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Serum Progesterone Measurement: Its Prediction of Pregnancy Loss In Women With First Trimester Threatened Miscarriage In A Medical Center In Owerri, Nigeria

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ABSTRACT
Background: *Threatened miscarriage is a cause of psychological and emotional trauma to the pregnant woman and her family. The unpredictability of its outcome makes it equally challenging to the health care professionals. Of the various biochemical markers that have been investigated, serum progesterone has shown great promise in predicting outcome following threatened miscarriage; however, the results have been conflicting.*
Objectives: *To determine the accuracy of serum progesterone measurement in predicting pregnancy loss in women with first trimester threatened miscarriage at Federal Medical Center, Owerri.*
Study design: *A prospective cohort study of pregnant women with threatened miscarriage at 6-10 weeks gestation (Group 1) and those without threatened miscarriage (Group 2) at the same gestational age.*
Methodology: *A total of 100 parturient who satisfied the inclusion criteria were recruited for the study by systematic sampling. These were equal number of 50 participants each as subject and control. They were matched for gestational age and social status. Serum progesterone measurement obtained and the pregnancy outcomes were evaluated for each participant. The results were analysed using SPSS version 25 with appropriate tables and figures generated.*
Results: *The overall median serum progesterone levels were higher in the control group than the subject (p=0.228). The median progesterone levels were significantly lower among those with threatened miscarriage who had pregnancy loss compared with those that had ongoing pregnancy [9.33ng/ml (4.56-14.75) vs. 20.72ng/ml (16.10-28.87) respectively, p<0.001]. Progesterone had 77.8% sensitivity with negative predictive value of 85.2% and 92% specificity with positive predictive value of 87.5% at optimum cut-off value of 14.80ng/ml. The area under the curve for progesterone was 0.89 (95% CI, 0.764-1.000).*
Conclusion: *Serum progesterone measurement in women with first trimester threatened miscarriage have some degree of accuracy in predicting pregnancy loss.*
Recommendation: *Serum progesterone estimation should be explored to help the health practitioners in the management of patients with first trimester miscarriage.*
KEYWORDS: *Pregesterone, Prediction, Serum, Miscarriage, Threatened, First, Trimester, Loss, Pregnancy.*

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I. INTRODUCTION

Threatened miscarriage is the most common complication of early pregnancy, occurring in approximately 20% of pregnant women.[1] It is a cause of anxiety to the patients and also poses a challenge to the attending physician because outcome is difficult to predict.[2] The diagnosis of threatened miscarriage is made when the woman presents in early pregnancy with vaginal bleeding, a closed cervix on clinical examination and subsequent ultrasound scan (USS) demonstrates fetal cardiac activity.[3, 4]

Pregnancy loss is a recognized sequelae of threatened miscarriage; as about 16.9% to half of women with vaginal bleeding in the first half of pregnancy will abort [5,6] but this risk is substantially less if there is fetal cardiac activitydemonstrable by ultrasonography.[7] A study reported pregnancy loss of 36.2% in North Central Nigeria amongst women with prior threatened miscarriage.[8] Most of these miscarriages occur in the first trimester as the rate of fetal death after 14 weeks gestation is much lower than the rate of pre-embryonic and embryonic loss.[9]

There are many causes of miscarriages of which chromosomal abnormalities have been reported to be the most common cause of first trimester miscarriage; accounting for 50% of the cases.[10]

However, the exact pathway leading to miscarriage are not always apparent. Ultrasonography and many other biomarkers, in isolation or combinations, including urine estrogens, urine HCG, estrone, estradiol (E2), progesterone, human placental lactogen, cortisol, serum human chorionic gonadotropin (HCG), estradiol (E2), and Cancer Antigen-125 (CA-125) have been investigated for the prediction of spontaneous abortion or subsequent outcome of pregnancy.

