

Role of Maternal Serum 6HCG in Prediction of Early Onset Pre Eclampsia and It's Correlation with Uterine Artery Doppler

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Abstract

Background: Hypertensive disorders during pregnancy remain amongst the most significant and intriguing unsolved problems in obstetrics. The study aims at testing the hypothesis that women with high Serum beta hCG levels and alternations in waveforms in uterine artery doppler in first and second trimester have high risk of developing pre eclampsia. **Methods:** Serum 6 hCG estimation was done by Sandwich chemiluminescence immunoassay method. All uterine artery waveforms were obtained using ultrasound machine attached to a 3.5 MHz curvilinear transducer, with color and pulsed Doppler abilities. **Results:** The mean maternal Serum 6 HCG level in non severe pre eclampsia in first and second trimester were 30517.5+-11076.2 and 48204.6+-12074.0 respectively and for severe pre eclampsia were 37213.4+-11968.4 and 52549.5+-12074.0 respectively which were significantly greater than normotensive (25819.9+-10017.8 and 32617.8+-6759.0 respectively p value<0.001). The number of complications in preeclampsia group were more than normotensive once. **Conclusion:** Mean 6HCG levels are higher in preeclampsia group as compared with normotensive and maternal and fetal complications associated.

Keywords: Gonadotropin, Preeclampsia, normotensive, eclampsia, 6hcg.

Introduction

Hypertensive disorders during pregnancy remain amongst the most significant and intriguing unsolved problems in obstetrics ^[1]. Pregnancy induced hypertension along with its sequelae that is pre eclampsia and eclampsia is a unique disease seen only in pregnancy, affecting 12 to 15% of all pregnant women ^[2].

Of all the Hypertensive disorders during pregnancy, pre eclampsia syndrome, either or superimposed on chronic hypertension is most dangerous ^[1]. It is a major cause of maternal and perinatal morbidity and mortality and is thought to be predominantly as the consequence of impaired placentation ^[3-5]. Pre eclampsia can be best described as a pregnancy specific syndrome

that can affect virtually every organ and widely varies in its clinical phenotypic expression.

It can be subdivided into early onset pre eclampsia, requiring delivery before 34 weeks of gestation and late onset pre eclampsia with delivery at or after 34 weeks, because the former is associated with higher incidence of adverse outcomes ^[6-9]. It is indeed a constant endeavor of obstetricians to identify the risk of pregnancy induced hypertension or pre eclampsia involved in pregnancy and if possible it's prediction. Because if prediction becomes possible prevention will follow naturally. Various attempts have been made to identify early markers of faulty placentation, impaired placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation. Hence, measurement during early pregnancy or

across pregnancy especially second trimester of various biological, biochemical, biophysical and radiological markers implicated in pre eclampsia syndrome has been proposed to predict its development. But none of the tests has been accepted widely due to their low predictive value.

The abnormal placentation has been considered as one of the initial events in disease process [10]. It has been hypothesized that during mid second trimester, immunological changes occur in the trophoblasts, resulting in secretory response, which is seen as a rise in the serum beta HCG levels.

The human chorionic Gonadotropin (hCG), synthesized from syncytiotrophoblastic cells of placenta, is a glycoprotein made up of two non-covalent linked subunits alpha and beta. It peaks in maternal serum at 8 to 10 weeks of GA and then gradually decreases to reach to a plateau at 18 to 20 weeks of GA. The free β subunit is produced from 3 sources namely direct trophoblastic cell secretions, splitting of hCG into free subunit, and by macrophage or neutrophil enzymes breaking the hCG molecules. The circulating levels of free β hCG only corresponds to only 0.3 to 4% of total [11].

Uterine artery doppler has more recently shown some promise, UA pulsatility index (PI) has been used as a marker of pre eclampsia and fgr, in presence of which PI increases due to the elevation in uterine artery impedance [12]. Hence in our study we have tried to compare predictive value of beta hCG levels as predictor of pre eclampsia.

