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Original Article

Serum anti mullerian hormone and renalase levels in predicting the risk of preeclampsia

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ABSTRACT

Objective: The aim of the study was to explore the association of serum AMH and Renalase with the risk of preeclampsia thereby assessing them as screening tools, reducing the risk of gravid consequences of preeclampsia.

Materials and methods: This cross-sectional study recruited n = 95 pregnant women between 14 and 32 gestational weeks. They were categorized as a) women with gestational hypertension (n = 45); b) women with pre-eclampsia (n = 20) and c) normotensive pregnant women (n = 30) according to the ACOG criteria. Anthropometrics data and blood and urine samples were collected. AMH and Renalase levels were measured by ELISA assay.

Results: The mean age of study cohort was 27.3 ± 6.2 year and weight was 65.1 ± 14.1 kg. Blood pressures were significantly higher in pre-eclamptic patients versus both the gestational hypertensive females and controls ($p < 0.05$). AMH was found to be significantly higher in controls but no difference was observed between gestational hypertensive and pre-eclamptic patients. No difference was seen for serum Renalase among the three groups ($p > 0.05$). AMH showed a negative weak correlation with diastolic blood pressure ($r = -0.272$; $p = 0.008$) that remained significant even after adjustment ($r = -0.236$; $p = 0.023$) whereas Renalase did not show any difference ($r = -0.051$; $p > 0.05$). Females with low levels of AMH were 1.07 times at risk of developing hypertension even after adjustment for age and BMI ($p < 0.05$).

Conclusion: Low AMH levels may lead to hypertension in pregnancy suggesting a role in detecting vascular diseases as well as its effect on ovarian aging. However, further research is required to establish a causal relationship.

Introduction

Preeclampsia (PE) is a maternal disorder and clinically defined as combination of hypertension and proteinuria after 20th week of pregnancy [1]. It effects 5–6% of pregnancies and is a major cause of morbidity and mortality for mother and child [2]. It can also lead to hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome [1]. Previously different screening tests were reported for predicting many pregnancy related outcomes, such as maternal serum placental protein-13 (PP-13), pregnancy-associated plasma protein-A (PAPP-A) and maternal serum placenta growth factor [3]. It is important to note that both PE and cardiovascular disorders share common risk factors such as chronic hypertension, obesity, and insulin resistance. Furthermore, association between early menopause and vascular disease has also been proved. Sub-fertile women with reduced ovarian reserve, appear to have an increased rate of vascular complications in a future pregnancy [4]. Similarly, in women with premature menopause, assisted reproduction has a similar vascular complication in pregnancy suggesting a link between ovarian physiology and cardiovascular health [5].

The anti-Mullerian hormone (AMH) is a member of the tissue growth factor beta superfamily. Main source of AMH is ovary but placenta may also produce AMH [6]. In females, the production of AMH correlates with rise in the number of growing ovarian follicles [7]. AMH has been found to modulate ovarian response to follicular

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stimulating hormone (FSH) but with unknown mechanisms. Furthermore, AMH receptors were also documented in other places like uterus and breast, proposing its physiological role which are not known at this time [8]. An interesting fact regarding AMH is that it can be used to reliably predict ovarian reservoir as it is produced by the granulosa cells of small antral and pre-antral follicles. Serum level of AMH corresponds to the size of the pool of these follicles in animal models as well as in the human ovary [9]. Evidence based studies show reduced AMH levels in pregnancies complicated by hypertensive disorders [10]. Association of lower levels of serum AMH with advancing maternal age have also been documented previously [11]. Furthermore, advancing age is a risk factor for adverse pregnancy outcomes such as stillbirth, pre-eclampsia, gestational diabetes and gestational hypertension [12]. However, for pre-eclamptic pregnancies, discriminated results of low or high AMH levels have been documented [13].

