

The Comparison of Serum CA-125 Levels in Women with Normal Pregnancy and Severe and Non-Severe Preeclampsia

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Article Type	ABSTRACT
Research Paper	Background and Objective: In pregnancies complicated by preeclampsia, it seems that failure of trophoblast invasion and induction of placental inflammation can lead to the production of biomarkers, one of which is CA-125. The aim of this study is to investigate serum CA-125 levels in non-severe and severe preeclampsia and compare it with normal pregnancy. Methods: This retrospective case-control study was conducted on 30 women with normal pregnancy, 27 women with mild preeclampsia and 30 women with severe preeclampsia referring to the midwifery clinic of Shahid Motahari Hospital in Urmia who met the inclusion criteria. The data evaluated in this study included gestational age, systolic and diastolic blood pressure, platelet, AST, ALT, serum creatinine, serum uric acid, serum CA-125 levels, urinary protein level and birth weight. Venous blood samples were collected at delivery for complete blood count, creatinine, uric acid and CA-125 concentration from all participants. Then the results were compared. Findings: The results of the present study showed that the mean CA-125 of women in the control group was 17.83 ± 5.37 u/ml, in the mild preeclampsia group was 40.64 ± 12.40 and in the severe preeclampsia group was 71.73 ± 48.90, which indicates that this value is high in mild preeclampsia compared to the control group as well as severe preeclampsia compared to the other two groups. Statistical comparisons showed that there is a significant relationship between serum CA-125 levels in women with normal pregnancy and non-severe and severe preeclampsia ($p < 0.001$). Conclusion: The results of the present study showed that CA-125 is associated with the occurrence of preeclampsia (mild and severe) and can be helpful as a marker in the diagnosis of preeclampsia, especially its severe type. Moreover, due to the relationship between this marker and a wide range of other variables, paying attention to its serum level along with other paraclinical variables can be helpful in better diagnosis and management of patients. Keywords: Serum CA-125 Level, Preeclampsia, Normal Pregnancy, Pregnancy.

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Introduction

Blood pressure disorders are the most common medical complications of pregnancy that occur in 5-10% of pregnancies. Blood pressure disorders and most importantly preeclampsia along with infections and bleeding are considered to be the most common factors associated with maternal mortality. According to the report of the World Health Organization, among the factors leading to maternal death, preeclampsia and its related complications are more common than others (1-5). The main cause of preeclampsia is unknown. Preeclampsia is more common in nulliparous and young mothers, while older mothers are at increased risk of chronic hypertension and preeclampsia. On the other hand, race and genetic factors have been reported as risk factors for preeclampsia (5-9).

Preeclampsia affects both the mother and the fetus. Decreased placental perfusion leads to decreased fetal growth and causes restrictions in growth. Premature delivery is an important complication of preeclampsia that occurs after intervention to terminate pregnancy and causes fetal damage, neurodevelopmental disorder and fetal death. The treatment of preeclampsia is the termination of pregnancy, and in the case of premature fetuses, pregnancy can be prolonged with proper care if possible (10-12).

CA-125 antigen is an epitope on a high molecular weight mucin-like glycoprotein. This antigen appears in 80% of ovarian epithelial carcinomas and non-malignant pelvic conditions such as endometriosis, fibroids, pregnancy and pelvic inflammation, liver disease, kidney failure, and lung, colon, breast, and adenomyosis cancers (13-15). Although fetal chorion, amniotic fluid and maternal decidua are potential sources of high serum CA-125 levels in the first trimester of pregnancy and the postpartum period, the dynamics of serum CA-125 levels in the perinatal period still need to be explained (14). In pregnancies complicated by preeclampsia, it seems that failure of trophoblast invasion and induction of inflammatory process within the placenta cause the production of biomarkers, one of which is CA-125 (16, 17). Therefore, CA-125 is a biomarker of the severity of the inflammatory process in preeclampsia and can be used as an additional and helpful test to detect atypical types of preeclampsia or early detection of severe types of preeclampsia from non-severe ones (18).