Methods

The study was carried out between December 2022 to December 2024(2yrs) among 329 pregnant women who attended antenatal clinics or were admitted in antenatal wards in department of Obstetrics and Gynecology of UISEMH, GSVM Medical college Kanpur uttarpradesh, India. Out of 329, 79 women were loss to follow up, 250 women who completed their pregnancy and delivered at our hospital were evaluated and statistically analysed.

Definition

PIH: Systolic BP 140mmHg or more with a >30 mmHg rise and or Diastolic BP of 90 mmHG or more with rise of >15 mmHg occurring on two or more occasions after 20 weeks of gestation.

Pre eclampsia: Gestational hypertension with proteinuria of at least 2+ or 1g/L in dipstick or 24 hrs urinary protein excretion >0.3g.

β hCG was done by Sandwich chemiluminescence method.

All uterine artery doppler were performed as per ISUOG Practice guidelines (2013) using RS80 ultrasound system from Samsung Healthcare with a curvilinear probe with 3.5 MHz.

The study includes pregnant women aged 18-45, antenatal women between 11-28 weeks gestation, and women willing to follow up.

Women with pre-existing renal disease, chronic hypertension, diabetes mellitus, multiple gestation, BMI >25, smoking habits, or unwilling to participate are excluded.

Control included were women who had normal range BP constantly throughout pregnancy. Remaining were considered case.

Results

The distribution of parity among normotensive women, those with preeclampsia with non-severe features, and those with preeclampsia with severe features was analyzed.

The chi-square test indicated a statistically significant difference in parity distribution among the three groups ($\chi^2 = 17.37$, $p = 0.008$), suggesting that primigravida women had a higher prevalence of severe preeclampsia compared to multiparous women (Table 1).

Despite these variations, the difference in mode of delivery across the groups was not statistically significant ($\chi^2 = 5.84$, $p = 0.211$). However, the trend suggests a higher proportion of LSCS in severe preeclampsia cases, likely due to maternal and fetal complications associated with the condition (Table 2).

The birth weight distribution varied across groups, though the differences were not statistically significant ($\chi^2 = 8.63$, $p = 0.196$). Extremely low birth weight (ELBW) babies (<1 kg) were seen only in the preeclampsia with non-severe features group (2.5%), while very low birth weight (VLBW, 1.0-1.4 kg) babies were more common in preeclampsia cases (7.5% in non-severe and 8.7% in severe) than in normotensive cases (3.7%). Low birth weight (LBW, 1.5-2.4 kg) was highest in preeclampsia with non-severe features (52.5%), followed by normotensive (45.5%) and preeclampsia with severe features (43.5%). The proportion of babies with normal birth weight (≥ 2.5 kg) was highest in normotensive cases (50.8%) and lowest in preeclampsia with non-severe features (37.5%).

Regarding gestational age (GA) at delivery, preterm births were highest in preeclampsia with severe features (43.5%), followed by preeclampsia with non-severe features (35.0%) and normotensive cases (23.0%). Term deliveries were most common in normotensive women (68.4%), followed by preeclampsia with non-severe features (65.0%) and severe features (47.8%). Postdated deliveries were rare, occurring in 8.6% of normotensive cases and 8.7% of preeclampsia with severe features cases, but absent in preeclampsia with non-severe features. Although the difference in gestational age was not statistically significant ($\chi^2 = 9.16$, $p = 0.057$), a trend toward higher preterm births in preeclampsia cases was observed (Table 3).

The condition of newborns at birth showed variations among the groups, though the differences were not statistically significant ($\chi^2 = 5.64$, $p = 0.228$) (Table 4).