Renalase is an enzyme that degrades circulating catecholamines. Human renalase is 342 amino acids long, and made up of a signal peptide, an amine oxidase domain and FAD-binding region [14]. Renalase circulates in the blood in an inactive form called as pro-renalase, which is secreted by kidney. Pro-renalase has no amine oxidase activity, and it is converted to renalase by increased catecholamines level and high blood pressure. Renalase decreases the blood pressure by degrading the catecholamines including dopamine, epinephrine and norepinephrine [15]. This cyclical activation of renalase and the resultant degradation of catecholamines helps control blood pressure in a normal individual [16]. Hence, renalase seem to indirectly regulate the cardiac function by controlling the sympathetic activity and blood pressure [17]. Additionally, ongoing studies have revealed a strong link between renalase, hypertension and ischemic heart diseases [18]. Li, X., et al. have observed that restricted renal blood flow resulted in down regulation of renalase and subsequent increase in catecholamine concentration [19]. Recently, some studies were conducted to accurately determine the levels of renalase in PE and also to speculate its predictive role [20]. Yilmaz and group reported low renalase levels in pre-eclamptic pregnancies relating to the decreased glomerular filtration rate and kidney function which are crucial organs affected by PE [21]. Furthermore, interesting facts have been documented in previous studies about renalase's expression in mouse gonads such as expression in testes, oocytes, granulosa, interstitial and luteal cells of ovary, showing a possible connection of its activity with reproduction [22,23]. The shared expression of both renalase and AMH and their possible involvement in reproductive health urged us to explore the possible role in pregnancy related disorders. To the best of our ability, we were unable to find any research that studied both biomarkers in any reproductive health malady including pre-eclampsia. Keeping this in mind, we designed a study with the aim to explore the association of serum markers AMH and Renalase with the risk of preeclampsia in our population. We compared the levels of both these markers with that of normotensive pregnant females and pregnancy induced hypertensive females. The goal of our study was to explore biomarkers that can be used as screening tools that could potentially help reduce the risk of gravid consequences of preeclampsia.

Materials and methods

This cross-sectional study was conducted at the Aga Khan University in collaboration with Basic Medical Science Institute, Jinnah Postgraduate Medical Center Karachi, Pakistan with the approval from the concerned ethical committees (ERC-4523-BBS-16 and F.2–81/GENL-2017-IRB/15107/JPMC). The study subjects were selected via convenient random technique from the antenatal clinics and also from the labor room of a tertiary care hospital in Karachi, between the periods of January to December 2017. Informed written consent was obtained from all participants of the study. Women having history of any chronic systemic disease, such as cardiovascular, urogenital, immunological, endocrinological and renal disease were excluded. Women with previous history of complication of pregnancy such as abortion, intra uterine fetal demise, antenatal bleeding was also not included in the study.

A total of 95 pregnant women, between the gestational ages of 14–32 weeks, were categorized into 3 groups according to their health status: Group I: women with gestational hypertension ($n = 45$); Group II: women with pre-eclampsia ($n = 20$); Group III: normotensive pregnant women ($n = 30$). Pre-eclampsia was diagnosed according to American College of Obstetricians and Gynecologists (ACOG) criteria 2013 as sudden onset of high systolic blood pressure (140 mmHg or more) or diastolic blood pressure (90 mmHg or more) confirmed by two readings 4–6 h apart, with ± proteinuria of 0.3 gm/l or ≥1 + proteinuria on urine dipstick in the absence of urine infection, after 20 weeks of gestation in a previously normotensive woman. Gestational hypertension was taken as blood pressure of 140/90 mmHg or greater at least two readings 4 h apart, appears after 20 weeks of gestation without proteinuria [24]. Patient data regarding maternal age, gestational age (calculated by first trimester ultrasound), systolic and diastolic blood pressure readings, weight and height for BMI calculation, reproductive history and medical history was collected. During the antenatal visit, 10 ml of maternal venous blood was collected, serum was separated by centrifugation at 4000 rmp for 15 min and stored at −80 °C until used for estimation of anti mullerian hormone (AMH) and serum Renalase by commercially available ELISA kits (cat number 10011 and G7203 from GloryScince Co. Ltd, USA). Proteinuria was estimated through urine dipstick method. Statistical software SPSS version 21.0 was used for data recording and analysis. A descriptive statistical analysis of continuous variables was performed. Statistical comparisons were performed by using Mann Whitney-U-test for quantitative variables, chi-square or Fisher exact test for categorical variables. Pearson correlation and regression analysis were conducted to identify the correlation of biomarkers with hypertension. In all statistical analysis only p-value < 0.05 was taken as significant.

