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EVALUATION OF SERUM LEVEL OF ANTI-MÜLLERIAN HORMONE IN PRE-ECLAMPSIA

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Pre-eclampsia is a multiorgan disease process characterized by hypertension and proteinuria after 20 weeks of gestation. The aim of the study was to assess the serum level of anti-Müllerian hormone (AMH) in pregnant women as a predictor for pre-eclampsia.

A case control study was carried out in Baghdad Teaching Hospital from 2020 to 2021. A sample of 192 pregnant women in the third trimester participated in the study and were divided into two main groups. The first group enrolled 96 normotensive pregnant women (control group), and the second group included 96 patients with pre-eclampsia (as a case group). The latter group was subdivided into 36 patients with mild to moderate pre-eclampsia, and 60 with severe pre-eclampsia. Blood samples were taken from each woman (case and control group) to test the AMH level, liver function tests, renal function tests, serum uric acid, serum lactate dehydrogenase (LDH), and complete blood picture. Urine samples were analyzed for albumin concentration and spot urine was assessed for protein-to-creatinine ratio.

Anti-Müllerian hormone levels were significantly lower in the case group than in the control group ($p < 0.001$). In the control group, the AMH level was 4.92 ± 1.79 ng/ml, while for mild to moderate pre-eclampsia group, it was 1.56 ± 0.21 ng/ml, and 0.42 ± 0.38 ng/ml for severe pre-eclampsia. Systolic and diastolic blood pressure showed significant higher values in the case group ($p < 0.001$). Gestational age, serum uric acid and serum albumin had moderate correlation with AMH in pre-eclampsia with significant association.

The level of AMH was decreased significantly in pregnant women with pre-eclampsia in comparison to healthy pregnancy.

Keywords: anti-Mullerian hormone, pre-eclampsia, blood pressure

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INTRODUCTION

Anti-Müllerian hormone (AMH) is a glycoprotein hormone primarily involved in growth differentiation and folliculogenesis. The expression of the AMH gene results in degeneration of Müllerian ducts during male sex development (1).

Recent years have allowed extensive research investigations examining the use of this hormone as a clinical measure for ovarian reserve and a predictor factor for responsiveness to gonadotropin-induced ovarian stimulation during ovulation induction (2). AMH has been proposed as a potential regulator of the cardiovascular system (3). Pregnancy causes the levels to drop because of ovarian suppression (4). Currently, it is unclear if the suppression of AMH is associated with placentation and whether elevated AMH levels might contribute to pre-eclampsia. Serum AMH levels markedly vary among women predisposed to pre-eclampsia. The findings indicated that elevated blood AMH levels correlate with a reduced chance of developing pre-eclampsia (5).

Even after accounting for factors such as age, hormonal contraceptive use and smoking, the ovarian reserve of women who have had pre-eclampsia is much lower than that of women whose pregnancies were normotensive. A connection was identified between hypertension at follow-up and C-reactive protein (CRP) levels, as well as serum AMH-based ovarian reserve status. These findings may corroborate the concept that vascular compromise serves as a catalyst in the ovarian aging process since pre-eclampsia, particularly early-onset pre-eclampsia, is seen as an indication of compromised vascular health (6).

The aim of the paper was to assess the serum level of anti-Müllerian hormone in pregnant women as a predictor of pre-eclampsia.

METHODS

Patients

A case control study was carried out in Baghdad Teaching Hospital between July 2020 and June 2021. A sample of 192 pregnant women in their third trimester participated in the study and were divided into two groups as follows: ninety-six patients with pre-eclampsia as a case group, which included 36 patients with mild to moderate pre-eclampsia, and 60 with severe pre-eclampsia. The second group involved 96 normal normotensive pregnant women as a control group.

The inclusion criteria comprised the following: 1. Women's age ranging from 18 to 39 years. 2. Singleton pregnancies in the third trimester (28–40 weeks). 3. Viable fetus.

The exclusion criteria were as follows: multiple pregnancies, gestational age < 28 weeks, history of other diseases (chronic hypertension, diabetes, thyroid disease, renal disease, liver disease, autoimmune disease, hematological diseases, cardiovascular diseases, and malignancy), any history of in-fertility, in vitro fertilization or ovulation induction, as well as the history of ovarian surgery.

