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Original Research Article

Prediction Of Pre-Eclampsia Among Pregnant Women In Usmanu Danfodio University Teaching Hospital, Sokoto, Using Maternal Serum Beta-Human Chorionic Gonadotropin

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Abstract

Previous attempts have been made to determine the role of maternal serum beta human chorionic gonadotropin (β-hCG) in the pathophysiology of pre-eclampsia. The objective of this study was to determine the correlation between maternal serum free β-hCG and the development of pre-eclampsia as well as to evaluate its utility as a predictive test for pre-eclampsia. This was a prospective cross-sectional study carried out in the antenatal clinic of Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria. A total of 200 pregnant women who fulfilled the inclusion criteria were recruited between 14-20 weeks of gestation. However, only 188 of them were completely followed up till delivery. A pretested questionnaire was used to obtain data of the subjects. Their blood samples were taken under aseptic technique for quantitative free β-hcg estimation using the ELISA technique. The subjects were then followed up till delivery and observed for development of pre-eclampsia. Correlation between serum free β-hCG concentration and blood pressure was studied while a logistic regression was used to determine a prediction model for pre-eclampsia. The result showed that there was statistically significant positive correlation between the maternal serum free β-hCG concentration with the mean systolic blood pressure (r= 0.432, p= 0.000) and mean diastolic blood pressure (r= 0.364, p= 0.000), among women with pre-eclampsia. The logistic regression model was statistically significant (Wald (X^2) = 26.13, P= 0.000). Using a Receiver Operating Characteristic Curve (ROC), the sensitivity and specificity of free β-hCG as a diagnostic test in pre-eclampsia was 61.1% and 96.5% respectively with cutoff point of 282.3mIU/ml. The study concluded that elevation of maternal serum free β-hCG in early second trimester is a useful indicator to identify women who are likely to develop pre-eclampsia in the same pregnancy.

Keywords: free β-hCG, correlation, prediction, second trimester, pre-eclampsia.

INTRODUCTION

Pre-eclampsia is a multisystemic disorder of unknown aetiology characterised by development of hypertension to the extent of 140/90 mmHg or more with significant proteinuria occuring after 20th week of gestation in a previously normotensive and non proteinuric woman [1]. Ten million women develop pre-eclampsia each year around the world while about 76,000 pregnant women die each year from pre-eclampsia and related hypertensive disorders [2].

Despite many active researches for years now, the exact aetiology of this potentially fatal disorder remains poorly understood. A number of theories have been put forward where different biochemical markers have been implicated in the causal association of pre-eclampsia. Most current hypotheses regarding the pathophysiologic mechanisms of pre-eclampsia points to early placental abnormalities [1]. Several studies have reported an association between unexplained increase in maternal serum β-hCG levels in the second trimester of pregnancy and subsequent development of pre-eclampsia [3-5]. Other biochemical markers that

have been studied for their roles in pre-eclampsia include: pregnancy associated plasma protein- A (PAPP-A), soluble FMS-like tyrosine kinase (s-Flt), placenta growth factor (PlGF), soluble endoglin (s-Endoglin), placenta protein-13 (PP-13), cystatin-C, foetal hemoglobin (HbF), α_1-microglobulin (A1M), Inhibin A and Activin A [6, 7].

The human chorionic gonadotropin (hCG) is a glycoprotein composed of two non-covalently linked subunits, α and β, and is produced by syncytiotrophoblast cells of the placenta [8]. Maternal serum hCG peaks at 8 - 10 weeks of gestation and then declines to reach a plateau at 18 - 20 weeks of gestation [9]. Its best known biologic function is the maintenance of corpus luteum of pregnancy. During pregnancy hCG also promotes: cytotrophoblast differentiation, immunosuppression and blockage of phagocytosis of invading trophoblast cells [10]. It appears that hCG plays an important embryonic signal which could trigger adaptive cardiovascular changes in early pregnancy and simultaneously preserving sufficient utero-placenta perfusion during the entire gestation by an endothelial independent mechanism.

Twin pregnancies and molar pregnancies produce higher levels of hCG and they are associated with a higher incidence of pre-eclampsia than uncomplicated singleton pregnancies. Furthermore, hCG secretion may be increased as a result of abnormal placental invasion or placental immaturity [10]. Production of hCG may also be linked to the trophoblast response to hypoxia, with the development of a hypersecretory state [10].