Results

The mean age of study cohort was 27.3 ± 6.2 year and weight was 65.1 ± 14.1 kg. On average the women were between 25.25 ± 7.3 weeks of gestation (Table 1). Table 2 compares the biophysical and biochemical variables of the cohort sub grouped according to the ACOG criterion. Diastolic as well as systolic blood pressures were significantly higher in pre-eclamptic patients as compared to both the gestational hypertensive females and controls ($p < 0.05$). Serum AMH was found to be significantly higher in

Table 1
Descriptive statistics of the study cohort.

Variables	Study Population Mean ± SD n = 95
Age (years)	27.3 ± 6.2
Weight (kg)	65.1 ± 14.1
BMI (kg/m^2)	25.49 ± 5.26
Gestational age (week)	25.25 ± 7.3
Diastolic BP (mmHg)	90 ± 16.9
Systolic BP (mmHg)	136.78 ± 24.22
Serum Renalase (ng/ml)	24.58 ± 2.37
Serum AMH (ng/ml)	1.04 ± 1.6

Where: AMH is Anti Mullerian hormone. BP is blood pressure. Data expressed as Mean ± S.D.

Table 2
Physical and Biochemical characteristics of study population stratified on the basis of blood pressure.

	Controls n = 30 Mean ± SD	Gestational hypertension n = 45 Mean ± SD	Preeclampsia n = 20 Mean ± SD
Age (year)	25.9 ± 5.3	27.2 ± 5.14	29.7 ± 9.1
Weight (kg)	67.2 ± 15.7	64.8 ± 14.8	66.2 ± 13.34
BMI (kg/m^2)	25.66 ± 5.45	25.08 ± 5.30	26.18 ± 5.07
Gestational age	24.3 ± 6.4	26.47 ± 3.3	25.25 ± 5.9
Diastolic BP (mmHg)	73.0 ± 13.17	95.1 ± 13.4	104 ± 10.9*
Systolic BP(mmHg)	114.3 ± 15.01	143.4 ± 11.6*	155.5 ± 14.7*
Renalase (ng/ml)	23.31 ± 1.38	27.34 ± 0.77	21.08 ± 0.89
AMH (ng/ml)	1.62 ± 2.29	0.73 ± 1.29	0.85 ± 1.07*
Urine Protein Absolute Count (%)			
0	26 (86.7)	40 (88.9)*	–
1+	4 (13.3)	5 (11.1)	–
2+	–		16 (80.0)*
3+	–	–	4 (20.0)*

Where: AMH is Anti Mullerian hormone. Data expressed as Mean ± S.D and absolute count with percentage in parenthesis. Mann Whitney U test and chi square test were used to compare the difference between groups and $p < 0.05$ considered significant. * means in comparison with controls.

controls but there was no significant difference while comparing gestational hypertensive and pre-eclamptic patients. No significance was found in the difference between serum Renalase among the three groups ($p > 0.05$). Urine dipstick assay for protein showed that 95% subjects with PE had high protein positivity in urine sample whereas 88.9% of GDM-HTN subjects showed no protein in urine.

AMH showed a negative weak correlation with diastolic blood pressure ($r = -0.272$; $p = 0.008$) that remained significant even after adjustment for age and BMI ($r = -0.236$; $p = 0.023$) whereas Renalase did not show any difference ($r = -0.051$; $p > 0.05$). Next we applied binary logistic regression to estimate the odds ratio of the effect of age and BMI on the serum AMH levels in predicting hypertension during pregnancy. In both, the unadjusted as well as adjusted mode for age and BMI results showed that females with low levels of AMH were 1.07 times at risk of developing hypertension ($p < 0.05$) (Table 3).