It has been suggested that abnormal levels of one or more of these biomarkers might help to forecast abortion. Of the biomarkers, serum progesterone has shown great promise as several

studies have suggested that serum progesterone level in early pregnancy is the most specific single predictive biomarker in natural conception for distinguishing viable from non-viable pregnancies; and measurable circulating progesterone levels in the first trimester are related to pregnancy outcome[11-13]. Low progesterone values are associated with miscarriages while high progesterone concentrations with viable pregnancies.[14,15]

Serum progesterone in pregnancy is a reflection of the progesterone production by the corpus luteum and placenta which is stimulated by a viable pregnancy. Corpus luteum maintains its capacity to synthesize the progesterone throughout pregnancy but at approximately 7th week of gestation its functional ability markedly decreases at the start of luteo-placental transition.[16] Progesterone prepares the uterus for implantation of the blastocyst by promoting endometrial decidualisation. It also helps in the maintenance of early pregnancy by stimulating the secretion of Th2 cytokines while reducing Th1 cytokines, thus, inhibiting immune responses like those involved in graft rejection[17]. Other physiological roles of progesterone in pregnancy are to inhibit smooth muscle contractility, decrease prostaglandin formation which help maintain myometrial

quiescence and prevent the onset of uterine contractions.[17-19]

Progesterone assays are currently available in most immunoassay platforms and have shown excellent performance in terms of assay sensitivity, specificity, accuracy and precision with rapid turnaround times.[19] Its ability as a single test to differentiate continuing from non-continuing intrauterine pregnancy in patients with threatened abortion will be very helpful. There are minimal studies on the effect of progesterone on pregnancy loss in Nigeria. This actually shows a knowledge gap which this study will fill. The aim of this study is to determine how the serum progesterone measurement predicts pregnancy loss in women with threatened first trimester miscarriage in a Tertiary Health Center in Owerri, Nigeria.

II. METHODOLOGY

Study Area: The study was conducted in the department of Obstetrics and Gynaecology of the Federal Medical Centre, Owerri, Imo State, South-East Nigeria. Federal Medical Centre Owerri is a tertiary health facility that trains Resident Doctors in all medical and surgical specialties and also provides health care to the people in the city of Owerri as well as nearby semi-urban settlements and neigbouring towns. It receives clients from other States in Nigeria such as Abia and River States as well. The average monthly antenatal attendance in the center are 153,580 pregnant women.

Study Population: The study population were pregnant women at 6-10 weeks gestational age who satisfied the inclusion criteria.

Inclusion Criteria: All parity, spontaneously conceived pregnancies, gestational age between 6 and 10 weeks, singleton intra-uterine pregnancy and demonstration of cardiac activity by ultrasonography.

Study Design: The study was a prospective cohort study; participants were pregnant women with threatened miscarriage at 6-10 weeks gestation (Group 1) and those without threatened miscarriage (Group 2) at the same gestational age.

Study Tool: The study tool was data collection sheets.

Sample Size: The sample size was 100 comprising 50 eligible participants with threatened miscarriage in the 6-10 weeks gestation and 50 eligible participants with no history of threatened miscarriage in the same gestational age. It was determined by a previously validated formula for cohort study[20].

Sampling Technique: The sampling method was systematic sampling. First, all pregnant women were screened to determine those who satisfied the inclusion criteria. Second, eligible women were screened to determine those who were having threatened miscarriage at 6-10 weeks gestation (Group 1). Those without threatened miscarriage (Group 2) were recruited after matching for gestational age and social status.

Patients Recruitment: Consenting and eligible pregnant women in their first trimester, between 6-10 weeks gestational age, who presented to the hospital either as their first antenatal booking or at the Gynaecological emergency unit or hospitalized for threatened miscarriage were enrolled into the study until the sample size was complete. They were categorized into two groups. Group 1 included women with threatened miscarriage in whom an ultrasonography report confirmed the presence of fetal cardiac activity and Group 2 consisting of consenting control population that were recruited from the antenatal booking clinic or general outpatient clinic after eligibility criteria were met.

Recruitments were done by the researcher with assistance from the research assistants.The research assistants were four junior resident Doctors who were trained about the study protocol (such as the contents of the information sheet, consent form, data collection sheet and also sample collection) daily for one week before commencement of the study.

Data Collection: Pregnant women in their first trimester between gestational ages of 6-10weeks, who meet the criteria were given detailed explanation of the study and a written informed consent obtained. Participants were subjected to history taking and examinationto determine age, parity, gestational age, any previous early pregnancy miscarriage; and to exclude general and systemic diseases.

Atransvaginal or abdominal ultrasonographic scanning was done to establish gestational age, presence of intrauterine pregnancy with demonstrable embryonic or fetal cardiac activity, and to exclude multiple pregnancies, and vesicular mole. Information obtained were recorded in the data collection sheet.

