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"ACCURACY OF SINGLE PROGESTERONE ASSAY TO PREDICT EARLY PREGNANCY OUTCOME"

Gynaecology

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ABSTRACT

OBJECTIVE: To study the accuracy of estimation of single serum progesterone level in predicting early pregnancy outcome in symptomatic women with inconclusive USG

MATERIALAND METHODS: 70 women with gestational age less than 12 weeks fulfilling the inclusion criteria were included in the study.

RESULTS: Out of 70 women, the follow up scan revealed 33 viable pregnancies and 37 non-viable pregnancies. Mean serum progesterone was significantly higher in viable pregnancy group (16.318± 7.29 ng/ml), compared with non-viable pregnancy group (8.07± 5.878ng/ml) and the association was found to be statistically significant with a 'p' value of 0.0001. Serum progesterone of 10ng/ml has sensitivity of 72.97% in predicting a non-viable pregnancy and specificity of 81.81% in predicting viable pregnancy.

CONCLUSION: Single serum progesterone value of less than 10ng/ml can be a useful test in predicting early pregnancy failure in symptomatic patients with inconclusive USG.

KEYWORDS

serum progesterone, viable pregnancy.

INTRODUCTION

Pregnancy is a dynamic ongoing process. First trimester is the most important of all. Vaginal bleeding and abdominal pain are the most common causes of consultation in early pregnancy; 20% of women will experience pain or bleeding in their first trimester[1].

Miscarriage occurs in about 15-20% of clinically diagnosed pregnancies[2]. If a lady has bleeding in her first trimester, incidence of abortion is about 30%, ectopic pregnancies is 10-15%and molar pregnancies is 0.2%.[3]

In patients presenting with bleeding per vaginum and/or pain abdomen,prompt diagnosis of whether the pregnancy is viable or not helps to determine the need for any intervention if required.

Most women seeking medical advice have a transvaginal ultrasound scan to confirm a viable pregnancy, a miscarriage, or an ectopic pregnancy. However, in pregnancies with inconclusive ultrasound results has shown that 50% spontaneously resolve (decreasing concentrations of beta hCG), 27% are subsequently diagnosed as viable, and 14% are diagnosed as ectopic pregnancies[4]. The high incidence of miscarriages and ectopic pregnancies warrants further tests to reach diagnosis. Measurement of serum beta-hCG can be useful, but often more than one beta-hCG measurements is needed to make a diagnosis[5].

Progesterone which is a C21 steroid hormone is required to maintain pregnancy. Role of progesterone in early pregnancy has been extensively studied. It is mainly the luteal phase progesterone which is responsible for maintenance of the developing trophoblast in the first 7 to 8 weeks of gestation[6,7].

Studies have shown that serum progesterone measurement in early pregnancy can be a useful predictor for pregnancy outcome in natural conception[8,9,10,11]. Low progesterone levels are associated with pregnancy failure, including miscarriages and ectopic pregnancies, where as viable pregnancies have high progesterone levels. It has been shown that single serum progesterone measurement was almost as effective as that compared to combination of biochemical markers[12].

The present study intends to check the accuracy of single serum progesterone level in predicting early pregnancy outcome in terms of viable or non-viable in patients presenting with pain abdomen and/or bleeding per vaginum in the first trimester with an inconclusive USG.

AIMOF THE STUDY:

To study the accuracy of estimation of single serum progesterone level in predicting early pregnancy outcome in symptomatic women with inconclusive USG

MATERIALS AND METHODS

Study setting:

This study was conducted on women registering in the Obstetrics and Gynaecological department over a period of one year, from October 2015 to October 2016 at Alluri Sita Rama Raju Academy of medical sciences, Eluru, which is a tertiary care centre.

Study population:

70 antenatal women, who met the inclusion criteria and were willing to participate, were included in the study.

Inclusion criteria:

Women with gestational age less than 12 weeks, presenting with vaginal bleeding and/or pain abdomen and having an inconclusive ultrasound report, which include:

- Mean sac diameter less than 16-24 mm with no embryo
- Foetal pole less than 7 mm with no cardiac activity
- Foetal heart rate less than 90/min at more than 7 weeks of gestation
- Mean sac diameter less than expected, indicating wrong dates
- Small gestational sac in relation to embryo (MSD-CRL<5mm)
- Enlarged (>7mm), irregular or abnormally shaped yolk sac or presence of sub chorionic haemorrhage

Exclusion criteria:

- Women with documented non-viable pregnancy
- Women who have received or is receiving exogenous progesterone support
- Women having any local causes of bleeding or any bleeding disorders.
- Pregnancy of unknown location
- Multi foetal gestation

- Suspected ectopic gestation or hydatiform mole.

Study design:
This was an observational study.

