removed the amount of proteinuria as a key criterion [6]. If the severity of proteinuria can be predicted at the time of diagnosis of preeclampsia, there may be additional time to prevent preterm labor and other poor obstetric outcomes.

Alpha-fetoprotein (AFP), the major plasma protein of the fetus is synthesized by the yolk sac and fetal liver, and it is presumably the fetal counterpart of serum albumin [7]. Unexpected increases in AFP in the second trimester may increase the risk of complications related to placental insufficiency, such as preeclampsia [8]. Impairments in the structure of placental capillary endothelial cells and the placental barrier in women with preeclampsia may cause elevated levels of AFP in maternal blood. Some studies have found a relationship between maternal serum AFP levels and the development of preeclampsia [9, 11]. Theories have been presented about its development. Faulty placentation, which is responsible for preeclampsia pathogenesis is one theory. For this reason, it has been suggested that AFP can move from the placenta to maternal circulation for many weeks before preeclampsia develops [12].

The increase in estrogen levels during pregnancy and the physiological increase in the half-life of thyroid-binding globulin lead to increased levels of thyroid-binding globulin. Patients with preeclampsia exhibit low estrogen levels, which can reduce the half-life of thyroid-binding globulin and lead to the reduction of serum T3 and T4 levels. It has been suggested that a high thyroid-stimulating hormone (TSH) level and low free Tri-iodothyronine (free T3) and free tetraiodothyronine (free T4) levels may be associated with the development and complication of preeclampsia [13, 14]. Therefore, this study explored the relationships of second-trimester AFP, TSH, and free T4 levels with the severity of proteinuria in 24-h urine samples from patients with preeclampsia. The effect of proteinuria level on maternal/perinatal outcomes in 24-h urine was also evaluated.

METHODS

This retrospective study was conducted in our hospital between January 2017 and October 2019. The study protocol was approved by the hospital's ethics committee. Informed consent was obtained from all participants prior to inclusion in the study.

Patients aged 20-44 years old with a singleton pregnancy who were diagnosed with preeclampsia and delivered after 20 weeks of gestation were included in the study. Pregnant women were excluded if they met the following criteria: delivery of an infant with a birth weight < 500 g; missing preconception TSH or second-trimester AFP data; body mass index (BMI) > 35; multiple pregnancies; gestational hypertension, chronic hypertension, or high blood pressure before the 20th week of pregnancy; known antepartum thyroid disease (e.g., Hashimoto's disease or Graves' disease); use of medication for hypothyroidism or hyperthyroidism; pre-pregnancy nephropathy; and diagnosis of congenital anomalies (e.g., neural tube defect), uterine fibroids, and bleeding during pregnancy. For the patients included in the study relevant data were retrieved from the hospital database.

In the diagnosis of preeclampsia, hypertension was defined as the first occurrence of a systolic blood pressure ≥ 140 mmHg and a diastolic blood pressure ≥ 90 mmHg after the 20th week of pregnancy, measured at least twice at 4-h intervals in the left lateral decubitus position. A pregnant woman with no kidney disease was determined to have < 0.3 g in a 24-h urine sample for protein measurement in the third trimester [4]. All patients diagnosed with preeclampsia were followed up for 12 weeks after birth. Patients with persistent hypertension were excluded from the study because of the possibility of a chronic hypertension diagnosis during pregnancy. Patients who met the diagnostic criteria for preeclampsia and provided 24-h urine samples for protein measurement in the third trimester were divided into three groups based on proteinuria level: (1) mild (0.3 to < 2 g, n = 94), (2) severe (2 to < 5 g, n = 38), and (3) massive (≥ 5 g, n = 11) [15]. We compared the groups demographic characteristics (i.e., maternal age, parity, BMI, secondary diseases, and smoking), laboratory findings (i.e., second-trimester AFP, preconception TSH, and free T4 levels), maternal outcomes (maternal postpartum conditions [i.e., use of magnesium sulfate, intensive care unit requirement, wound infection, placenta abruption, acute

kidney failure, and dialysis]; cesarean section rate; cesarean section indication [e.g., persistent high blood pressure that did not decrease below 160/110 mmHg despite medical treatment, abnormal labor, placenta previa, placenta abruption, eclampsia, breech presentation, fetal distress, and/or previous cesarean history]; and length of stay), and neonatal outcomes (fetal weight, first minute Apgar score, fifth minute Apgar score, small for gestational age, neonatal intensive care unit [NICU], respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, neonatal death, and NICU duration). In addition, we evaluated the effects of these factors on severe and massive proteinuria using multivariate and univariate logistic regression analyses.