Two milliliters of peripheral venous blood was taken once, at recruitment, for serum progesterone measurement following selection of a consenting eligible participant. While in sitting or lying position, the cubital vein was identified having prepared the required materials for the procedure. The puncture site was aseptically prepared and tourniquet applied at the upper arm. The venipuncture procedure was completed by collection of blood after removal of the tourniquet. The puncture site and the overall condition of the participant were observed for complications that could arise, and all contaminated materials were disposed of. The samples were collected at the antenatal clinic, general outpatient clinic, gynaecologic emergency unit and ward into a plain bottle and taken to the laboratory where the serum was separated by centrifugation at 2000rpm and stored at -20°C until hormonal level measurement; which were done in batches, to minimize analytical variation.

Serum progesterone was analyzed using a fully-auto chemiluminescence immunoassay (CLIA) analyzer MAGLUMI 1000 which uses competitive immunoluminometric assay principle.

Patients Follow up: All participants in group I who presented with threatened miscarriage were advised to have physical rest. Both groups were followed up to observe participants whose pregnancies would be on-going or abort at the end of the first trimester. The follow up information were condumented in the data collection sheet.

Data Analysis: The data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 25. Kolmogrov- Smirnov test was used to evaluate normality of Data distribution. The values of progesterone was expressed as median values and interquartile ranges as data was not normally distributed. Comparative analysis of serum progesterone in the different groups was done using Mann-Whitney test. Receiver Operator Characteristic (ROC) curve was constructed to evaluate the level of serum progesterone in distinguishing ongoing pregnancies from those that resulted in pregnancy loss. The accuracy of progesterone in predicting pregnancy loss was established by determining the area under the ROC curve; and the optimal predictive cut-off value of serum progesterone for pregnancy loss determined by the best sensitivity and specificity from the Receiver Operator Characteristic (ROC) curve analysis. In all statistical analyses, $p<0.05$ (95% confidence interval) was considered significant. Results were presented using tables and figures.

Ethical Consideration: An institutional approval for this study was obtained from the Ethical Review Committee of Federal Medical Center, Owerri. Informed written consent was obtained from each participant after adequate counselling and the data obtained from the study were treated with confidentiality and used solely for the purpose of the study.

Limitation of the study:

1. The study was a single centre study; a multicentre study with a larger number of participants may be more representative.
2. Serial serum progesterone analysis would have shown the trend of progesterone changes during the course of the pregnancy than a single serum progesterone evaluation.
3. Pregnancy outcome was only followed up to the end of the first trimester. Monitoring till delivery would have been more informative.

III. RESULTS

The study was conducted over a period of 24 months (October, 2018 to October, 2020). A total of 100 participants were enrolled comprising 50 participants in each group. Two women, one in each group, had induced termination of pregnancy while ten women; one in group 1 and 9 in group 2 were lost to follow up. Five women in the study group were excluded from the analysis because they received progesterone medication. A total of 43 women with threatened miscarriage and 40 participants without threatened miscarriage were included in the analysis.

Table 1: Demographic profile of the participants

	Study group	Control group	p- value
	Mean(SD)	Mean(SD)	
Age (years)	28.81 (4.98)	27.7 (5.15)	0.224
Gravidity	2.07 (0.99)	2.11 (0.92)	0.776
Parity	1.00 (1.11)	1.18 (1.09)	0.425
Gestational Age	7.77 (1.34)	7.83 (1.36)	`0.848
BMI(Kg/m^2)	24.31 (4.78)	27.65 (5.15)	0.750

BMI = Body mass index

Analysis by Student's t-test

The demographic profile of each group is shown in table 1.The mean ages for the maternal groups with threatened abortion and control were 28.81 (21-40) years with SD ± 4.98 and 27.70 (21-35) years with SD ± 5.15 respectively. No significant differences were noted between the maternal ages, gestational ages, BMI and parity between the two groups.

Table 2: Pregnancy outcome of participant at gestational age of 13 weeks

	Ongoing pregnancy n (%)	Pregnancy loss n (%)
Study group(n=43)	25 (58.1)	18 (41.9)
Control group (n=40)	38 (95.0)	2 (5.0)

Study group: women with threatened miscarriage

Table 2 illustrates the proportion of women with ongoing pregnancy or pregnancy loss in both groups by 13 weeks.

