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Role of single serum progesterone assay in threatened abortion as a predictor of viable pregnancy.

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ABSTRACT

Background: Low progesterone levels have been linked to increased risk of miscarriage in first trimester of pregnancy. **Methods**: The observational, cross-sectional study was conducted over 100 pregnant females in first trimester of pregnancy < 12 weeks. All patients were subjected to sonography to confirm pregnancy & serum progesterone level testing immediately after admission and before initiation of treatment. **Result:** After analysis of the results, cut off value of serum progesterone as determined in this study came out to be 9.9 ng/ml with 94.9% sensitivity & 92.7% specificity. **Conclusion**: The value of serum progesterone estimation was of great help in differentiating between viable and non-viable pregnancy.

Keywords: Pregnancy, Progestrone, Threatened Abortion.

INTRODUCTION

World Health Organisation defines abortion as pregnancy termination before 20 weeks of gestation or with a foetus born weighing <500g. Threatened abortion, where uterine bleeding and/or cramping with cervix closed, is very common in the first trimester of pregnancy.[1-5] Every woman with an early pregnancy vaginal bleeding and pain should be evaluated.[6] The diagnosis of pregnancy can be made by history and physical examination, laboratory evaluation and ultrasonography. There is no single test currently available which can immediately differentiate continuing from non-continuing intrauterine or tubal pregnancy.[7] Ultrasound scanning is probably the best single diagnostic and prognostic test available for diagnosing early pregnancy failure but this technique is dependent on the skill of the operator and thus the results are not always consistently reproducible. Although serum hCG is helpful in diagnosing ectopic pregnancy, it cannot discriminate between viable and non-viable intrauterine pregnancies, moreover, a wide range of hCG levels are recorded in pregnancy with a very long half time in blood following pregnancy demise. In addition, miscarriages may occur at any time during the first trimester, which further contributes to the variability of hCG measurements.

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In very early pregnancy, the corpus luteum produces progesterone. By seventh week of gestation there is luteo-placental shift of production of progesterone during which placenta may not produce sufficiently and thus decreasing levels during pregnancy may trigger an episode of vaginal bleeding and limit successful maintenance of pregnancy. Thus, bleeding at this time in pregnancy may signal that the early placenta has not developed optimally.[8] Insufficient progesterone secretion by the corpus luteum or placenta has been associated with an increased incidence of abortion .It has been suggested that abnormal levels of one or more hormones might help to forecast abortion.[3] Viable intrauterine pregnancy can be diagnosed with 97.5%sensitivity if the serum progesterone levels are greater than 25ng/ml (>79.5nmol/L).Conversely, serum progesterone levels of less than 5ng/ml (<15.9nmol/L) can aid in the diagnosis of a nonviable pregnancy with 100% sensitivity. Hence, finding serum progesterone level less than 5ng/ml allow diagnostic evaluation of the uterus in a stable patient, further testing using ultrasound, additional hormonal assays or serial examinations is warranted to establish viability of pregnancy.[7] Thus to observe the role of single progesterone assay in prediction of viability of pregnancy in threatened abortion cases and to find out a cut off value for the same.

MATERIALS AND METHODS

The present observational, cross-sectional study conducted in the department of Obstetrics and Gynaecology, NIMS hospital, Jaipur over 100 pregnant females in first trimester of pregnancy < 12 weeks, as documented by positive Urine pregnancy test and/ or ultrasound, presenting with complaints of; bleeding per vaginum, lower abdomen pain or both, and on per speculum examination cervical os was closed. Patients with positive finding suggestive of Missed abortion/ Incomplete abortion/ complete abortion, patients with Ectopic pregnancy and patients with ART induced pregnancy were excluded from the study. Thereby, determining and ascertaining the ways to improve the perinatal outcome.

Demographic data like age, obstetric history along with relevant history were recorded on a predesigned and pretested proforma.

Investigations:

In addition to all routine investigations like Complete blood counts, urine examination, Viral markers (HIV, HBsAg, VDRL), Blood Sugar, Thyroid Function tests in suspected cases, and Glucose tolerance test, if required were carried out.

