

# Threatened Miscarriage and Adverse Fetomaternal Outcome Late in Pregnancy—A Prospective Study

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## ABSTRACT

**Aim:** The study was aimed to analyze the effect of threatened miscarriage on fetomaternal outcomes late in pregnancy and thereby reduce the morbidity through better antenatal care.

**Materials and methods:** A 1-year prospective observational study on 50 pregnant women with threatened miscarriage and 50 pregnant women with no history of vaginal bleeding was undertaken at Pushpagiri Institute of Medical Sciences and Research Centre from August 2016 to July 2017. Adverse fetomaternal outcomes late in pregnancy were evaluated in both groups. Relative risk was assessed, and the association between threatened miscarriage and various outcomes was analyzed using the Chi-square test.  $p$  value  $<0.05$  was considered statistically significant.

**Results:** The outcomes found to be significantly increased in threatened miscarriage group were preterm labor [18% vs 2%,  $p = 0.016$ , OR 10.75 (CI 1.3–88.4)], NICU admission [30% vs 10%,  $p = 0.023$ , OR 3.857 (CI 1.278–11.638)], and low birth weight (mean 2.67, SD = 0.53 vs mean 3.03, SD = 0.42). Most of the other outcomes studied were increased in the exposed group compared to the normal pregnancies, but the association was not significant.

**Conclusion:** Preterm labor, low birth weight, and NICU admissions were significantly increased in the threatened miscarriage group.

**Clinical significance:** Anticipation of such outcomes and measures for prediction and prevention is a question to be considered in such pregnancies to optimize the fetomaternal outcome.

**Keywords:** Fetomaternal outcome, Prospective study, Threatened miscarriage, Vaginal bleeding in pregnancy.

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## INTRODUCTION

Threatened miscarriage is diagnosed when vaginal bleeding occurs before 24 weeks, with a closed cervix and a documented fetal cardiac activity on ultrasound scan. Bleeding is usually in a slight amount and of unknown source. Though it causes less physical morbidity, the psychological impact and the stress and anxiety, it renders to the mother and family members are to be considered. The presence of cardiac activity with fetal heart rate more than or equal to 120 beats per minute, is a strong predictor that the pregnancy will proceed normally. The risk of threatened miscarriage to proceed to full miscarriage depends on gestational age and is diminished to 2–14% after confirmation of cardiac activity.<sup>1–3</sup> In some cases, ultrasound may reveal a subchorionic hematoma. Larger hematomas have been implicated in an increased risk of miscarriage and other poor pregnancy outcomes.<sup>4</sup>

When bleeding occurs between chorionic membranes and uterine walls, it may progress and produce local necrosis, leading onto uterine contraction and expulsion, resulting in the process of miscarriage. In the rest of the pregnancies that continue, it is postulated that such a process in early pregnancy can lead onto a spectrum of effects on pregnancy and its outcome by various mechanisms. Some of these may be:

- Chronic inflammation eventually causing rupture of the membrane or stimulating myometrial activity.<sup>5</sup>
- Bleeding acting as a nidus causing subclinical uterine infection and leading to preterm labor.
- Impaired invasion of cytotrophoblasts and remodeling of spiral arteries in early placentation, which are complicated by preterm delivery, preterm premature rupture of membranes (PPROM), and placental abruption.<sup>6</sup>

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**Ethical and humane considerations:** The study was initiated after approval from the Institutional Research and Ethics Committee. The study subjects were counseled, informed consent taken, enrolled, and given a serial number for identification.

- Iron deposit due to bleeding may provoke excess oxidative stress that is linked to preterm delivery, preeclampsia, and premature rupture of membranes (PROM).<sup>6</sup>
- Excess amount of thrombin may be released in response to tissue factor activation due to the bleed, which could impede the ongoing implantation.<sup>6</sup>

As does a threatened miscarriage may result in loss of pregnancy, similarly, the probability that the common initial trigger causing a significant adverse pregnancy outcome and fetal effects cannot be neglected. Various studies suggest emerging evidence that such association exists with many late pregnancy complications.

There are only a few well-designed prospective studies available. Whether such pregnancies need to be considered high risk, in order to foresee such complications and carry out early interventions, is still unclear.

## MATERIALS AND METHODS

A hospital-based prospective observational study, enrolling 100 women who visited the antenatal clinic at the Department of Obstetrics and Gynaecology, Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, Kerala from August 2016 to July 2017, was initiated. Sample size was calculated using the incidence of PROM for alpha = 5% and power of 90%. Fifty booked pregnant women with threatened miscarriage and 50 booked pregnant women without any vaginal bleed whose pregnancy continued beyond 24 weeks were included by purposive sampling after age, parity, and BMI were matched. Threatened miscarriage was diagnosed based on documented fetal cardiac activity on ultrasound after a history of vaginal bleeding, in the presence of closed cervix. The enrolled women were followed up, and data were collected by pretested semi-structured questionnaire, direct observation/examination, and case records of mother and baby, and documented on the proforma.

