Research article

A study protocol of maternal serum anti-mullerian hormone levels in antenatal women as predictor of preeclampsia

Krutika Bhalerao*, Sandhya Pajai

Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi, Wardha, Maharashtra, India

ABSTRACT

Pre-eclampsia is a pregnancy disease that affects many systems in women who were previously normotensive and develop high blood pressure after 20 weeks of pregnancy. This study aims to see if serum anti-malarial hormone levels between 11 and 14 weeks of pregnancy have any link to preeclampsia, and if so, what function it plays in the pathogenesis and prevention of preeclampsia and subsequent cardiovascular abnormalities later in life. This study will be conducted on 350 antenatal women who will be subjected for serum anti-malarial hormone (AMH). Women with altered values will be divided into two groups and will be followed till 7 days postpartum for development of pre-eclampsia and pregnancy outcome. Various studies have been carried out in developed countries have proven the association between AMH and preeclampsia but also the long-term effect on the cardiovascular system. This study will emphasize the role of AMH in a developing country like India where the burden of pre-eclampsia is high and one of the third important cause of maternal mortality. The prospective outcomes of this will help in prediction of preeclampsia and timely treatment with low dose aspirin which may prevent life threatening complications.

Keywords: Anti-Mullerian hormone, preeclampsia, Antenatal, women, Predictor, fetal and maternal outcome.

Received - 20-10-2021, Accepted- 02-05-2022

Correspondence: Dr. Krutika Bhalerao* krutika.bhalerao@yahoo.in, Orcid Id: https://orcid.org/ 0000-0001-6979-7052

INTRODUCTION

Preeclampsia is a disease of pregnancy which affects various organs of those who were previously normotensive but now have a raised blood pressure of more than 140/90 mm Hg and substantial proteinuria after 20 weeks of pregnancy [1,2]. Preeclampsia affects about 5% - 8% of all pregnant women [3]. Preeclampsia is believed to affect 8-10% of pregnant women in India. According to the WHO, hypertensive diseases, particularly preeclampsia, are the second leading cause of maternal death (14%) after hemorrhage (27%) [4].

Preeclampsia before 34 weeks of pregnancy is termed early onset preeclampsia and is caused by flaws in subsequent invasion of the vessel by trophoblastic tissue, which renders the vessel insensitive to pressure drugs, and thrombosis, which affects the thromboxane/PGI2 ratio, resulting in vasoconstriction. Late-onset preeclampsia is one that develops after 34 weeks of pregnancy and is caused by maternal endothelium and vascular damage linked to oxygen free radicals and vasoconstriction. Both forms of thrombosis are present [5,6,7]. Preeclampsia with early onset has a worse prognosis than preeclampsia with late onset. Placental abruption, Eclampsia, Postpartum hemorrhage, disseminated intravascular coagulation, preterm labour, intrauterine growth restriction, and intrauterine mortality are all complications of preeclampsia.

Various causes, such as genetic, vascular, immunological, and oxidative stress, have been proposed in an etiology of preeclampsia, although the results are mixed. Many factors, such as serum uric acid, serum triglycerides, uterine artery doppler, PAPP-A, placental growth factor, and others, have been explored for the prediction of preeclampsia, but the results have been inconsistent [8,9]. Preeclampsia has recently been linked to a biomarker called maternal serum anti-Mullerian hormone. A glycosylated glycoprotein Anti-Mullerian hormone (AMH) is released from granulosa cells in the ovary [10]. As the pregnancy progresses, AMH levels decrease, and levels rise again in puerperium. Anti-Mullerian hormone levels are low during pregnancy due to elevated estrogen levels, hence prenatal women should be tested between 11 and 14 weeks of pregnancy. As AMH is associated with placenta and cardiac muscle its role is proposed in preeclampsia and cardiovascular risk in later life.

Preeclampsia patients have low amounts of AMH in their blood. Anti Mullerian Hormone (AMH) is protective for endothelium, and the presence of AMH receptors on the placenta and cardiac tissues suggests that vascular problems associated with preeclampsia may have an impact on ovarian ageing, increasing cardiovascular risk in
women with preeclampsia later in life [11,12].

Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality, as well as increased cardiovascular alterations and risk in women later in life. As a result, early detection and appropriate management of these problems are essential. This will be useful in determining its function in the pathophysiology of preeclampsia and subsequent cardiovascular hazards later in life.

Some researchers discovered that biomarker serum AMH levels in pre eclamptic prenatal women were lower (2.001.87 g/L vs. 2.262.56 g/L) at 11-14 weeks of pregnancy as compared to women with normal blood pressure [13]. Few studies have been published that suggest an inconsistent link between maternal serum AMH levels at 11-14 weeks of pregnancy and preeclampsia [14-16]. There is paucity of Indian data regarding anti Mullerian hormone levels as a predictor of preeclampsia. The study aims at finding the association between Serum Anti Mullerian hormone levels at 11-14 weeks of gestation and development of Preeclampsia.

