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Serum Biochemical Markers Combined With Uterine Artery Doppler during Second Trimester as a Predictor of Pre-Eclampsia

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ABSTRACT

Pre-eclampsia is a pregnancy specific syndrome characterized by the onset of hypertension and proteinuria after the 20th week of gestation. It is the leading cause of the fetal growth restriction, premature delivery and is responsible for over 50,000 maternal deaths annually worldwide. To evaluate the association between abnormal levels of serum biochemical markers (Alpha Fetoprotein, -HCG, Uric Acid, Liver function test and Renal function test) combined with uterine artery Doppler in 2nd trimester in the prediction of pre-eclampsia and eclampsia This Hospital based Prospective observational study was conducted in Department of Obstetrics and Gynecology S.C.B medical College and Hospital, Cuttack during the study period from March 2021-March 2022 Our study showed that, mean Age of patients was [24.0865±4.2268], mean Gestational Age (Weeks/days)of patients was [19.9913±1.1747], mean BMI of patients was [24.0208±3.1991], mean MAP of patients was [86.7475±7.8911], mean Sr. ß-HCG of patients was [31557.7212±17649.6158], mean Sr. LDH of patients was [441.2115±86.1059], mean Sr. AFP of patients was [87.0673±45.5231], mean Sr. Uric Acid of patients was [5.0615±1.4377], mean Sr. Bilirubin(Total) of patients was [.8875±.2606], mean Sr. Bilirubin(Direct) of patients was [.3825±.1464], mean Sr. Bilirubin (Indirect) of patients was [.5019±.2547], mean SGOT of patients was 25.2788±9.4216, mean SGPT of patients was[75.3654±27.2033], mean Sr. ALP of patients was [221.7788±52.5259], mean Sr. Urea of patients was [27.5962±8.1913], mean Sr. Creatinine of patients was [.6067±.1553], mean Sr. Sodium of patients was [137.8250±14.0400], mean Sr. Potassium of patients was [3.9481±.3066], mean Uterine Artery PI of patients was [1.1044±.1856]. Sr. ß-HCG was higher in pregnant women with PE compared to without PE which was statistically significant. Sr. LDH was more in women without PE compared to with PE but this was not statistically significant. Sr. AFP was higher in women with PE compared to without PE but this was not statistically significant. Uterine Artery PI was more in women with PE compared to without PE which was statistically significant.

INTRODUCTION

Pre-eclampsia here is a significant contributor of maternal and fetal mortality and it affects 2-8% of all pregnancies worldwide. A screening test that could identify, early in pregnancy, those women who would later develop the pre-eclampsia would allow increased surveillance of those at risk and reduced surveillance for more unlikely to develop the syndrome. Pre-eclampsia is a two stage phenomena resulting in the systemic pre-eclampsia syndrome in women who are sensitive to the insult. Initial insult is thought to be abnormal placentation leading to maldevelopment of uteroplacental perfusion that then leads to the increased inflammatory response and endothelial dysfunction of the syndrome. Doppler measurements of the uteroplacental vasculature preformed in the 2nd trimester reportedly could identify women who subsequently develop pre-eclampsia. Pre-eclampsia prediction studies included all in which the overall objective was to identify potential biochemical markers for predication of pre-eclampsia. Preeclampsia (PE) affects about 2-8% of pregnancies and is the biggest cause of maternal and perinatal morbidity and mortality[1]. In India, it is responsible for about a quarter of maternal deaths[2]. Severe hypertensive disorders were the main cause of severe maternal morbidity and the mortality index was 10.7% in a Brazilian multicentre study[3]. Besides the impact on mortality, PE is one of the main causes of severe maternal morbidity. This disease causes multi system commitment due to a generalized vasospasm associated with endothelial lesions and a change in microcirculation at the level of the central nervous system, kidneys, lungs, liver, retina and other organs. For this reason, it has the potential to cause multiple organ failure and sequelae. Despite numerous studies in the last decades, the physiopathology of PE is not completely known. It has a multifactorial pathogenesis which involves immunological, genetic, hormonal and environmental factors. Until now, the only cure for PE has been the removal of the placenta, which seems to be the pathogenic root of all of the disease's manifestations[4]. In PE, trophoblastic invasion is deficient and causes an increase in the resistance of uterine and placental circulation, placental hypoxia and local oxidative stress[5]. This process leads to a systemic inflammatory response and vasospasms which result in hypertension, edema and proteinuria. Several studies have been conducted in an attempt to identify high risk PE patients in the first trimester of pregnancy so that they may benefit from an effective prophylaxis with acetylsalicylic acid (ASA) before 16 weeks[6]. In order to obtain a higher sensitivity in identifying these patients, the following variables have been combined maternal characteristics, mean arterial pressure (MAP), uterine artery pulsatility index (PI) and biochemical markers. The Fetal Medicine Foundation (FMF) has developed a prediction algorithm for PE in the first trimester. Since it uses all variables, it achieves expressive results in detecting preterm PE, with a sensitivity of 76% (false positive [FP], 10%). Although the combined method has an acknowledged superiority, in developing countries such as India biochemical markers are unavailable in the public health system and are thus unavailable for the majority of the population. Unfortunately, without these biomarkers, the sensitivity rate for identifying patients at high risk for PE is lower.