Relevant information about the bleeding episode, ultrasound finding, antenatal period, obstetric history, and presence of risk factors was collected. The outcomes studied were:

**MATERNAL:** Preterm labor, PPRM, PROM, pregnancy-induced hypertension (PIH), abruptio placentae, placenta praevia, retained/adherent placenta, and emergency cesarean section.

**FETAL:** *Intrauterine growth restriction* (IUGR), IUD, neonatal death/morbidity, anomalies, NICU admission, low birth weight, and low Apgar.

Exclusion criteria considered were multifetal gestation, pre-existing diabetes mellitus, chronic hypertension, unsure dates/irregular menstrual cycles, and lost to follow-up.

## Statistical Analysis

Data collected were entered in Microsoft Excel spreadsheet. Discrete variables were expressed in frequency and percentage. Continuous variables were expressed as mean and standard deviation. Outcomes in both groups were compared to see for any significant association of threatened miscarriage on the late pregnancy outcome. Data were analyzed using SPSS version 16. Relative risk was assessed, and the association between threatened miscarriage and various outcomes was analyzed using the Chi-square test.  $p$  value <0.05 was considered statistically significant.

## RESULTS

The total number of subjects studied was 100. Fifty women with threatened miscarriage and 50 without threatened miscarriage were studied, and the age, parity, and BMI wise distribution of both groups were comparable.

Figure 1 shows the distribution of age. About half of the studied subjects in each category belonged to the age group 26–30 years. Figure 2 depicts the distribution of parity of both groups. The majority of the subjects studied were nulliparas and of normal BMI. Figure 3 shows similar distribution of BMI among the groups. Various risk factors that might have an effect on the outcome were also studied. Figure 4 shows the distribution of the risk factors of equal prevalence in both groups.

