Role of serum progesterone in threatened miscarriage

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ABSTRACT

Background: Miscarriage is the inadvertent loss of a pregnancy before the fetus is viable. The World Health Organization defines this un-survivable state as an embryo or fetus weighing 500 grams or less, which typically corresponds to a fetal age (gestational age) of 20 to 22 weeks or less.

Methods: The present study was conducted in the Department of Obstetrics and Gynaecology, M. G. M. Medical College and M.Y. Hospital, Indore, from October 2013 to October 2014 on 100 patients.

Results: The incidence of first trimester threatened miscarriage, in the Gynaec O.P.D. of M.Y. Hospital, Indore, was 8.8%. The most common risk factor was a history of previous miscarriages in 38% of cases while 9% had advanced maternal age and 35% had advanced paternal age. History of preterm labour was positive in 25% cases and that of congenital anomaly in previous pregnancy in 7% cases. UTI and vaginitis were diagnosed in 10% and 11% cases respectively. Systemic illness was in 24% cases while 6% cases had endocrine disorders. On USG missed miscarriage was found in 8% inconclusive ultrasound was found in 34% cases, rest were normal. Of the 38 cases giving history of previous 1, 2, 3 and more than or equal to 4 miscarriages were 22%, 6%, 8% and 2 % respectively. 36% of the patients presented with bleeding per vaginum, only while 30% had bleeding with pain and 33% cases had only pain in abdomen. On USG 58% had normal scans. USG scan was inconclusive in 34% and only 35% continued with viable pregnancy, rest aborted. 7 of the 100 cases had preterm labour and 51 cases continued to term. Rest 42 aborted. H/o contact, travel, trauma, heavy work did not have any statistically proven effect on outcome of pregnancy.

Conclusions: 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. Furthermore, the cost per test for progesterone assay is affordable. Several studies have shown that progesterone is the most specific biomarker for distinguishing viable from nonviable pregnancies. The downfall of progesterone as a biomarker is due to the different cut-off values used by researchers. The cut-off values were also determined on different study populations.

Keywords: Miscarriage, Preterm labour, USG, UTI, Vaginum

INTRODUCTION

Threatened miscarriage is very common in the first trimester; about 25-30% of all pregnancies have some bleeding during the pregnancy.1,2 12% to 20% of all clinically recognized pregnancies end up as miscarriages.3,4 On examination, blood or brownish discharge may be present in the vagina. The cervix is not tender, and the cervical os is closed. No foetal tissue or membranes have passed. The ultrasound shows a continuing intrauterine pregnancy. If an ultrasound was not performed previously, it is required at this time to rule out an ectopic pregnancy, which could present similarly. Ultrasound scanning is probably the best single
diagnostic and prognostic test available for diagnosing early pregnancy failure. However, there were certain conditions where both the ultrasonographic evidence and clinical findings were indeterminate.\(^5\) In addition, this technique is dependent upon the skill of the operator and thus the results are not always consistently reproducible. Therefore, a highly sensitive and specific biomarker is required to determine the pregnancy viability for early intervention.

Progesterone is a C-21 steroid hormone secreted by granulosa cells of the ovary. This hormone is important to promote endometrial decidualization by preparing the uterus for implantation of the blastocyst and in maintaining the pregnancy.\(^6,7\) The downfall of progesterone as a biomarker is due to the different cut-off values used by researchers.\(^7,8,11\) The cut-off values were also determined on different study populations. Other important physiological function of progesterone is to inhibit smooth muscle contractility, decrease prostaglandin formation which help maintain myometrial quiescence and prevent the onset of uterine contractions, and inhibit immune responses like those involved in graft rejection.\(^12\)

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. Furthermore, the cost per test for progesterone assay is affordable. Several studies have shown that progesterone is the most specific biomarker for distinguishing viable from nonviable pregnancies.\(^7,8,13,14\)

The aims and objectives are to study the incidence of threatened miscarriage; to study the various etiological factors functional in patients of threatened miscarriage and to study the pregnancy outcome and role of USG and chief complaints in these patients and to study the role of single serum progesterone assay and determine the cut off level of serum progesterone in detecting the viability of pregnancy.

**METHODS**

The present study was conducted in the Department of Obstetrics and Gynaecology, M. G. M. Medical College and M.Y. Hospital, Indore. The period of study was October 2013 to October 2014. The study was conducted on 100 patients. These patients were selected from all age groups, parity, socioeconomic and educational status from the patients attending Gynae OPD, presenting in first trimester of pregnancy.

