Original Article

Role of Maternal Serum Unconjugated Oestriol as Predictive Marker for Pre-eclampsia and Poor Clinical Neonatal Outcome in Sokoto, North-West Nigeria

***Abubakar AF[1], Bello A[1]**

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

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***Correspondence:** Dr. Abdullahi Abubakar Fakku

Email: abdullahifakku@gmail.com, Tel: +2348068144285

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 role of maternal serum unconjugated oestriol (uE3) as a predictive marker for pre-eclampsia and poor clinical neonatal outcome in Sokoto. It was prospective case-control study conducted in some selected hospitals in the Sokoto metropolis. Two hundred participants were recruited for this study. The data obtained were analysed using SPSS 25 version statistical software. Variables were compared using an unpaired Student t-test analysis, and the predictive value for developing preeclampsia and poor clinical neonatal outcome was determined using a Receiver Operating Characteristic analysis. The results showed that maternal serum levels of uE3 for preeclamptic women were significantly lower compared to the controls (11.34 ± 0.58 vs 32.05 ± 1.04 ng/ml, $p=0.000$). Mothers with poor clinical neonatal babies, had lower uE3 than mothers with normal babies. A cut-off value of ≤ 25.50 ng/ml for uE3, the predictive power for developing pre-eclampsia was excellent, and at cut-off value of ≤ 16.50 ng/ml for uE3, the predictive power for developing poor neonatal outcomes was good. In conclusion, maternal serum uE3 levels at the second trimester and above may be useful in predicting preeclampsia and poor clinical neonatal outcomes.

Keywords: Maternal, Preeclampsia, Serum, Sokoto, uE3

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 uE3 is such a marker.[2,3]

Maternal serum unconjugated oestriol (uE3) 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 predict other adverse pregnancies, which include: preeclampsia, large/small size for gestational age, low birth weight, 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]

Oestrogens are natural endogenous hormones with many functions in humans. Its involved in the development and maintenance of female phenotype, germ cell maturation,

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and pregnancy.[13] They are also important in various other non-gender specific roles in men and women. These include growth, nervous system maturations, bone metabolism, and endothelial responsiveness.[13] Three major biologically active oestrogens were recognized in humans, which include; oestrone (E1), oestradiol (E2), and oestriol (E3).[13] Like other members of the steroid hormones family, oestrogens diffuse into the cells and bind to specific nuclear receptors, which in turn changes gene transcription in a tissue. [13] Oestriol (E3) is a dominant oestrogen during pregnancy and is secreted mainly by the placenta, with minimal contribution from the ovaries. [13,14]

Oestriol test for the foeto-placental function is widely used, especially in high-risk pregnancies to predict adverse pregnancy outcomes.[15, 16] Low maternal serum unconjugated oestriol (uE3) is associated with poor maternal/neonatal outcomes, especially preeclampsia and preterm birth.[15-20]

The present study aimed at assessing the role of maternal serum uE3 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[21].

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. [22]

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%)[23], 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.

Data Management and Analysis

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 $\pm$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 based on the Helsinki Declaration. Before being included in the study, the participants were fully informed and their agreement was obtained under standard protocol.

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 tests and 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 uE3 in (Mean ±SEM) between subjects with 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 uE3, were significantly low in preeclamptic women than in controls (11.34 ± 0.58 vs 32.05 ± 0.40, p=0.000). The maternal mean serum uE3, concentrations in women with live birth babies and those with stillbirth babies, showed that uE3, in women with stillbirth babies, were significantly lower compared to the women who had live birth babies (22.63 ± 0.98 vs 10.13 ± 1.56, p=0.000).The maternal mean serum concentrations of uE3 in women who had preterm babies and those with full-term babies, showed that uE3 of women with preterm babies were significantly lower compared to the women who had full-term babies (22.90 ± 1.01 vs 11.95 ± 1.36, p=0.000). The maternal mean serum concentrations of uE3 in women who had low Apgar score babies and those with normal Apgar scores, showed that uE3 levels in women with low Apgar score babies were significantly lower compared to those with normal Apgar score babies (24.25 ± 1.13 vs 16.00 ± 1.50, p=0.000). The maternal mean serum concentrations of uE3 in women who had low birth weight babies and those with normal birth weight babies, showed that uE3 of women with low-birth-weight babies were significantly higher compared to the women who had normal birth weight babies (23.28 ± 1.04 vs 13.38 ± 1.51, p=0.000).