The growth pattern of newborns varied significantly among the groups ($\chi^2 = 34.26$, $p < 0.001$). Normal growth was observed in 94.7% of newborns from normotensive mothers, compared to 65.0% in preeclampsia with non-severe features and 69.6% in preeclampsia with severe features. Conversely, intrauterine growth restriction (IUGR) was notably higher in preeclampsia cases, affecting 35.0% of newborns in the non-severe group and 30.4% in the severe group, compared to only 5.3% in normotensive pregnancies. This highlights the significant impact of preeclampsia on fetal growth, with a higher prevalence of IUGR in affected pregnancies (Table 5).

The amniotic fluid status showed a significant difference among the groups ($\chi^2 = 32.41$, $p < 0.001$). Adequate liquor was present in 96.8% of normotensive pregnancies, whereas it was reduced in preeclampsia cases, with 75.0% in the non-severe group and 69.6% in the severe group. Oligohydramnios was significantly more common in preeclampsia cases, affecting 25.0% in the non-severe group and 30.4% in the severe group, compared to only 3.2% in normotensive pregnancies. This suggests a strong association between preeclampsia and reduced amniotic fluid levels, which can have implications for fetal well-being and pregnancy outcomes (Table 6).

The maternal outcomes were compared based on β -HCG levels at two time points (T1 and T2). For normotensive mothers, the mean β -HCG at T1 was 25,819.9 mIU/ml (SD = 10,017.8), and at T2, it increased to 32,617.8 mIU/ml (SD = 6,759.0). In mothers with pre eclampsia with non-severe features, the mean β -HCG at T1 was

30,517.5 mIU/ml (SD = 11,076.2), and at T2, it significantly rose to 48,204.6 mIU/ml (SD = 10,594.7). For mothers with pre eclampsia with severe features, the mean 6-HCG at T1 was 37,213.4 mIU/ml (SD = 11,968.4), and at T2, it further increased to 52,549.5 mIU/ml (SD = 12,074.0). The ANOVA results indicated significant differences in 6-HCG levels across the groups at both time points, with F-values of 14.20 ($p < 0.001$) for T1 and 108.8 ($p < 0.001$) for T2 (Table 7 Figure 1).

The ROC analysis was conducted to determine the optimal cut-off values for Serum β -HCG levels at T1 and T2, as well as Uterine Artery Doppler (UAD), for predicting preeclampsia with non-severe features. The predictive performance of these biomarkers was then compared. Serum β -HCG at T1 had an AUROC of 0.626 (95% CI: 0.53-0.73), indicating a low predictive ability. The optimal cut-off value was β -HCG $> 36,230$, with a sensitivity of 42.5% (95% CI: 36.4-48.6) and a specificity of 81.4% (95% CI: 76.6-86.2). The positive predictive value (PPV) was 32.8% (95% CI: 27.0-38.6), while the negative predictive value (NPV) was 87.0% (95% CI: 82.8-91.2). In contrast, Serum β -HCG at T2 showed a much stronger predictive ability, with an AUROC of 0.856 (95% CI: 0.80-0.91). The optimal cut-off value was β -HCG $> 39,503$, with a sensitivity of 80% (95% CI: 75.0-85.0) and specificity of 81% (95% CI: 76.1-85.9). The PPV was 47.4% (95% CI: 41.2-53.6), while the NPV was the highest at 95% (95% CI: 92.3-97.7). Uterine Artery Doppler (UAD) had a moderate predictive ability, with an AUROC of 0.783 (95% CI: 0.70-0.86). The optimal cut-off value was UAD > 0.87 ,

with a sensitivity of 67.5% (95% CI: 61.7-73.3) and specificity of 87.1% (95% CI: 82.9-91.3). The PPV was 52.8% (95% CI: 46.6-59.0), and the NPV was 93% (95% CI: 89.8-96.2) (Table 8 Figure 2).