The availability of highly sensitive and specific physiologic and biochemical markers would not only detect patients at risk but also permit a close surveillance, an early diagnosis, timely intervention, as well as simplified recruitment for future studies looking at therapeutic medications and additional prospective markers. This study evaluates the role of serum β hCG in development of pre-eclampsia and its utility as a predictive test for pre-eclampsia.

METHODOLOGY

This was a prospective cross-sectional study carried out in the antenatal clinic of Usmanu Danfodiyo University Teaching Hospital Sokoto (UDUTH), Nigeria. All pregnant women in the early second trimester, (between 14-20 weeks of gestation) presenting at the antenatal clinic and who consented to participate in the study were recruited consecutively until the desired sample size of 200 was achieved. Exclusion criteria were pregnant women with pre-existing hypertension, multiple gestations in present pregnancy, heart disease, renal disease, diabetes mellitus and those who did not give consent to participate in the study.

The information that was obtained and entered into the questionnaire include: socio-demographic characteristics, gestational age, parity, obstetrical, gynaecological, medical and social histories. The weight, height, and sitting blood pressure were also recorded. Their blood samples were taken under aseptic technique for quantitative serum free β-hcg estimation using the GenWay Biotechnology β-hCG ELISA test kit. The subjects were followed up till delivery and observed for development of pre-eclampsia. Pre-eclampsia was defined as sustained hypertension with blood pressure of at least 140/90 mmHg measured at least 4 hours apart, after 20 weeks of gestation with significant proteinuria of at least 2+ on urinalysis. Urine samples were collected from the subjects who were noticed to have elevated blood pressure after 20 weeks of gestation for qualitative analysis of proteinuria. The subjects were divided into two groups: group A - women who developed pre-eclampsia and group B- women who did not develop pre-eclampsia till delivery.

Data analysis was performed using statistical package for social sciences (SPSS) version 20. Data on maternal age, weight, height, serum β-hCG, and blood pressure were presented as mean with standard deviation. The mean of these variables were compared between the subjects that developed pre-eclampsia and those that did not develop pre-eclampsia, using independent t-test. The presence or absence of significant proteinuria between the pre-eclamptic group and women with no features of pre-eclampsia was compared using Fisher's exact test.

The outcome variables were maternal blood pressure and presence or absence of significant proteinuria. Correlation between serum β-hCG concentration and blood pressure was studied using the Pearson correlation to see whether the two variables exhibit any linear correlation. In order not to allow for the effects of the potentially confounding variables, age, parity, gestational age, weight, and height were included as simple linear covariates to determine if they exhibit any significant correlation with serum β-hCG concentration.

Stepwise binomial logistic regression was then used to determine whether serum β-hCG can predict pre-eclampsia. The area under a Receiver Operating Characteristic Curve (ROC) generated was used to define a cut off value of serum β-hCG above which pre-eclampsia can be predicted. The level of significance (P value) was set at < 0.05.

The study was fully funded by the researcher. Ethical clearance was obtained from the Ethical and Research Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto. Informed consent was obtained from all participants in this study. Participants were reassured that data collected will be used for research purpose only.

RESULTS

A total of 200 pregnant women who fulfilled the inclusion criteria were recruited into this study from the Antenatal Care Clinic of Usmanu Danfodiyo University Teaching Hospital, Sokoto. However, only 188 (94 %) of them were completely followed up till delivery. Out of a total 188 cases who were finally followed up till delivery, 18 (9.6%) developed preeclampsia (group A), while 170 (90.4%) of them did not develop pre-eclampsia (group B).

Table-1 shows the comparison of the mean age, parity, gestational age at recruitment, weight, height among the pre-eclamptic group and normal pregnancy group. The mean age of the women with features of preeclampsia was (29.2 ± 5.31 years) compared with women with no features of preeclampsia (27.6 ± 5.23 years). The difference was not statistically significant (t=1.24, p= 0.217). The mean parity of the patients in the pre-eclamptic group was 0.6 ± 1.09 and 2.0 ± 1.71 in the group who did not develop pre-eclampsia. The difference was statistically significant (t = 3.21, p = 0.001). The mean gestational age of the patients at recruitment was 18.7 ± 1.67 weeks in the pre-eclamptic group and 18.5 ± 1.89 weeks in the group who did not develop pre-eclampsia. The difference was also not statistically significant (t = 0.39, p = 0.696). In the pre-eclamptic group the mean weight was 68.3 ± 11.94 kg compared to the group who did not develop pre-eclampsia, 68.2 ± 15.08 kg. The difference was not statistically significant (t = 0.004, p = 0.997). The mean height was 1.6 ± 0.05m in the pre-eclamptic group which was comparable to that of the group who did not develop pre-eclampsia, 1.6 ± 0.06m. There was no statistically significant difference (t = 0.33, p = 0.743).