Abnormal labor included an active-phase arrest in the first or second stage of labor. The arrest of labor in the first stage was defined as ≥ 6 cm of dilation with ruptured membranes and failure to progress despite (a) 4 h of adequate uterine activity or (b) at least 6 h of oxytocin administration with inadequate uterine activity and no cervical change. Arrest of labor in the second stage was diagnosed after at least 2 hour of pushing in multiparous women and at least 3 hour of pushing in nulliparous women. All women with abnormal labor underwent cesarean delivery. Deliveries before 37 weeks were classified as premature. Intrauterine growth restriction was diagnosed if the estimated fetal weight was below the 10th percentile for gestational age. Fetal distress was diagnosed by the International Federation of Gynecology and Obstetrics (16). The second-trimester prenatal screening test was performed between 16 and 20 weeks of gestation for all participants. Maternal serum AFP (ng/ml) was measured in the same laboratory by enzyme-linked immunosorbent assay. TSH (mIU/ml; reference range, 0.27–4.2) and free T4 (ng/dl; reference range, 0.8–1.9) were determined by immunoassay (Immulite

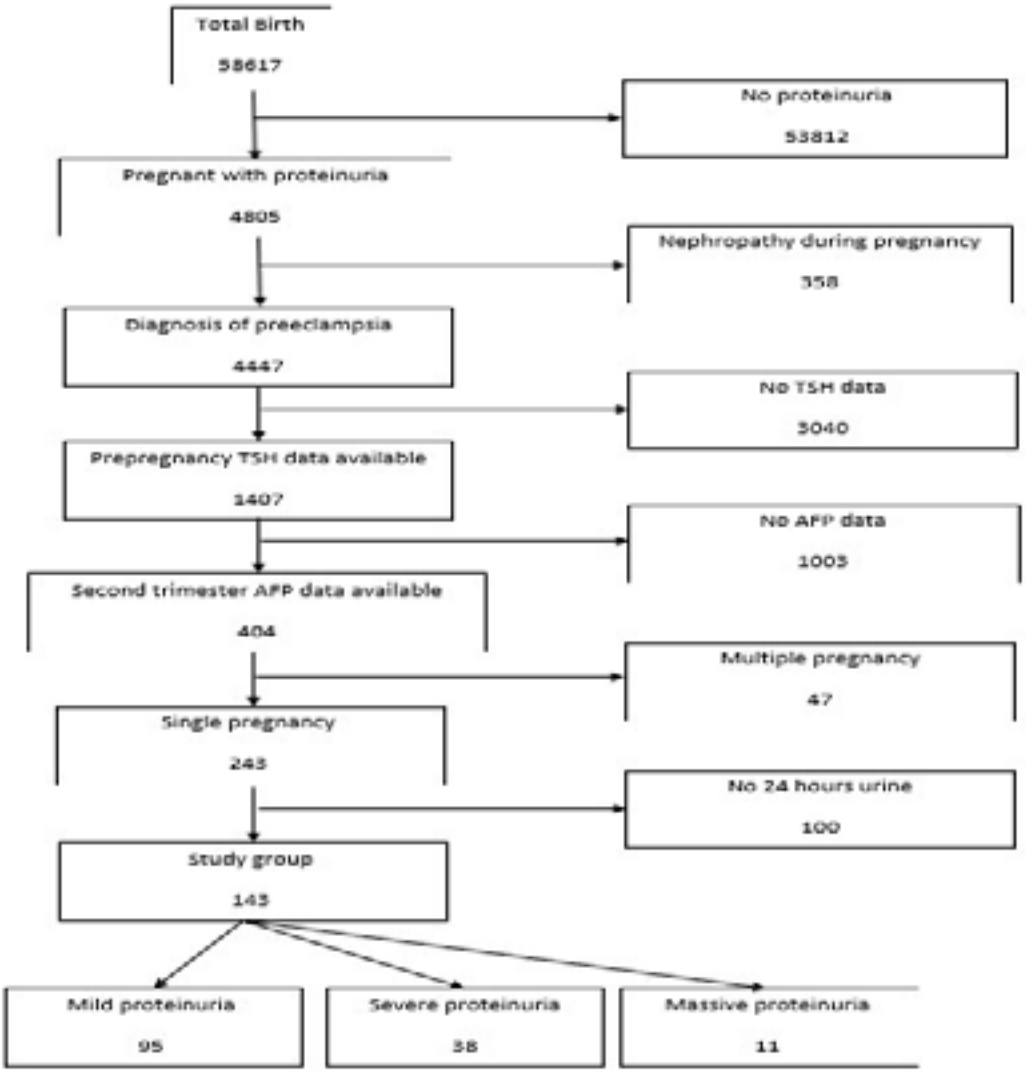

Figure 1. Flow chart.

2000, USA). The TSH values in the three months before pregnancy were taken.

The primary outcomes were the ability of preconception second-trimester AFP, TSH, and free T4 levels to predict the severity of proteinuria in 24-h urine samples from patients with preeclampsia. The secondary outcomes were the effects of proteinuria levels on maternal and neonatal outcomes in patients with preeclampsia.

Statistical Analysis

The statistical package program SPSS 20 (IBM SPSS Statistics for Windows version 20.0, IBM Corp., Armonk, NY, USA) was used to evaluate the data. Data were expressed as the mean ± SD and in percentages. Continuous variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilks test) to determine whether they were normally distributed. If the numerical data were non-parametric, the Kruskal-Wallis test would be conducted; if they were parametric, a one-way ANOVA test would be performed. The Bonferroni correction was used for the post-hoc assessment. The relationships between categorical variables were analyzed by the chi-square test. The bivariate correlations were investigated by Spearman's correlation analysis. For the multivariate analysis, the possible factors identified using univariate analyses were further entered into the logistic regression analysis to determine independent predictors of proteinuria. