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MATERNAL SERUM ALPHA-FOETOPROTEIN AS A PREDICTIVE MARKER FOR PRE-ECLAMPSIA AND POOR NEONATAL OUTCOMES IN SOKOTO, NORTHWEST NIGERIA

Abdullahi Abubakar Fakku[1,*], Muhammad Bashir Abdulrahman[1,*], Bello Aminu[1], Kasimu Saidu[1], Aminu U Abdullahi[1], Abubakar A Panti[2*], Ibrahim S Aliyu[3*], Abubakar SAkuyam[3*]

[1]Department of Chemical Pathology and Immunology, Faculty of Basic Clinical Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.
[2]Department of Obstetrics and Gynaecology, Faculty of Clinical Sciences, Usmanu Danfodiyo, University, Sokoto, Nigeria.
[3]Department of Chemical Pathology, Faculty of Basic Clinical Sciences, Ahmadu Bello University, Zaria, Nigeria.

***Corresponding Author: Abdullahi Abubakar Fakku**

Department of Chemical Pathology and Immunology, Faculty of Basic Clinical Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.

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ABSTRACT

Background: Pre-eclampsia is defined as hypertension that occurs at or after the 20th week of gestation in a previously normotensive woman, accompanied with proteinuria. Pre-eclampsia and neonatal complications associated with it has remained a significant public health threat with global economic concern. The impact of the disease is felt more severely in developing countries, where medical interventions may be ineffective due partly to delay in presentation of cases to the health centre and also due to inadequate health facilities for management of obstetric emergencies. There is, therefore the need for biochemical markers that will predict the development of pre-eclampsia, with a view to applying preventive measures against its development or reduce the severity of the disorder. Alpha foetoprotein is one of such markers that has potential for use in the prediction of pre-eclampsia. **Aim**: The study aimed to evaluate the role of maternal serum Alpha-Foetoprotein (MSAFP) concentration as a predictive marker for developing pre-eclampsia and its correlation with maternal variables and neonatal outcome. **Methods:** This was a cross-sectional, case-control study that was carried out on pregnant women who attended antenatal clinic at three selected hospitals in Sokoto metropolis. A total of two hundred subjects (one hundred pre-eclamptic and one hundred apparently healthy singleton pregnant women), matched for gestational age, gravidity, parity and age range were recruited for the study. The pre-eclamptic were further grouped into severe and mild, based on the blood pressure level and urinary protein/ creatinine ratio. Blood pressure was measured and recorded. Maternal blood and urine samples were taken at the time of enrollment and were used to determine the MSAFP levels and urinary protein and creatinine respectively. At delivery, pregnancy outcomes were documented. **Results:** MSAFP was found to be significantly different (*P*=0.000*)* between the three groups (303.10 ± 20.41, 186.80± 10.65 and 88.10± 5.77 for severe pre-eclampsia, mild pre-eclampsia and controls respectively. MSAPF was significantly higher in pre-eclamptic women than controls, and significantly higher (*P*=0.000*)* in severe pre-eclampsia than mild pre-eclampsia. Likewise, urinary protein/creatinine ratio was significantly different between the three groups (1.4±0.75, 1.27±0.65 and 0.04±0.24, p= 0.000) for severe pre-eclampsia, mild pre-eclampsia and controls respectively. There was a strong significant positive correlation between the MSAFP and maternal mean arterial blood pressure (r = 0.713, p< 0.000) and with urinary protein/creatinine ratio (r = 0.651, p = 0.000). MAFP excellently predicted pre-eclampsia (Area Under the Curve=0.972, 95%CI is 0.948 to 0.005, p=0.001), at a cut-off point of 114.5ng/ml and above. The birth weight (BW), birth length[1] and Apgar scores (AS) for neonates of pre-eclamptic patients were significantly lower than those of the controls (BW 2.86±0.64kg vs 3.42±0.59kg; BL 48.80±2.64cm vs 49.96±1.97cm; AS 5.85±2.63 vs 7.65±0.98, p < 0.05). There was a negative correlation between MSAFP and birth BW (r = −0.399, 0.000) and also with AS (r −0.399, 0.000). **Conclusion**: Elevated MSAFP at 20 weeks an above is associated with the risk of pre-eclampsia and poor neonatal outcomes.

KEYWORDS: Pre-eclampsia; Neonatal outcomes; Alpha-Foetoprotein; Sokoto.