The ROC analysis was performed to determine the optimal cut-off values for Serum β -HCG levels at T1 and T2, as well as Uterine Artery Doppler (UAD), for predicting preeclampsia with severe features. Their predictive performances were then compared. Serum β -HCG at T1 had an AUROC of 0.772 (95% CI: 0.66-0.88), indicating a moderate predictive ability. The optimal cut-off value was β -HCG $> 36,726.5$, with a sensitivity of 60.9% (95% CI: 54.9-66.9) and a specificity of 87.7% (95% CI: 83.6-91.8). The positive predictive value (PPV) was 51.4% (95% CI: 45.2-57.6), while the negative predictive value (NPV) was 91.0% (95% CI: 87.5-94.5). Serum β -HCG at T2 showed a stronger predictive ability, with an AUROC of 0.893 (95% CI: 0.84-0.95). The optimal cut-off value was β -HCG $> 40,316.0$, with a high sensitivity of 87% (95% CI: 82.8-91.2) and a specificity of 78.4% (95% CI: 73.3-83.5). The PPV was 46.3% (95% CI: 40.1-52.5), while the NPV was the highest at 97.0% (95% CI: 94.9-99.1). Uterine Artery Doppler (UAD) also showed strong predictive accuracy, with an AUROC of 0.855 (95% CI: 0.75-0.96). The optimal cut-off value was UAD > 0.93 , with a sensitivity of 78.3% (95% CI: 73.2-83.4) and the highest specificity of 89.4% (95% CI: 85.6-93.6). The PPV for UAD was 47.6% (95% CI: 40.8-59.0), while the NPV was 97% (95% CI: 94.7-99.3) (Table 9 Figure 3).

Table 1: Distribution of Cases according to Parity

Parity	Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
	No.	%	No.	%	No.	%	chi sq	p-value
G1	64	34.2%	9	22.5%	11	47.8%	17.37	0.008
G2	72	38.5%	12	30.0%	2	8.7%		
G3	33	17.6%	15	37.5%	5	21.7%		
> G3	18	9.6%	4	10.0%	5	21.7%		

Table 2: Distribution of Cases according to Mode of Delivery

Mode of delivery	Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
	No.	%	No.	%	No.	%	chi sq	p-value
TVD	87	46.5%	19	47.5%	9	39.1%	5.84	0.211
Assisted	0	0.0%	1	2.5%	0	0.0%		
LSCS	100	53.5%	20	50.0%	14	60.9%		

Table 3: Distribution of Cases according to Neonatal outcome

Baby Characteristics		Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
		No.	%	No.	%	No.	%	chi sq	p-value
Birth Weight	ELBW (<1 kg)	0	0.0%	1	2.5%	0	0.0%	8.63	0.196
	VLBW (1.0-1.4 kg)	7	3.7%	3	7.5%	2	8.7%		
	LBW (1.5-2.4 kg)	85	45.5%	21	52.5%	10	43.5%		
	Normal (≥ 2.5 kg)	95	50.8%	15	37.5%	11	47.8%		
GA at time of delivery	Preterm	43	23.0%	14	35.0%	10	43.5%	9.16	0.057
	Term	128	68.4%	26	65.0%	11	47.8%		
	Postdated	16	8.6%	0	0.0%	2	8.7%		

Table 4: Distribution of Cases according to Condition of Newborn

Condition of Newborn	Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
	No.	%	No.	%	No.	%	chi sq	p-value
Bedside	145	77.5%	26	65.0%	14	60.9%	5.64	0.228
NICU Admission	41	21.9%	14	35.0%	9	39.1%		

Table 5: Distribution of Cases according to Baby Growth

Baby Growth	Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
	No.	%	No.	%	No.	%	chi sq	p-value
Normal	177	94.7%	26	65.0%	16	69.6%	34.26	<0.001
IUGR	10	5.3%	14	35.0%	7	30.4%		

Table 6: Distribution of Cases according to Liquor

Liquor	Normotensive		Preeclampsia with non-severe features		Preeclampsia with severe features		significance	
	No.	%	No.	%	No.	%	chi sq	p-value
Adequate	181	96.8%	30	75.0%	16	69.6%	32.41	<0.001
Oligohydramnios	6	3.2%	10	25.0%	7	30.4%		