Table-: Mean ±SD of age, parity, gestational age, weight, height among normal and pre-eclamptic group

Variable	Group A Mean ± SD	Group B Mean ± SD	T test	P- value
Age (years)	29.2 ±5.31	27.6 ±5.23	1.24	0.217
Parity	0.6 ±1.09	2.0 ±1.71	3.21	0.001
Gestational age (weeks)	18.7 ±1.67	18.5 ±1.89	0.39	0.696
Weight (Kg)	68.3 ±11.94	68.2 ±15.08	0.004	0.997
Height (m)	1.6 ±0.05	1.6 ±0.06	0.33	0.743

Table-2 below shows the mean systolic blood pressure, mean diastolic blood pressure and urine protein qualitative analysis of pre-eclamptic group and the group who did not develop pre-eclampsia. The mean systolic blood pressure in women with pre-eclampsia was 157.2 ±7.52mmHg, while it was 111.3 ±10.91mmHg in the women with no features of pre-eclampsia. This was statistically significant (t = 17.41, p = 0.000). The mean diastolic blood pressure was also higher in the pre-eclamptic group (92.2 ±6.47mmHg) compared to women with no features of pre-eclampsia (70.5 ±7.36mmHg). The difference was statistically significant (t = 12.05, p = 0.000). The entire pre-eclamptic group had urine dipstick protein of at least 2+, but none of the normotensive pregnant women had significant proteinuria (Fisher's exact test, p = 0.000).

Table-2: Comparison between the Mean blood pressure and urine protein qualitative analysis of pre-eclamptic group and normal pregnancy group

Parameter	Group A Mean ± SD	Group B Mean ± SD	Test	P- value
Systolic blood pressure (mmHg)	157.2 ±7.52	111.3 ±10.91	t = 17.41	0.000
Diastolic blood pressure (mmHg)	92.2 ±6.47	70.5 ±7.36	t = 12.05	0.000
Urine protein (≥2+)	n=18	n=0	Fisher's exact test	0.000

Table-3 shows the comparison of the mean maternal serum β-hCG concentration between the pre-eclamptic group and the women with no features of pre-eclampsia. The mean level of maternal serum β-hCG in the pre-eclamptic group was significantly higher compared to women with no features of pre-eclampsia (283.47 ± 46.64 mIU/ml vs. 211.90 ± 39.09 mIU/ml). The difference was statistically significant (t= 7.25, p=0.000).

Table-3: Comparison between the mean maternal serum β-hCG of pre-eclamptic group and normal pregnancy group

Serum β-hCG	Group A Mean ± SD	Group B Mean ± SD	T test	P- value
β-hCG (mIU/ml)	283.47±46.64	211.90±39.09	7.25	0.000

Table-4 below shows that there was statistically significant positive correlation between the

maternal serum β-hCG concentration with the systolic blood pressure (r= 0.432, p= 0.000) and diastolic blood pressure (r= 0.364, p= 0.000).

Table-4: Correlation between serum level of β-hCG with systolic blood pressure and diastolic blood pressure

Variable		Systolic Blood Pressure	Diastolic Blood Pressure
Serum β-hCG level (mIU/ml)	r	0.432	0.364
	p	0.000	0.000

The scatter diagram in Figure 1 and 2 below shows positive linear correlation between maternal serum β-hCG concentration and systolic and diastolic blood pressure.