Methodology:
After taking an informed consent from the women meeting the inclusion criteria, a semi structural proforma was filled. 2 ml venous blood sample was drawn from the women for serum progesterone estimation using automated radioimmunoassay technique. Women were followed with an ultrasound examination after 2 weeks and pregnancy was grouped into viable or non-viable pregnancy.

RESULTS:
Descriptive statistical analysis was carried out in this study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). The outcomes were dichotomized into viable and non-viable pregnancy categories.

Comparison of means of continuous variables was performed using unpaired t test. Chi-square test has been used to find the significance of study on categorical scale between two groups. Yates correction is used if >20% values in the contingency table are <5. A value of 'p'<0.05 was considered statistically significant.

The statistical software namely SPSS 16.0 was used for analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

70 antenatal women who met inclusion criteria were included in the study. The mean age of the studied population was 26.01 ± 4.055 years and the mean gestational age was found to be 7.41 ± 1.28 weeks. Most common symptom the patient presented with was found to be vaginal bleeding, accounting for 42.8%. On follow up scan, we had 33 viable and 37 non-viable pregnancies.

It was found in the study that significant number of patients had non-viable pregnancy when they presented with both pain abdomen and vaginal bleeding ('p' value:0.00062). Also, the regularity of the gestational sac was significantly associated with the viability of pregnancy (p value:0.000).

TABLE 1: SERUM PROGESTERONE LEVELS IN RELATION TO VIABILITY:

Serum progesterone	Viable (n=33)	Non-viable (n=37)	Total
<10.1 ng/ml	6	27	33
10.1-15 ng/ml	9	5	14
15.1-20ng/ml	13	4	17
>20.1ng/ml	5	1	6
Mean ± SD	16.318± 7.29 ng/ml	8.07± 5.878ng/ml	70
Range of serum progesterone	6.81- 40ng/ml	0.299-25.7ng/ml	

With Unpaired t test results: t = 5.2349; 'p' value = 0.0001.

Serum progesterone levels were statistically associated with viability of gestation Serum progesterone levels when compared with maternal age, parity, previous abortion, gestational age and regularity of menstrual cycles, no statistical association was found. However, serum progesterone levels were statistically associated with gestational sac regularity in the study.

TABLE 2: MATENAL AGE, GESTATIONAL AGE, PARITY, PREVOUS ABORTIONS, MENSTRUAL CYCLES IN RELATION TO SERUM PROSGESTERONE:

Variables	Number	Serum progesterone (ng/ml) Mean ± SD	P value Unpaired t test
Maternal age <30 years >30 years	56 14	11.81±7.75 12.56±7.92	0.7481
Gestational age 5-7.6weeks ≥8weeks	48 22	11.409± 7.59 13.16 ±8.08	0.3830
Parity Primi Multi	38 32	12.109± 7.44 11.7 ±8.18	0.8633
Previous abortion Yes No	15 55	10.7±7.48 12.30 ± 7.83	0.4830
Menstrual cycle Regular Irregular	60 10	11.95 ±7.79 11.98 ± 7.77	0.9927
Gestational sac Regular Irregular	40 30	14.76 ± 7.96 8.21 ± 5.64	0.0003

TABLE 3: CORRELATION OF SERUM PROGESTERONE WITH VIABILITY AT DIFFERENT CUT OFF VALUES – AN OBSERVATION

Serum Progesterone	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≤ 5 ng/ml	35.13	100	100	57.89
≤ 10 ng/ml	72.97	81.81	81.81	72.97
≤ 15 ng/ml	86.48	54.54	68.08	78.26
≤ 20 ng/ml	97.29	15.15	56.25	83.33

In the present study, it was noted that none of the pregnancies were viable when the progesterone level was less than 5 ng/ml. With a cut-off value of 5ng/ml, it is 100% specific in diagnosing viable pregnancy. But at this level, sensitivity of the test to predict non-viable pregnancy was only 35.13 %.

At a cut off value of 10 ng/ml, serum progesterone was 72.97% sensitive in diagnosing non-viable pregnancy and 81.8% specific in detecting a viable pregnancy with a positive predictive value of 81.8%. It was observed that when 15 ng/ml was taken as cut-off level, the sensitivity improved to 86.48% in detecting a non-viable pregnancy but specificity was reduced to 54.54%.

When a cut off value for serum progesterone was taken as 20 ng/ml, the sensitivity of progesterone in predicting a non-viable pregnancy was 97.29% but specificity of predicting viable pregnancy was only 15.15%.

DISCUSSION
70 women, who came with vaginal bleeding and/or pain abdomen to ASRAM medical college, were taken into the study when ultrasound showed inconclusive features.

Mean age of study population was 26.01 ± 4.055 years and mean gestational age was 7.41 ± 1.28 weeks.