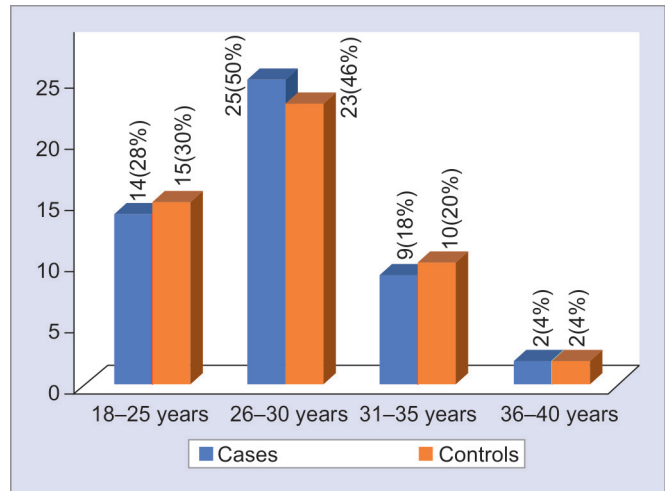


Fig. 1: Distribution of age

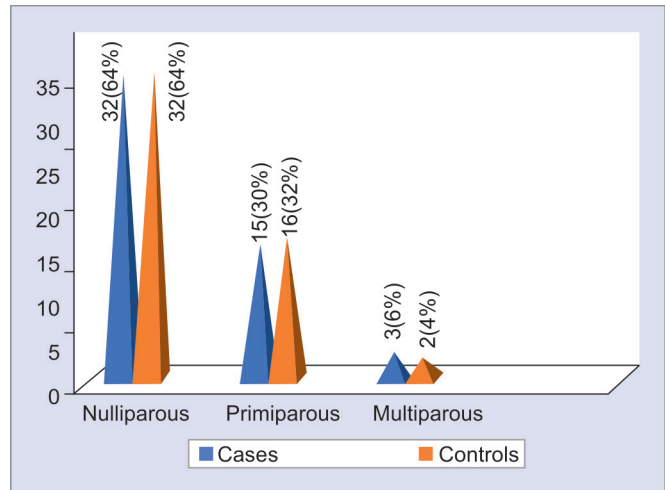


Fig. 2: Distribution of parity

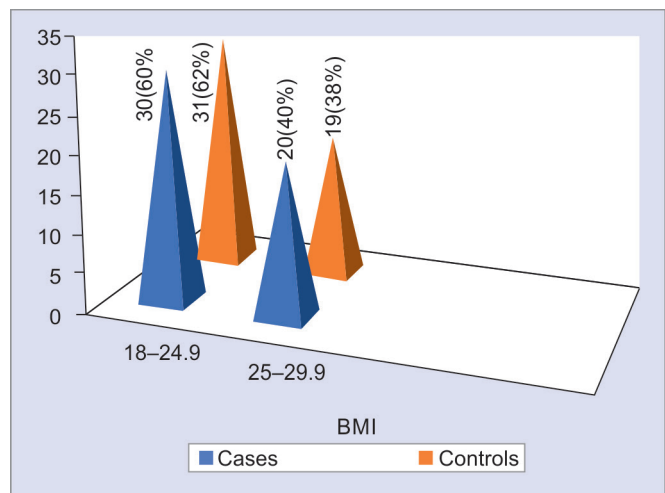


Fig. 3: Distribution of BMI

## Maternal Outcomes

Table 1 shows a summary of the association between threatened miscarriage and maternal outcome. Preterm labor was significantly

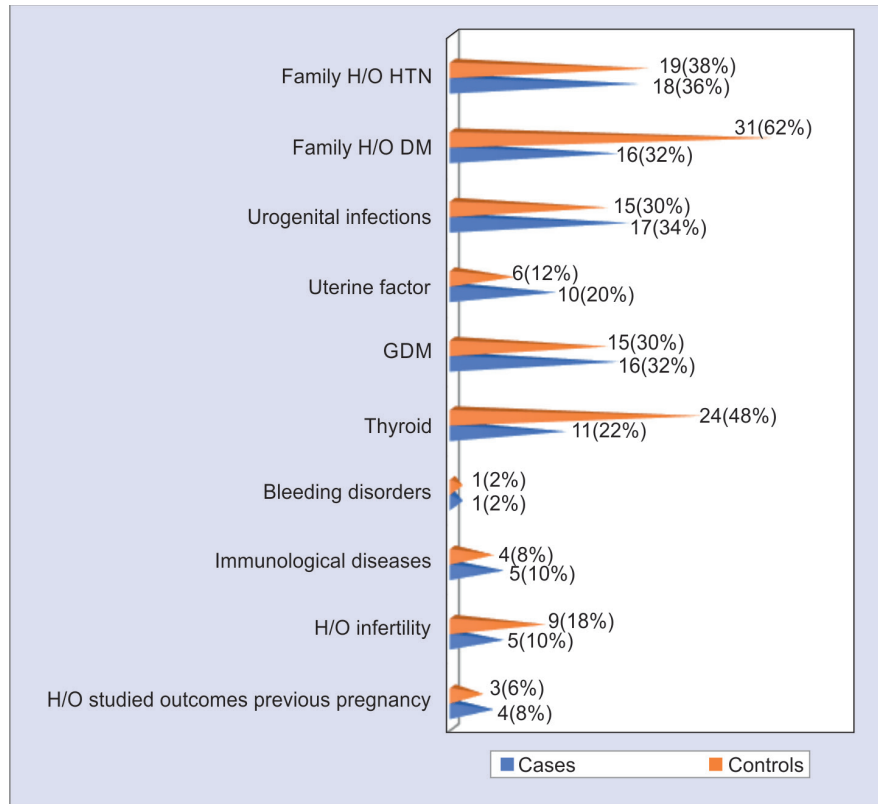


Fig. 4: Distribution of risk factors

Table 1: Summary of association of threatened miscarriage and maternal outcomes

Characteristic	Threatened abortion	Normal pregnancy	p value	OR (95% CI)
Preterm labor				
Yes	9 (18%)	1 (2%)	0.016	10.75 (1.3–88.4)
No	41 (82%)	49 (98%)		
PPROM				
Yes	2 (4%)	0 (0%)	0.495	
No	48 (96%)	50 (100%)		
PROM				
Yes	2 (4%)	2 (4%)	1.000	1.000 (0.135–7.392)
No	48 (96%)	48 (96%)		
PIH				
Yes	5 (10%)	3 (6%)	0.715	1.741 (0.393–7.713)
No	45 (90%)	47 (94%)		
Abruptio placentae				
Yes	2 (4%)	1 (2%)		2.042 (0.179–3.266)
No	48 (96%)	49 (98%)	1.000	
Placenta praevia				
Yes	3 (6%)	2 (4%)		1.532 (0.245–9.587)
No	47 (94%)	48 (96%)	1.000	
Retained/adherent placenta				
Yes	3 (6%)	0 (0%)	0.242	
No	47 (94%)	50 (100%)		
Emergency CS				
Yes	18 (36%)	8 (16%)	0.242	2.953 (1.141–7.646)
No	32 (64%)	42 (84%)		