Discussion

Pre-eclampsia is considered to be the leading cause of maternal and neonatal morbidity and mortality. Maternal cardiovascular system, placenta and the fetus are susceptible to organ damage by pre-eclampsia. Furthermore, women with a history of preeclampsia are at an increased risk of chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism and impaired memory [25]. AMH role as a marker of ovarian reserve and ovarian aging has been well established by previous studies [26–29], however its role in PE is still not well understood.

AMH levels have been used in detecting the role of vascular diseases as a causative factor of ovarian aging, particularly in women with past preeclampsia [30]. In turn, ovarian aging has been recognized as a source of increase incidence of cardiovascular disease (CVD) [31]. Moreover, detection of AMH receptors on cardiac tissue proposes the linkage of AMH with cardiac physiology [32]. In our study, we found reduced levels of AMH in pre-eclamptic and gestational hypertensive subjects thus signifying its role in prediction of ovarian aging, which is a strong risk factor for development of preeclampsia. Previous studies have shown similar results with AMH levels found to be lower in pre-eclamptic patients than in normal patients [33]. Low AMH levels were found to have a moderate association with gestational hypertension, and women with a history of preeclampsia along with low ovarian reserve [10,30]. However, another study showed no difference in AMH levels between women with preeclampsia and controls [13].

Table 3
Logistic regression analysis for AMH.

Variables	Unadjusted	p value	Adjusted for Age and BMI	p value
	OR (95% C.I)		OR (95% C.I)	
AMH	1.076 (1.010–1.145)	0.023	1.073 (1.007–1.143)	0.029

Where: Anti mullerien hormone (AMH). $p < 0.05$ considered significant.

There was no significant difference in the mean Renalase levels of the three groups in our study. These findings are not consistent with those presented by Yilmaz et al. [21] who suggested that high blood pressure in pregnant females were associated with low serum Renalase levels. They also proposed a direct relation of serum renalase with glomerular filtration rate and an inverse relationship with blood pressure levels. Recent study by Stoumpos et al. showed that reduced AMH levels could be a predictor of preeclampsia in pregnant women with a history of renal disease [34]. One of the possible explanations for the observed difference in results could be attributed to the fact that we were unable to measure and control for the glomerular filtration rate in our study subjects. It might be possible that all women included in our study had a glomerular filtration rate within normal range therefore had normal circulating Renalase. A second explanation for this difference in findings could be that the participants in the 'Gestational hypertension' and the 'pre-eclampsia' group were hypertensive for only a few months with little or no impact on their kidney function. In comparison to the conclusions drawn by Yilmaz et al. and Stoumpos et al., Wang et al. has stated that there was no correlation in serum Renalase levels and high blood pressure or arterial stiffness in the Chinese Han population with normal renal function [35]. Although the authors excluded all cases of secondary hypertension, their results were consistent with the results of ours.

Obesity is considered a risk factor for pre-eclampsia [36], being a prime factor for development of hypertension, causes increased sodium reabsorption through renal tubules [37]. Most of our subjects were overweight according to the South Asian guidelines; hence this finding supports the association of weight with hypertension. Furthermore, obesity also seem to affect serum AMH levels in women of reproductive age, and is also a cause of an–ovulatory cycles with abnormal uterine bleeding, endometrial hyperplasia/cancer, infertility and other pregnancy complications such as

miscarriage or preeclampsia [38]. Therefore, we conducted logistic regression to assess the effect of age and BMI; females with low levels of AMH were 1.07 times at risk of developing hypertension even after adjustment for age and BMI ($p < 0.05$). Though we report lower AMH levels and normal Renalase levels in pre-eclamptic females and its independent association with blood pressure, further studies needs to be conducted to establish a causal relationship.

Conclusion

In our study population, hypertensive disorders of gestation and ovarian aging were associated with low serum AMH levels, suggesting that the biomarker has a role in detecting vascular diseases. However, no inference can be drawn for the same regarding Serum Renalase levels. Further work up is needed to establish a causal and correlational relationship.

Author contribution

ZJ and SSF were involved in study design and concept, questionnaire design, data analysis, data interpretation and manuscript writing. EB, RA and FS performed the literature search and drafting of the manuscript. SS was involved in data collection and manuscript writing.

Conflict of interest statement

All authors declare that they have no potential conflict of interest.

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