

# Efficacy of Progesterone in the Management of Threatened Miscarriage

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## ABSTRACT

### BACKGROUND

There is a great probability of foetal demise and abnormal outcomes in the first trimester of a recognized pregnancy. 20% pregnancies have first trimester complications out of which the most common is miscarriage. Threatened miscarriage is a risk factor occurring in about 20-25% of confirmed pregnancies which may progress or resolve. Inadequate progesterone secretion has been implicated in the aetiology of miscarriage. The current study was undertaken to study the efficacy of progesterone in the management of first trimester threatened miscarriage.

### METHODS

A prospective randomized clinical trial was conducted in a rural tertiary health care center from Jan 2018 to March 2019. A total of 100 pregnant women who had a viable pregnancy who were admitted for threatened abortion in the first trimester, fulfilling the inclusion and exclusion criteria, were selected after taking an informed consent. Patients were further divided into 2 groups of 50 patients each. Group A was treated with progesterone and Group B was given supportive treatment without progesterone. They were observed for relief of symptoms, and progression to second trimester or spontaneous miscarriage.

### RESULTS

Parameters like age, gravidity, period of gestation and body mass index at the time of admission did not have a significant difference between the two groups. Symptoms like vaginal bleed and abdominal pain reduced in 54% and 52% of patients who received progesterone respectively; while, vaginal bleed and abdominal pain reduced only in 40% and 38% of patients who received only symptomatic treatment respectively. 54% of patients who received progesterone and 38% of patients who received only symptomatic treatment could continue the pregnancy further.

### CONCLUSIONS

Pregnant women with first trimester threatened miscarriage have a great risk for spontaneous loss of pregnancy. Progesterone may help clinically, but has no statistically significant improvement in the outcome of pregnancy. Further trials are required utilizing other forms and dosages of progesterone and other routes of administration.

### KEYWORDS

Threatened Miscarriage, Progesterone, Outcome

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## BACKGROUND

Threatened miscarriage is when the process of miscarriage has started but not progressed to the stage of irreversibility. A diagnosis is made on the basis of foetal cardiac activity documented on ultrasound along with a history of vaginal bleeding with a closed cervix on examination. It complicates at least a quarter (25%) of pregnancies.<sup>1,2</sup> Out of which half of the cases progresses to miscarriage.<sup>3</sup> In over 50% of cases miscarriage is associated with chromosomal abnormality of the conceptus.<sup>4,5</sup> Other risk factors include maternal age over 35 years,<sup>6</sup> maternal infections like vaginal colonization of group B streptococci, human immunodeficiency virus and genital herpes simplex,<sup>7</sup> maternal autoimmune factors like phospholipids antibodies, maternal abnormalities of the endocrine system including uncontrolled diabetes mellitus<sup>8,9</sup> polycystic ovary syndrome and inadequate corpus luteum production of progesterone<sup>4</sup> and a previous history of two or more miscarriages.<sup>10</sup>

Progesterone is a hormone secreted by the corpus luteum which prepares the uterus for implantation of fertilized egg. Progesterone promotes implantation, affects cytokine balance, inhibits activity of natural killer cell at the foeto-maternal interface, inhibits arachidonic acid release, promote PIBF synthesis which favours the production of asymmetric, pregnancy-protecting antibodies, and prevents myometrial contractility and cervical dilatation.<sup>11</sup> There are many documented theoretical data on the physiological role of progesterone in maintenance of pregnancy and have been prescribed in order to prevent miscarriages since the 1950s. Progestogens are medications that mimic progesterone action. Progestogens can be administered orally, vaginally, or intra-muscularly. But there is no sufficient evidence to support the therapeutic value of progesterone for the treatment of threatened miscarriage.<sup>12</sup>

Miscarriages takes a profound toll on the physical and psychological wellbeing of the mother. These includes depression, sleep disturbances, marital discord, acute hypovolemic shock, death. Any treatment which might help in reducing the serious morbidity and mortality associated with it is worth further investigation. This study has been conducted keeping in view of this problem about the efficacy of progesterone in management of threatened miscarriage in first trimester.

## METHODS

A prospective randomized clinical trial was conducted over a one year period from Jan 2018- March 2019 in the Department of Obstetrics and Gynaecology, in a rural tertiary care hospital, MVJMC and RH, Dandupalya, Bangalore, India.