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 58,617 deliveries were recorded in our hospital between January 2017 and October 2019. Among them, 358 patients were excluded because they had been diagnosed with nephropathy during pregnancy. Among the remaining patients, 4,447 had been diagnosed with preeclampsia after the 20th week of pregnancy. Pre-pregnancy TSH data were only available for 1,407 pregnant women with preeclampsia. Second-trimester AFP data were available for 404 of these patients. After the exclusion of 47 patients with multiple pregnancies and 100 patients diagnosed with preeclampsia without a urine protein/creatinine ratio, 143 patients with preeclampsia remained and were included in the study. The flow charts of the study are shown in Figure 1. Among these patients, 94 had mild proteinuria (0.3 to <2 g), 38 had severe proteinuria (2 to <5 g), and 11 had massive proteinuria (≥5 g).

Table 1 presents the demographic characteristics and laboratory findings of patients with preeclampsia, stratified by severity of proteinuria. BMI (mild: 29.91±2.5 kg/m2; severe: 28.98 ±2.78 kg/m2; massive: 27.85±1.53 kg/m2 [p=0.017]), parity (mild: 0.66±0.48; severe: 0.53±0.51; massive: 0.27±0.47 [p=0.029]), and a gestational week at birth (mild: 35.53±3.11; severe: 34.45±3.22; massive: 33.55±3.42 [p=0.027]) were significantly lower in the massive proteinuria group. Patients with higher protein levels in the 24-h urine samples had an earlier gestational week at birth and exhibited lower parity. In addition, the second-trimester AFP levels increased with the

Table 1. Demographic characteristics and laboratory findings of preeclamptic patients classified according to the severity of proteinuria.

Variables	Mild proteinuria group (n:94)	Severe proteinuria group (n:38)	Massive proteinuria group (n:11)	*p*
Maternal age(n)*	30.19±5.7	30.26±7.89	27.73±8.61	0.461 γ
BMI (kg/m2) *	29.91±2.5[c]	28.98±2.78	27.85±1.53	0.017&
Parity (n)*	0.66±0.48[c]	0.53±0.51	0.27±0.47	0,029 γ
Gestational week at birth*	35.53±3.11[c]	34.45± .22	33.55±3.42	**0.027** γ
DM	3 (3.1)	1 (2.6)	-	0.697 γ
Smoking**	20 (21.3)	8 (21.1)	2 (18.2)	0.972 δ
TSH (mIU/ml)*	1.91±1.55[c]	2.61±1.77	2.92±1.71	**0.012** γ
Free T4 (ng/dl)*	1.07±0.44	6.89±2.51	0.97±0.17	0.492 γ
AFP (ng / ml)*	47.97±16.33[b,c]	60.52±15.01	65.5±26.52	**<0.001** γ