Table 7: Comparison of S. b HCG level by Maternal Outcome

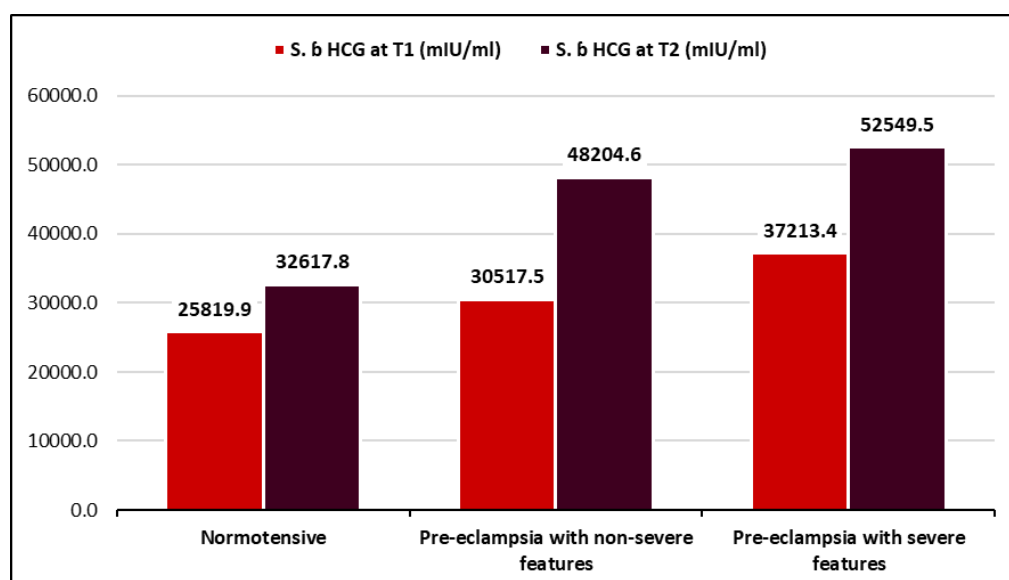
Maternal Outcome	S. b HCG at T1 (mIU/ml)		S. b HCG at T2 (mIU/ml)	
	Mean	SD	Mean	SD
Normotensive	25819.9	10017.8	32617.8	6759.0
Pre-eclampsia with non-severe features	30517.5	11076.2	48204.6	10594.7
Pre-eclampsia with severe features	37213.4	11968.4	52549.5	12074.0
ANOVA	F=14.20, p<0.001		F=108.8, p<0.001	

Table 8: ROC Analysis to find optimum cut off of S. b HCG Level & UAD for Prediction of Preeclampsia with non-severe features and Compare their Precisions

Prediction of Preeclampsia with non-severe features			
Parameter	S. b HCG at T1	S. b HCG at T2	UAD
AUROC (95% CI)	0.626 (0.53-0.73)	0.856 (0.80-0.91)	0.783 (0.70-0.86)
optimum cut off	bHCG > 36230	bHCG>39503	UAD > 0.87
Sensitivity	42.5 (36.4-48.6)	80 (75.0-85.0)	67.5 (61.7-73.3)
Specificity	81.4 (76.6-86.2)	81 (76.1-85.9)	87.1 (82.9-91.3)
PPV	32.8 (27.0-38.6)	47.4 (41.2-53.6)	52.8 (46.6-59.0)
NPV	87.0 (82.8-91.2)	95 (92.3-97.7)	93 (89.8-96.2)

Table 9: ROC Analysis to find optimum cut off of S. b HCG Level & UAD for Prediction of Preeclampsia with severe features and Compare their Precisions