After taking a written informed consent explaining in detail about the drug, a total of 100 patients with a diagnosis of threatened abortion made on the history, examination and viability confirmed on ultrasonography during first twelve weeks of gestation after considering inclusion and

exclusion criteria were studied over the course of pregnancy to determine the efficacy of progesterone in the management of threatened abortion. All patients in the age group 19-40 years and with gestational age within 12 weeks with viability confirmed on ultrasound were included. Patients unwilling for registration, hydatidiform mole, recurrent pregnancy loss, multiple pregnancies, uterine anomalies, local cervical and vaginal lesions and pre-existing medical disorders e.g. hypothyroidism, diabetes mellitus, chronic hypertension, diagnosed thrombophilia and other bleeding disorders, autoimmune disease like APLA syndrome were excluded.

A prior prepared proforma was used to collect data from patients who were admitted. Patients were randomly divided into two groups of 50 cases each. Group-A was given natural progesterone 200 mg twice daily till 14 weeks of gestation. Group-B was advised only bed rest and no progesterone was administered as treatment. These patients were observed after management for relief of symptoms like vaginal bleeding, abdominal pain and progression of pregnancy to second trimester or had a spontaneous miscarriage.

## Statistical Analysis

The collected data was entered in SPSS version 10 for statistical analysis. Frequencies were determined for the cessation of symptoms like vaginal bleeding and abdominal pain and for the number of patients reaching the second trimester in each group. Mean and Standard deviations was calculated for gestational age. Statistical significance was calculated between two groups by using Chi square test to compare the outcome. A 'p' value of <0.05 was considered as significant.

## RESULTS

Majority of the patient belonged to the age group of 21-25 years of age (60%). The mean age of the patient was found to be  $23.56 \pm 3.98$ . Mean BMI of patient was found to be  $27.2 \pm 3.84$  kg/m<sup>2</sup> which is similar in both the groups. Majority of the patients who presented with threatened abortion were between 5-8 weeks of gestation in both groups. Mean period of gestation is  $8.04 \pm 2.55$  in Group A and in Group B is  $7.86 \pm 1.99$ . One of the main variables taken into consideration is the resolution of symptoms like vaginal bleed and abdominal pain. The bleeding settled in 27 patients (54%) in Group-A after treatment with progesterone and 20 patients (40%) in Group-B after receiving only bed rest. There is no significant difference in outcome in both groups. p value is 0.31. The abdominal pain settled in 26 patients (52%) in Group-A and 19 patients (40%) in Group-B. There is no significant difference in both groups. p value is 0.436. Another study variable compared was the progression of pregnancy to second trimester. Even though Group A patients who received progesterone had a better clinical prognosis than Group B patients who did not receive the same, it is statistically insignificant as p value is 0.194.

Age	N	%
15-20	20	20%
21-25	60	60%
26-30	16	16%
31-35	2	2%
36-40	2	2%

**Table 1**

Duration of Gestation	Group A (With Progesterone)		Group B (Without Progesterone)	
	N	%	N	%
5-8 weeks	31	62	33	66
9-11 weeks	14	28	15	30
12-14 weeks	5	10	2	4
Total	50	100	50	100
Mean/ SD	8.04 ± 2.55		7.86 ± 1.99	

**Table 2. Comparison of Gestational Age in Both Groups (Before Receiving Treatment)**

Cessation of Vaginal Bleed	Group A (With Progesterone)		Group B (Without Progesterone)	
	N	%	N	%
Settled	27	54	20	40
Persisted	23	46	30	60
Total	50	100	50	100

**Table 3. Comparison of Cessation of Per Vaginal Bleeding in Both Groups (After Receiving Treatment)**

p value = 0.301

Relief of Abdominal Pain	Group A (With Progesterone)		Group B (Without Progesterone)	
	N	%	N	%
Settled	26	52	19	38
Persisted	24	48	31	62
Total	50	100	50	100

**Table 4. Comparison of Relief of Abdominal Pain in Both Groups (After Receiving Treatment)**

p value = 0.436

Pregnancy Outcome	Group A (With Progesterone)		Group B (Without Progesterone)	
	N	%	N	%
Progressed	27	54	19	38
Aborted	23	46	31	62
Total	50	100	50	100

**Table 5. Comparison of Pregnancy Outcome in Both Groups (After Receiving Treatment)**

p value- 0.194

## DISCUSSION

Pregnancy is a major life event with the purpose of developing a healthy baby while keeping the mother healthy. Miscarriage is defined as the spontaneous or induced termination of pregnancy before foetal viability. Spontaneous miscarriage occurs in about 15-20% of pregnancies. Threatened miscarriage is evidenced by bleeding per vagina, with or without abdominal pain, while a viable foetus is inside the uterine cavity with a closed cervix.<sup>12</sup> Miscarriage is a deeply distressing event that can affect the physical, psychological and social bearing of a mother and her family. Thus an event of threatened miscarriage requires meticulous attention and adequate care to fulfil a successful pregnancy.