γKruskal Wallis test, & One-way ANOVA test, δChi-square test. Values were presented as *mean±SD or ** n (%). p-value <0.05 statistically significant. SD: Standard deviation; BMI: body mass index; DM: diabetes mellitus; TSH: Thyroid Stimulating Hormone; AFP: Alpha-fetoprotein; T4: thyroxine.

[b]There was a significant difference with the compared Severe proteinuria group in post-hoc comparison. [c]There was a significant difference with compared Massive proteinuria group in post-hoc comparison.

Table 2. Maternal and neonatal outcomes of preeclamptic patients classified according to the severity of proteinuria

Variables	Mild proteinuria group (n:94)	Severe proteinuria group (n:38)	Massive proteinuria group (n:11)	*p*
Cesarean section ratio, n (%)	74 (78.7)	33 (86.8)	11 (100.0)	0.153 [δ]
Cesarean section indication, n (%)				0.334 [δ]
Persistent high blood pressure	11 (14.9)	11 (33.3)	2 (18.2)	
Abnormal labor	8 (10.8)	-	1 (9.1)	
Placenta previa	2 (2.7)	-	-	
Placenta abruption	3 (4.1)	2 (6.1)	1 (9.1)	
Previous cesarean	11 (14.9)	6 (18.2)	1 (9.1)	
Fetal distress	34 (45.9)	10 (30.3)	4 (36.4)	
Eclampsia	3 (4.1)	4 (12.1)	2 (18.2)	
Breech presentation	2 (2.7)	-	-	
Fetal weight (gr) (± SD)	2554.3 (802.8)	2226.1 (688.3)	1835.5 (678.6)[b]	0.005 [γ]
IUGR	10 (10.6)	14 (36.8)	9 (81.8)	<0.001 [δ]
1st minute Apgar score ± SD	7.06 ± 1.50	6.63 ± 1.48	6.27 ± 1.85	0.058 [γ]
5th minute Apgar score ± SD	8.18 ± 1.29	7.97 ± 1.28	7.73 ± 1.35	0.247 [γ]
Neonatal complications, n (%)				0.001 [δ]
RDS	10 (10.6)	5 (13.2)	3 (27.4)	
IVH	-	1 (2.6)	2 (18.1)	
NEC	1 (1.1)	1 (2.6)	2 (18.1)	
Neonatal sepsis	-	1 (2.6)	1 (9.0)	
Neonatal death	1 (1.1)	-	1 (9.0)	
Composite adverse neonatal outcome	12 (12.8)	8 (21)	9 (81.8)	< 0.001 [δ]
Use of magnesium sulfate	30 (31.9)[b]	20 (52.6)	10 (90.9)	< 0.001 [δ]
ICU requirement	3 (3.2)[b]	5 (13.1)	8 (72.7)	< 0.001 [δ]
Wound infection	6 (6.4)	3 (7.9)	1 (9.0)	0.915 [δ]
Placenta abruption	3 (4.1)	2 (6.1)	1 (9.1)	0.607 [δ]
Acute kidney failure and dialysis	1 (1.0)[b]	1 (2.6)	3 (27.4)	< 0.001 [δ]
Length of hospital stay (days) ± SD	6.27 ± 3.74[b]	7.05 ± 3.00	8.18 ± 2.09	0.007 [γ]

[γ]Kruskal Wallis test, [δ]Chi-square test. Values were presented as mean ± SD or numbers and percent (%). *p* value < 0.05 statistically significant. SD: Standard deviation; IUGR: Intrauterine growth restriction; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ICU: Intensivecare unit. [b]There was a significant difference with compared Massive proteinuria group in post-hoc comparison.

severity of proteinuria (mild: 47.97 ng/ml; severe: 60.52 ng/ml; massive: 65.50 ng/ml [p<0.001]). In addition, there was a significant relationship between preconception TSH levels and severity of proteinuria (p=0.012). Conversely, no significant relationship was found between preconception free T4 levels and severity of proteinuria (p=0.492).