The primary objective of this research is to correlate the occurrence of preeclampsia in women with normal and altered serum antimullerian hormone levels at 11-14 weeks of gestation. While the secondary objectives will be comparing the Fetal and Maternal outcome in women with normal and altered serum Anti-Mullerian Hormones level as well as to correlate the pregnancy outcome in normal and low levels of AMH in preeclampsia patients.

MATERIALS AND METHODS
The enrolment and assessment of this study will be followed as standard protocol for intervention trial. The present study will be done in the outdoor and indoor department of Obstetrics and Gynecology of a tertiary care hospital situated in central India. The study design for this research will non-blinded randomized control trial. The subjects were selected for study by convenience sampling. The ethical approval is obtained from Institutional ethical committee of Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, India with the reference no DMIMS (DU) IEC/2020-21/9341.

350 antenatal women between 11-14 weeks of gestation with singleton pregnancy and willing to deliver at the same place and stay for 7 days will be recruited after informed consent and counselling.

Pregnant women with systemic disorders such as cardiovascular, kidney, immunological, endocrinological disease, diabetes mellitus, past history of preeclampsia, abortion, intra uterine fetal demise, multiple pregnancy hydatidiform mole, women <11 weeks gestation and >14 weeks gestation will be excluded from the study.

Evaluation
Sociodemographic particulars of antenatal women will be noted such as name, age, address, husbands’ occupation, contraception, spontaneous or IVF conception, education level, diet habits, age of marriage, premonitory warning symptoms of preeclampsia, last menstrual period, obstetric history including gravida, para, abortions, history of hypertensive disorders, diabetes mellitus, intrauterine growth restriction, prematurity, pregnancy loss, previous neonatal deaths will be asked. Last menstrual period (LMP) and first trimester ultrasound will be used for calculation of gestational age. History of diabetes, thyroid disorder and autoimmune disorders will be asked in past history. Any specific surgical history, family history, nutrition history will be asked for. Weight, pulse, pedal oedema, thyroid enlargement etc. will be clinically seen. Following the guidelines to measure blood pressure, BP will be taken every time and MAP (Mean Arterial blood Pressure) calculation will be done in all trimesters. Gestational age of women will be confirmed by last menstrual period, menstrual cycle regularity, clinical examination and/or early ultrasound scan. Routine antenatal investigations as, Complete blood count, peripheral smear, HIV, HbSAg, VDRL, blood group, Rh Type hemoglobin electrophoresis, Sc-rum TSH, Post glucose blood sugar, Urine for sugar, albumin and pus cells, Urine culture -sensitivity and special investigations like maternal serum AMH will be taken at 11-14 weeks of gestation.

Intervention
Serum AMH levels will be done from our hospital. 2 cc of blood will be taken and subjected for immunofluorescence technique for serum AMH level. Results will be expressed as ng/ml. The normal value of serum anti-Mullerian hormone in first trimester of normotensive pregnancy is 1.54 ng/ml-2.66 ng/ml. Women with values less than 1.54 ng/ml will be considered to have low AMH levels. Antenatal Women with Altered serum anti-Mullerian hormone levels will be included in Group A and Antenatal women with Normal serum anti-Mullerian Levels will be included in Group B.

All women will be followed till delivery and 7 days after delivery. Blood pressure will be taken every time when the woman comes for follow up. The diagnosis of preeclampsia will be made as per NHBPEP (National high blood pressure education Programme) criteria [17,18], and comparison will be made between the two groups of women with low anti-Mullerian hormone levels and those with normal anti-Mullerian hormone levels, with respect to Maternal outcome as Antenatal, Intra-natal and Postnatal complications such as Antepartum hemorrhage, eclampsia, HELLP syndrome, Mode of delivery, Indication for caesarean section and Postpartum hemorrhage. Foetal outcome as intrauterine growth restriction, intrauterine death, APGAR, NICU admission. Data will be entered in excel sheet and confidentiality will be maintained.

Statistical Analysis
Data will be stored in an excel sheet, verified by another
The patient information including her name, phone number, will be taken and the data will be verified and entered in our own laptop/ computer to keep the data secured. The data will then be reviewed and entered in a backup file, and evaluated periodically. Data analysis will have both descriptive and inferential statistics. Data will be coded and analysed in statistical software STATA, version10.1, 2011. Descriptive statistics will be carried out where categorical variables will be summarized as frequency and percentage. Inferential analysis will include test of significance for comparing parameters in 2 groups. P value < 0.05 will be considered statistically significant for assessing the association between low AMH and maternal complications.