All patients were subjected to sonography to confirm pregnancy & its location & viability & later for follow-up.

Serum Progesterone:

All cases underwent serum progesterone level testing. Blood samples were collected immediately after admission and before initiation of treatment or any surgical intervention.

Statistical analysis:

The data was analyzed using Chi-Square Test & Fischer Test. (probability limit was 0.05). P value <0.05 was taken significant.

Serum progesterone levels were analysed by Risk of curve analysis (ROC) and cut-off value was determined.

RESULTS

The Table 1 and Figure 1 enumerates the various high risk factors present in the cases under study on presentation & their percentage. The most common risk factor was history of previous abortions seen in 37 cases.

Table 1: Risk Factors Associated with Threatened Abortion

Risk factor	No.of cases	Percentage
Advanced maternal age >30 yrs	9	9.00
Advanced paternal age >30 yrs	29	29.00
Previous Preterm Labour	28	28.00
Previous Abortion	37	37.00
H/o Contact	12	12.00
H/o Travel	25	25.00
H/o Trauma	12	12.00
H/o Heavy work	5	5.00
Any Systemic diseases	24	24.00
Known Endocrine disorder	10	10.00
H/o Bacterial vaginosis	11	11.00
H/o UTI	10	10.00
Total	100	100.00

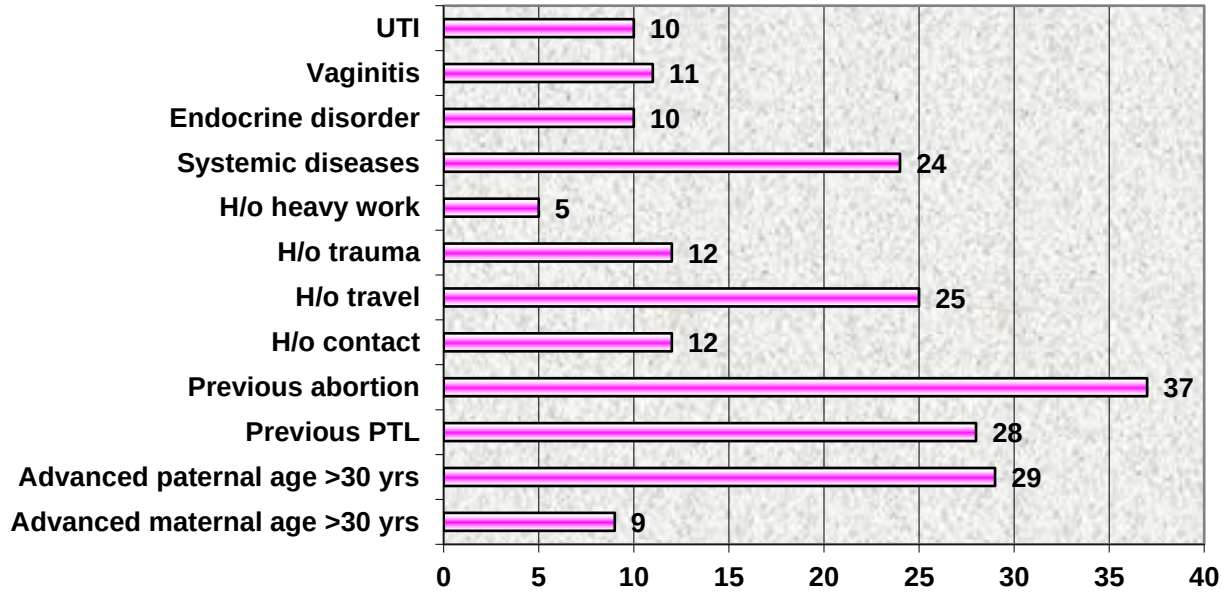


Figure 1: Risk Factors Associated with Threatened Abortion

Table 2 shows that in cases who continued the pregnancy, mean serum progesterone level was 18.18 ± 6.09, with a minimum value of 7.9 and maximum value of 34. While those who aborted had mean serum progesterone 6.56 ± 2.94, with a minimum value of 1.5 and maximum value of 14.8. This association came out to be statistically significant (P value <0.001).