Table 3 Shows Cut-off values, multiple of median (mom), area under the curve, sensitivity and specificity of maternal serum level of unconjugated oestriol (uE3) for predicting preeclampsia and poor neonatal outcomes (preterm, still birth, low birth weight, and low Apgar score).

This shows that, the cut-off values, multiple of median (MOM), area under the curve, sensitivity and specificity of maternal serum level for uE3, (≤ 1.03, ≤ 25.50 ng/ml, 0.936, 97% and 72%), for predicting preeclampsia respectively. Based on the area under the curve, at cut-off value of ≤ 25.50 ng/ml for uE3, showed excellent predictive power.

This shows the cut-off values, multiple of median (mom), area under the curve, sensitivity and specificity of maternal serum level of uE3 (≤ 1.47, ≤ 16.50 ng/ml, 0.757, 86% and 64 %), for predicting poor clinical neonatal outcomes respectively. Based on the area under the curve, at cu-off value of ≤ 16.50 ng/ml for uE3, showed good predictive power.

Smaller values of the test result of unconjugated oestriol (uE3), indicate stronger evidence for a positive actual state. a positive actual state, ($p < 0.0001$).

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)				
. . . . .	18(18%)	18(18%)		
. . . . .	58(58%)	55(55%)	0.804	0.422
. . . . .	24(24%)	27(27%)		
. . . . .	15 to 42	15 to 42		
. . . . .	53(53%)	97(97%)		
. . . . .	47(47%)	3(3%)	0.213	0.004
History of risk factors for Preeclampsia				
NO	7(7%)	79(79%)		
YES	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				
Low Apgar score(< 7 score)	49(49%)	13(13%)	4.112	0.000
Normal Apgar score(≥ 7 score)	51(51%)	87(87%)		

Table 2: Serum levels of uE3 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.

Subjects	Number of subjects	uE3(ng/ml)	p-value
Preeclampsia	100	11.34 ± 0,58	0.000
Controls	100	32.05 ± 0.40[a]	
Live babies	185	22.63 ± 0.98	0.000
Still-birth	15	10.13 ± 1.56[a]	
Full-term	178	22.90 ± 1.01	0.000
Preterm	22	11.95 ± 1.36[a]	
Normal Apgar score	138	24.25 ± 1.13	0.000
Low Apgar score	62	16.00 ± 1.50[a]	
Normal birth weight	168	23.28 ± `1.04	0.000
Low birth weight	32	13.38 ± 1.51[a]	

Table 3 Cut-off values, multiple of median (MOM), area under the curve (AUC), sensitivity and specificity of maternal serum unconjugated oestriol(uE3) for predicting preeclampsia and poor neonatal outcomes (preterm, still birth, low birth weight, and low Apgar score)

Subjects	MOM	uE3 cut-off value	AUC (95%CI)	Sensitivity	Specificity
Preeclampsia	≤ 1.03	≤ 25.50 ng/ml	0.936 (0.900 to 0.971)[a]	97	72
Poor neonatal out comes	≤ 1.47	≤ 16.50 ng/ml	0.757(0.659 to 0.854)[a]	86	64

a= p < 0.0001

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. [24,25]

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.[25,26]

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[27-33]

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 studies.[33,34] This is in disagreement with a study done by Jain, and Patel. (2016), who reported that the most frequent indications for emergency cesarean section were severe anaemia, malpresentation, oligohydramnios, foetal distress, and eclampsia in that order.[34] This could be due to differences in methodology. In their study, they used both booked and unbooked subjects,and they excluded those women with previous cesarean sections.[33] While in the present study, unbooked mothers were excluded, and mothers with previous cesarean sections were included.