Recently, in some studies, the role of maternal serum CA-125 in the differentiation of severe and non-severe preeclampsia has been mentioned, which can help differentiate between severe and non-severe types of preeclampsia along with blood pressure measurement and clinical symptoms and other laboratory tests and can be used in the selection of treatment (18). In a study, the level of CA-125 in preeclampsia was investigated and this study showed that there is a significant relationship between the serum CA-125 levels and the severity of preeclampsia. This biomarker can be used to distinguish mild from severe types (19). In another study, the level of CA-125 was compared in normal pregnancy and severe and non-severe preeclampsia; this study showed that the level of this biomarker is normal in non-severe type of preeclampsia and normal pregnancy, but increases in severe type (20). Other studies showed that CA-125 levels are higher than normal in both severe and non-severe types of preeclampsia (21-24). In a study, it was shown that there was no significant difference between CA-125 level in non-severe preeclampsia and normal pregnancy. There was no significant difference between severe and non-severe preeclampsia (25).

Given the importance of preeclampsia and the resulting maternal and fetal complications, and considering the lack of clinical studies on the relationship between CA-125 serum levels and hypertensive disorders in pregnancy, as well as the contradictory results of these studies, we were motivated to conduct this study at Motahari Hospital in Urmia, which is a level III center of the province and a referral hospital for most cases of preeclampsia.

Methods

After approval by the Ethics Committee of Urmia University of Medical Sciences with the ethics code IR.UMSU.REC.1399.279, this case-control study was conducted on pregnant women with preeclampsia referred to Motahari Hospital in Urmia in 2020-2021. The study subjects included 90 pregnant women in three groups of 30 (healthy pregnant women, non-severe and severe preeclampsia) who were selected from among pregnant women referring to Motahari Hospital in Urmia. Pregnant women were matched in three groups according to age and body mass index (BMI). In this study, the Guidelines of the American College of Obstetricians and Gynecologists were used to diagnose and classify preeclampsia into severe and non-severe types (14).

Patients with overt diabetes and gestational diabetes, chronic high blood pressure, known history of peripheral vascular disease and BMI less than 19 and more than 30 kg/m² at the onset of pregnancy and multiple pregnancy, history of ovarian cyst, adenomyosis, uterine fibroids, kidney stones, and endometriosis based on their history, history of intrauterine mass and history of intrauterine adhesion, history of IBD and cholecystitis, and malignancies such as lung, colon, kidney, and breast cancer were excluded from the study. Pregnant women referred to Motahari Hospital who signed the informed consent form and did not meet any of the exclusion criteria were included in the study.

Patients with preeclampsia were divided into two groups of non-severe and severe. Mild preeclampsia was defined as blood pressure greater than or equal to 140/90 and less than 160/110 and the absence of headache, visual disturbance, upper abdominal pain, oliguria, seizures and normal creatinine and absence of thrombocytopenia, normal level of transaminases and absence of growth restriction and pulmonary edema. Severe preeclampsia was defined as blood pressure greater than or equal to 160/110 and the presence of headache, visual disturbance, upper abdominal pain, oliguria, seizures and high creatinine and the presence of thrombocytopenia, significantly high transaminases and growth restriction and pulmonary edema (2, 14).

Venous blood samples were collected from all participants at delivery for evaluation of complete blood, creatinine, uric acid and CA-125 concentration. CA-125 titer was measured using quantitative method of luminescence of Ario Pharma Ltd using Liaison device in Motahari Hospital. Additionally, 24-hour urine was collected from each participant to determine urine protein excretion. Data collection was done by means of a pre-designed questionnaire. The information evaluated in this study included gestational age, systolic and diastolic blood pressure, AST, ALT, platelets, serum creatinine, serum uric acid, serum CA-125 level, urinary protein level and fetal weight.

To calculate the sample size using the corresponding formula to estimate the mean difference, with 99% confidence ($Z_{1-\alpha/2} = 2.575$) and 95% power ($Z_{1-\beta} = 1.28$) and using the results of the study of Ozat et al. (19), ($S_1 = 3.34$, $S_2 = 8.72$, $X_1 = 48.25$, $X_2 = 55.7$) and the probability of 30% miscarriage, 30 women in each group and 90 pregnant women in total were selected from among pregnant women referring to the midwifery clinic of Shahid Motahari Hospital in Urmia according to the inclusion criteria.