RR with 95 confidence intervals will be calculated. Difference in means will be analysed by 2 independent samples to test and p values less than 0.05 will be statistically significant.

Odds ratio will be calculated. Confidence Interval of 95% will be considered as statistically significant. This study aims to see if serum anti-Mullerian hormone levels between 11 and 14 weeks of pregnancy have any link to preeclampsia, and if so, what function it plays in the pathogenesis and prevention of preeclampsia and subsequent cardiovascular abnormalities later in life. Will be expressed in terms of relative risk. A ROC curve will be plotted to get the reference value for Indian population.

RESULTS AND DISCUSSION

The study aims to correlate the levels of anti-Mullerian hormone with frequency of preeclampsia. We expect from our results that lower serum anti-Mullerian hormone levels between 11-14 weeks of gestation will have higher frequency of preeclampsia.

Preeclampsia can result in maternal and perinatal death and morbidity as well as an unfavorable pregnancy outcome. This disease's specific a etiology is still unknown. Several factors have been investigated. The anti-Mullerian hormone's role is most likely due to a thrombotic, vascular factor that reduces blood flow to the ovaries, lowering anti-Mullerian hormone levels throughout pregnancy. As a result, ovarian ageing can occur thus worsening cardio-vascular problems in women who have preeclampsia.

Low anti Mullerian hormone levels during the 11-14 weeks of gestation are associated with increased risk of preeclampsia in a few studies14-15. A prospective case-control research conducted by few authors discovered that maternal AMH levels were lower in women with preeclampsia than in women with normal blood pressure. The preeclampsia group had an AMH value of 0.620.51 ng/ml, while the control group had an AMH value of 0.930.83 ng/ml. There was no link between maternal AMH levels and any changes in maternal or perinatal outcomes16.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age in yrs PE/N</th>
<th>Type of study</th>
<th>Exclusion criteria</th>
<th>Sample size PE/N</th>
<th>AMH Levels PE/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birdir et al14</td>
<td>32.6 (29.4–37.1) vs 31.9 (26.9–35.9)</td>
<td>Case control</td>
<td>Gestational age less than 11 weeks and more than 13 weeks</td>
<td>50/150</td>
<td>2.140 (1.968–2.273) vs 2.062 (1.938–2.181) ng/L</td>
</tr>
<tr>
<td>Tokmak et al15</td>
<td>28.7 ± 6.2 vs 27.0 ± 4.2</td>
<td>Case control</td>
<td>Early onset preeclampsia, gestational age less than 20 weeks</td>
<td>45/42</td>
<td>0.62 ± 0.51 vs 0.93 ± 0.83 ng/ml</td>
</tr>
<tr>
<td>Shand et al16</td>
<td>NA</td>
<td>Retrospective cohort</td>
<td>Multiple pregnancy, pregnancy more than 1st trimester, Birth less than 20 weeks</td>
<td>11/23</td>
<td>4.7 (1.8–13.2) vs 5.5 (1.4–16.1) pmol/L</td>
</tr>
</tbody>
</table>

A study in Sydney, Australia 2017 AMH was detected at 10–13 + 6 weeks of pregnancy. The risk of hypertension during pregnancy was shown to be 3.3 times higher in the study by few authors.16 In a large study of 336 women with preeclampsia and 329 normotensive women were considered. The study showed significantly lower ovarian reserve in women with preeclampsia with low AMH levels than women with normal blood pressure [15]. In another study AMH levels were found to be low during third trimester in women with preeclampsia compared to women with normal blood pressure (0.79±0.40 ng/ml vs. 1.45±0.93 ng/ml). Art of obstetric care involves improvement of pregnancy outcome.

All these studies have been done in developed countries and since the frequency of preeclampsia is higher in developing country like India it is essential to conduct such study and decrease maternal and perinatal morbidity and mortality due to same.

In women predisposed to preeclampsia, low serum anti Mullerian hormone levels at 11-14 weeks of gestation will help in starting low dose aspirin in antenatal women but it would also help in preventing mothers from future cardiovascular risks.

CONCLUSIONS

Low maternal serum anti-Mullerian hormone levels taken at 11-14 weeks of gestation have higher frequency of preeclampsia. Maternal serum anti-Mullerian hormone should be incorporated into the model for predicting the frequency of preeclampsia. This will be helpful to know its role in the pathogenesis and thus prevention of preeclampsia and further cardiovascular risks in later years of life. Considering the modest prognostic value further studies should validate the clinical usefulness of anti-Mullerian hormone as predictor of preeclampsia

REFERENCES

1. Which anticonvulsant for women with eclampsia? Evidence from

How to cite this article