Prediction of Preeclampsia with severe features			
Parameter	S. b HCG at T1	S. b HCG at T2	UAD
AUROC (95% CI)	0.772 (0.66-0.88)	0.893 (0.84-0.95)	0.855 (0.75-0.96)
optimum cut off	bHCG > 36726.5	bHCG>40316.0	UAD > 0.93
Sensitivity	60.9 (54.9-66.9)	87 (82.8-91.2)	78.3 (73.2-83.4)
Specificity	87.7 (83.6-91.8)	78.4 (73.3-83.5)	89.4 (85.6-93.6)
PPV	51.4 (45.2-57.6)	46.3 (40.1-52.5)	47.6 (40.8-59.0)
NPV	91.0 (87.5-94.5)	97.0 (94.9-99.1)	97 (94.7-99.3)

**Figure 1: Showing comparison of S. b HCG level by Maternal Outcome**

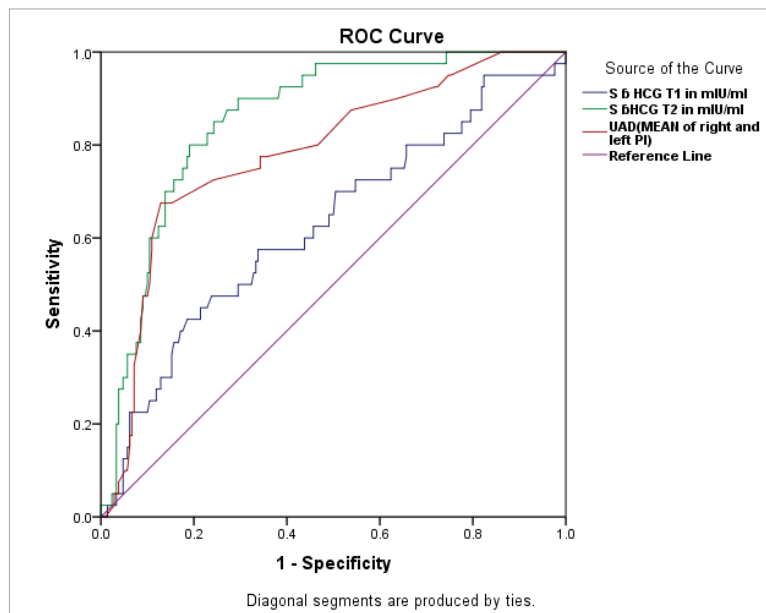


Figure 2: ROC Analysis to find optimum cut off of S. b HCG Level & UAD for Prediction of Preeclampsia with non-severe features and Compare their Precisions