For quantitative variables, centrality and dispersion (Mean $\pm$ SD) were calculated, and for qualitative variables, frequency and percentage were calculated. Appropriate statistical tables and graphs were used as needed to display data and results. Parametric statistical tests such as Chi-Square, t-testone, ANOVA, and multivariate linear regression were used to compare and investigate relationships, and for pairwise comparisons, Post Hoc was used based on the Bonferroni method. Furthermore, to evaluate the diagnostic value of relevant indicators including sensitivity, specificity, and positive and negative predictive value were calculated. All data were analyzed using SPSS 21 and $p < 0.05$ was considered significant.

Results

In this study, 30 women in the control group, 27 women in the mild preeclampsia group, and 30 women in the severe preeclampsia group were evaluated. According to the results, the mean age of women in the control group was 31.37 ± 5.54 years, in the mild preeclampsia group was 30.78 ± 4.99 years, and in the severe preeclampsia group was 30.73 ± 5.18 years. The mean systolic and diastolic blood pressure of women showed a statistically significant difference between the control group, the mild preeclampsia group and the severe preeclampsia group ($p < 0.001$). The results showed that the control group compared with mild preeclampsia ($p < 0.001$) and mild compared with severe preeclampsia ($p < 0.001$) and the control group compared with severe preeclampsia showed a statistically significant difference ($p < 0.001$). The mean birth weight of infants in the control group was 3146.67 ± 337.31 , in the mild preeclampsia group was 2997.78 ± 409.60 and in the severe preeclampsia group was 2164.28 ± 970.39 grams. The control group did not show a statistically significant difference compared with the mild preeclampsia group, but there was a statistically significant difference between the mild preeclampsia and severe preeclampsia ($p < 0.001$) and the control group compared with the severe preeclampsia group ($p < 0.001$) (Table 1).

There was a statistically significant difference in the mean platelet count of women between the three groups ($p < 0.001$). The results showed that the control group compared with mild preeclampsia ($p < 0.001$) and the control group compared with severe preeclampsia had a statistically significant difference ($p < 0.001$), but no significant statistical difference was observed in the mild preeclampsia group compared with severe preeclampsia ($p = 0.187$). Comparing the mean creatinine, ALT, AST and Hb of women in the control group, the mild preeclampsia group and the severe preeclampsia group showed a statistically significant difference between the three groups ($p < 0.001$). No statistically significant difference was observed between the control group compared with mild preeclampsia, but there is a significant statistical difference between the control group and the severe preeclampsia group and between the mild preeclampsia group and severe preeclampsia group ($p < 0.001$) (Table 2).

The mean CA-125 and mean uric acid of women showed statistically significant differences between the three groups ($p < 0.001$). In addition, there were statistically significant differences between the control group compared with mild preeclampsia and the control group compared with severe preeclampsia and the mild preeclampsia group compared with severe preeclampsia group.

There was no statistically significant difference between the three groups in terms of the type of delivery and mother's education. In addition, the results showed that there is a statistically significant difference between the three groups in terms of IUGR and receiving blood pressure medication ($p < 0.001$).

To control the effect of confounding factors, multivariate analysis was used based on linear regression using backward technique. In this analysis, CA-125 as a dependent variable and the variables of uric acid, mother's age, systolic and diastolic blood pressure, ALT, AST, Cr, Hb, Plt, BMI and studied groups (three groups) as independent variables were entered into the model. The results showed that only the variables of IUGR and receiving blood pressure medication in the preeclampsia group had a significant effect on CA-125 ($\beta = 27.01$, S.E = 3.88, Beta = 0.58, $p < 0.001$, CI 95% for B = 19.30-34.72, ADJ.R² = 0.359, R² = 0.366, R = 0.605).