Clinical assessment and data collection: The sample size included 192 pregnant women. The sample was divided in two groups. The case group consisted of 96 pregnant women with pre-eclampsia (36 patients with mild to moderate pre-eclampsia, and 60 with severe pre-eclampsia) diagnosed according to the National Institute for Health and Care Excellence (NICE) criteria 2019. The control group consisted of 96 pregnant women with similar gestational age without any complaint or complication. They all fulfilled the inclusion criteria.

A detailed history was taken from all pregnant women including maternal age, number of pregnancies, and parity. Gestational age was confirmed according to the last menstrual period, or with early pregnancy ultrasound when available, as well as abdominal and obstetrical ultrasound (Philips HD 11 ultrasound machine) performed by radiologist at the time of admission. The case group had signs and symptoms of pre-eclampsia.

General, abdominal, and obstetrical examinations were performed, followed by measuring blood pressure using mercury sphygmomanometer. The blood pressure measurement was accomplished with the patient in a seated position, back supported, and the right arm kept at the level of the heart.

Sample collection and analyses

Blood samples were collected in the labor ward at Baghdad Teaching Hospital and were sent for complete blood analysis in order to estimate the platelet count. In addition to renal function tests (blood urea nitrogen (BUN), serum creatinine (s. creatinine)), liver function tests–aspartate amino-transferase (AST) and alanine transaminase (ALT), serum albumin (s. albumin), serum uric acid (s. uric acid),

serum lactate dehydrogenase (s. LDH) were also checked. Midstream urine samples were collected for albumin measurement, and spot urine specimens were analyzed for the protein-to-creatinine ratio.

Samples of venous blood were taken from each woman (case and control). 5 mL were collected into plain tubes, and each tube was labeled with name of the participant to measure the anti-Müllerian hormone level. The samples were allowed to clot, centrifuged for 10 min at 3000 rpm, and then stored at -20 °C and analyzed by AMH/MIS ELISA KIT, (Bioactive Diagnostica, Germany).

A second tube with five milliliters of venous blood was collected from the same participants to detect the biochemical parameters (AST, ALT, s.albumin, BUN, s. creatinine, s. uric acid, s. LDH, and platelet count). All these tests were done in laboratory of Baghdad Teaching Hospital.

For general urine examination, midstream samples were collected for albumin measurement, while spot urine specimens were obtained to assess the protein-to-creatinine ratio.

Ethical consideration

The study was approved by the Ethical Committee in the College of Medicine, University of Baghdad in accordance with the Declaration of Helsinki for clinical studies (registration no–526, May 11, 2020). An informed written consent was obtained from all participants.

Statistical analysis

We used the SPSS application (version 23), to evaluate the gathered data. Percentages and frequencies for the qualitative variables and measures of dispersion (standard deviation) were used, as well as the central tendency for quantitative variables. A Chi-square test was used for the inferential statistics, with a significance level of $p \leq 0.05$.

According to statistics, the R-value may be anywhere from zero (showing no connection at all) to one (perfect correlation), with values closer to one indicating a higher link. In addition, a signed negative R denotes an inverse correlation and a non-signed positive denotes R direct correlation.

RESULTS

The mean age of patients in mild to moderate pre-eclampsia was 26.02 ± 5.1 years, and in severe type of pre-eclampsia, it was 25.94 ± 5.1 years, whereas in the control group, the mean age was 26.01 ± 4.1 years. There were no significant differences between groups (p = 0.7), as shown in Table 1.

The mean of pregnancies was 3.1 ± 1.7 in mild to moderate pre-eclampsia, 3.1 ± 1.2 in severe type of pre-eclampsia, 3.2 ± 1.4 for the control group with no significant differences (p value = 0.5). For the parity mean in the studied groups, the mean in mild to moderate pre-eclampsia was 2.4 ± 0.8, in severe type it was 2.4 ± 0.6, and in the control group, it was 2.3 ± 0.2 with no significant difference between the studied groups (p = 0.2).