Levels of uE3 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 present study demonstrated that maternal serum levels of uE3 were significantly lower in women with preeclampsia 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.[35] Contrary to Gu *et al.* (2015), who reported a low level of AFP(38 ± 15µg/L vs 47 ± 18µg/L), and a high level of uE3 (0.98 ± 0.3 µg/L vs 1.17 ± 0.39 µg/L) in preeclampsia compared to controls for cases and controls respectively.[36] This could be due to disparity in the region, race, diet, knowledge of the importance of antenatal booking, methodology of the study, and gestational age at which the study was done. Their study was done in the first trimester, on Caucasians, who eat a balanced diet and book early, with regular antenatal visits and intake of routine medications and its prospective observational study. The present study was cross-sectional prospective, done in black races that book late, not regular in antenatal visits, and couples with noncompliant of routine medications due to financial constraints[37-39]

The maternal serum uE3 levels 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 Settiyanan *et al.* (2016) and Benn *et al.* (2000) who reported that first-trimester high maternal serum AFP and low levels of uE3 were largely associated with the risk of stillbirth.[36,37]

The maternal serum uE3 of women with preterm babies was significantly lower compared to that of women who had full-term babies. This corroborates previous studies, which reported that preterm birth before 34 weeks of gestation was associated with higher maternal AFP, βhCG, INH-A, and low uE3. [40-42]

The maternal serum uE3 of women with low Apgar score babies were significantly lower compared to the women who had normal Apgar score babies. Similar findings were observed in previous studies.[43]

The maternal serum uE3 of women with low-birth-weight babies were significantly lower compared to the women who had normal birth weight babies. This corroborates the previous study done by Sirikunalai *et al.,* (2016), who reported that elevated maternal serum concentrations of βhCG, and low uE3 in the first trimester were associated with poor neonatal outcomes, including low birth weight. [44]

A cut-off value for unconjugated Oestriol of 25.50ng/ml or multiple of the median of $\leq$ 1.45 the sensitivity and specificity for predicting preeclampsia were 99% and 72% respectively. This agrees with a previous study done by Kim *et al.* (2000), who reported that a multiple of the median of $\leq$ 1.5 for unconjugated oestriols, the sensitivity, and specificity for predicting preeclampsia and pre-term birth were all above 80%.[45] This contrary to the previous study done by Karakış *et al.,* (2021), who reported that the multiple of median of >2.0 for maternal serum uE3, the sensitivity and specificity were 66.66% and 54.78% respectively. The variations observed could be due to differences in race, lifestyle, and gestational age at which the study was conducted. Their study was carried out in the first trimester and Western countries, while this present study was conducted in the late second trimester. [46–50.]

The significance of this study is to identify pregnant women who could be at risk of adverse pregnancy, particularly preeclampsia and poor neonatal outcomes so that measures will be applied to prevent or at least attenuate the severity of the disorders. Considering the management of complications related to PE and poor clinical neonatal outcomes has economic challenges in Sokoto due to limited resources.

CONCLUSION

Our study has shown that the maternal serum level of uE3 was significantly lower among preeclamptic women, mothers with low-birth babies, low Apgar score babies, preterm babies and stillbirth babies. The maternal serum uE3 level at second trimesters and above may be useful in predicting preeclampsia and poor clinical neonatal outcomes.

RECOMMENDATIONS

1. Unconjugated oestriol (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 uE3 is lower in otherwise normal pregnancy; a multicenter randomized controlled trial with a larger sample size be carried out to further evaluate the applications of maternal uE3 as predictor for preeclampsia and poor neonatal outcomes;
3. 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 serum uE3 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 uE3 level at first trimester and post-delivery are missing.

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Conflict of Interest: None

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