Based on the correlation matrix between measured quantitative variables, CA-125 variable had a significant direct correlation with systolic and diastolic blood pressure, Cr and uric acid variables, and a significant inverse correlation with Plt and fetal weight at birth. Moreover, birth weight had a significant direct correlation with Plt, Hb and gestational age at delivery and a significant inverse correlation with systolic and diastolic blood pressure, uric acid, Cr, ALT, AST, CA-125, BMI. In the comparison of mean quantitative variables measured in terms of IUGR, mean number of births, mean maternal age, mean ALT, mean AST and BMI, the two groups with IUGR and the group without IUGR had no significant

statistical differences. In terms of mean gestational age at delivery, mean systolic and diastolic blood pressure, mean Plt, mean Cr, mean Hb, mean fetal weight, mean CA-125 and mean uric acid in the group with IUGR and the group without IUGR, it was shown that there is a significant difference between the two groups ($p<0.05$).

Med Calc statistical software was used to investigate the diagnostic value of CA-125 in preeclampsia and severe preeclampsia. First, the analysis was done without taking into account the severity of preeclampsia. According to the results, the calculated sensitivity was equal to 45.61%, specificity was equal to 100% and positive predictive value was equal to 100% and negative predictive value was equal to 49.18%. For severe preeclampsia according to the results, sensitivity was equal to 73.33%, the specificity was equal to 100% and the positive predictive value was equal to 100% and the negative predictive value was equal to 78.95% (Table 3).

Table 1. Comparison of the mean quantitative variables in studied patients

Groups	Number	Mean $\pm$ SD	95% confidence interval	p-value
Number of births				
Control	30	1.53 $\pm$ 0.78	1.24-1.82	0.966
Mild preeclampsia	27	1.56 $\pm$ 0.85	1.22-1.89	
Severe preeclampsia	30	1.50 $\pm$ 0.78	1.21-1.79	
Number of pregnancies				
Control	30	1.53 $\pm$ 0.78	1.24-1.82	0.966
Mild preeclampsia	27	1.56 $\pm$ 0.85	1.22-1.89	
Severe preeclampsia	30	1.50 $\pm$ 0.78	1.21-1.79	
Mother's age				
Control	30	31.37 $\pm$ 5.54	29.30-33.44	0.875
Mild preeclampsia	27	30.78 $\pm$ 4.99	28.80-32.75	
Severe preeclampsia	30	30.73 $\pm$ 5.18	28.80-32.67	
Height				
Control	30	161.07 $\pm$ 5.66	158.95-163.18	0.055
Mild preeclampsia	27	164.04 $\pm$ 4.48	162.26-165.81	
Severe preeclampsia	30	160.24 $\pm$ 7.58	157.36-163.12	
Weight				
Control	30	74.38 $\pm$ 9.57	70.81-77.96	0.127
Mild preeclampsia	27	78.81 $\pm$ 6.77	76.14-81.49	
Severe preeclampsia	30	75.93 $\pm$ 7.89	72.93-78.93	
Gestational age at delivery				
Control	30	5.99 $\pm$ 36.20	33.96-38.44	0.033
Mild preeclampsia	27	35.67 $\pm$ 3.06	34.45-36.88	
Severe preeclampsia	30	33.47 $\pm$ 2.57	32.51-34.43	
Systolic blood pressure				
Control	30	115 $\pm$ 10.17	111.20-118.80	<0.001
Mild preeclampsia	27	146.48 $\pm$ 4.96	144.52-148.45	
Severe preeclampsia	30	171.67 $\pm$ 13.35	166.68-176.65	
Diastolic blood pressure				
Control	30	70 $\pm$ 8.51	66.82-73.18	<0.001
Mild preeclampsia	27	92.78 $\pm$ 6.10	90.37-95.19	
Severe preeclampsia	30	105.83 $\pm$ 8.21	102.77-108.90	
Fetal weight				
Control	30	3146.67 $\pm$ 337.31	3020.71-3272.62	<0.001
Mild preeclampsia	27	2997.78 $\pm$ 409.60	2835.75-3159.81	
Severe preeclampsia	30	2164.28 $\pm$ 970.39	1795.16-2533.39	
BMI				
Control	30	28.63 $\pm$ 3.06	27.49-29.78	0.414
Mild preeclampsia	27	29.34 $\pm$ 2.80	28.23-30.45	
Severe preeclampsia	30	29.65 $\pm$ 3.11	28.47-30.83	