Table 1. *Relation between demographic parameters in the studied groups*

Variables (mean ± SD)	Pre-eclampsia (n = 96)		Control (n = 96)	P-value
	Mild to moderate (n = 36)	Severe (n = 60)		
Age (years)	26.02 ± 5.1	25.94 ± 5.1	26.01 ± 4.1	0.7
Pregnancy	3.1 ± 1.7	3.1 ± 1.2	3.2 ± 1.4	0.5
Parity	2.4 ± 0.8	2.4 ± 0.6	2.3 ± 0.2	0.2
GA (weeks)	34.39 ± 2.1	34.31 ± 2.2	34.4 ± 2.7	0.7
Systolic BP	141.7 ± 20.8	167.7 ± 20.8	105 ± 15.2	< 0.001
Diastolic BP	102.3 ± 3.7	121.3 ± 10.7	72.4 ± 9.9	< 0.001

**n = number, *SD = standard deviation, *p = probability, *GA = gestational age, *BP = blood pressure*

Table 2. *Relation between AST, ALT, BUN, s. creatinine, s. uric acid, s. albumin, level of LDH, platelets, and protein/creatinine ratio parameters in the studied groups*

Variables (mean ± SD)	Pre-eclampsia (n = 96)		Control (n = 96)	P-value
	Mild to moderate (n = 36)	Sever (n = 60)		
AST	29.83 ± 10.6	83.3 ± 12.9	18.4 ± 5.2	< 0.001
ALT	34 ± 4.2	67.4 ± 13.8	17.2 ± 3.8	< 0.001
BUN (mg/dl)	24.3 ± 6.2	39.2 ± 19.7	18.2 ± 6.7	< 0.001
S. creatinine (mg/dl)	1.1 ± 0.5	1.5 ± 0.32	0.5 ± 0.2	< 0.001
S. uric acid (mg/dl)	7.5 ± 0.8	9.7 ± 2.4	4.1 ± 1.2	< 0.001
S. albumin (g/dl)	2.1 ± 0.31	1.61 ± 0.05	4.1 ± 0.035	< 0.001
LDH (U/L)	408.5 ± 128.1	586.6 ± 342.8	299.2 ± 112.1	< 0.001
Platelets	121.6 ± 56.4	110 ± 26.19	237.7 ± 28.2	< 0.001
Protein/Cr Ratio (mg/dl)	1.9 ± 0.62	3.06 ± 1.6	0.22 ± 0.05	< 0.001

Abbreviations: AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; BUN = Blood Urea Nitrogen; LDH = Lactate dehydrogenase; Protein/Cr = Protein/Creatinine.

The mean of gestational age was 34.39 ± 2.1 weeks in mild to moderate pre-eclampsia, 34.31 ± 2.2 weeks in severe type of pre-eclampsia, 34.4 ± 2.7 weeks in the control group with no significant differences (p = 0.7).

Systolic blood pressure mean was 141.7 ± 20.8 in mild to moderate pre-eclampsia, 167.7 ± 20.8 in severe type of pre-eclampsia, 105 ± 15.2 in the control group, with significant difference (p < 0.001).

As for diastolic blood pressure, the mean was 102.3 ± 3.7 in mild to moderate pre-eclampsia, 121.3 ± 10.7 in severe type of pre-eclampsia, 72.4 ± 9.9 in the control group with high significance (p < 0.001).

A significant difference (p < 0.001) was seen in AST levels. They were 29.83 ± 10.6 in the mild to moderate group and 83.3 ± 12.9 in the severe pre-eclampsia group, compared to 18.4 ± 5.2 in the control group. ALT levels were significantly different in the groups with mild to moderate pre-eclampsia (34 ± 4.2) and severe preeclampsia (67.4 ± 13.8), compared to the control group (17.2 ± 3.8) (p < 0.001), as shown in Table 2.

There was a significant difference (p < 0.001) in blood urea nitrogen (BUN) levels between the mild to moderate group (24.3 ± 6.2 mg/dl) and the severe pre-eclampsia group (39.2 ± 19.7 mg/dl), while in the control group the level was 18.2 ± 6.7 mg/dl. The control group had the level of s. creatinine of 0.5 ± 0.2 mg/dl, while the mild to moderate and severe pre-eclampsia groups had levels of 1.1 ± 0.5 mg/dl and 1.5 ± 0.32 mg/dl, respectively, with a significant difference (p < 0.001). In the mild to moderate group, the level of s. uric acid was 7.5 ± 0.8 mg/dl, in the severe pre-eclampsia group it was 9.7 ± 2.4 mg/dl, and in the control group it was 4.1 ± 1.2 mg/dl, with a very significant difference (p < 0.001).

There was a significant difference (p < 0.001) in the levels of s. albumin, which were 2.1 ± 0.31 g/dl in the mild to moderate group and 1.61 ± 0.05 g/dl in the severe pre-eclampsia group, compared to 4.1 ± 0.035 g/dl in the control group.