Out of 70 women in the study, the follow up scan revealed 33 (47.17%) viable pregnancies and 37 (52.85%) non-viable pregnancies.

In present study, 33 women had serum progesterone levels <10.1ng/ml, 14 women had serum progesterone levels between 10.1-15ng/ml, 17 women had serum progesterone levels between 15.1-20 ng/ml and 6 women had serum progesterone levels >20.1ng/ml.

The relationship between serum progesterone and maternal age or gestational age of the studied population was statistically insignificant and this is in agreement with Hahlin et al., study which reported that the discriminatory efficacy of a single progesterone determination was not increased by serial estimation of progesterone level. No association between gestational age and serum progesterone levels also confirms that serum progesterone levels change little during early pregnancy which is in agreement with the study by Al Jufairi et al[13].

On comparing the gestational sac characteristics with serum progesterone level, it was noted that 21 out of 30 women with irregular gestational sac had serum progesterone of ≤ 10 ng/ml and none of them had serum progesterone > 20.1 ng/ml, which was statistically significant (p value: 0.0003).Hence, non-viable pregnancy is characterised by irregular gestational sac and low progesterone levels which was proved to be statistically significant.

The mean serum progesterone levels in primi gravida was 12.1±7.44 and in multigravida was 11.78 ± 8.18. With a 'p' value of 0.863, parity was not significantly associated with serum progesterone levels

indicating that serum progesterone levels do not alter with parity of the women.

In the present study, mean serum progesterone was significantly higher in viable pregnancy group (16.318± 7.29 ng/ml), compared with non-viable pregnancy group (8.07± 5.878ng/ml) which correlated with other studies[13,15,18,20]. This association was found to be statistically significant with a p value of 0.0001.

In the present study, it was noted that, out of 33 women who had serum progesterone of ≤ 10 ng/ml, 27 (81.81%) had non-viable pregnancy. Taking 10 ng/ml as cut off level, serum progesterone was 72.97% sensitive in predicting a non-viable pregnancy and 81.81% specific for predicting viable pregnancy, with a PPV of 81.81% and NPV of 72.97% .

When 15 ng/ml was taken as cut off level for serum progesterone, it was noted that the sensitivity was 86.48% but specificity was only 54.54%. Similarly, by taking 20 ng/ml as cut off value for serum progesterone, sensitivity of diagnosing non-viable pregnancy improved to 97.29% but specificity of diagnosing viable pregnancy was only 15.15%.

However, in the present study there were 13 patients with serum progesterone value of less than 5 ng/ml, out of which none of them had a viable pregnancy. This is in agreement with the results of **Al Jufairi et al**[13].Hence, serum progesterone values >5ng/ml are 100% specific in diagnosing viable pregnancy.

After analysing the results, it was found from the study that 10 ng/ml can be taken cut off level of serum progesterone.

The thresholds of serum progesterone used in many studies ranged from 3.2-11ng/ml.[10,13,14,15,17,18,19]This is in agreement with present study threshold level of 10ng/ml. Also, serum progesterone levels >5ng/ml are 100% specific to diagnose viable pregnancy.

Early studies on the use of progesterone in early pregnancy complications focused on its potential value in the diagnosis of ectopic pregnancy. However, the results were not encouraging.[11] This may be explained by wide spectrum of ectopic pregnancy presentations, which range from cases resembling healthy intrauterine pregnancies to spontaneous tubal miscarraiges.[11]

It has been suggested that in early pregnancy the production of progesterone by the corpus luteum is dependent on the slope of hCG increase in serum. If this theory was correct, serum progesterone should be a measure of pregnancy viability, rather than an indication of its location.[11]Moreover, progesterone levels do not change significantly during early pregnancy unlike βhCG

Through this study it was noted that measurement of serum progesterone is a valuable test to assess pregnancy viability. Result of this study is in agreement in other studies which have shown single serum progesterone level to be useful in predicting an early pregnancy failure.

However, when applying the model in clinical practice it is important that the population under observation is similar to that used in the present study. To allow for differences between ultrasound operators and biochemistry laboratories the initial implementation of the model should be carefully audited. This would enable the necessary adjustments to be made to define the optimal cut-offs for each individual unit.

CONCLUSIONS

The conclusions that can be drawn from our study are as follows:
Gestational age, maternal age, parity, history of previous abortions,regularity of menstrual cycles does not significantly change the serum progesterone value.

Feature of an irregular gestational sac on USG is more likely associated with low level of serum progesterone and non-viable pregnancy.

Single serum progesterone value of less than 10ng/ml can be a useful test in predicting early pregnancy failure in symptomatic patients with inconclusive USG.

Serum progesterone value more than 10 ng/ml may need follow up USG to diagnose the outcome.

Serum progesterone value less than 5 ng/ml predicts non-viable pregnancy almost to certainty.

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