**Inclusion criteria**

- Attending gynae OPD during the period
- In first trimester of pregnancy <12 weeks
- Chief complaints of bleeding P/V, Lower abdomen pain or both
- UPT positive
- Cervix-closed os.

**Exclusion criteria**

- Multifetal gestation
- Ectopic pregnancy
- ART Induced pregnancy.

**Methodology**

Detailed history of patient was taken. During history taking special importance was given to few salient features.

- Previous obstetric history and prior pregnancy losses and Menstrual history.
- History of any risk factors contributing to threatened miscarriages or any systemic diseases and medications during prenatal and antenatal period.
- Relevant Family history, especially regarding pregnancy losses in the family, any chromosomal or genetic disorder running in the family, or a history of diabetes, hypertension.

Physical examination was carried out with particular attention to:

- Obesity, hirsutism and acanthosis
- Breast and thyroid examination were conducted.
- A Per speculum examination was conducted. Status of os, any evidence of infection nature of bleeding or discharge per vaginum was noted.

**Investigations**

- Complete Blood count, RFT, LFT, ABO Rh, Urine Routine Microscopy, VDRL, HIV, HbsAg, blood urea, and FBS, PPBS, GTT if required were carried out.
- All patients were subjected to sonography to confirm pregnancy and its location and viability and later for follow-up.

**Serum progesterone**

All cases undergo serum progesterone assay. Blood samples were collected immediately after admission and before initiation of treatment or surgical intervention. A maximum of 5ml venous blood was collected in a plain tube, centrifuged and the serum were aliquoted and stored at -70°C until analysis was carried out.

Serum progesterone was measured on a fully automated analyzer (Architect i2000sr) using Chemiluminescent Microparticle Immunoassay (CMIA). The Architect progesterone assays measure progesterone concentrations between 0.1ng/ml to 36.0ng/ml. All cases underwent
USG and were under follow up till either Miscarriage or continued pregnancy.

**Statistical analysis**

The data was analyzed using Chi-square test and Fischer test (probability limit was 0.05). Serum progesterone levels were analysed by risk of curve analysis and cut-off value determined.

**RESULTS**

This table shows the incidence of first trimester threatened Miscarriage among cases attending Gynaec OPD. The incidence was 8.8%.

Table 2 showing the maximum cases with pregnancy continued i.e. 61.3% and 56.7% cases in maternal age groups of 21-25 years and 26-30 years respectively.

**Table 1: Incidence of threatened miscarriage.**

| Parameters studied | Total cases in 1st trimester of pregnancy attending gynae O. P. D in study duration | Total cases of threatened miscarriage attending gynae O. P. D in study duration | Incidence of 1st trimester threatened miscarriage in gynae O. P. D |
|--------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|
| Maternal age (in years) | Frequency Continued Percentage Aborted Percentage |
| <20 | 10 | 5 | 50 | 5 | 50 |
| 21-25 | 44 | 27 | 61.3 | 17 | 29.7 |
| 26-30 | 37 | 21 | 56.7 | 16 | 43.2 |
| >30 | 9 | 5 | 55.5 | 4 | 44.4 |

| Paternal age (in years) | Frequency |
|-------------------------|-----------|
| <20 | 1 | 1 | 100 | 0 | 0 |
| 21-25 | 24 | 14 | 58.4 | 10 | 41.6 |
| 26-30 | 40 | 23 | 57.5 | 17 | 42.5 |
| >30 | 35 | 20 | 57.1 | 15 | 42.8 |

| Parity | Total cases |
|--------|-------------|
| Primiparity | 52 | 40 | 76.9 | 12 | 23.1 |
| Multiparity | 38 | 18 | 47.3 | 20 | 52.6 |

**Figure 1:** showing comparison of serum progesterone levels with respect to weeks of gestation with mean progesterone levels of 18.09 ng/ml for viable pregnancy.

However, in the paternal age groups 21-25, 26-30 and >30 years pregnancy continued in 58.4, 57.5 and 57.1 % cases respectively. The test result variable(s): serum progesterone has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

**Figure 2:** ROC curve for serum progesterone.

Under the nonparametric assumption,
Null hypothesis: true area = 0.5.

The smallest cut off value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1.

