Original Article

Assessment of the Usefulness of Maternal Serum Beta-Human Chorionic Gonadotrophin as Predictive Marker for Pre-Eclampsia and Poor Clinical Neonatal Outcome in Sokoto, North-West Nigeria

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ABSTRACT

Preeclampsia and its related maternal and neonatal complications remain a significant global public health threat and economic concern, especially in developing countries. It contributes to the high maternal and neonatal morbidity and mortality in Sokoto. Some of the analytes evaluated had low predictive power for preeclampsia and poor neonatal outcomes in Sokoto. The present study assessed the application of maternal serum beta human chorionic gonadotrophin (βhCG) levels as a predictive marker for preeclampsia and poor neonatal outcomes in Sokoto. This was a prospective case-control study conducted in some selected centres in the Sokoto metropolis. Two hundred participants (one hundred cases and one hundred controls) were recruited for this study. The data obtained were analysed using SPSS 25 version statistical software. The association between the variables was assessed using Pearson's linear correlation and unpaired student t test analysis, and predictive value for developing preeclampsia, and poor clinical neonatal outcome was determined using Receiver Operating Characteristic analysis. The results showed that maternal serum levels of βhCG of preeclamptic women were significantly higher compared to the controls (5189.91±7.35, 3943.71±53.21 mIU, p=0.000). There were significant negative correlations between βhCG, with birth weight (r=-0.371, p=0.000), and Apgar score (r= -0.385, p=0.000). The predictive power of βhCG for developing pre-eclampsia and poor neonatal outcomes was excellent and good, respectively. In conclusion, maternal serum βhCG levels at second trimesters and above may be useful in predicting preeclampsia and poor clinical neonatal outcomes.

Keywords: βhCG, Maternal Preeclampsia, Serum, Sokoto.

INTRODUCTION

Preeclampsia and its related maternal and neonatal complications remain significant global public health threats and economic concerns, especially in developing countries[1]. The management of complications related to preeclampsia has economic challenges in developing countries, especially Nigeria, due to limited resources and inadequate healthcare facilities[1]. For now, the only effective treatment of preeclampsia is delivery of the placenta or preventing it from occurring by assessing biomarkers that will predict the development of adverse pregnancy, in which quadruple analytes are such markers[2,3]

Maternal serum beta-human chorionic gonadotrophin (βhCG) is one of the quadruple analyte tests performed in the early 1980s to identify foetuses with structural deformity and chromosomal aneuploidy [4]. It has been used in recent years to

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predict numerous unfavourable outcomes for mothers and foetuses, including preeclampsia, large/small size for gestational age, preterm delivery, and stillbirth[5].

Normally, all pregnant women should be offered quadruple screening tests, however, it is highly recommended for women with a high risk of developing adverse pregnancy outcomes, such as primigravida, and pregnant women with a previous history of adverse pregnancy outcomes, among others[6]. During pregnancy, a woman undergoes dramatic physiological and hormonal changes[7]. These orchestrated changes can go wrong at some stage of pregnancy, leading to adverse pregnancy[7]. One of the hypertensive disorders that is commonly seen during pregnancy is preeclampsia (PE) [8]. Other hypertensive disorders that fall under this category are gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension [8,9]. Preterm birth, placental abruption, stillbirth, low birth weight, low Apgar scores, intrauterine foetal growth restrictions, and many other adverse pregnancy outcomes are frequently linked to it [10, 11]. Preeclampsia is a multisystem disorder characterised by widespread vascular endothelial abnormalities. It remains a major cause of morbidity and mortality for both mothers and infants, especially in low- and middle-income countries[11,12].

Human chorionic gonadotropin (hCG) is a glycoprotein with a molecular weight of 36.7 kDa and 244 amino acids [13]. The syncytiotrophoblast produces βhCG, which stimulates the corpus luteum to secrete progesterone and maintain pregnancy[13 - 15]. Maternal serum βhCG reaches its maximum concentration of 100,000 iu/l at about 8-10 weeks of gestation, and it declines as placental steroid synthesis commences [14]. It is a heterodimeric molecule composed of an alpha subunit that is identical to luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, and the beta subunit is unique to human chorionic gonadotrophin[15]. Unexplained elevation of maternal serum βhCG concentration in the second and third trimesters (cut-off values of > 2 multiples of median) is associated with adverse pregnancy outcomes, particularly preeclampsia[16].