Table 2. Comparison of the mean quantitative paraclinical variables in studied patients

Groups	Number	Mean±SD	95% confidence interval	p-value
Plt				
Control	30	209366.67±71223.05	182771.54-235961.79	<0.001
Mild preeclampsia	27	142037.04±26383.97	131599.89-152474.19	
Severe preeclampsia	30	116933.33±39591.83	102149.50-131717.16	
Cr				
Control	30	0.72±0.15	0.67-0.78	<0.001
Mild preeclampsia	27	0.79±0.15	0.73-0.85	
Severe preeclampsia	30	0.97±0.18	1.04-0.90	
ALT				
Control	30	30.87±30.44	19.50-42.23	0.017
Mild preeclampsia	27	26.30±9.22	22.65-29.94	
Severe preeclampsia	30	69.1±58.85	31.93-107.24	
AST				
Control	30	26.17±6.05	23.91-28.42	0.026
Mild preeclampsia	27	29.44±9.21	25.80-33.09	
Severe preeclampsia	30	62.93±13.81	27.11-97.16	
Hb				
Control	30	12.12±0.92	11.78-12.46	<0.001
Mild preeclampsia	27	11.80±1.05	11.39-12.22	
Severe preeclampsia	30	10.94±0.99	10.57-11.31	
CA-125				
Control	30	17.83±5.37	15.82-19.83	<0.001
Mild preeclampsia	27	40.64±12.40	35.74-45.54	
Severe preeclampsia	30	71.73±48.90	53.47-89.99	
Uric acid				
Control	30	3.85±1.22	3.40-4.31	<0.001
Mild preeclampsia	27	5.41±1.09	4.98-5.84	
Severe preeclampsia	30	3.63±1.39	6.11-7.15	

Table 3. Results of CA-125 diagnostic value indices in preeclampsia and severe preeclampsia

Index	Preeclampsia CI 95%	Severe preeclampsia CI 95%
Sensitivity	45.61 (32.36-59.34)	73.33 (54.11-87.72)
Specificity	100 (88.43-100)	100 (88.43-100)
AUC	0.73 (0.62-0.82)	0.87 (0.75-0.94)
Positive Likelihood Ratio	-	-
Negative Likelihood Ratio	0.54 (0.43-0.69)	0.27 (0.15-0.48)
Disease prevalence	65.52 (54.56-75.39)	50 (36.81-63.19)
Positive Predictive Value	100	100
Negative Predictive Value	49.18 (43.28-55.11)	78.95 (67.44-87.16)
Accuracy	64.37 (55.38-74.35)	86.67 (75.41-93.79)

ROC Curve was used to determine the best cut-off point based on the data of this study, and the results showed that the best cut-off point for preeclampsia was 26.85 with a sensitivity of 0.877 and a specificity of 0.933, a value of 28.89 with a sensitivity of 0.877 and a specificity is 0.967. In addition, with a cut-off point of 50.5, sensitivity was equal to 0.456 and specificity was equal to 1 (Figure 1).