MATERIALS AND METHODS

This Hospital based Prospective observational study was conducted in Department of obstetrics and gynecology S.C.B medical College and Hospital, Cuttack during the study period from March 2021-March 2022, Patient was selected after taking into account the inclusion and exclusion criteria, study was carried after obtaining ethical clearance and consent from the patients.

Sample Size: Formula=4pq/n2 where P=Prevalence in previous study (7%) q=1-p, n=Standard error (5%). Result=4pq/n2=104(minimum number of cases).

Inclusion Criteria: All booked and unbooked cases of pregnant women in 2ndtrimester of pregnancy willing for a hospital delivery at SCB Medical College and Hospital.

Exclusion Criteria: Women with K/c/o- Renal diseases, Previous liver diseases, Chronic hypertension, DM, Autoimmune D/O women who didn't give written informed consent. It was a prospective cross-sectional study consisting of 104 patients. Blood Samples for Investigation (-HCG, LDH, AFP, Serum Uric Acid, LFT, RFT) drawn at 18-22 wks. Uterine Artery Doppler was done at18-22wks along with TIFFA Scan. Then the patient is asked to visit for regular ANC in every 4wks up to 28 wks of pregnancy, then in every 2 wks up to 36 wks, then once in every week till delivery. Blood sample was taken and sent to the biochemistry department and patient was treated accordingly on the basis of the report. The study was carried out according to a predefined proforma. All data was collected, charged out and analyzed thereafter. Then result was compared by using statistical parameters and statistical analysis was performed using statistical package for the social sciences (SPSS) software version 22, SPSS Inc., Chicago, IL), $P<0.05$ was considered significant. Implications (a) Screening by a combination of serum biochemical markers and uterine artery Doppler can identify the risk of developing pre-eclampsia (b) By identifying these patients with high risk for pre-eclampsia, appropriately tailored antenatal surveillance can be integrated and prophylactic pharmacological interventions can be

prescribed to improve placentation and ultimately the outcome for both the mother and fetus(c) As pre-eclampsia is in an increasing trend during pregnancy that adds considerable physical, psychological and financial burden to the lady, her family and community. Knowledge of the risk factors, proper use of prophylactic and therapeutic medications and adequate monitoring will help in preventing morbidity and mortality associated with it.

RESULTS AND DISCUSSIONS

In our study, 20 (19.4%) patients were<20 years of age, 74 (71.8%) patients were 21-30 years of age and 9 (8.7%) patients were >31 years of age. The value of z is 9.2035. The value of p<00001. The result is significant at p<0.05. In our study, 40 (38.5%) patients had multigravida and 64 (61.5%) patients had primigravida. The value of z is 3.3282. The value of p is 0.00086. The result is significant at p<0.05. In our study, 8 (7.7%) patients had PE. The value of z is 12.2034. The value of p<0.00001. The result is significant at p<0.05. The mean Age (mean±s.d.) of patients was 24.0865±4.2268 and the mean BMI of patients was 24.0208±3.1991. The mean MAP (mean±s.d.) of patients was 86.7475±7.8911. The mean Sr. Uric Acid (mean±s.d.) of patients was 5.0615±1.4377.