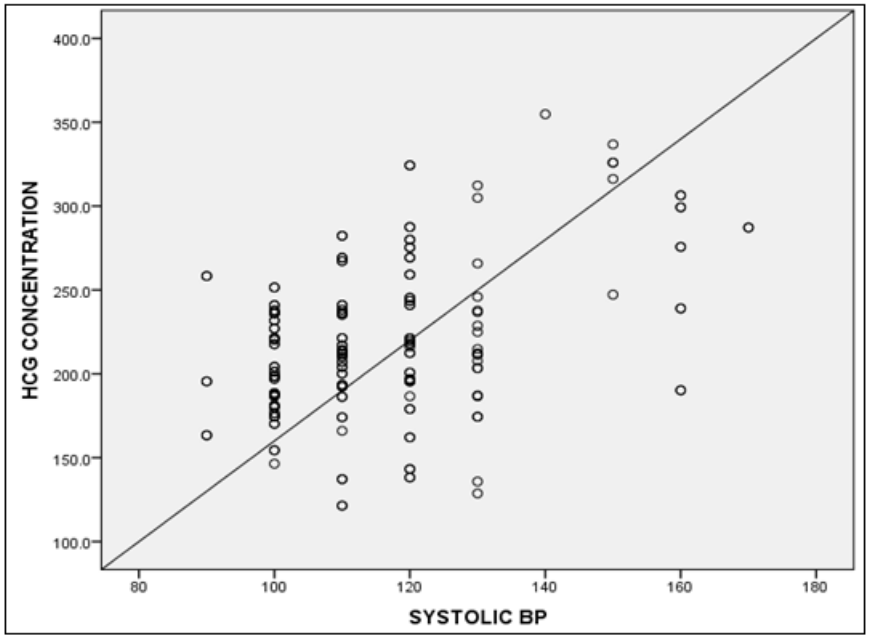

Fig-1: Scatter diagram showing positive linear correlation between maternal serum β-hCG concentration and systolic blood pressure

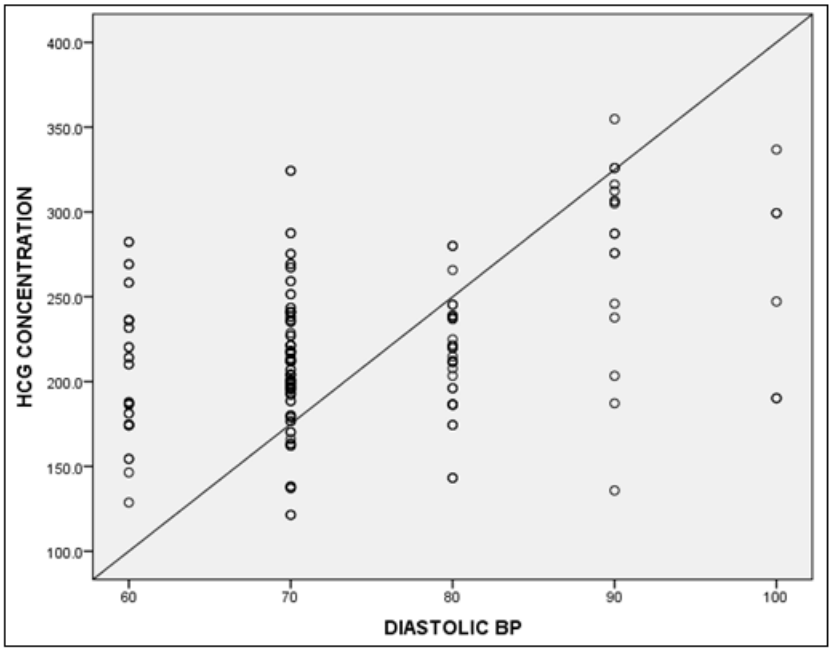

Fig-2: Scatter diagram showing positive linear correlation between maternal serum β-hCG concentration and diastolic blood pressure

Table-5 below shows correlation between serum level of β-hCG with maternal age, gestational age, parity, weight and height in pre-eclamptic women. There was no statistically significant correlation between β-hCG concentration with maternal age (r= -0.003, p= 0.963), parity (r= -0.086, p= 0.243), gestational age, (r= 0.002, p= 0.979), weight, (r= 0.067, p= 0.362) and height, (r= 0.010, p= 0.896).

Table-5: Correlation between serum level of β-hCG with maternal age, gestational age, parity, weight and height

Variable		Age	Gestational age	Parity	Weight	Height
Serum β-hCG level (mIU/ml)	r	-0.003	0.002	-0.086	0.067	0.010
	p	0.963	0.979	0.243	0.362	0.896

The area under the curve (AUC) was 0.873 with 95% confidence interval (0.769-0.976) which was significantly different from 0.5 (p=0.000). Receiver operating characteristic curve (ROC) identified that with cutoff point of 282.3mIU/ml, the sensitivity and specificity of β-hCG as a predictive test in pre-eclampsia was 61.1% and 96.5% respectively. This is shown in Figure-3 below.