The maternal and neonatal outcomes are shown in Table 2. All neonatal outcomes and composite adverse neonatal outcomes differed significantly among groups. The cesarean rates were high in all three groups (mild proteinuria group, 78.7%; severe proteinuria group, 86.8%; massive proteinuria group, 100%). The length of hospital stay was the longest in the massive proteinuria group (mild: 6.27±3.74 days; severe: 7.05±3.00 days; massive: 8.18±2.09 days [p=0.007]). Postpartum maternal complications were the most common in the massive proteinuria group. The use of magnesium sulfate, intensive care unit requirement, acute kidney failure, and dialysis were more common among women with preeclampsia who had massive proteinuria (p values <0.001, <0.001, <0.001, respec-

Table 3. Factors affecting patients with proteinuria greater than 2 g were evaluated by multivariate and univariate logistic regression analysis.

	Multivariate					Univariate				
	B	**S.E.**	***p***	**OR**	**95% C.I.**	**B**	**S.E.**	***p***	**OR**	**95% C.I.**
Maternal age	0,126	0,054	0,021	1,134	1,020- 1.262	-0,012	0,027	0,666	0,988	0,938- 1.042
BMI	-0,200	0,111	0,073	0,819	0,658- 1.018	-0,191	0,075	0,011	0,826	0,713 – 0.957
Parity	-1,513	0,692	0,029	0,220	0,057- 0.854	-0,784	0,360	0,029	0,457	0,226 – 0.924
TSH	0,094	0,128	0,463	1,098	0,855- 1.411	0,281	0,111	0,012	1,324	1,065 – 1.647
AFP	0,040	0,012	0,001	1,041	1,016- 1.066	0,045	0,011	<0,001	1,046	1,023 – 1.069

B: Standardized regression coefficient SE: Standard error. OR: odds ratio. CI: confidence interval. p values with statistical significance ($p < 0.05$) are shown in bold. BMI: body mass index; TSH: Thyroid Stimulating Hormone; AFP: Alpha-fetoprotein.

tively). With the severity of proteinuria, birth weight decreased (mild: 2,554.3 (802.8) g; severe: 2,226.1 (688.3) g; massive: 1,835.5 (678.6) g [p=0.005]), and the frequency of IUGR increased (mild: 10 (10.6); severe: 14 (36.8); massive: 9 (81.8) [p<0.001]).

The factors affecting the outcomes of patients with proteinuria >2 g (Table 3) were examined using multivariate and univariate logistic regression analysis. AFP was identified as the most important independent predictor of severe proteinuria with an odds ratio of 1.041 (p<0.001). TSH was not predictive of severe proteinuria (odds ratio =0.463; p=1.098). Correlation analysis showed that increased proteinuria was associated with significant increases in AFP and TSH levels and with significant reductions in age, BMI, and parity (Table 4). The strongest association was found between AFP and proteinuria as shown in Figure 2. The correlation of TSH with proteinuria was showned in Figure 3.

DISCUSSION

AFP and preconception TSH were found to be valuable markers for predicting the severity of proteinuria in 24-h urine samples from patients with preeclampsia. As AFP and preconception TSH increased, the severity of proteinuria increased. Higher levels of proteinuria were associated with composite adverse maternal and neonatal outcomes.

Li and colleagues [17] found that maternal age and BMI were negatively correlated with increased 24-h proteinuria levels and that gestational age at delivery became noticeably younger as the level of proteinuria increased. By contrast, Tanacan and colleagues [3] found no significant relationships between proteinuria and each of the following factors: maternal age, BMI and parity. In our study, maternal age, BMI, and parity significantly decreased as the severity of proteinuria increased. Moreover, the incidences of early birth and preterm labor increased with the severity of proteinuria. These findings show that severity of proteinuria is a valuable predictor of preterm labor. Preterm labor, which occurs in 10%–12% of pregnancies, is the leading cause of neonatal mortality and morbidity [18]. Therefore, the accurate prediction of severe proteinuria in patients with preeclampsia can improve maternal and neonatal outcomes.

The cesarean rates in our study were high consistent with the published literature [2]. Although we did

Table 4. Correlation of some values with proteinuria.