Previous studies reported that high maternal serum concentrations of βhCG, in the second trimester, were associated with preeclampsia, preterm birth, low birth weight and stillbirth [17,18]. The present study was aimed at evaluating the application of maternal serum βhCG concentration at the second, and above trimester, as a predictive marker for preeclampsia and poor clinical neonatal outcomes in Sokoto.

MATERIALS AND METHODS

The study was conducted in the Department of Chemical Pathology and Immunology, Faculty of Basic Clinical Sciences and Obstetrics and Gynaecology, Faculty of Clinical Sciences, Usmanu Danfodiyo University, Sokoto, in collaboration with Usmanu Danfodiyo University Teaching Hospital (UDUTH), Specialist Hospital (SHS) and Maryam Abacha Women and Children Hospital (MAWCH) Sokoto. These Hospitals (UDUTHS, MAWCHS, and SHS) are located within the Sokoto metropolis and serve as referral centre for more than ten million people of the Nigerian states of Sokoto, Kebbi, and Zamfara and neighbouring countries like Niger and Benin Republic in West African sub-region[19].

A total of two hundred (200) study Participants, consisting of one hundred preeclamptic singleton women (cases) and one hundred healthy singleton pregnant women(controls), matched for gestational age, gravidity, parity, and age range were recruited for this study. These were consecutively selected from among the population of pregnant women who attended the Antenatal Care Clinic during the period of study at UDUTH, SHS, and MAWCH all in the Sokoto metropolis. At delivery, pregnancy outcomes (maternal and neonatal outcomes) of the recruited participants were documented.

Inclusion criteria include; confirmed cases of classical preeclampsia that agreed to participate, healthy singleton pregnant women with normal blood pressure and whose gestational age was greater than 20 weeks and who agreed to participate (controls). The exclusion criteria include; Healthy pregnant women who were less than 20 weeks of gestation, pregnant women who consume alcohol/or smoke cigarettes, multiple gestations for both cases and controls, chronic hypertension with

superimposed preeclampsia and other atypical preeclampsia, and pregnant women with chronic medical diseases such as diabetes mellitus, chronic hypertension, sickle cell disease, connective tissue disorders, renal disease, and liver disease, among others, pregnant women with overt urinary tract infections, un-booked pregnant women, and those who refuse to consent. Before being included in the study, the participants were fully informed and their agreement was obtained under standard protocol.

The sample size for the study was determined using a standard formula for the calculation of minimum sample size [20].

Sample size n is given by the formula.

$n=Z^2pq/d^2$

Where n = minimum sample Size, Z = Standard normal deviate (SND) at the confidence interval (1.96) which corresponds to a 96% confidence level, P =Prevalence of preeclampsia obtained from a previous study in Sokoto, is six percent (6%) (Singh *et al.,* 2014), q = 1- P (1-0.06 =0.94), d = degree of precision is (0.05)

Therefore: $n = \frac{(1.96)^2(0.06)(0.94)}{(0.05)^2}$

$n = \frac{3.8416 \times 0.0564}{0.0025}$

$n = \frac{0.2166324}{0.0025}$

$n = 87$

In addition, 10% (9 patients) were added as attrition rate, which implies 87 plus 9 equals 96.

Therefore, the minimum sample size required for the study was 96. However, 100 subjects were recruited for better precision and statistical analysis.

The study was a prospective, case-control study. At the respective location, the participants who satisfied the study inclusion criteria were consecutively selected from the population of pregnant women who attended the antenatal care clinic at three selected centres in Sokoto Nigeria, during the period of study.

A study questionnaire was designed, and was used for the collection of information about the subject's demographic characteristics of mothers that includes; age, ethnic group, religion, level of education, and occupation. Obstetric history of the mother which includes; a history of preeclampsia in a previous pregnancy, parity, gestational age, history of premature delivery, stillbirth, inter-pregnancy interval, and recent change of partner were recorded. Similarly, anthropometric measurements of mothers (weight, height, and body mass index), and blood pressure were taken.