INTRODUCTION

Maternal adverse pregnancy such as pre-eclampsia and poor neonatal outcomes related to it. remains a significant public health threat that is of economic concern in both developed and developing countries.[2] It contributes to global maternal and neonatal morbidity and mortality.[3] The impact of the disease is felt more severely in developing countries, where medical interventions may be ineffective due to delay in presentation of cases to the health centres, inadequate/insufficient health facilities for management of obstetric emergencies and the unpredictable nature of the disease.[4] Unlike the huge investment in research on pre-eclampsia with a view to reducing the burden related to the disorder in developed countries, the situation is different in developing countries. Currently, the only remedy for pre-eclampsia is prevention of its development by instituting appropriate antenatal measures or the delivery of the placenta.[5] In recent years, pregnancy related analytes are being used as biomarkers for predicting adverse pregnancy events.[6] Alpha-Foetoprotein is one of the pregnancy related analytes that is used as part of a quadruple screening test to predict the development of adverse pregnancy events, pre-eclampsia inclusive.[7] Elevated maternal serum alpha foeto-protein (MSAFP), a component of the quadruple screening test has been associated with adverse pregnancy outcomes like still birth, pre-eclampsia, low birth weight and low Apgar scores among others.[8-13]

Alpha foeto-protein (AFP), also known as alpha-1-foeto-protein or alpha-foetoglobin, is a glycoprotein made up polypeptide that are single in chain, with a molecular weight of about 75 kilo-Dalton.[14] AFP is produced by the yolk sac of the developing embryo.[15,16] Foetal liver begins to synthesize it (AFP) from the sixth week of gestation onward, reaching a peak in foetal plasma at about 13 weeks and then falling progressively from then until term.[17] MSAFP levels in pregnancy on the other hand start to rise from 14 weeks of gestation until it reaches a peak at about 32 weeks gestation, then progressively declines.[14] MSAFP concentration is usually very low at birth and is absent or undetectable in maternal serum two weeks post-delivery.[14,17] MSAFP is affected by gestational age and some maternal modifiable and non-modifiable variables such as weight, race, cigarette smoking and diabetes mellitus.[18-20]

Low birth weight as a poor neonatal outcome is a common health problem in the developing world especially sub Saharan Africa.[21,22] Low birth weight is defined as any birth weight less than the 10th percentile for that gestational age, or when it is less than 2500 grams in a full term neonate.[21]

Apgar score is a scoring method that quickly summarizes the health status of a newborn. Apgar scoring is routinely performed in most delivery rooms in order to identify a baby that needs immediate medical intervention.[23] Apgar score is determined by assessing the new born on five criteria on a scale from zero (0) to two (2), then summing up the five values thus obtained.[23, 24] The score ranges from zero to ten; scores of seven and above are generally normal, four to six are fairly low and a score of less than or equal to three is regarded as critically low and needs urgent medical intervention.[23,24] Most studies reported that unexplained increased MSAFP in the first, second and third trimesters were strongly associated with subsequent risk of developing pre-eclampsia, preterm delivery, intrauterine growth restriction and other complications related to utero-placental insufficiency.[25-28] However, some studies show contradicting findings, such as low MSAFP being associated with adverse pregnancy events and elevated first trimester MSAFP having poor prediction for adverse pregnancy. Additionally, these studies were done in developed countries with none in Nigeria.[25, 29-33] MSAFP concentration is part of a quadruple analytes used as a screening test for adverse pregnancy outcomes like birth defect, pre-eclampsia, premature rupture of membrane, placenta previa and placental abruption, which are usually interpreted based on the age, race, body mass index and gestational age.[1, 34] High MSAFP appear to be associated with high incidence of poor pregnancy outcomes.[1, 13] The purpose of this study was to assess the association between the MSAFP and pre-eclampsia and poor neonatal outcome (low birth weight, low Apgar score).