(Table 1) Distribution of mean Sr.Bilirubin (Total) In above table showed that the mean Sr.Bilirubin (Total) (mean±s.d.) of patients was 0.8875±.2606. The mean *Sr. Bilirubin* (Direct) of patients was 0.3825±.1464. The mean Sr. Bilirubin (Indirect) of patients was 0.5019±.2547. The meanSGOT (mean±s.d.) of patients was 25.2788±9.4216. The mean SGPT of patients was 75.3654±27.2033. The mean Sr. ALP of patients was 221.7788±52.5259. The mean *Sr. Urea* of patients was 27.5962±8.1913. The mean *Sr. Creatinine* of patients was .6067±.1553. The mean *Sr. Sodium* of patients was 137.8250±14.0400. The mean *Sr. Potassium* of patients was 3.9481±.3066. In Without PE, the mean Sr. ß-HCG (mean± s.d.) of patients was 29831.2083 ± 14297.7359. In With PE, the mean Sr.ß-HCG of patients was 49869.2500± 36744.3130. Distribution of mean Sr.ß-HCG with PE was statistically significant (p = 0.0016). In without PE, the mean Sr.LDH (mean±s.d.) of patients was443.1563± 85.5354. In ith PE, the mean Sr.LDH (mean±s.d.) of patients was 431.3750± 88.7387. Distribution of mean Sr.LDH with PE was not statistically significant (p = 0.7097). In without PE, the mean Sr.AFP (mean±s.d.) of patientswas84.8021±45.6021.In With PE, the mean Sr.AFP (mean±s.d.) of patients was 106.0000±37.6146. Distribution of mean Sr.AFP with PE was not statistically significant (p = 0.2044). In without PE, the mean Uterine Artery PI (mean±s.d.) of patients was 1.0774±.1389. In with PE, the mean Uterine Artery PI (mean±s.d.) of patients was1.4375±.3285. Distribution of mean Uterine Artery PI with PE was statistically significant (p<0.0001).

Hymavathi *et al.*[7]: Found that study results showed a strong association between gestational age at delivery and neonatal outcome (neonatal birth weight and APGAR) with pre-eclampsia. In our study, out of 104 patients most of the patients were 21-30 years old [74 (71.8%)]. Which was statistically significant (p<0.00001), (z = 9.2035). We found that, higher number of patients had Primigravida [64 (61.5%)] followed by Multigravida [40 (38.5%)] though itwas statistically significant (p = .00086), (z = 3.3282).

Kuc *et al*[8]: Showed that pre-eclampsia (PE) affects 1% to 2% of pregnant women and is a leading cause of maternal and perinatal morbidity and mortality worldwide. The clinical syndrome of PE arises in the second half of pregnancy.

Kuc *et al*.[9]:Found that the model predicted detection rates (DR) for fixed 10% false-positive rates were calculated for EO-PE and LO-PE with or without the presence of a small for gestational age infant (SGA,birth weight <10th centile). The best prediction model included maternal characteristics, MAP, PAPP-A, ADAM12 and PlGF, with DR of 72% for EO-PE and 49% for LO-PE. Prediction for PE with concomitant SGA was better than for PE alone (92% for EO-PE and 57% for LO-PE).

DG *et al*[10]: Observed that the patients were followed up to detect PE and IUGR. PE developed in 14 cases (5.26 %), 2 cases early-onset 2 cases and late-onset 12 cases and IUGR in 19 cases (7.14 %), early-onset 3cases and late-onset 16 cases. We observed that, lower number of patients had PE [8 (7.7%)] and it was statistically significant (p<0.00001), (z = 12.2034).

Saha *et al*[11]: observed that booking BMI and Uristix protein had significant association with pre-eclampsia. Among the biochemical and sonological markers maternal serum -HCG, uterine artery doppler RI (22-24 wks.) and notching (22-24 wks.) had the best sensitivity, specificity and predictive value.

De Freitas Leite J *et al*[12]: Showed that to evaluate the performance of the pre-eclampsia(PE) screening algorithm of the Fetal Medicine Foundation (FMF) during the first trimester in a Brazilian population using maternal characteristics, mean arterial pressure (MAP) and uterine artery Doppler data.

Dane *et al*[13]: This study was to assess the correlation between first trimester maternal serum free beta-human chorionic gonadotropin (fBHCG),

Table 1: Distribution of mean *Sr.Bilirubin* (Total)

	Number	Mean	SD	Minimum	Maximum	Median
Sr. Bilirubin (Total)	104	.8875	.2606	0.3000	1.3000	0.9000
Sr. Bilirubin (Direct)	104	.3825	.1464	0.1000	0.7000	0.4000
Sr. Bilirubin (Indirect)	104	.5019	.2547	0.1000	1.1000	0.5000

Table 2: Distribution of mean Sr.ß-HCG: PE

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Sr.ß-HCG	No	96	29831. 2083	14297.7359	8135.0000	88000.0000	29234.5000	0.0016
	Yes	8	49869.2500	36744.3130	11022.0000	108000.0000	42133.0000	

Table 3: Distribution of mean Sr.LDH: PE

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Sr.LDH	No	96	443.1563	85.5354	306.0000	594.0000	438.0000	0.7097
	Yes	8	431.3750	88.7387	311.0000	583.0000	438.0000	