The nature of pregnancy outcomes (full-term delivery, preterm delivery, stillbirth, small-for-gestational-age, low birth weight, Apgar score, and congenital malformation), and anthropometric measurements of babies (birth weight and birth length were taken).

Maternal serum levels of human chorionic gonadotrophin were also measured. All the findings were included in a study questionnaire.

The data obtained were sorted out manually, entered into a Microsoft Office Excel for Windows 2010 spreadsheet, and analyzed using SPSS version 23 statistical computer software. The results were expressed as the Mean , ±SEM a two-tailed unpaired Students, Receiver Operating Characteristics (ROC) analysis and Pearson's correlations. A *p*-value of less than or equal to 0.05 ($p \leq 0.05$) was considered significant.

Ethical Considerations

The ethical approvals were obtained from the Ethics and Research Committees of Usmanu Danfodiyo University Teaching Hospital (UDUTH/HREC/2019/NO.822), Specialist Hospital (SHS/SUB/2019/133/VOL1). and Maryam Abacha Women and Children Hospital (MAWCH/SUB/2019/018/VOL2) all in Sokoto by the Helsinki Declaration. Anonymity of every study subject was ensured.

RESULTS

The General characteristics of preeclamptic women, controls and their neonatal outcomes are shown in table 1. The age range of preeclamptic women in this study was between 15 and 42 years. Of eighteen preeclamptic women, 18 (18%) were less than 19 years, 24 (24%) were above 35 years, and 58 (58%)

were within the range of 20 to 34 years. No significant difference between the controls (t^2 0.804, p=0.422). Fifty-three, 53 (53%) of preeclamptic women had regular antenatal care visits, and 47 (47%) had less than four visits before delivery, while 97 (97%) of controls had regular antenatal care visits and 3 (3%) had less than four visits before delivery.

There was a significant difference between controls and preeclamptic women in terms of antenatal care visits (t^2 0.213, p= 0.004). Ninety-three, 93 (93%) of the preeclamptic women had high-risk factors for preeclampsia, and 7 (7%) had no risk factors, while the majority, 78 (78%) of controls had no such high-risk factors. There was a significant difference between the two groups (t^2 0.912, p=0.002). Most preeclamptic women were primigravida, which accounts for 42 (42%), followed by grand multigravida (gravidity of five and above), which was 35 (35%), and gravidity between 2 and 4 accounted for 23 (23%). Fifty-two, 52 (52%) of preeclamptic women had a spontaneous vaginal delivery, 2 (2%) had assisted vaginal delivery, and 46 (46%) had an emergency cesarean section, while for controls, 86 (86%) had a spontaneous vaginal delivery, 5 (5%) had assisted vaginal delivery and 9 (9%) had an emergency cesarean section. There was a significant difference between the two groups (t^2 6.118, p=0.000).

Fifty-eight, 58 (58%) of babies delivered by preeclamptic women were females and the remaining 42(42%) were males, while among controls, 63 (63%) of the babies delivered were females, and the remaining 37 (37%) were males, with no significant difference between the two groups (t^2 -0.286, p=0.775).

In terms of viability, eighty-five percent 85 (85%) of the babies of preeclamptic women were live births and 15 (15%) were stillbirths. As for the controls, all 100 (100%) were live births, with no stillbirths. There was a significant difference between babies of preeclamptic women and controls (t^2 4.180, p=0.000). The majority, 80 (80%) of babies of preeclamptic women were full-term and 20 (20%) were pre-term. Ninety-seven, 97(97%) of the babies of control subjects were full-term and 3 (3%) were pre-term, with a significant difference between babies of preeclamptic and control women (t^2 4.226, p=0.000).

Seventy-two, (72%) of the babies of preeclamptic women had appropriate birth weight for their gestational age, and 28(28%) had low birth weight, while 96 (96%) of the babies of control subjects had appropriate birth weight for their gestational age and 4 (4%) had low birth weight. There was a significant difference between the two groups (t^2 3.782 p= 0.000). Almost half, 49(49%) of babies of preeclamptic women had Apgar scores of less than seven, and 51 (51%) had Apgar scores of seven and above (normal), while 13(13%) of babies of control subjects had low Apgar score (Apgar score less than seven) and 87 (87%) had normal Apgar score. There was a significant difference between babies of preeclamptic mothers and those of control mothers in terms of maturity, birth weight, and Apgar score (t^2 4.226, p=0.000; t^2 3.782, p=0.000 and t^2 4.112, p=0.000) respectively.