Subjects and Methods

The study was a cross-sectional, case-control study that was carried out on pregnant women who attended antenatal clinic at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Maryam Abacha Women and Children Hospital (MAWCH) and Specialist Hospital (SHS) all in Sokoto, Nigeria, between July 2019 to November, 2020. The study was approved by the local ethical committees of the enrolled hospitals (UDUTH, MAWCH and SHS). The study was conducted in accordance with the principle of the Helsinki declaration. A total of two hundred subjects (one hundred pre-eclamptic and one hundred apparently healthy singleton pregnant women), matched for gestational age, parity and age range were recruited for the study. The pre-eclamptics were further grouped into two, sixty three mild pre-eclamptics and thirty seven severe pre-eclamptics, based on the level of blood pressure and urinary protein /creatinine ratio. The enrolled pregnant women were weighed using a weighing health scale (model ZT120, Seca Gmbh and Co., Germany) which was set at zero reading. The height of the subjects was determined using a standiometer (model 220, SecaGmbh and Co., Germany). The body mass index (BMI) was determined by dividing the weight in kilograms, by the square of the height in meters (kg/m^2). The blood pressure of enrolled subjects was measured at rest with the pregnant women in sitting position using a sphygmomanometer (Accoson's mercury sphygmomanometer model MK3, United Kingdom). At delivery, pregnancy outcomes (maternal and neonatal) were documented. The newborn babies were weighed (Digital infant beam scale modal ZT420, Republic of China) and a weight of less than 2.5 kilograms was regarded as low birth weight. The babies' Apgar scores were assessed at one- and 5-minutes interval using five parameters vis; **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration. Each parameter has a score of zero to two, with a maximum total score of ten and minimum total score of zero. A score of less than seven is regarded as low.

Inclusion and exclusion criteria

The inclusion criteria were: confirmed cases of pre-eclampsia, apparently healthy normotensive singleton pregnant women who were at or greater than the 20th week of gestation, that consented to participate (as controls). The following categories of pregnant women were excluded from the study: apparently healthy pregnant women who were less than twenty weeks of gestation, pregnant women that consume alcohol/or smoke cigarette, multiple gestation for both cases and controls and pregnant women with chronic medical diseases such as diabetes mellitus, atypical pre-eclampsia, chronic hypertension, sickle cell disease, connective tissue disorders, renal disease and liver disease.

Statistical Analysis

The data obtained was sorted out manually and entered into Microsoft office excel for windows 2010 spread sheet and analyzed using SPSS version 23 statistical software. The serum concentration of AFP and uPr/Cr ratio of pre-eclamptic patients and healthy pregnant women were compared using unpaired t-test**.**

The predictive values for MSAFP and uPr/Cr ratio level for development of pre-eclampsia were determined using receiver operating characteristics (ROC) analysis.

The association between AFF and uPr/Cr ratio with maternal and neonatal variables were determined using Pearson' correlation.

RESULTS

Table1 shows the socio-demographic characteristics of the recruited subjects (cases and controls). The age range was between 15 to 42 years. Participants that were less than 20 years of age and above 35 years of age were eighteen and twenty-seven respectively. These two categories accounted for forty five percent of respondents. Majority of the subjects had primary and secondary education.

Table 2 shows the obstetric characteristics of the pre-eclamptic women and controls. Majority of cases were primigravidae 41% while multigravidae made up 35%. Forty six percent of the pre-eclamptic women were delivered through caesarean section due to complications developed such ante-partum haemorrhage (from placental abruption, placenta previa), fetal distress, eclampsia and intrauterine growth restriction.

Table 3 shows the general characteristics of neonatal outcomes of pre-eclamptic women and control subjects. Fifty two percent of pre-eclamptic babies were delivered spontaneously per vaginam as against 86 percent of babies of controls. All the controls had live births, unlike the pre-eclamptic babies, where fifteen still births were recorded. Twenty percent of pre-eclamptic babies were born preterm as against three percent for babies of controls. Twenty eight percent of pre-eclamptic babies had low birth weight as against four percent for babies of controls. Forty nine percent of pre-eclamptic babies had low Apgar score as against thirteen percent for babies of controls.

Table 4 shows the MSAFP and uPr/Cr level in severe pre-eclamptics, mild pre-eclamptics and controls. MSAFP was found to be significantly different between the three groups (303.10 ± 20.41, 186.80± 10.65 and 88.10± 5.77) for severe pre-eclamptics, mild pre-eclamptics and controls respectively. MSAPF was significantly higher (p 0.000) in pre-eclamptic women than controls, and significantly higher (p 0.000) in severe pre-eclamptics than mild preeclamptics. Likewise, urinary protein/creatinine ratio was observed to be significantly different between the three groups (1.4±0.75, 1.27±0.65 and 0.04±0.24, p= 0.000) for severe preeclampsia, mild preeclampsia and controls respectively.

Table 5 shows the best cutoff value, area under the curve, sensitivity, specificity and false positive rate of AFP in predicting pre-eclampsia. MSAFP had an excellent predictive power for developing pre-eclampsia, considering the area under the curve (0.972). Values greater than or equal to 0.9 are considered excellent in the prediction of disease. At cutoff a value of 165.7ng/ml and above, for MSAFP, the sensitivity, specificity and false positive rates were 94%, 94% and 6% respectively.

