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AN OBSERVATIONAL STUDY ON ASSOCIATION OF CELL FREE FETAL HEMOGLOBIN LEVEL WITH PREECLAMPSIA IN PREGNANT WOMEN AT SMS MEDICAL COLLEGE, JAIPUR

Obstetrics & Gynaecology

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ABSTRACT

Background: Preeclampsia is a significant cause of maternal and fetal morbidity and mortality, particularly in developing countries like India. It is a complex syndrome with no definitive predictive test for its onset. Emerging evidence suggests that cell-free fetal hemoglobin (Hb) plays a role in the pathogenesis of preeclampsia by inducing oxidative stress and vasoconstriction.**Objective:** This observational study aimed to investigate the association between cell-free fetal hemoglobin levels and the development of preeclampsia in pregnant women. **Methods:** A total of 213 pregnant women between 6 and 20 weeks of gestation were enrolled from the Department of Obstetrics and Gynecology at SMS Medical College, Jaipur. Participants were followed until delivery, and their cell-free fetal hemoglobin levels were measured using ELISA. Blood pressure and urine albumin were monitored throughout pregnancy to track the development of preeclampsia, classified according to ISSHP 2018 criteria. **Results:** The mean age of participants was 25.2 ± 3.83 years. Out of 213 participants, 17 (8%) developed preeclampsia. The mean value of cell-free fetal hemoglobin was significantly higher in participants who developed preeclampsia (1.59 ± 0.2 ng/ml) compared to those who did not (0.95 ± 0.28 ng/ml), with a p-value of 0.005. **Conclusion:** Elevated levels of cell-free fetal hemoglobin in early pregnancy are significantly associated with the subsequent development of preeclampsia. This suggests that cell-free fetal hemoglobin could serve as a potential serum marker for early detection, allowing timely intervention to improve maternal and fetal outcomes.

KEYWORDS

Preeclampsia, cell-free fetal hemoglobin, oxidative stress, maternal morbidity, pregnancy

INTRODUCTION

Preeclampsia is a serious pregnancy-related condition that contributes to significant maternal and fetal morbidity and mortality globally, especially in countries like India where healthcare access is limited. Despite extensive research, the condition remains a challenge in terms of prediction and treatment. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has classified hypertensive disorders in pregnancy, including chronic hypertension, gestational hypertension, and preeclampsia, among others. Notably, preeclampsia, which may develop after 20 weeks of gestation, can cause severe complications without warning, leading to maternal and fetal death. Proteinuria is no longer a mandatory criterion for diagnosing preeclampsia, with other symptoms like hypertension, kidney injury, and liver dysfunction playing key roles in diagnosis.

The HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets) is a severe manifestation of preeclampsia, while white coat and masked hypertension are related conditions that require careful monitoring. Early detection and preventive measures, such as aspirin and calcium supplementation for high-risk women, are essential strategies, though no treatment can completely prevent preeclampsia.

Preeclampsia is considered a syndrome rather than a single disease, with two distinct types: early onset (before 34 weeks) and late onset (after 34 weeks), each having different pathophysiological processes. Globally, 3-10% of pregnancies are affected by preeclampsia, with long-term consequences including cardiovascular diseases in mothers and premature birth in infants. The condition is rooted in placental dysfunction, with abnormal spiral artery remodeling leading to placental ischemia and hypoxia, particularly in early-onset cases. Addressing preeclampsia requires a multidisciplinary approach to reduce maternal and fetal risks.

No predictive test is available to identify women who will subsequently develop preeclampsia-eclampsia. Cell-free fetal hemoglobin (Hb) and its metabolites, such as free heme and ferrous ions, are toxic due to their ability to induce oxidative stress. Cell-free fetal Hb binds strongly with nitric oxide (NO), a potent vasodilator, leading to vasoconstriction and reduced NO availability. Oxidative stress, an imbalance between oxidative substances and antioxidants, is driven by reactive oxygen species (ROS) such as free radicals and peroxides, which can damage DNA, proteins, and cell membranes. In preeclampsia, oxidative stress is evident in both the placenta and maternal circulation.

Extracellular fetal Hb accumulates in the placental vasculature in preeclampsia, causing oxidative damage and leaking into maternal circulation. This free Hb, due to its iron content, generates oxygen radicals and promotes neutrophil and cytokine synthesis. Haptoglobin, a Hb-clearing molecule, binds to cell-free Hb in the placenta, forming a Hb-Hp complex, which is cleared from the blood by hepatocytes. Elevated levels of fetal hemoglobins (HbA and HbF) in the first trimester are associated with tissue damage in maternal circulation.

Given the prevalence of preeclampsia in Indian pregnancies, this study aims to investigate cell-free fetal hemoglobin as a serum indicator for early detection, improving timely referral and saving lives of both mother and fetus.