Table 2 Shows serum levels of βhCG in (Mean ± SEM)

between preeclampsia and controls, live birth and still birth, full term and preterm babies, normal and low Apgar score babies and babies with normal and low birth weight. The results showed that the levels of βhCG, were significantly higher in preeclamptic women than in controls (5189.91±75.35 vs 3942.71, p=0.000). The maternal mean serum βhCG, concentrations in women with live birth babies and those with stillbirth babies, showed that βhCG, in women with stillbirth babies, were significantly higher compared to the women who had live birth babies (4499.0 ± 06.48 vs 54082.70±19.23, p=0.000).

The maternal mean serum concentrations of βhCG in women who had preterm babies and those with full-term babies, showed that βhCG of women with preterm babies were significantly higher compared to the women who had full-term babies (4471.16 ± 06.57 vs 5332.23 ± 15.73, p=0.000). The maternal mean serum concentrations of βhCG in women who had low Apgar score babies and those with normal Apgar scores, showed that βhCG levels in women with low Apgar score babies were significantly higher compared to those with normal Apgar score babies (4387.50±75.74 vs 4964.20±101.99,

p=0.000). The maternal mean serum concentrations of βhCG in women who had low birth weight babies and those with normal birth weight babies, showed that βhCG of women with low-birth-weight babies were significantly higher compared to the women who had normal birth weight babies (4441.0±06.70 vs 5224.1±14.050, *p*=0.000).

Table 1: General characteristics of preeclamptic women, controls and their neonatal outcomes

Parameters	Preeclampsia 100(100%)	Controls 100 (100%)	t^2	*p*-value
Age (Years)				
≤19 years	18(18%)	18(18%)		
20 to 34 years	58(58%)	55(55%)	0.804	0.422
≥ 35 years	24(24%)	27(27%)		
Age range (Years)	15 to 42	15 to 42		
Antenatal visit	53(53%)	97(97%)		
Adequate	47(47%)	3(3%)	0.213	0.004
Not adequate				
History of risk factors for Preeclampsia				
NO				
YES	7(7%)	79(79%)		
	93(93%)	21(21%)	0.912	0.002
Nature of Delivery				
Spontaneous vaginal delivery	52(52%)	86(86%)		
Assisted vaginal delivery	2(2%)	5(5%)	5.622	0.000
Cesarean sections	46(46%)	9(9%)		
Gender				
Male	42(42%)	37(37%)	-0.286	
Female	58(58%)	63(63%)		
Viability				
Live birth	85(85%)	100(100%)	4.180	0.000
Stillbirth	15(15%)	0(0%)		
Maturity				
Full term	80(80%)	97(97%)	4.226	0.000
Preterm	20(20%)	3(3%)		
Birth weight				
Low birth weight	28(28%)	4(4%)	3.782	0.000
Normal birth weight	72(72%)	96(96%)		
Apgar Score			4.112	0.000
Low Apgar score(< 7 score)	49(49%)	13(13%)		
Normal Apgar score(≥ 7 score)	51(51%)	87(87%)		

Table 2: Shows serun levels of βhCG in (Mean ± SEM) between preeclampsia and controls in relation to various pregnancy outcomes

Subjects	Number of subjects	βhCG(mUI/ml)	p value
Preeclampsia	100	5189.91±75.35	0.000
Controls	100	3942.71±53.21[a]	
Live babies	185	4498.00±06.48	0.000
Still-birth	15	54082.70±19. 23[a]	
Full-term	178	4471.16±06.57	0.000
Preterm	22	5332.23±15. 73[a]	
Normal Apgar score	138	4387.50±75.74	0.000
Low Apgar score	62	4964.20±101.99[a]	
Normal birth weight	168	4441.0± 06.70	0.000
Low birth weight	32	5224.1±14.050[a]	

DISCUSSION

The age range of preeclamptic women in this study was between 15 years and 42 years, eighteen percent of them were less than 19 years of age, which consider a teenage pregnancy, which is a known risk factor for preeclampsia. Twenty four percent of preeclamptic women were above 35 years of age, which is also a risk factor for preeclampsia. This corroborates with previous studies, which observed that advanced maternal age and teenage pregnancy are at risk of adverse pregnancy outcomes, including preeclampsia [21,22]