Of the 59 cases that continued their pregnancy, 25 cases currently are between 28-34 weeks of

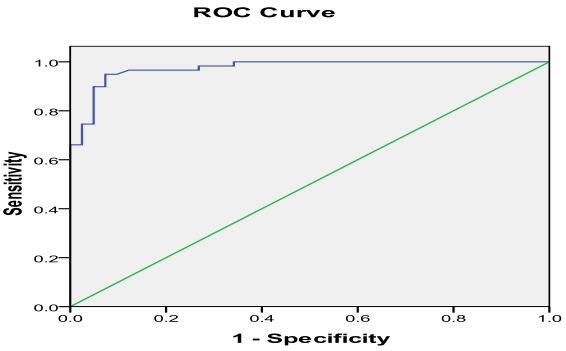
gestation, 30 cases are above 34 weeks of gestation. 2 delivered vaginally as preterm and 2 delivered vaginally as term pregnancy.

Table 2: Association with Serum Progesterone Levels.

Pregnancy Outcome		N	Mean	Std. Error of Mean	Std. Deviation	Minimum	Maximum
Continued	**S. Progesterone**	59	18.18	0.79	6.09	7.9	34
Aborted	**S. Progesterone**	41	6.56	0.46	2.94	1.5	14.8
Total	**S. Progesterone**	100	13.42	0.76	7.63	1.5	34

Table 3: Current Gestational Age of Cases (Continuing Pregnancy).

Current gestational age	No. of patients
28-34 weeks	25
>34 weeks	30
Pre-term vaginal delivery	2
Full-term vaginal delivery	2
Total continuing cases	59



Diagonal segments are produced by ties.

In this study, at serum progesterone level of 9.9 ng/ml, Youden's index, i.e. difference between sensitivity and false positive rate was found highest so this was taken as cut-off value (sensitivity 94.9% & specificity 92.7%).

The Table 4 shows that 38 cases with serum progesterone level less than the cut off value (9.9ng/ml) aborted while only 3 continued their pregnancy. And 56 cases with serum progesterone above the cut off value continued their pregnancy and 3 cases aborted.

Area Under the Curve

Test Result Variable(s):Progesterone

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.975	.013	.000	.949	1.000

The test result variable(s): Progesterone has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 4: Cut off Value of Serum Progesterone

S. Progesterone	Aborted	Continued	Total
<9.9ng/ml	38	3	41
>9.9ng/ml	3	56	59
Total	41	59	100

DISCUSSION

There have been only a few studies that assessed the value of progesterone in very early gestations.[9] 100 women who reported to NIMS OPD with chief complaints of vaginal bleeding and/or lower abdominal pain during the first trimester of their pregnancies and who met the inclusion criteria were included in the study.

Out of 100 patients incorporated in my study, 28 cases had previous history of preterm labour. Out of these 28 patients, 20 patients aborted while only 8 patients continued their pregnancy. This association was found to be statistically significant in my study. Many investigators have reported increase incidences of preterm birth and low birth weight following threatened miscarriage. As shown in studies by Goldstein et al. (1983), Batzofin et al. (1996 and 1984), Ball RH et al.(1996), Salah Roshdy Ahmed et al.(2010), this risk is specially increased

for PROM, Preterm labour and birth and low neonatal birth weight. However, there have been no studies to draw a reverse conclusion, that whether previous preterm labour is significantly associated with increased risk of threatened abortions in future pregnancies, as shown significantly in my study.[10]

As far as association with previous history of abortion is concerned, there were 37 cases with history of previous abortion. Of these, 21 cases aborted while 16 continued their pregnancy. It is concluded from many studies in the past that previous abortion increases the risk of subsequent abortions. Data from a study done by Bhattacharya et al. (2010) suggests that in the absence of any previous miscarriage, risk of subsequent miscarriage is 7%. However, this risk increases to 14%, 26% and 28% in the presence of previous 1, 2 and 3 miscarriages, respectively.[11]

As concluded by studies done by Hasan et al. (2010)[8], Gracia et al. (2005)[12], Chunk et al.(1999)[13], Everett et al.(1997)[5]; Heavy bleeding in the first trimester, particularly when accompanied by pain, is associated with higher risk of miscarriage. Spotting and light episodes are not, especially if only lasting 1–2 days.[8] My study showed the similar results. Out of 100 cases taken in the study, 34% had bleeding per vaginum as the chief complaint, of which 26.83% aborted; 34% had both bleeding per vaginum and lower abdominal pain, of which 51.22% aborted. This finding was statistically significant and comparable to studies done in the past.