MATERIAL AND METHODS

Study was conducted in the department of Obstetrics and Gynecology, Pandit Deen Dayal Upadhyay Hospital, attached to S.M.S. medical College, Jaipur, from October 2017 onwards. The gestational length of 250 study participants was calculated from the last menstrual period and confirmed by ultrasound scan by the crown rump measurement. The gestational age was taken between six to twenty weeks (6^{+0} to 19^{+6}) of pregnancy.

After consent all routine investigations were performed e.g. CBC, LFT, RFT, Blood group, urine routine and microscopic, HIV, HbsAg, VDRL, DIPSI, serum TSH, Blood pressure was checked on the first visit. Ultrasound scan was performed on all the pregnant women to decide the duration of gestation and exclude multifetal gestation. Women with 6^{+0} to 19^{+6} weeks of duration and singleton pregnancies were included in the study. Women who had inter delivery interval more than 60 months were not included in the study.

Woman, who had high blood pressure on the first visit or known case of essential hypertension, high TSH value or known case of hyper- or hypothyroidism and high sugar values in DIPSI results, were excluded from study. Women who had preeclampsia/eclampsia or GDM in previous pregnancies or overt diabetes mellitus type I or type II were also excluded from the study.

Cell free fetal hemoglobin test was done by ELISA method on the maternal blood sample of all the participants after being included in the study. Follow up visits were recorded till delivery. On each visit blood pressure and urine albumin were measured to track the development of

preeclampsia till 48 hours after delivery. According to, 2018 classification of ISSHP (International Society for the Study of Hypertension in Pregnancy) study participants were labeled preeclampsia.

RESULTS

Out of total 213 study subjects, maximum participants were from age group 23-27 years (46%) and groups of 19-22 years and 28-32 years had about 28% and 21% participants respectively. Mean age of participants was 25.2±3.83 years.

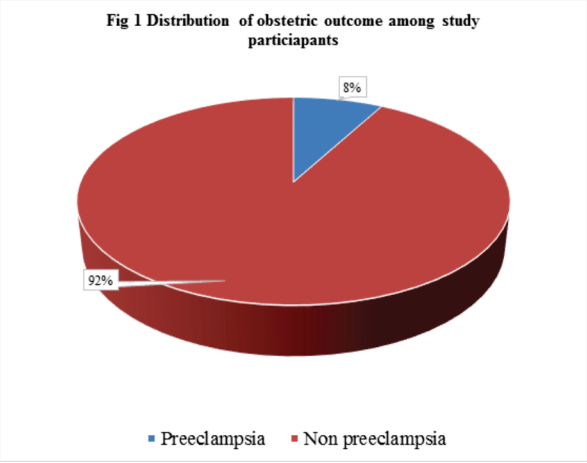

Table 1 Association Of Cell Free Fetal Hemoglobin With Preeclampsia

Status	frequency	Mean value of cell free fetal Hb (ng/ml)	t test	P value
Preeclampsia	17	1.59±0.2	2.82	0.005
Non Preeclampsia	196	0.95±0.28		

Distribution of cell free fetal haemoglobin in the serum of study participants was tabulated, Mean value of cell free fetal haemoglobin in serum of study participants was statistically significant higher in those who developed preeclampsia in present pregnancy (P =0.005).

DISCUSSION

Cell free fetal hemoglobin levels of all the candidates were tabulated and it was found that mean value of the above parameter was significantly higher in the study participants who eventually developed preeclampsia. As seen by Fatma A et al during their study that level of cell free fetal hemoglobin was higher in severe preeclampsia patients as compared to mild preeclampsia cases. The concentration of cell free fetal hemoglobin was significantly raised in early pregnancy in those females who subsequently developed preeclampsia. In the present study, around 8% of study participants developed preeclampsia.

Socio-demographic details of the study participants were taken and analyzed to see the effect of demographic variation on the development of preeclampsia. Mean age of study participants at the time of their marriage was 20 years. In the age group 19-25 years of age, around 62% participants got married and 30% got married before that age. Over all literacy rates in female population in Rajasthan according to census book of India, 2011 is 43% and 65% in the urban area. In present study, only 16% participants were illiterate and 30% had education up to primary level. Post-graduation and more degrees were achieved by only 13% of subjects. This discrepancy might be there because this study was done in an urban tertiary care hospital.

Preeclampsia is more common at extreme of ages and in Rajasthan mean age of marriage of girls is less than other parts of India. In present study, around 92% participants got married in 18 to 25 years of age group and only 1% of participants got married after 33 years of age. 93% cases of preeclampsia in our study were seen in 19-25 years of age group participants.

Cell free fetal hemoglobin was tested in all the study participants, between 6 weeks to 20 weeks duration of pregnancy. It was seen in the result that mean value of test was higher in subjects, who consequently developed preeclampsia in any time during pregnancy. The difference was statistically significant. Out of 213 participants 17 participants developed preeclampsia and mean value of cell free fetal hemoglobin was higher in these cases. Out of these 17, five subjects developed early preeclampsia and rest had late preeclampsia.

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