All the other cutoff values are the averages of two consecutive ordered observed test values. Cut off value with maximum sensitivity and specificity: 10.05 (sensitivity 93 % and specificity 90.5%).

Table 3: Serum progesterone.

| Total cases | Viable | Non-viable |
|-------------|--------|------------|
| 100         | 58     | 42         |
| Mean progesterone levels (ng/ml) | 18.09 | 6.7 |

The incidence of first trimester threatened Miscarriage, in the Gynae O.P.D. of M.Y. Hospital, Indore, was 8.8%. There were 9 cases with maternal age >30 years. These cases showed a significantly higher Miscarriage rate of 44%.

The study thus, proves that increased maternal age is a definite adverse factor in prognosis of threatened Miscarriage. The most common risk factor was a history of previous Miscarriages in 38% of cases.

Table 4: ROC curve and their relation to level of serum progesterone.

| Area | Std. error | Asymptotic sig. | Asymptotic 95% confidence interval |
|------|------------|-----------------|-----------------------------------|
|      |            |                 | Lower bound | Upper bound |
| 0.971 | 0.014 | 0.000 | 0.944 | 0.997 |

The test result variable(s): serum 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.

Advanced maternal age was seen in 9% of cases and advanced paternal age in 35%. History of preterm labour was positive in 25% cases and that of congenital anomaly in previous pregnancy in 7% cases.

Table 5: Factors and the level of significance with respect to p-value.

| Factors               | P-value         |
|-----------------------|-----------------|
| Maternal age          | 0.539 (non-significant) |
| Paternal age          | 0.534 (non-significant) |
| Socioeconomic status  | 0.115 (non-significant) |
| Serum progesterone    | 0.000 (Significant) |

UTI and vaginitis were diagnosed in 10% and 11% cases respectively. Systemic illness was elicited on history in 24% cases, while 6% patients gave history of suffering from various endocrine disorders. On ultrasound examination missed Miscarriage was found in 8% inconclusive ultrasound was found in 34% cases, rest were normal. Of the 38 cases giving history of previous Miscarriage 22% had previous 1 Miscarriage, previous 2 Miscarriage were seen in 6% and previous 3 Miscarriages in 8% patients.

Table 6: Risk factors associated with abortion.

| Risk factor                        | Number | Percentage of cases |
|------------------------------------|--------|---------------------|
| Advanced maternal age >30 years    | 9      | 9                   |
| Advanced paternal age >30 years    | 35     | 35                  |
| H/o contact                        | 14     | 14                  |
| H/o heavy work                     | 5      | 5                   |
| H/o travel                         | 25     | 25                  |
| H/o trauma                         | 15     | 15                  |
| UTI                                | 10     | 10                  |
| Vaginitis                          | 11     | 11                  |
| Previous PTL                       | 25     | 25                  |
| Previous Miscarriage               | 38     | 38                  |
| H/o congenital anomaly in previous pregnancy | 7  | 7                  |
| Systemic diseases                  | 24     | 24                  |
| Endocrine disorder                 | 12     | 12                  |
| Addictions                         | 17     | 17                  |

Those having 4 or more Miscarriages comprised only 2%. Most (36%) of the patients presented with complaint of bleeding per vagina, while 30% had bleeding with pain and 33% cases had only pain in abdomen. On USG maximum patients 58% had normal scans. Among these patients the Miscarriage rate was 20.6%. 34% of the patients showed inconclusive scan and only 35% continued with viable pregnancy, rest aborted. About 7 of the 100 cases had preterm labour and 51 cases continued to term.

Rest 42 aborted. H/o contact, travel, trauma, heavy work did not have any statistically proven effect on outcome of pregnancy. Of the 58 cases reaching term 9 landed up in caesarean section, while 44 had normal vaginal delivery. The caesarean rate is 17.6%.

The perinatal outcome in these 58 cases was such that 48 babies were of birth weight >2.5 kg and 3 had birth weight <2.5 kg. Of these 2 were very low birth weight and 4 had IUGR. Serum progesterone varies between 1.5 to 34.