Table 3: Comparison of median progesterone of participants with ongoing pregnancyand those with pregnancy loss

	Ongoing pregnancy	Pregnancy loss	P-value
	Median(IQR)	Median(IQR)	
Study group	20.72 (16.10-28.87)	9.33 (4.56-14.75)	< 0.001
Control group	21.93 (17.57-30.16)	18.10*	0.352

IQR: Interquartile range

Median progesterone is measured in ng/ml

* No interquartile range because there was only two values.

Table 3 depicts the median progesterone of participants with ongoing pregnancy by 13 weeks and those with pregnancy loss in both groups as analysed by the Mann-Whitney U test.

The progesterone distribution in both groups were not normally distributed as determined by the Kolmogorov smirnov test (p=<0.001). Progesterone values ranged from 4.25 – 64.21ng/ml and 3.21 – 68.33ng/dl with median (IQR) values of 21.55 (17.44 – 29.38)ng/ml and 16.00 (10.65 – 24.92)ng/ml for the control and study groups respectively. The overall serum progesterone median value was higher in the control

group compared with those with threatened miscarriage but this difference was not statistically significant (p= 0.228). In the threatened abortion group, median serum progesterone level was significantly lower in patients who went on to miscarry (9.32ng/ml) as compared to those who did not miscarry (20.72ng/ml) (p< 0.001) there was no statistically significant difference between the median progesterone across the categories of gestational ages (p= 0.311).

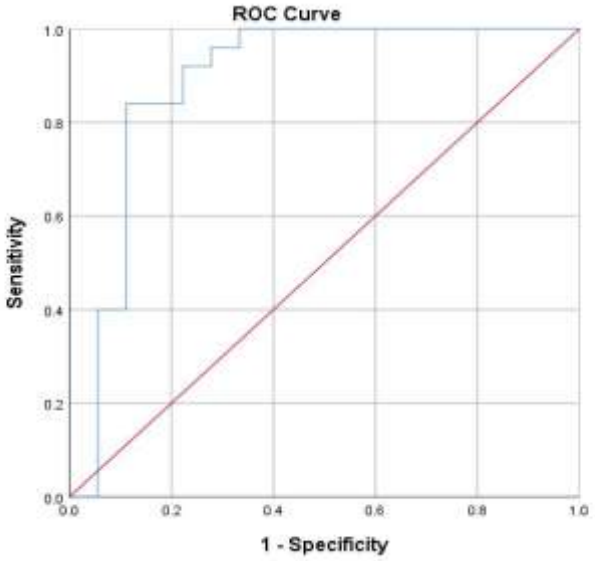

Figure 1: Receiver operator characteristic (ROC) curve of progesterone concentration as a predictive test for pregnancy loss.

Figure 1 illustrates receiver operator characteristic (ROC) curve of serum progesterone concentration in predicting pregnancy loss in women with threatened miscarriage. Single serum progesterone estimation was able to significantly discriminate between those threatened miscarriages that continued with those that failed as demonstrated by the ROC curve analysis.

The area under the curve (AUC) for progesterone as derived from the ROC curve was 0.89 (95% C1, 0.764-1.000). The optimum cut-off value of progesterone concentration from the ROC analysis of below 14.80ng/ml for the prediction of pregnancy loss established sensitivity, specificity, positive predictive and negative predictive value as shown in table 3.

Table 4: Number of Pregnancy loss and ongoing pregnancy at serum progesterone cut-offpoint of 14.80ng/ml

	Pregnancy loss(n)	Ongoing pregnancy(n)	Total
Progesterone level(ng/dl)			
<14.80	14	2	16
≥14.80	4	23	27
Total	18	25	43

Table 5: Sensitivity, Specificity, Positive predictive value and Negative predictive value of Progesterone cut-off point of 14.80ng/ml in predicting pregnancy loss in women with threatened miscarriage at 95% CI

Measurement		Estimate (%)
Cut-off point 14.80ng/ml	Sensitivity	77.8
	Specificity	92.0
	Positive predictive value	87.5
	Negative predictive value	85.2

IV. DISCUSSION

In this study evaluation of the median progesterone levels in women who went on having miscarriage with those with ongoing viable pregnancies in both groups showed that while there was no statistically

significant difference in the progesterone concentration between those with threatened miscarriage and the control, it was determined that the median concentration of progesterone was significantly higher in those whose pregnancies were still viable by 13weeks of gestation following a threatened miscarriage. These findings were in agreement with reports from other studies.[14,19]

The accuracy of serum progesterone measurement in the prediction of pregnancy viability or failure by the end of 13 weeks of gestation in women diagnosed with first trimester threatened miscarriage was evaluated in this study. As demonstrated by the ROC curve analysis, serum progesterone concentration showed a significant ability to discriminate between pregnancies that continued and those that eventually miscarried.