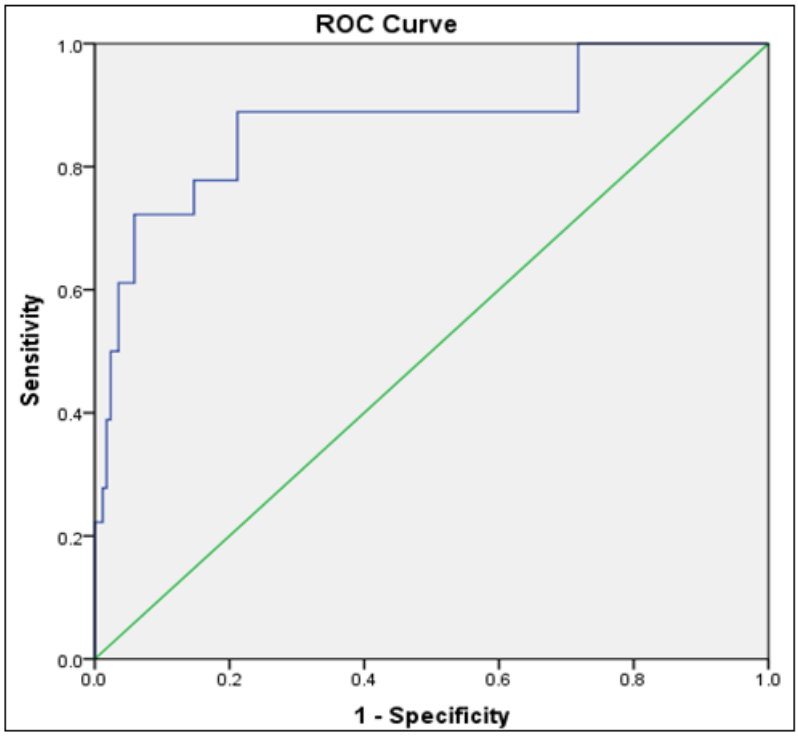

Fig-3: Sensitivity and Specificity level of β-hCG in the prediction of pre-eclampsia

Table-6 below shows the logistic regression model for the prediction of pre-eclampsia using serum free β-hCG.

Table-6: Logistic Regression Model

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	HCG	.039	.008	26.126	1	.000	1.040	1.024	1.055
	Constant	-11.815	2.043	33.460	1	.000	.000		
a. Variable(s) entered on step 1: HCG.									

DISCUSSION

In this study, the mean parity in the pre-eclamptic group was lower compared to the normotensive group with higher proportion being nulliparous among the pre-eclamptic group. This was corroborated by reports from previous studies [11]. However, yakasai & Morhason-Bello and Ganiyu *et al*., reported contrary findings [12, 13]. It is believed that immune maladaptation of the primigravida is responsible for the higher incidence of preeclampsia in this group. This maladaptation is lost in subsequent pregnancies, hence the decreasing incidence of preeclampsia in the multipara. The mean gestational age of the patients at which serum β-hCG was estimated for both groups of women was compared and there was no statistically significant difference (p = 0.696). This may provide adequate basis for comparison between the two groups.

The mean systolic blood pressure in women with preeclampsia was significantly higher compared to the women without features of pre-eclampsia (p = 0.000). The mean diastolic blood pressure was also higher in the pre-eclamptic group compared to women without features of pre-eclampsia (p = 0.000). The entire pre-eclamptic group had urine dipstick protein of at least 2+, but none of the normotensive pregnant women had significant proteinuria. Proteinuria is a specific feature of preeclampsia and in the presence of hypertension it is the standard criterion upon which the diagnosis hinges [1]. It is a result of the pathological changes in the glomeruli as part of the widespread endothelial dysfunction characterized in pre-eclampsia [1].

In our study, the mean level of maternal serum β-hCG in the pre-eclamptic group was significantly higher compared to women with no features of pre-eclampsia (p < 0.000). This finding is corroborated by the results of some studies done elsewhere [3-5, 14]. However, in a recent study carried out to determine potential indicators of pre-eclampsia in African black women, Adeosun *et al*., reported lower maternal serum β-hCG in pre-eclamptic subjects compared to controls [15]. The study was conducted in the third trimester and there was significant difference in the mean gestational age when serum β-hCG was estimated, between the pre-eclamptic group and the controls. Furthermore, there was no correlational study to control for this difference in gestational age which may be a significant confounding factor in the study. In addition, when the serum β-hCG was measured in the postpartum period at the same day for both groups, there was significant elevation of serum β-hCG among the pre-eclamptic subjects compared to the controls.