	Proteinuria	
	r	**P**
AFP	0.418	< 0.001
TSH	0.282	0.001
Maternal age	-0.101	0.231
BMI	-0.237	0.004
Parity	-0.175	0.036

Spearman's correlation analysis was used. p values with statistical significance ($p < 0.05$) are shown in bold. r: correlation coefficient; BMI: body mass index; TSH: Thyroid Stimulating Hormone; AFP: Alphafetoprotein.

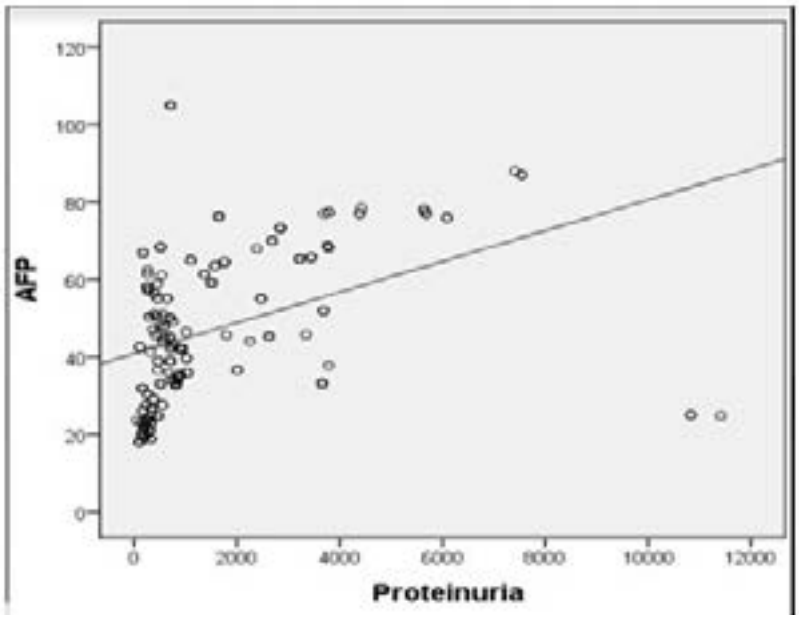

Figure 1. The correlation of AFP with proteinuria.

not stratify the symptoms according to the severity of preeclampsia. This study results suggest a meaningful association between the severity of preeclampsia and the severity of proteinuria. The diagnosis of the patients in the group with massive proteinuria was made earlier in the gestational weeks and the neonatal complication rates in this group were high in the study, consistent with other studies [3, 15, 19, 20]. The rates for the usage of magnesium sulfate, admission to ICU, acute kidney failure and dialysis, and length of hospital stay were higher in the severe and massive proteinuria groups. Similarly, IUGR and preterm delivery rates were higher in the massive proteinuria group. These results are compatible with the literature [3, 15, 19, 20]. Whereas retrospective studies found a significant relationship between severity of proteinuria and negative maternal/neonatal outcomes, this relationship was not found in prospective studies. However, the severity of proteinuria should not be used alone to determine the time of birth in preeclampsia [21].

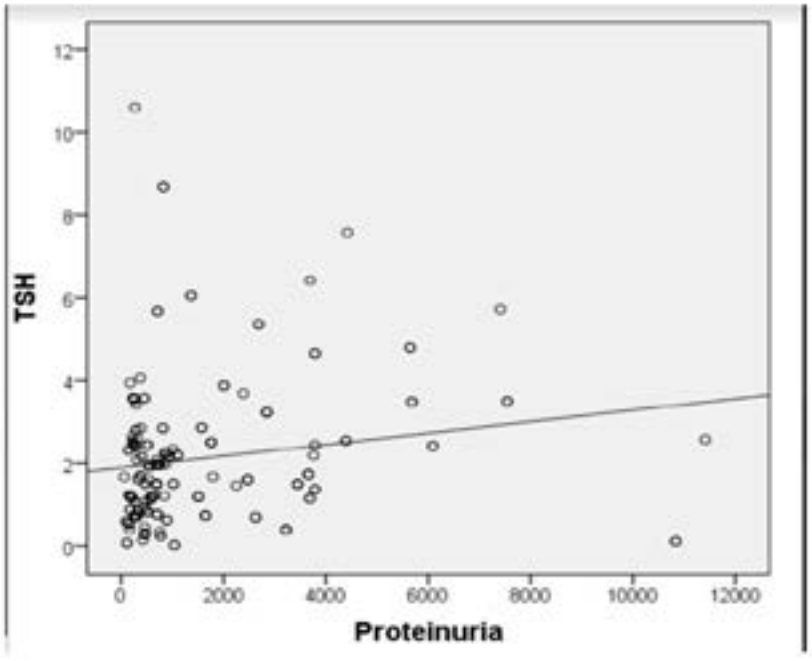

Figure 1. The correlation of TSH with proteinuria.