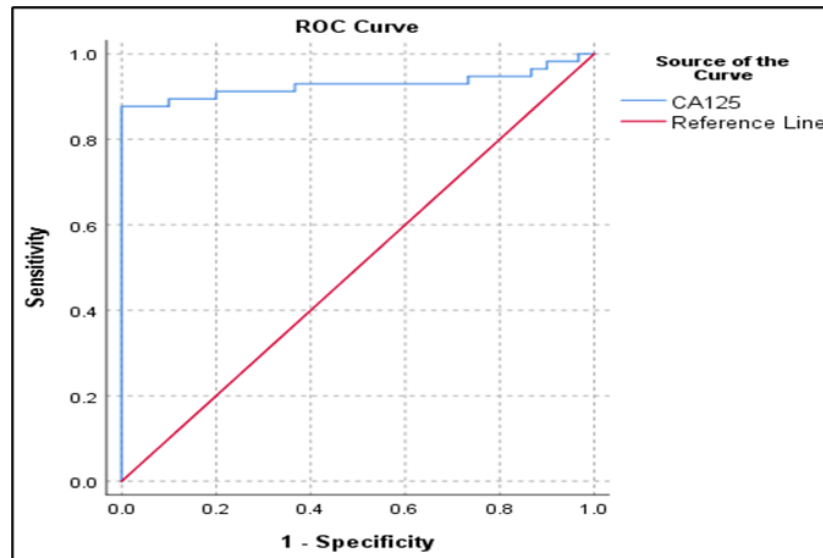


Figure 1. ROC curve related to the diagnostic value of CA-125 in mild preeclampsia

To determine the best cut-off point based on the data of the present study for severe preeclampsia, the results showed that the best cut-off point was 43.71 with a sensitivity of 0.833 and a specificity of 0.860, a value of 43.435 with a sensitivity of 0.833 and a specificity of 0.842. Furthermore, with a cut-off point of 50.5, sensitivity was equal to 0.733 and specificity was equal to 0.93 (Figure 2).

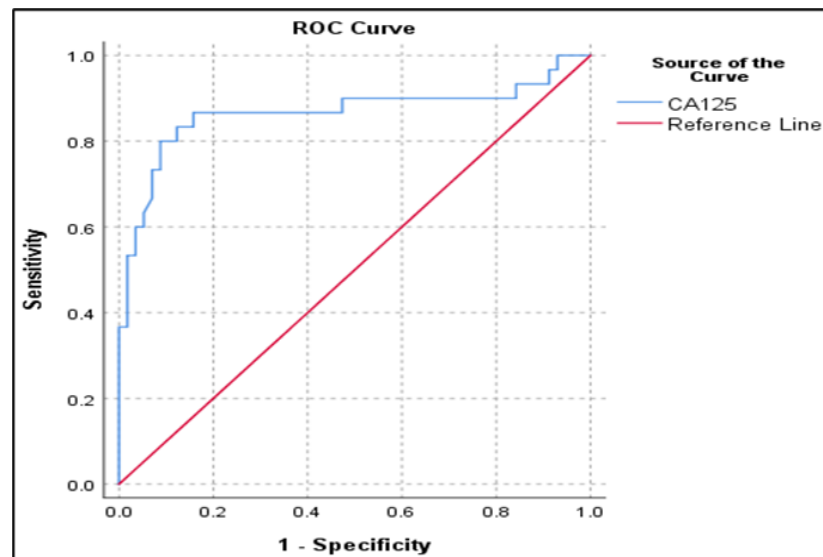


Figure 2. ROC curve related to the diagnostic value of CA125 in severe preeclampsia

Discussion

The present study showed that the mean age of the patients, the number of births and the body mass index in the three studied groups showed no statistically significant difference. The mean CA-125 in women in three groups shows that this value is high in mild preeclampsia compared to the control group as well as severe preeclampsia compared to the other two groups (control and mild preeclampsia) and this difference was statistically significant. In previous studies, the mean range of CA-125 in women without preeclampsia was reported as 14.4 to 48.25 (IU/ml), and the mean value calculated in the present study (17.83) is in this range. In addition, the mean range of CA-125 in women with mild preeclampsia is reported as 18.8 to 55.70 (IU/ml), and the mean value calculated in the present study (40.64) is in this range. The mean range of CA-125 of women with severe preeclampsia is reported as 37.35 to 59.11 (IU/ml), and the mean value calculated in the present study (71.73) is higher than similar studies. In all similar studies, a significant difference was reported in the mean CA-125 between the control group and severe preeclampsia (19, 20, 23-25), which is similar to the results of the present study. Furthermore, in the present study, the results showed that the mean CA-125 had a significant difference in women of the control group compared with mild preeclampsia, which was similar to the results of other studies (19, 23-25). Only in the study conducted by Karaman et al., no significant difference was reported between the two groups of control and mild preeclampsia (20) and this could be due to genetic differences in the studied populations in recent studies compared to the present study, or the lack of control of confounders and also the method of conducting the study.