There was a significant difference (p < 0.001) in the levels of LDH between the control group (299.2 ± 112.1) and the groups with mild to moderate pre-eclampsia (408.5 ± 128.1) and severe pre-eclampsia (586.6 ± 342.8). There was a very significant difference (p < 0.001) in the platelet mean between the mild to moderate group (121.6 ± 56.4) and the severe pre-eclampsia group (110 ± 26.19), and between the control group (237.7 ± 28.2).

There was a significant difference (p < 0.001) in protein/creatinine ratio between the control group and the groups with mild to severe pre-eclampsia, with the former having a ratio of 1.9 ± 0.62 and the latter having a ratio of 3.06 ± 1.6.

The level of AMH in the control group was 4.92 ± 1.79 ng/ml, while for mild to moderate pre-eclampsia group, it was 1.56 ± 0.21 ng/ml, and 0.42 ± 0.38 ng/ml for severe pre-eclampsia with highly significant decrease in the case group than that in the control group (p < 0.001), as shown in Table 3.

Table 4 and Figure 1 show the validity test and ROC curve of maternal AMH in pre-eclampsia, respectively. The validity test of the level of maternal AMH at the cutoff value (≤ 0.651 (ng/ml) to detect pre-eclampsia in ROC (AUC = 0.9) shows the following: sensitivity was 92%, specificity 82%, NPV 91%, PPV 88%, and the accuracy of the test was 87%.

Table 3. *The association between the studied groups regarding AMH*

Variables (mean ± SD)	Control (n = 96)	Pre-eclampsia (n = 96)		P-value
		Mild to moderate (n = 36)	Sever (n = 60)	
AMH (ng/ml)	4.92 ± 1.79	1.56 ± 0.21	0.42 ± 0.38	< 0.001

Abbreviations: AMH = Anti-Müllerian hormone.

Table 4. *Validity test of maternal AMH in pre-eclampsia*

Cut off value of AMH (ng/ml)	Sensitivity	Specificity	NPV	PPV	Accuracy
≤ 0.651	92	82	91	88	87

Abbreviations: AMH = Anti-Müllerian hormone; NPV = negative predictive value; PPV = positive predictive value.

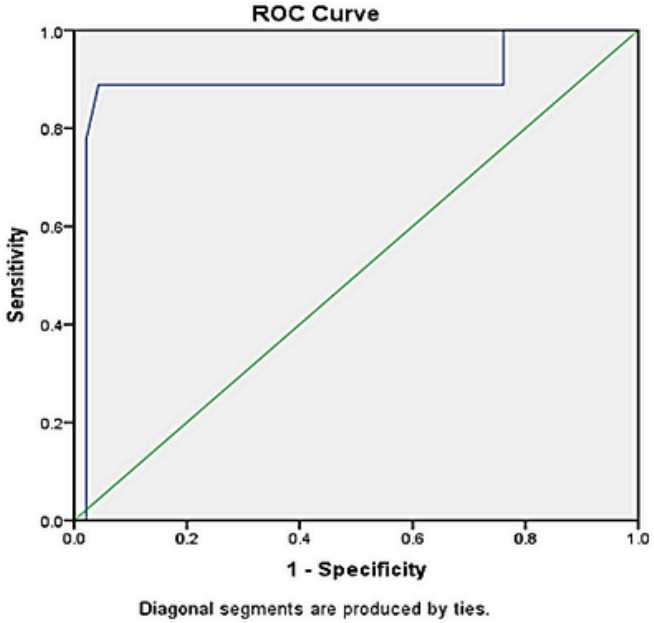

Figure 1. *Receiver operating characteristics (ROC) curve for AMH in pre-eclampsia (AUC = 0.9)*

Regarding the correlation between AMH and different parameters in pre-eclampsia group, the gestational age, s.uric acid and s.albumin have moderate correlation with AMH in pre-eclampsia with significant association ($p \leq 0.05$), as shown in Table 5.

Table 5. *Correlation between AMH and different parameters in pre-eclampsia group*

Variables	AMH (ng/ml)	
	Pre-eclampsia	
	r	P-value
Age (years)	0.193	0.284
Parity	0.0352	0.31
GA (weeks)	0.625	0.01 [S]
S. uric acid (mg/dl)	0.467	0.003 [S]
S. albumin (g/dl)	0.382	0.01 [S]
Pregnancies	0.156	0.5
LDH (U/L)	0.164	0.407
BUN (mg/dl)	0.119	0.452
ALT	0.038	0.841
S. creatinine	0.02	0.112
AST	0.13	0.5

Abbreviations: GA = gestational age; LDH = Lactate dehydrogenase; BUN = Blood Urea Nitrogen; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; r= correlation coefficient.