Table 4:DistributionofmeanSr.AFP:PE

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Sr. AFP	No	96	84.8021	45.6021	12.0000	200.0000	76.5000	0.2044
	Yes	8	106.0000	37.6146	42.0000	140.0000	124.0000	

Table 5: Distribution of mean Uterine Artery PI: PE

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Uterine Artery PI	No	96	1.0774	0.1389	0.8300	1.2900	1.0900	<0.0001
	Yes	8	1.4375	0.3285	1.0200	1.8000	1.5000	

pregnancy-associated plasma protein A (PAPP-A), second-trimester uterine artery (UA) Doppler measurements and adverse pregnancy outcomes. Serum levels of PAPP-A and free Beta HCG were determined at the first trimester and patients underwent bilateral UA Doppler assessments at 20-25 weeks of gestation.

Mohammed *et al*[14]: Examined that pre-eclampsia accounts for 15% of maternal deaths and may cause fetal morbidity and mortality. The aim of this research was to evaluate the efficacy of maternal uterine artery Doppler versus serum beta-human chorionic gonadotropin (ß-hCG), during the first trimester, in predicting preeclampsia and intrauterine growth restriction (IUGR). In our study, Sr. ß-HCG was higher in with PE [49869.2500±36744.3130] compared to without PE [29831.2083±14297.7359] but this was statistically significant (p = 0.0016).

Kuc *et al*[8]: Showed that theaimofthis systematicreviewwas to study the literature on the predictive potential of first-trimester serum markers and of uterine artery Doppler velocity waveform assessment (Ut-A Doppler).

Desai *et al*[15]: Observed that in normal pregnancy almost always at 12 to 14 weeks of duration, the uterine artery shows presence of a diastolic notch. In high-risk subjects, disappearance of diastolic notch at mid-trimester in uterine artery Doppler waveform analysis if used alone may not be a good screening method for obstetric vasculopathies.

DG *et al*[10]: To assess the accuracy of first-trimester uterine artery Doppler indices combined with maternal serum placental growth factor (PlGF) and pregnancy associated plasma protein- A (PAPP-A) in the prediction of pre-eclampsia (PE) and intrauterine growth restriction (IUGR) in low risk pregnancy.

Li *et al*[16]: Found that first-trimester screening may be a major advantage over a second-trimester approach since it opens prospects for early and more efficient interventions. Second-trimester uterine artery PI and marker levels were expressed as multiples of the median (MoM). The uterine artery PI was increased in pregnancies with pre-eclampsia compared with controls. In pregnancies that developed pre-eclampsia, the uterine artery PI was increased (1.61±0.047 vs. 1.02±0.049, p<0.001), as was the level of inhibit A (1.72±0.023 vs. 1.03±0.063, p<0.001) and the level of activin A (1.68±0.38 vs.1.06±0.42, p<0.001) compared with the controls. In contrast, the level of PlGF was decreased in pregnancies that developed pre-eclampsia compared with the controls (0.69±0.23 vs. 1.00±0.26, p<0.001). We found that, Sr. LDH was more in without PE [443.1563±85.5354] compared to with PE [431.3750±88.7387] but this was no statistical significant (p = 0.7097).

Saha *et al*[11]: Observedthatpre eclampsia and eclampsia is a very common cause of maternal and perinatal mortality and morbidity. Serum parameters AFP, -HCG, inhibit A, urinary parameters like urinary albumin- creatinine ratio (spot sample), sonological parameters like uterine artery doppler study, RI, PI, notching were measured. In our study, Sr. AFP was higher in with PE [106.0000±37.6146] compared to without PE [84.8021±45.6021] but this was not statistically significant (p=0.2044).

Hymavathi *et al*[17]: Showed that this study was conducted to evaluate the efficacy of different biochemical and biophysical markers in the early weeks ofgestationasscreeningtoolsforearlypredictionofpre-

eclampsia. This hospital-based prospective observational study conducted on 52 pregnant women, at <13 weeks of gestation were recruited. Maternal serum inhibit A and uterine artery PI levels were analyzed among the pregnant women who subsequently developed PE and compare with those who did not develop PE. We found that, Uterine Artery PI was more in with PE [1.4375±.3285] compared to without PE [1.0774±.1389] but this was statistically significant (p<0.0001).

CONCLUSION

In our study, Sr. ß-HCG was higher in pregnant women with PE compared to without PE which was statistically significant. We found that, Sr. LDH was more in women without PE compared to with PE but this was not statistically significant. In our study, Sr. AFP was higher in women with PE compared to without PE but this was not statistically significant. We found that, Uterine Artery PI was more in women with PE compared to without PE which was statistically significant.

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