The results of the present study showed that the mean CA-125 had a direct significant correlation with systolic and diastolic blood pressure, Cr and uric acid, and these relationships were found in the study of Karaman et al. with systolic and diastolic blood pressure (20) and in the study of Ozat et al. with systolic and diastolic blood pressure and platelet count, uric acid and urine protein concentration (19). In the study of Bhattacharya et al., a significant direct correlation was reported with systolic and diastolic blood pressure and platelet count, uric acid and urine protein concentration (24).

In the multivariate analysis based on multivariate regression to control the effects of confounding factors in the present study, the results showed that only the variables of IUGR and receiving blood pressure medication in the preeclampsia group had a significant effect on CA-125. This indicates the difference in mean CA-125 based on the studied groups despite controlling all factors. Moreover, the comparison made according to the presence of IUGR showed that the mean variables of systolic and diastolic blood pressure, platelet count, Cr and uric acid, CA-125, Hb and birth weight were significantly different. The results of the present study showed that the mean CA-125 had a significant inverse correlation with platelets count and birth weight. These relationships were found in the study of Karaman et al. with birth weight, fetal weight, and age at delivery (20) and in the study of Ozat et al. with birth weight and fetal weight (19). In the study of Bhattacharya et al., a significant inverse correlation was reported with birth weight and fetal weight (24).

In the present study, evaluating the diagnostic value of CA-125 for preeclampsia without considering the severity showed these results: sensitivity was equal to 45.61%, specificity was equal to 100%, positive predictive value was equal to 100%, and negative predictive value was equal to 49.18%. For severe preeclampsia, sensitivity was equal to 73.33%, specificity was equal to 100%, positive predictive value was equal to 100% and negative predictive value was equal to 78.95%. This indicates that CA-125 can be helpful for severe preeclampsia. However, the normal limit is considered to be less than 50 IU/ml. Compared to similar articles, in the study of Ibrahim et al., sensitivity was equal to 96.7%, and specificity was equal to 98.7% (23). In the study by Bhattacharya et al., where the same cut-off point was considered as the present study, sensitivity was equal to 91%, specificity was equal to 80.2%, positive predictive value was equal to 88.7% and negative predictive value was equal to 80.2% (24).

To calculate the best cut-off point based on the data of this study, the ROC Curve was used, and for preeclampsia, the best value of CA-125 was 28.89 with a sensitivity of 0.877 and a specificity of 0.967, and for the diagnosis of severe preeclampsia, the value was 43.71 with sensitivity of 0.833 and specificity of 0.860. In the study of Ozat et al. with the same cut-off point as the present study, sensitivity was equal to 93.7% and specificity was equal to 88% (19).

The advantages of the present study include focusing on the mild and severe preeclampsia groups and the control group and matching the demographic variables in the three groups (mother's age, mother's education, body mass index and number of births) and also performing a multivariate analysis in order to control the probable confounding factors and multiplicity of factors under investigation. However, the small sample size might have affected the results and evaluation of relationships and the presence of significant relationships. New clinical methods with different approaches and the integration and combination of clinical knowledge and experience will play an important role in generalizing the results of evidence-based clinical studies regarding the treatment and survival of patients (26, 27).

The results of the present study showed that CA-125 is associated with the occurrence of preeclampsia (mild and severe) and can be helpful as a marker in the diagnosis of preeclampsia, especially its severe type. Moreover, due to the relationship between this marker and a wide range of other variables, paying attention to its serum level along with other paraclinical variables can help in better diagnosis and management of patients.

Suggestions: According to the results of the present study, it is suggested that in future studies, while increasing the sample size, and taking into account other effective factors, as well as measuring other important factors, other studies should be carried out in order to help clinical decisions.

Ethical Considerations: First of all, sufficient information was provided to all participants regarding the goals and stages of the research. Subjects were included in the study if they were willing. All collected information remained confidential. All stages of the project were carefully examined by the University Research Ethics Committee. None of the patients were charged any fees.

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