In Yadav *et al*.'s study [22], the second-trimester AFP levels were 151.04±7.2 ng/ml in women with severe preeclampsia and 52.50±15.52 ng/ml in healthy pregnant women; thus, unexplained high levels of maternal serum AFP were presumably associated with preeclampsia. In another study that stratified patients into healthy, non-severe preeclampsia and severe preeclampsia groups, the only significant differences among the groups were observed in maternal serum AFP and AFP multiples of the median values [23]. The average AFP level for pregnant women with severe preeclampsia, including those with progressive renal insufficiency, was 50.11±33.81 U/ml; conversely, the average AFP level in the non-severe preeclampsia group was 42.47±15.46 U/ml. We identified AFP as the most important independent predictor of severe proteinuria, with an odds ratio of 1.041. AFP multiples of the median values were not included in our study, but we found that a linear increase in maternal serum AFP level corresponded to the severity of proteinuria. A study that calculated AFP levels, adjusted for maternal age and BMI, revealed a linear relationship with severity of proteinuria [23]. The study performed multivariate regression analysis to ensure that the interactions among these factors did not result in bias.

Deshpande *et al*. [24] showed that serum albumin was positively correlated with T3 and T4 levels but was negatively correlated with serum TSH levels in women with preeclampsia. Some studies have shown a statistically significant positive relationship between thyroid hypofunction and preeclampsia [25]. However, Arbib and colleagues [25] found that firsttrimester TSH levels were not a significant predictor of preeclampsia. They conducted a regression analysis and determined that subclinical hypothyroidism approximately doubled the risk of preterm birth. Our study found a significant relationship between preconception TSH levels and proteinuria levels in pregnant women with preeclampsia but not between preconception free T4 levels. TSH levels tended to increase as proteinuria increased and their association was statistically significant. This result may be related to the collection of these data three months prior to conception. Perhaps if investigators had collected first-trimester data, as in other studies, might have found a strong association similar to that between AFP and proteinuria.

Limitations

The main limitation of this study is its retrospective nature. In addition, this study hospital's birth rates were particularly high during the study period. These factors may have limited the accessibility of patient data. Moreover, this study is limited by the patients not stratified according to severity of preeclampsia. The study did not analyze the symptoms and laboratory findings associated with severe preeclampsia. As clinical results not only depend on the severity of proteinuria, this might have caused bias. Another limitation is the relatively small sample size and the singlecenter experience.

The strength of our study is that the frequent application of TSH and free T4 screening in the preconceptional period in our country increased the number of patients containing this data. Especially, it assessed the AFP and TSH levels in patients with preeclampsia stratified according to severity of proteinuria. Moreover, the observance of differences in maternal and neonatal outcomes among these groups demonstrated the usefulness of proteinuria levels in assessing the severity of preeclampsia.

CONCLUSION

The second-trimester serum AFP level may be a valuable predictor in predicting the severity of proteinuria in 24 hour urine samples in patients with preeclampsia. This study findings suggest that second-trimester AFP levels can assist providers in preparing for adverse obstetric outcomes. Maternal and neonatal outcomes can be improved by incorporating earlier preparations for obstetric complications. Given that AFP may be a valuable predictor of complications, it may be advisable to measure second-trimester AFP levels in maternal blood, regardless of the ability to perform a triple test. A similar situation was observed between high TSH levels seen in the preconceptional period and massive proteinuria. In addition, the presence of higher levels (> 5 g) of 24-h urinary protein was closely related to adverse maternal/neonatal outcomes. Multicenter observational cohort studies involving more patients are required for stronger results.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Harran University, Urfa,

Turkey. (Decision number: 07, date: 16.12.2019).

Authors' Contribution

Study Conception: NNY; Study Design: EB; Literature Review: NB; Critical Review: FE; Data Collection and/or Processing: SK; Analysis and/or Data Interpretation: EB; Manuscript preparing: SK.

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