The percentage of preeclamptic women who had no adequate antenatal visit was higher compared to the control group, and their reasons include; financial constraints, cultural beliefs, cumbersome protocols nature of the antenatal visit, knowledge about antenatal care so they can apply it at home, (like taking haematinics and checking blood level), Similar reasons were reported by previous studies[23-25]

Ninety-seven per cent (97%) of preeclamptic women had at least one or more risk factors for preeclampsia, which include previous preeclampsia, first pregnancy, multigravida, history of preeclampsia in the first-degree family, recent change of spouse, advanced maternal age and teenage pregnancy. The most frequent risk factors observed in the present study were first pregnancy, previous history of preeclampsia, history of preeclampsia in first-degree families, advanced maternal age, and teenage pregnancy in that order. These were also observed in previous studies[26-30]

Fifty-two per cent (52%) of preeclamptic women had a spontaneous vaginal delivery, 2% had assisted vaginal delivery and 46% had an emergency cesarean section, and the indications for emergency cesarean section were eclampsia, foetal distress, haemorrhage, and previous cesarean section in that order. A similar finding was observed in previous.[31,32]

Levels of βhCG were found to be significantly higher in preeclamptic women than in controls. This finding corroborates a previous study by Yue *et al.* (2020). They reported that those pregnant women with increased maternal serum βhCG, AFP, INH-A, and low uE3 at first and second trimesters were at risk of preeclampsia, preterm delivery, and low birth weight.[33]

Beta-hCG in women with stillbirth babies were found to be significantly higher compared to the women who had live birth babies. This corroborates with previous studies carried out by Bhattacharjee *et al.* (2016) and Smith *et al.* (2007) who reported that first-trimester high maternal serum APF, βhCG, was largely associated with the risk of stillbirth.[34,35]

This study also found that βhCG levels of women with preterm babies were significantly higher compared to the women who had full-term babies. This corroborates with previous studies which reported that preterm birth before 34 weeks of gestation was associated with higher maternal AFP, βhCG, and INH-A.[36-39]

Levels of βhCG of women with low Apgar score babies were significantly higher compared to the women who had normal Apgar score babies. Similar findings were observed in previous studies.[40] Similarly, this study found that the levels of β-hCG in women with low-birth-weight babies were significantly higher compared to those in women who had normal-birth-weight babies. This corroborates the previous studies done by Canini *et al. (*2008) and Sirikunalai *et al.*, who reported that elevated maternal serum concentrations of βhCG in the first trimester were associated with poor neonatal outcomes, including low birth weight. [41,42]

In conclusion, the maternal serum level of βhCG was significantly higher among preeclamptic women, mothers with low-birth babies, low Apgar score babies, preterm babies, and stillbirth babies. A cut off value of ≥ 4125IU/ml, for maternal serum concentrations at second trimesters for βhCG, had the excellent predictive ability for preeclampsia. A cut-off value of ≥ 4685IU/ml, for maternal serum concentrations at second trimester for βhCG had the good predictive ability for poor neonatal outcomes. The maternal serum βhCG level at second trimesters and above may be useful in predicting preeclampsia and poor clinical neonatal outcomes.

The recommendations:

1. Beta human chorionic gonadotrophin (Part of quadruple analytes) tests should be included as part of routine antenatal investigations, especially in high-risk pregnancies;
2. Development of preeclampsia and poor clinical neonatal outcome be suspected by health professionals if maternal serum concentrations of βhCG are higher in an otherwise normal pregnancy;
3. A multicenter randomized controlled trial with a larger sample size should be carried out to further evaluate the applications of maternal βhCG as a predictor for preeclampsia and poor neonatal outcomes.
4. A longitudinal study of pregnancy from the first

trimester to the post-delivery period is also desirable to identify the point at which the alteration of maternal quadruple analytes becomes significant to suspect preeclampsia and poor neonatal outcomes.

Limitations

The present study was a cross-sectional case-control study at 20th weeks of gestation and above; as such, the values of maternal serum βhCG level at first trimester and post-delivery are missing.

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