The best combined sensitivity and specificity of serum progesterone estimation in predicting pregnancy loss following a threatened miscarriage agreed with the reports by Hanita et al[19] and Kant etal[21]. However, Pillai et al[22] concluded that progesterone assay is not useful in predicting outcome of a pregnancy with viable fetus.This contrary view could be due to non-specific methods used in serum progesterone measurement of the individual studies included in the analysis as differences in progesterone assay measurement, standardization and performance may affect outcome[19].

A progesterone cut-off value of 14.80ng/ml obtained from the ROC analysis was shown in this study to be optimum in discriminating between pregnancies that are likely to continue with those at risk of miscarriage. At this cut-off value, the highest combined sensitivity and specificity was obtained. The positive predictive value (PPV) and negative predictive value (NPV) for the prediction of pregnancy loss were 87.5% and 85.2% respectively. A similar cut-off of 14.15ng/ml was shown by another study[23], in a prospective comparative study to assess the role of a single maternal serum progesterone measurement in the immediate diagnosis of early pregnancy failure and in the long-term prognosis of fetal viability, to make a distinction between threatened-continuing and non-continuing pregnancies with 87.6% sensitivity and specificity of 87.5%. This study unlike the index study included ectopic gestations and women with threatened miscarriage in the first 18 weeks of pregnancy. Lower discriminating cut-off values of 10ng/ml have been reported by some studies [24,25]. However, these studies did not give data on fetal heart activity at presentation and included participants with missed miscarriage, ectopic pregnancy and those with inconclusive ultrasound findings in their analysis which were all excluded in our study. This can explain the lower cut-off as compared with that obtained in the index study as serum progesterone concentrations have been noted to be lower in ectopic and non-viable pregnancies[26,27]. Leket al.[28] in a large cohort study validated progesterone concentration of 11.0ng/ml as a cut-off for spontaneous miscarriage following a first trimester miscarriage sensitivity 92.0%, specificity 92.0%, PPV 67.7% and NPV 91.3%. The cohorts were followed up to 16 weeks as opposed to ours that were followed up to 13 weeks of pregnancy. Other studies reported higher progesterone cut-off values. In a study by Abdelazim et al.[29], serum progesterone was 95.1% sensitive for diagnosing non-viable pregnancy and 98.9% specific for the diagnosis of viable pregnancy at a cut-off level of 20ng/ml. However, the study included those with abdominal pain without vaginal bleeding. This could explain the higher cut-off value reported as women with bleeding tends to have lower serum progesterone level.[14]

When using a progesterone concentration of less than 32.7ng/ml as a cut-off value for the diagnosis of non-viable pregnancy, it was noted by Hanita et al.[19], in a cross sectional study, that sensitivity was 90% , specificity 92% , while the positive predictive value was 97% and the negative predictive value 75%. The study design of this study was different from that of the index study. Differences in data collection or study design have a significant impact on the estimated discriminative capacity of serum progesterone measurement[3]. Variation in progesterone values among women from different geographic background may affect the outcome of a study.[30]

V. CONCLUSION:

Serum progesterone concentration was significantly higher in women who eventually carried their pregnancies beyond the first trimester as opposed to those that had pregnancy loss. Serum progesterone measurement in women with first trimester threatened miscarriage have some degree of accuracy in predicting pregnancy loss.

VI. RECOMMENDATIONS

1. Serum progesterone estimation should be explored to help the health practitioners in the management of patients with first trimester miscarriage.
2. Further studies with follow-up period beyond the first trimester to ascertain viability and as well validate the cut-off of 14.80ng/ml in the locality are required.
3. Studies in which progesterone supplementation is offered to women with first trimester miscarriage in whom serum progesterone is below 14.80ng/ml to determine outcome are needed.

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