Table 6 shows the correlation of MSAFP with some maternal variables. There were statistically significant positive correlations between MSAFP and systolic blood pressure (r= 0.678, P=0.000), diastolic blood pressure (r=0.679, P=0.000), mean arterial blood pressure (r = 0.713, p< 0.000), and urinary protein/creatinine ratio (r=0.651, P=0.000). No significant correlation was observed between MSAFP and body mass index (r=0.126, P0.198).

Table7 shows the correlation of neonatal birth weight (BW), gestational age (GA) and Apgar score (AS) with MSAFP (ng/ml). A significant negative correlation was observed between MSAFP and birth weight (r=-0.399, P=0.000) and Apgar score (r=0.389, P=0.000), but no significant correlation was observed with gestational age (r= -0.112, P=0.116).

Table 8 shows the birth weight[27], birth length (cm) and Apgar score for neonates of pre-eclamptic women and controls. The birth weight[27], birth length (cm) and Apgar score of neonates born to pre-eclamptic cases were significantly lower than neonates of controls (BW 2.86±0.64 vs 3.42±0.59; BL 48.80±2.64 vs 49.96±1.97; AS 5.85±2.63 vs 7.65±0.98, $p < 0.05$).

Figure 1: The receiver characteristics curve of MSAFP shows Sensitivity and false positive rate for predicting pre-eclampsia.

Table1: Socio-demographic characteristic of subjects (cases and controls).

Parameters	Control n (%)	Preeclampsia n (%)	P-Value
Age group (years) <20	18(18)	18(18)	
20-24	19(19)	21(21)	
25-29	15(15)	15(15)	0.07
30-34	21(21)	20(20)	
35 and above	27(27)	26(26)	
Total	100(100)	100(100)	
Age range(years)	15 to 42	15 to 42	
Mean Age (years)	27.84±7.48	27.98±7.35	0.894
Educational Status Nil Informal Primary Secondary Tertiary	0(0) 6(6) 46(46) 38(38) 10(10)	0(0) 18(18) 37(37) 33(33) 12(12)	0.677
Occupation Student Trading Full time house wives Civil servant	18(18) 37(37) 34(34) 11(11)	26(26) 8(8) 58(58) 9(9)	0.556

Table 2: Obstetric characteristics of the pre-eclamptic and control subjects.

Parameters	Preeclamptic Women N (%)	Control Subjects N (%)
Gravidity Primigravida Between 2 to 4 5 and above	42(42) 23(23) 35(35)	42(42) 23(23) 35(35)
Nature of Delivery Spontaneous vaginal delivery Assisted vaginal delivery Caesarean Section	52(52) 2(2) 46(46)	86(86) 5(5) 9(9)
Complications {Eclampsia, placental abnormalities and Intrauterine growth restriction (IUGR)}		
Nil Complication One Complication Two Complication Three Complication Eclampsia Placental abnormalities - IUGR	41(41) 41(41) 15(15) 3(3) 33/100 36/100 10/100	85(85) 15(15) 0(0) 0(0) 15/100 0/100

IUGR; Intrauterine growth restriction.

Table 3: General characteristics of neonatal outcomes of pre-eclamptic and control subjects.

Parameters	Preeclamptic Women N (%)	Control Subjects N (%)
Nature of Delivery		
SVD	52(52)	86(86)
AVD	2(2)	5(5)
C/S	46(46)	9(9)
Gender		
Male	42(42)	40(40)
Female	58(58)	60(60)
Viability		
Live Birth	85(85)	100(100)
Still birth	15(15)	0(0)
Maturity		
Full term	80(80)	97(97)
Pre term	20(20)	3(3)
Birth Weight		
Low birth weight (<2.5 kg)	28(28)	4(4)
Normal birth weight	72(72)	96(96)
Apgar Score		
Low Apgar score (< 7)	49(49)	13(13)
Normal Apgar score (≥7)	51(51)	87(87)

SVD = Spontaneous vaginal delivery
AVD = Assisted vaginal delivery
C/S = Caesarean section

Table 4: Maternal serum Alpha-Foeto-protein concentration and urinary protein/creatinine levels in severe and mild pre-eclamptic patients and controls

Analytes	Severe Preeclampsia (n=37)	Mild Preeclampsia (n=63)	Control (n=100)	P- Value
AFP(ng/ml)	303.10±20.41	186.80± 10.65	88.10 ± 5.77 [a]	0.000
uPr/Cr ratio	1.4±0.75	1.27 ± 0.65	0.04 ± 0.24 [a]	0.000

AFP = Alpha foeto protein, uPr/Cr= Urinary Protein/ Creatinine ratio. Data expressed as Mean ± Standard Error of Mean.