DISCUSSION

Despite AMH's potential as a surrogate indicator of ovarian reserve, it's role in pregnancy in Iraq has not been investigated in any research up to date. In this study, the AMH level and its effect on pre-eclampsia was investigated.

In the current study, the mean age, pregnancies, parity, and gestational age of women in both pre-eclampsia and controls group were nearly similar with no significant differences, while the systolic and diastolic BP were increased significantly in the case group compared to those in the healthy pregnancy group.

Women with a history of pre-eclampsia had a substantially lower blood AMH level compared to normotensive women in the third trimester. The same conclusion was reached by Yarde F et al. They proposed that pulmonary embolism (PE) is indicative of reduced vascular health, which may serve as a causal factor in the onset of early ovarian aging (5).

Tokmak A et al. shown that AMH levels are reduced in pre-eclamptic individuals compared to those without the condition (7). Research conducted by Shand A et al. in 2014 showed a modest correlation between low AMH levels and gestational hypertension, particularly in women with a history of pre-eclampsia and diminished ovarian reserve. Shand AW et al. discovered that women with pregnancy-induced hypertension have reduced AMH levels throughout the first trimester; however, no correlation exists between low AMH levels and negative pregnancy outcomes. Their conclusion indicated that pregnancy outcomes are often favorable in women with low first trimester AMH levels (8).

Mathyk et al. observed that AMH levels are diminished in pre-eclamptic pregnant women throughout the third trimester, and there exists a negative association between serum AMH levels and systolic blood pressure (9). Jamil et al. revealed that hypertensive diseases of gestation and ovarian age were correlated with decreased blood AMH levels. Furthermore, they proposed that the biomarker is essential in identifying vascular disorders (10).

The results of this study are not in agreement with a study done by Bhide et al (11). The study found that AMH increased in patients with previous history of severe pre-eclampsia group more than that in pregnancies without history of pre-eclampsia but with no significant difference. This may be attributed to the differences in study design and patient population. The research by Bhide P et al. assessed AMH levels post-delivery across a follow-up period of six months to five years, while this study evaluated AMH during the third trimester of pregnancy. The average age of women and the duration from the index pregnancy in both studies varied, indicating a reduced maternal age at index pregnancy in that research.

Agabain et al. investigated the maternal serum anti-Müllerian hormone level in Sudanese women with pre-eclampsia and healthy control (12). The results showed no significant difference in age, parity, and gestational age. These findings agree with the current study results. Regarding the AMH level between the studied groups, there was no significant difference in the previous study, and this is not in agreement with this study finding. AMH level was not associated with age, parity, gestational age, and BMI.

The current study revealed that there is a significant correlation between AMH and pre-eclampsia after adjustment of age and other baseline characters.

Previous studies investigated the level of AMH in pre-eclampsia and normotensive women. The current study

showed that the AMH level is decreased in pre-eclampsia and it is lower in severe than in mild to moderate cases. This decline may reflect underlying vascular dysfunction—a hallmark of pre-eclampsia—which is increasingly recognized as a contributing factor to accelerated ovarian aging and diminished ovarian reserve.

Regarding the validity test of maternal AMH level at the cutoff value of ≤ 0.651 ng/ml to detect pre-eclampsia in ROC (AUC = 0.9), the sensitivity was 92%, specificity 82%, NPV 91%, PPV (88%), while the accuracy of the test was 87%. This indicates that AMH is a good predictor for pre-eclampsia. Results from the study by Tokmak A et al. showed that the cut-off value for AMH was 0.365 ng/ml, and the area under the curve (AUC) was 0.590 (95% CI: 0.469-0.710; p = 0.149). The sensitivity for AMH was 67.4%, and the specificity was 47.1%. It was concluded that AMH did not serve as a strong discriminant in patients who were at risk of eclampsia. This might be because there is no statistically significant difference between AMH and perinatal outcome or maternal complications (7).

The level of AMH was decreased significantly in pregnant women with pre-eclampsia in comparison to healthy pregnancy.

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Competing interest

The authors declare no relevant conflicts of interest.

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