**Table 2:** Summary of association between threatened miscarriage and fetal outcomes

Characteristic	Threatened abortion	Normal pregnancy	<i>p</i> value	OR (95% CI)
IUGR				
Yes	10 (20%)	4 (8%)	0.148	2.875 (0.837–9.881)
No	40 (80%)	46 (92%)		
IUD				
Yes	0 (0%)	0 (0%)		
No	50 (100%)	50 (100%)		
NICU admission				
Yes	15 (30%)	5 (10%)	0.023	3.857 (1.278–11.638)
No	35 (70%)	45 (90%)		
Neonatal death/morbidity				
Yes	0 (0%)	1 (2%)	1.000	
No	50 (100%)	49 (98%)		
Anomalies				
Yes	0 (0%)	0 (0%)	1.000	
No	50 (100%)	50 (100%)		
Apgar at 1 min	8.34 (0.77)	8.32 (0.99)	0.911	
Birth weight	2.67 (0.53)	3.03 (0.42)	<0.001	

increased in those with threatened miscarriage, with odds' ratio for threatened abortion 10.756 (95% CI 1.308–88.473) and the *p* value 0.016.

Though there was an increased incidence of PPROM and PIH in the threatened miscarriage group, it could not be accounted as statistically significant. The incidence of PROM was found to be the same in both groups.

The incidence of abruption with OR 2, placenta praevia, was not found to be significantly increased, *p* value 1.000, though there was a minor difference in the incidence between the two groups.

The association between threatened miscarriage and retained/adherent placenta was not significant. Similarly, increased rate of IUGR and emergency cesarean deliveries in the study group compared with the control group was not statistically significant.

### Fetal Outcomes

Table 2 shows a summary of the association between threatened miscarriage and fetomaternal outcome. The NICU admission in threatened miscarriage cases was increased with odds ratio of 3.857 and was found to be significant, *p* value 0.023. The incidence of low birth weight in women with threatened miscarriage was statistically significant, *p* <0.001.

The difference in Apgar score between the two groups was not found to be significant. There were no cases of IUD or anomalous babies in both groups. There was only one case of NND, which was in the control group, where no significant association was seen.

### DISCUSSION

The main drawback of the earlier studies on threatened miscarriage was the retrospective, case-control methodology chosen. Very few studies have taken into account the various risk factors and thus have derived varying results. Thus, drawing definite conclusions from these studies remains still controversial.

The baseline characteristics of the study subjects in this study were adequately matched, and the risk factors that might have

influenced the outcomes studied were found to be almost of equal prevalence in both groups.

### Preterm Labor

In this study, 9 of 50 women (18%) with threatened abortion had preterm labor while only 1 of 50 women (10%) without threatened miscarriage had preterm labor. The odds' ratio for preterm labor is 10.756 (95% CI 1.308–88.473) and the *p* value is 0.016, which shows significant association of preterm labor for those with threatened miscarriage.

The association between threatened miscarriage and preterm labor has been demonstrated in many other large studies.<sup>6–14</sup> Williams et al. in their study of 1174 women who had first-trimester bleeding alone, the risk of having a preterm delivery was doubled compared with those without any bleeding (adjusted risk ratio = 2, 95% CI 1.6–2.5).<sup>15</sup> Hossain et al. had found a three-fold increased risk of preterm delivery (OR = 3, 95% CI:1.84–4.89).<sup>8</sup> Saraswat et al. in their meta-analysis reported the increased incidence.<sup>13</sup> The reported risk varied between 1.5 and 4.5 across various studies. The overall adjusted risk of preterm delivery risk was 2.05 (95% CI 1.76, 2.4) in women who experienced first-trimester bleeding (*p* <0.0001).<sup>13</sup> Strobino and Pantel-Silverman did not find any such association.<sup>16</sup>

### PPROM

Preterm premature rupture of membranes occurred in 2 of 50 (4%) women with threatened abortion and none in the control group, significant association could not be derived, *p* value 0.495. In the systematic review by Saraswat et al., PPROM was significantly higher in women whose pregnancy was complicated with threatened miscarriage (OR 1.78, 95% CI 1.28–2.48), (*p* = 0.01).<sup>13</sup> Wijesiriwardana et al. did not conclude in such association.<sup>17</sup>