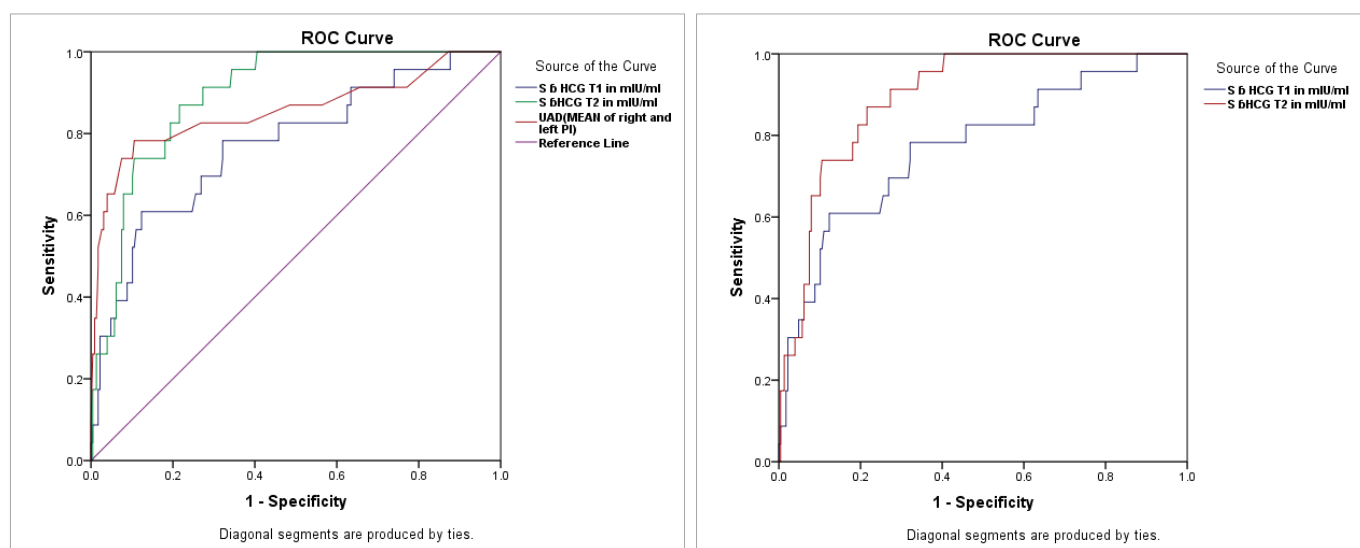


Figure 3: ROC Analysis to find optimum cut off of S. b HCG Level & UAD for Prediction of Preeclampsia with severe features and Compare their Precisions

Discussion

In Gestational hypertension the rise of the blood pressure is due to constriction of blood vessels and impaired angiogenesis which leads to hypoxia and hyperplasia of trophoblastic cells which leads to increased production of placental hormone ultimately leading to more levels of circulating 6 hCG. In our study we found that elevated 6 hCG levels in both trimester are related to raised maternal blood pressure as was also stated by Zygmunt et al (2002) [13]. It was evident from our study that raised Serum 6 hCG T1 mean 37213.4+-11968.4 and in T2 mean 52549+-12074.0 were significantly related to PIH similar to studies as Vidyabati et al (2014)(14), Towner et al (2006) (15), Tache et al (2014) (16), Davidson et al (2003) (17). We also found that Parity 1 and higher parity (more than 3) are susceptible to pre eclampsia similar to Rangkuti study in Indonesia 2022. The rates of LSCS in PIH group was found to be higher 60.9% in comparison to normotensive group where it was 53.5% similar to Tuffnel et al (2005) (1), Sibai. Results obtained were analyzed using Chi – square test, and P value was found to be 0.211 which was statistically insignificant. It was analysed that there is significant

impact of pre eclampsia on fetal growth, with higher prevalence of IUGR in affected pregnancies similar to “A study to assess the impact of pregnancy induced hypertension on Fetal outcomes among PIH patients delivered at Tertiary care hospital dadra & Nagar Haveli” [19-21] studies. And amniotic fluid was also estimated to be reduced in this pre eclampsia group with significant differences as in Heikkida et al [22], Harrington et al [23].

Conclusion

The study found that uterine artery Doppler indices are effective predictors of pre eclampsia, with higher mean 6 hCG levels in the pre eclampsia group. The Pearson correlation analysis showed moderately positive correlation between uterine artery doppler pulsatility index and serum 6 hCG levels at the first trimester and strongly positive correlation in the second trimester. The study also found that serum 6 hCG at the second trimester had the highest specificity, suggesting that a combination of these indices could improve prediction accuracy. Further research is needed to validate these findings.

Declarations

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Conflict of interest declaration

There is no conflict of interest among authors.

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Ethical Clearance

Approved by Institutional ethics committee

Contributors

Prof. Shaily Agarwal; Concept design, Supervision, Patients enrollment, Patients treatment.

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Dr. Divya Dwivedi; Help of paper writing, Data interpretation Supervision, Patients enrollment

Dr. Ashok Kumar Verma; Supervision, Patients enrollment, Case management, Radiological investigations

Dr. Deepak Anand; Supervision, Patients enrollment, Analysis

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