ROC analysis came up with the cut off of 10.05 with a sensitivity of 93.1% and specificity of 90.5%. 4(6.8%) out of 58 viable pregnancies have s. prog. <10.05 and 4 (9.5%) out of non-viable pregnancies have s. prog. >10.05. Mean serum progesterone in viable group is 18.09 and in non-viable group it is 6.707.
Table 7: Significant previous history.

| Previous history          | Continued | Percentage | Aborted | Percentage |
|---------------------------|-----------|------------|---------|------------|
| Preterm labour            | 58        | 58         | 42      | 42         |
| Spontaneous abortion      | 40        | 76.9       | 12      | 23.1       |
| Abortion                  | 18        | 47.3       | 20      | 52.6       |
| **Congenital Anomaly**    |           |            |         |            |
| Yes                       | 1         | 1.7        | 6       | 14.3       |
| No                        | 57        | 98.3       | 36      | 85.7       |
| **History of contact**    |           |            |         |            |
| Yes                       | 7         | 12.1       | 7       | 16.7       |
| No                        | 51        | 87.9       | 35      | 83.3       |
| **History of Travel**     |           |            |         |            |
| Yes                       | 15        | 25.9       | 10      | 23.8       |
| No                        | 43        | 74.1       | 32      | 76.2       |
| **History of Trauma**     |           |            |         |            |
| Yes                       | 6         | 10.3       | 9       | 21.4       |
| No                        | 52        | 89.7       | 33      | 78.6       |
| **History of Heavy Work** |           |            |         |            |
| Yes                       | 4         | 6.9        | 1       | 2.4        |
| No                        | 54        | 93.1       | 41      | 97.6       |
| **Vaginitis**             |           |            |         |            |
| Yes                       | 7         | 12.1       | 4       | 9.5        |
| No                        | 51        | 87.9       | 38      | 90.5       |
| **UTI**                   |           |            |         |            |
| Yes                       | 5         | 8.6        | 5       | 11.9       |
| No                        | 53        | 91.4       | 37      | 88.1       |

Table 8: Chief presenting complaints.

| Chief Presenting complaints | Continued | Percentage | Aborted | Percentage |
|-----------------------------|-----------|------------|---------|------------|
| Pain                        | 24        | 72.7       | 9       | 27.2       |
| Bleeding                    | 25        | 69.5       | 11      | 30.5       |
| Both complaints             | 9         | 29         | 22      | 70.9       |
| Total                       | 58        |            | 42      |            |
| **USG Findings**            |           |            |         |            |
| Normal                      | 46        | 79.3       | 12      | 20.6       |
| Inconclusive                | 12        | 35.2       | 22      | 64.7       |
| Missed                      | 0         | 0          | 8       | 100        |
| Total                       | 58        |            | 42      |            |

**DISCUSSION**

Recent studies suggest that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions (Elson et al, Zainab Ali et al, Phipps et al) The incidence of threatened Miscarriage among first trimester pregnancy cases presenting to Gynaecology O.P.D was 8.8% in my study. Threatened Miscarriage is very common in the first trimester; about 25-30% of all pregnancies have some bleeding during the pregnancy. Less than one half proceed to a complete Miscarriage. The overall miscarriage rate is reported as 15-20%. About 80% of miscarriages occur within the first trimester. Miscarriage, also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently.² Miscarriage, also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently. As per Table 2 represents effect of demographic profile on Pregnancy. However, with maternal age distribution with 37, 44 and 10 cases of threatened miscarriage between the age group of 26-30 years, 21-25 years and less than 20 years of age respectively. Authors had 9 cases of more than 30 years who were form high risk group, as with advancing age the oocyte quality decreases, risk of congenital malformation increases, and chances of successful pregnancy decrease. According to distribution of cases according to their husband’s age. 25 patients reported their husband’s age to be less than 25 years while 40 and...
35 cases had paternal age in the range of 26-30 years and between 31-35 years respectively. However, among primiparous 76.9% of pregnancies continued and about 52.6% cases aborted in cases of multiparous pregnancy.

In Tables 3,4 and 5, The mean age of the studied population was 25.7±4.35 years, the mean gestational age at progesterone assay was 9.7±0.5 week and women were tested for serum progesterone and USG and followed up to term. Women included in this study were classified according to the viability of their pregnancies into; viable pregnancy group 58 cases (58%) and non-viable pregnancy group (ended by miscarriages) 42 cases (42%).