### PROM

Premature rupture of membranes was not seen to be significantly associated in this study. Williams et al. also did not find any such association.<sup>15</sup> But Hosseini et al. found a 10-fold [OR 10 (6.4–10.6)]

increase in the incidence of PROM in women with threatened miscarriage but was not statistically significant,  $p$  value  $>0.001$ . Similar association was found in the study by Yang et al.<sup>18</sup>

### PIH

The incidence of PIH was 10% in women with threatened miscarriage when compared with the control group 6%, with odds' ratio 1.741 (0.393–7.713), it was not found to be significant ( $p$  value = 0.715). Preeclampsia was weakly associated with first-trimester bleeding in the study by Lykke et al.<sup>6</sup> The association was not statistically significant in the study by Wijesiriwardana et al. and Saraswat et al.<sup>13,17</sup> Hosseini et al. did not find any association between early pregnancy bleeding and pre-eclampsia, but gestational hypertension was found to be significantly associated. Significant association of preeclampsia with early pregnancy vaginal bleeding was documented in a large study by Weiss et al. and in many other studies.<sup>2,11,13</sup>

### Abruptio Placentae

While 2 of 50 women (4%) with threatened miscarriage had abruption placentae, only 1 of 50 (2%) women without threatened miscarriage had abruption with odds' ratio of 2.042 (0.179–23.266). But the association was not significant,  $p$  value of 1.000. Though studies by Johns et al. and Wijesiriwardana et al. revealed the same finding,<sup>17,19</sup> the significant association of abruption in pregnancies complicated by vaginal bleeding in early pregnancy in many other studies refuted this result.<sup>1,6,13</sup>

### Placenta Praevia

The incidence of placenta praevia was not found to be significantly increased,  $p$  value 1.000 (6% in cases and 4% in controls). This was supported in the study by Hossain et al.,<sup>8</sup> but contradicted in some other studies.<sup>6,8,11</sup> The systematic reviews by Saraswat et al. and van Oppenraaij also drew significant association with the incidence of placenta praevia.<sup>13,20</sup>

### Adherent Placenta

Adherent placenta was seen in 3(6%) of 50 women with threatened abortion, but the association was not significant,  $p$  value 0.242.

### Emergency Cesarean Delivery

Though there was an increase in the emergency cesarean in the study group of 18 of 50 women (36%) than in the control group, 8 of 50 (16%) with odds' ratio of 2.953 (1.141–7.646), it was not significantly associated,  $p$  value 0.242. The increased incidence of cesarean deliveries in pregnancies complicated by threatened miscarriage was statistically found to be significant in a large study by Weiss et al. and few other studies.<sup>1,7,11,17</sup>

### IUGR

The increased incidence of IUGR in pregnancies complicated with threatened miscarriage, 10 (20%) compared to control group 4 (8%), with odds' ratio of 2.875 (0.837–9.881) was not found to be significant,  $p$  value 0.148. Similarly, no significant association was found in the study by Batzofin et al.<sup>12</sup> There was an increased rate of IUGR in many studies.<sup>11,13,17</sup>

### Neonatal Outcomes

The NICU admission in threatened miscarriage cases was increased, 15 (30%) in comparison with control group 5 (10%), with odds' ratio of 3.857, and was found to be significant,  $p$  value 0.023. The risk of

perinatal mortality in women with threatened miscarriage was significantly increased in some studies,<sup>8–10,15</sup> but few other studies did not find such association.<sup>7,9,11</sup>

There were no cases of IUD or neonatal anomalies. There was 1 case of neonatal death in the control group. Though Sipila et al.<sup>7</sup> found an increased risk of congenital malformations, such association was not seen in studies by Batzofin et al.<sup>12</sup> and Hertz et al.

There was a difference in mean birth weight between the two groups, where the mean in the threatened abortion was lower than 2.67 compared with the control group mean of 3.03, and the incidence of low birth weight in women with threatened miscarriage was statistically significant with a  $p$  value  $<0.001$ . This was in accordance with the finding of significant increased incidence of low birth weight in women with early pregnancy vaginal bleed in many other studies.<sup>7,9–11,15,16,12</sup> But the study by Mulik et al. though showed that increase in LBW was not independently affected.<sup>21</sup>

### Limitation of the Study

The impact of a smaller sample size due to the prospective nature of the study might have affected the results. The varying pharmacologic management for threatened miscarriage, implemented in most of these cases might have influenced the various adverse fetomaternal outcomes.

### CONCLUSION

Threatened miscarriage was seen to have significant association with increased incidence of preterm labor. Most of the other maternal outcomes studied were increased in the threatened miscarriage group compared with the normal pregnancies, but the association was not significant.

The fetal outcomes of low birth weight and NICU admission also showed significant association with increased incidence in the threatened miscarriage group.

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