In another study carried out by Dugoff, there was no correlation between maternal serum β-hCG concentration and pre-eclampsia [16]. This may probably be related to the conduct of the study in the first trimester. In the first trimester, placental damage may be insufficient to cause an increase in serum β-hCG levels associated with pre-eclampsia [16]. In a prospective case control study to determine whether maternal second trimester serum hCG concentrations will predict development of preeclampsia, Keikkala E *et al.*, reported lower concentrations of hCG in women with preeclampsia compared to controls [17]. The lower concentration of hCG reported may be due to the fact that the hyperglycosylated form of hCG (hCG-h) was measured which is an independent molecule to β-hCG measured in this study [17].

There was a statistically significant positive correlation between serum β-hCG concentration and increase in both systolic (r= 0.432, p= 0.000) and diastolic blood pressure (r= 0.364, p= 0.000) in our study. However, there was no significant correlation between β-hCG concentration and potentially confounding variables like maternal age, parity, gestational age, weight, and height. These findings are in accordance with the results conducted by other studies [3, 4].

Contrary to the results of our study, Yadav *et al*., did not find any correlation between maternal serum β-hCG concentration and elevated blood pressure [18]. The divergent points of maternal serum β-hCG with wide range of cutoff values in the study may be responsible for this result. Also, the relatively smaller sample size could be a contributing factor.

The predictive power of maternal serum β-hCG in our study was assessed using an ROC curve. It identified that with cutoff point of 282.3mIU/ml, the sensitivity and specificity of β-hCG as a predictive test in pre-eclampsia was 61.1% and 96.5% respectively. Similarly, the accuracy of serum β-hCG in predicting pre-eclampsia has been determined by other studies using a ROC curve [3-5].

Lukas *et al.*, reported a sensitivity of 79% and specificity of 54% when free β-hCG was used to predict pre-eclampsia [3]. In the study, only primigravid women were recruited which may account for why β-hCG as a predictive test in pre-eclampsia had higher sensitivity and lower specificity compared to our study.

Sahar *et al*., reported that with cutoff point of 50,000 mIU/ml of maternal serum β-hCG, the sensitivity was 56.25% and specificity was 91.43% in the prediction of pre-eclampsia [19]. The lower value of serum β-hCG concentration in our study is probably because only the free beta (β) component of the hCG was assayed unlike the study by Sahar et al where total β-hCG was measured. In the normal second trimester maternal sera, the level of intact hCG range from 20,000 mIU/ml to 50,000 mIU/ml [20]. In contrast, the levels of either free α or free β-hCG are on average 0.5 to 1% of hCG levels [20, 21]. Free β-hCG has also been used by other studies to predict pre-eclampsia with smilar findings [3, 22].

The real advantage of using free β-hCG instead of the intact molecule is still open to debate. The sensitivity and specificity of the test may change according to the method of assay, the clinical and epidemiological background of the subjects, the gestational age at which samples were collected, and the cutoff chosen to distinguish high from normal hCG levels [23]. Nonetheless, it has been suggested that the effectiveness of free beta-hCG methodology is superior to that of total hCG in maternal serum screening with higher sensitivity [24]. The beta subunit is unique to hCG and it confers biological and immunological specificity to the hCG molecule [20]. Its clearance in the blood is more slowly when compared to the intact hCG molecule [24].

The pathophysiologic process that causes changes in the serum β-hCG usually becomes overt in the mid trimester [25]. Therefore this period was decided upon for the evaluation of maternal serum β-hCG. This is important because, for any biomarker to have any usefulness in the prediction of pre-eclampsia, it has to be detected prior to the manifestation of the disease at 20 weeks of gestation. Although the ultimate cure for pre-eclampsia is delivery, nevertheless early identification of women at increased risk is of value as targeted surveillance and intervention may lead to improved outcome. In this study the serum β-hCG was estimated once for each subject and not repeated serially to identify the point at which the alterations of the β-hCG becomes significant to suspect pre-eclampsia.

CONCLUSION

In conclusion, this study showed that the maternal serum free β-hCG level was significantly higher among the pre-eclamptic group compared to the women with no features of pre-eclampsia. It also demonstrated that there was statistically significant positive correlation between the maternal serum free β-hCG concentration with systolic and diastolic blood pressure. In addition with cutoff point of 282.3mIU/ml, serum free β-hCG can be considered as marker for predicting pre–eclampsia in the early second trimester of pregnancy with sensitivity of 61.1% and specificity of 96.5%.

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