The mean serum progesterone of the studied population was significantly high in viable pregnancy group (18.09±5.9 ng/ml) compared to non-viable pregnancy group (6.707±3.02 ng/ml). The relations between serum progesterone and maternal age or gestational age of the studied population were statistically insignificant; also, the relation between serum progesterone and past history of early miscarriage was statistically insignificant. The ROC curve analysis demonstrated a significant ability of serum progesterone to differentiate between viable and nonviable pregnancies.

The area under curve (AUC) for progesterone was 0.971 (95% CI, 0.944-0.997) with the parameters calculated from the ROC curve shown in Figure 1. In this study; 6.8% of viable pregnancies had serum progesterone level <10.05 ng/ ml, while 9.5% of non-viable pregnancies had serum progesterone level >10.05ng/ml, the serum progesterone at cut off level 10.05 ng/ml was 93.1% sensitive to diagnose non-viable pregnancy and was 90.5% specific to diagnose viable pregnancy. Below is table showing various study and their reference progesterone values with sensitivity and specificity.

As signified in Table 6, History of contact a was found in 14 cases out of which 7 aborted and with History of travel and history of trauma was seen in 25 cases and 15 cases out of which 10 and 9 cases aborted respectively. History of heavy work was noticed in 5 cases of which 1 aborted. None of the factors were found significant. (P value > 0.05). History of vaginitis and UTI was positive in 11 and 10 cases respectively but both were not significantly associated. (P value >0.05).

The most common risk factor among present cases was a history of previous Miscarriages. 38% cases had a history of previous miscarriage. This indicates that previous pregnancy loss is an important risk factor for 1st trimester miscarriage.

One percent of cases aborted for recurrent causes and 17% for non-recurrent causes in subsequent pregnancy. Table 9 represents associated systemic diseases, out of which it was found that nearly 6 cases of PCOS aborted and none continued, and Rest 10 cases were not significantly associated with viability.

### Table 9: Associated systemic diseases.

| Systemic diseases | Continued | Aborted |
|-------------------|-----------|---------|
| Asthma            | 3         | 1       |
| Epilepsy          | 4         | 2       |
| Gastroenteritis   | 2         | 1       |
| Hyperemesis       | 4         | 2       |
| Koch’s            | 3         | 0       |
| Hydronephrosis    | 0         | 1       |
| RHD               | 0         | 1       |
| None              | 42        | 34      |
| DM                | 1         | 1       |
| Hypothyroid       | 3         | 1       |
| PCOS              | 0         | 6       |
| Total             | 62        | 50      |

In Table 7 showing History of spontaneous pregnancy loss that 22,6,8 and 2 women were associated with previous 1,2,3 and 4 pregnancy losses respectively. There were 62 cases of no previous history of Miscarriage. Thus, majority of women had no previous pregnancy losses. Recurrent miscarriage, defined as the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive, as per Stirrat G M.17

According to a study by Regan L et al, the risk of a further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses, and the prognosis worsens with increasing maternal age.18

As shown in Table 8, The most common symptom of a miscarriage is bleeding.19 36% of the cases presented with bleeding PV and 33% of patients presented. However, both symptoms were present in 31% cases. According to a study of women who seek clinical treatment for bleeding during pregnancy, about half will go on to have a miscarriage.19

### Table 10: Pregnancy outcome.

| Pregnancy Outcome | Continued |
|-------------------|-----------|
| Term              | 51        |
| Preterm           | 7         |
| Normal            | 49        |
| VLBW              | 2         |
| LBW               | 3         |
| IUGR              | 4         |
| Normal Labour     | 44        |
| LSCS              | 9         |
| PTL               | 5         |

As per USG findings, 58% cases showed a normal scan out of which about 79% normal scans continued as viable pregnancy while about 20% aborted. It was inconclusive in 34% cases were having inconclusive USG findings requiring follow up USG after 1 week and 8% cases were diagnosed as missed miscarriage.
The percentage of Miscarriage was reduced with normal scans in my study. Most prospective series report a loss rate of 3.4-5.5% if bleeding occurs after fetal heart activity starts, and identification of fetal heart activity by ultrasound in primary healthcare settings carries 97% likelihood for the pregnancy continuing beyond 20 weeks.20

Table 10 showing the pregnancy outcome of which 42 aborted, 7 cases ended as preterm labour and 51 pregnancies reached up to term. Thus, the overall Miscarriage rate of present study was 42%.

The cut off level of serum progesterone in the present study was 10.05 ng/ml and the sensitivity and specificity for the test was 93.1% and 90.5 % respectively.

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