In my study, 58% cases with normal USG findings resulted in 77.97% of viable pregnancies and 48.78% of those which stayed inconclusive aborted. Real-time ultrasound scanning has made it possible to ascertain whether the fetus is alive in women who have bleeding in early pregnancy, as concluded by Everett et al.(1997)[6] and Jauniaux et al.(2005).[14] Our findings are consistent with the above studies and this association was found to be statistically significant.

In my study, 59% cases continued their pregnancy while 41% resulted in abortion. Mean progesterone levels in the continuing group was 18.18 ± 6.09 ,with a minimum value of 7.9 and a maximum value of 34. Mean progesterone level in the group that aborted was 6.56 ± 2.94, with a minimum value of 1.5 and a maximum value of 14.8.

In my study, at serum progesterone level of 9.9 ng/ml, Youden's index, i.e. difference between sensitivity and false positive rate was found highest so this cut off value may be used to discriminate likely viable and non-viable pregnancies. (sensitivity 94.9% & specificity 92.7%).

This is comparable to studies done by Hahlin et al.(1991)[15], Daily et al. (1994)[16]. Plante BJ et al.(2008) also concluded that among single biomarkers, progesterone had the greatest diagnostic accuracy in predicting viability.[17]

As concluded by Duan et al.(2011) , the mean serum levels of progesterone in patients with inevitable miscarriages (13.76 ± 5.52 ng/ml), was significantly lower than the levels in normal intrauterine pregnancies (31.67 ± 5.86 ng/ml) and ongoing pregnancies (25.47 ± 6.18 ng/ml) (P < 0.001).[18]

Verhaegen J et al. (2012) also concluded that a single progesterone measurement for women in early pregnancy presenting with bleeding or pain and inconclusive ultrasound assessments can rule out a viable pregnancy.[19]

In a study done by Abdelazim IA et al.(2013), the mean serum progesterone of the studied population was significantly higher in the viable pregnancy group (46.5±7.4 ng/mL) compared to non-viable pregnancy group (9.9±4.8 ng/mL; p<0.05).[20]

In my study, progesterone supplements (Oral micronized progesterone twice daily) were given to all the cases, irrespective of their serum progesterone levels, as per the institute protocol, however nothing could be proven as regards to decreased rate of abortions. Those with initial serum levels of serum progesterone < 9.9ng/ml still aborted the case except 3 cases. Statistically, this difference was insignificant.

This is comparable to a study done by Fakhrolmolouk Yassaee et al. (2014) which demonstrated that the rate of abortion was reduced in women treated with progesterone, irrespective of their gestational age. Nevertheless, its effect on prevention of abortion was not statistically meaningful.[21] These results are also comparable to studies done by El-Zibdeh et al.(2009), Gerhard et al. (1987), Palagiano et al.(2004), Pandian et al. (2009), Omar et al. (2005).

CONCLUSION

The present study showed that single serum progesterone assay can be used as a reliable marker for predicting viability in pregnancies with threatened abortions.

After analysis of the results, cut off value of serum progesterone as determined by my study came out to be 9.9 ng/ml with 94.9% sensitivity & 92.7% specificity.

According to recent literature, role of progesterone support in threatened abortions has yielded conflicting results, available evidences are of low quality and suggest its use in cases with luteal phase defects only. However, it has no harm to the fetus or neonatal outcome, also, it is found to be better than placebo as per the available data. So, progesterone supplements were given in all the patients as per the institute protocol. Although, whether it affected the outcome of pregnancy remains unclear. This is comparable to recent data and guidelines on progesterone supplementation. However, a lot more work is required to come to a conclusion in this

regards with a larger sample size and eliminating various other confounding factors.

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