Table 5: The cutoff value, area under the curve, sensitivity and false positive rate of MSAFP in predicting pre-eclampsia.

Cutoff value for MSAFP and uPr/Cr ratio	AOC	Sensitivity (%)	False positive rate (%)	Specificity (%)
≥ 162.5 ng/ml	0.972	94	6	94
≥ 0.62	0.954	94	30	70

MSAFP=Maternal serum Alpha foetoprotein
uPr/Cr ratio = urinary protein/ Creatinine ratio
AOC= Area under the curve

Table 6: Correlation of MSAFP (ng/ml) with SBP, DBP, MAP, uPr/Cr ratio and BMI in pre-eclamptics.

Analytes	r value	P-Value
SBP(mmHg)	0.678	0.000
DBP(mmHg)	0.679	0.000
MAP (mmHg)	0.713	0.000
uPr/Cr ratio	0.651	0.000
BMI(Kg/Ht^2)	0.126	0.198

MSAFP= Maternal serum Alpha-foeto protein, uPr/Cr = urinary protein /creatinine ratio, BMI=Body Mass Index, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP =Mean Arterial Pressure.

Table 7: Correlation of neonatal birth weight (BW), gestational age (GA) and APGAR score (AS) with MSAFP

Parameters	r- value	P-Value
Birth Weight	-0.399	0.000
pgar score	-0.389	0.000
Gestational Age	-0.112	0.116

MSAFP= Maternal Serum Alpha-foetoprotein.

Table 8: Anthropometric data for neonates of preeclamptic women and controls.

Parameters	Pre-eclamptics (n =100)	Control (n= 100)	P-Value
Birth weight(kg)	2.86 ± 0.64	3.42 ± 0.59	0.000
Birth length (cm)	48.80 ± 2.64	49.96 ± 1.97	0.001
Apgar Score	5.85 ± 2.63	7.65 ± 0.98	0.000

Data expressed as mean ± SEM, n= 100 per group.

DISCUSSION

In this current study, the age ranges of the subjects were similar to what was reported in similar studies.[35-37] Teenagers, women at 35 years or older, primigravidae and multigravidae constituted the majority of cases in this study, and these groups of subjects have been shown to be at risk of adverse pregnancy outcomes, particularly pre-eclampsia and poor neonatal outcomes.[38-43]

The indications for caesarean section in this study were as result of complications developed by the subjects such as eclampsia, placental abnormalities, ante partum haemorrhages, intrauterine growth restriction and fetal distress. Similar findings were observed in the studies carried out by Igberase et al.,[30] and Amorim et al.[44,45] In this study, the MSAPF was found to be significantly higher in pre-eclamptic women than control. A similar finding was observed in several studies where an elevated MSAPF was associated with adverse pregnancy outcomes, particularly pre-eclampsia and poor neonatal outcomes.[25,46,47] Anfuso et al.,[35] in their retrospective study found out that an unexplained elevation of second trimester MSAPF was associated with an adverse maternal/foetal outcome. Also Hu et al.,[36] in their retrospective study found that elevated MSAFP was associated with increased risk of adverse pregnancy outcomes in both mothers and neonates [31] In another prospective study on the impact of elevated second trimester MSAFP on pregnancy outcomes, pre-eclampsia, preterm birth, still birth and oligo-hydramnios were found to have significant positive correlation with high MSAFP.[48] Kiran et al.,[38] in their study reported an association between low birth weight, prematurity and ante partum haemorrhage with unexplained high second trimester MSAFP similar to the findings in this study. The sensitivity, specificity and false positive rate of MSAFP was 94%, 94% and 6% respectively, which is in contrast to what was reported by Basbug et al.[25] They reported a sensitivity and specificity of 17.9% and 85.6% respectively. The sensitivity in their study was low compared to that reported in this study probably due the method of determination and gestational age employed in the different studies.

CONCLUSION

Elevated second and third trimester MSAFP may be a useful marker for predicting the development of pre-eclampsia and poor neonatal outcomes in a developing country like Nigeria.

Declaration of patient consents

The authors certify that all the appropriate patient consent forms were signed. In the forms, the patients gave their informed consent for their clinical information to be reported in any resulting publication.

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Conflicts of interest

The authors declare no conflict of interest.

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