In our study the mean gestational age was similar in both the groups with 8.04 and 7.86 weeks respectively. These results are also in agreement with the studies of Hayfaa A Wahabi et al,<sup>4</sup> Omar MH et al.<sup>13</sup> and Everett et al,<sup>14</sup> where the mean gestational age was 7 weeks, which is very close to our findings. In our study an elevated mean BMI was noted in both groups (27.27±3.84 kg/m<sup>2</sup>) which is comparable to studies conducted by Everett et al.<sup>13</sup>

Progesterone is a hormone secreted from the ovary by functional corpus luteum which bind to the progesterone receptors. These receptors bind to both natural and synthetic forms of progesterone. During early pregnancy, human chorionic gonadotropin rescues the corpus luteum, hence maintaining progesterone secretion which is essential for the implantation and maintenance of early pregnancy. However, after the 8th week of gestation, production of progesterone shifts to the placenta wherein, maternal cholesterol is utilized as an initial substrate to produce most of the progesterone that enters the maternal circulation.

Besides inducing secretory changes in the endometrium and supporting early pregnancy, they play a major role in modulating immune response of the mother to prevent rejection of the foetus and relaxes smooth muscles of the uterus. Most doctors prescribe bed rest and progesterone as management of threatened miscarriage. The rationale being that progesterone deficiency has been implicated to hamper pregnancy and cause first trimester miscarriages. Furthermore, PIBF have an inhibitory effect on immune reaction, causing a shift and increase in production of cytokine 2. Be that as it may, in our study there was no significant relief of symptoms in the patients who took progesterone as compared to those who did not. Settlement of per vaginal bleeding and abdominal pain in Group A patients who were administered with progesterone alone was 54% and 52% cases respectively; while in Group B patients who were treated with only bed rest and not given progesterone, per vaginal bleeding and abdominal pain settled in 40% and 38% cases respectively. These findings were corroborated with studies done by Hayfaa A Wahabi and colleagues,<sup>4</sup> Omar MH and colleagues<sup>12</sup> and Julius Szerkes-Bartho.<sup>15</sup> In our study 53% of Group A patients who received progesterone progressed to second trimester while only 38% of Group B patients who received only bed rest and not given progesterone progressed to second trimester. However even though there was a clinical reduction in the rate of abortion, there is no statistically significant improvement on receiving progesterone as compared to women who received.

In a study done by Giobbe M of 226 women, 16% of 146 women in that study who were under bed rest eventually miscarried compared to a fifth of women who did not follow this option.<sup>16</sup> However, some of the embryos have structural malformations or karyotypic aberrations which are incompatible with life which is not corrected with administration of progesterone but and helps only to retain a normal embryo. As these confounding factors were not taken into account in the study, some patients in the treated and control groups with such abnormal embryos might have been treated raising the number of miscarriages in both groups. Moreover in our study only natural progesterone was used. In studies conducted by El-Zibdeh MY et al and Pandian RU, other progestogens like dydrogesterone, have been shown to have better effect.<sup>17,18</sup> Thus further trials are required utilizing other forms and dosages of progesterone and other routes of administration.

Information regarding the potential harm to the mother or child, or both, with the uses of progesterone in the treatment of threatened miscarriage is lacking. However, no documented side-effects were noted on intake of Progesterone in the mother or child in this study.

### CONCLUSIONS

Miscarriage is a debilitating condition morbidly affecting maternal wellbeing. Threatened miscarriages are alarming and demands for any treatment that can reduce the probability of progression to miscarriage. Although use of progestogens in the management of threatened miscarriage doesn't significantly improve outcome, progesterone may have some clinical benefit in reducing the risk for miscarriage, and hence can be used by physicians in the management of first trimester threatened miscarriage.

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