RESEARCH REPORT

THREATENED ABORTION: A RISK FACTOR FOR POOR PREGNANCY OUTCOME

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Abstract- The scientific literature regarding threatened abortion is relatively limited on the subject of outcomes and viability at term. To investigate prospectively the risk of adverse pregnancy outcome in women presenting with first-trimester threatened miscarriage, a prospective case control study was performed on 600 subjects, 150 women presenting with bleeding in the first trimester and 450 asymptomatic age-matched controls. Main outcome measures included gestational age and weight at delivery as well as incidence of adverse pregnancy outcome such as preterm labor, preterm prelabor rupture of membranes (PPROM), placental abruption, and low birth weight (LBW). The first-trimester miscarriage rate in the threatened miscarriage group was 42.7%. Compared with controls, women presenting with threatened miscarriage were more likely to deliver prematurely, 14.7% compared with 52.9%, respectively (relative risk 3.6, 95% confidence interval [CI] 2.4-4.8). They were also more likely to have PPROM, 6.4% compared with 27.5%, respectively (relative risk 4.2, 95% CI 2.6-6.9); placental abruption, 5.7% compared with 1.5%, respectively (relative risk 3.6, 95% CI 1.2-11.3); LBW, 14.9% compared with 7.1%, respectively (relative risk 2.1, 95% CI 1.1-3.8) and low lying placenta, 1.1% compared with 18.2%, respectively. birth weight 2866 ± 523.3 g compared with 312.45± 591.4 respectively, gestational age 35.71 ± 4.3 compared with 38.07 ± 3.2 respectively. First-trimester vaginal bleeding is an independent risk factor for adverse obstetric outcome and this risk factor should be taken into consideration when deciding upon antenatal surveillance and management of their pregnancies.

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Key words: Threatened abortion, spontaneous pregnancy loss, preterm delivery, preterm premature rupture of membranes

INTRODUCTION

Threatened miscarriage, defined as vaginal bleeding before 24 weeks of gestation, is a common complication affecting about 20% of pregnancies. It has been shown to be associated with an increased risk of poor obstetric outcomes such as preterm labor, low birth weight, and premature rupture of membranes. Moreover, when pregnant women have bleeding, it may cause stress and anxiety for the mother-to-be about the outcome of pregnancy. So, it is necessary to be diagnosed and managed to prevent maternal or fetal mortalities and morbidities (1).

The scientific literature regarding threatened abortion is relatively limited on the subject of outcomes and viability at term. Small number of patients and significantly biased data collection have limited previous studies of pregnancies that were complicated by threatened abortion (2-4). Many studies suggest that first-trimester vaginal bleeding is associated with a worse outcome (2-9). However, there have been few studies that evaluated outcomes other than viability at term, after the documentation of a living embryo. In general, the incidence of

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spontaneous abortion after first-trimester bleeding is quoted to be 50% before sonographic evaluation for fetal viability (5, 6). If a viable fetus is noted at ultrasound examination after first-trimester vaginal bleeding, 95% to 98% of such pregnancies will still continue beyond 20 weeks of gestation (5, 10).

The diagnosis of threatened miscarriage is frequently made in clinical practice as a result of taking a history of vaginal spotting and the finding of a closed cervix at subsequent vaginal examination. A definitive diagnosis of threatened miscarriage should be made following ultrasonographic examination, confirming the presence of fetal heart activity in an intrauterine pregnancy (11).

Because bleeding originates from the placenta in most cases of threatened abortion, we hypothesized that pregnancies complicated by a first-trimester threatened abortion could be at increased risk for other "placental related" complications. To evaluate this risk of first-trimester bleeding, we evaluated a variety of outcomes that included pregnancy loss, preterm delivery, intrauterine growth restriction (IUGR), preeclampsia, preterm premature rupture of membranes (PPROM), placental abruption, placenta previa, and Cesarean delivery (12).

First-trimester vaginal bleeding is common, occurring in 15-20% of all viable pregnancies. Despite its common occurrence, the risk of adverse outcome for pregnancies with first-trimester threatened abortion and a living embryo has been defined incompletely (13). However, unexplained prenatal haemorrhage, similar to threatened miscarriage, probably exerts an indirect effect (as they were not independent risk factors for early neonatal death) on perinatal outcome through the increased risk of preterm delivery. This suggests that a threatened miscarriage is possibly related to uteroplacental dysfunction. This assumption is supported by the fact that threatened miscarriage was associated independently with the risk of placental abruption and unexplained antenatal haemorrhage. The former remained a risk factor even in term pregnancies and contributed independently to early neonatal deaths (1, 14).

The current study was conducted on patients with first-trimester threatened abortion to evaluate the outcome.

MATERIALS AND METHODS

A prospective case-control study was preformed in 150 women presenting with bleeding in the first trimester and 450 age-matched control subjects who attended for routine dating or delivery at MKH Hospital of Tehran University Medical Sciences from October 2004 to November 2006. The study was approved by Ethics Committee of Tehran University of Medical Sciences and written informed consent was obtained from all subjects.

Baseline data were recorded by questionnaire and patient interview. Subjects were divided into two groups: 1) no bleeding, 2) bleeding (defined as spotting or as similar to menses). Post delivery follow-up was performed by telephone interview or medical record review by the research coordinator at each site.

Any incident of preeclampsia, IUGR, intrauterine fetal distress (IUFD), low birth weight (LBW), low lying placenta, placenta previa or low lying placenta, birth weight and neonatal sex were recorded. Potential confounding factors were identified and adjustment was made in the statistical models. These factors included: maternal age, gravidity and previous recurrent abortion. The following pregnancy outcomes between the two groups were compared: abortion, low lying placenta, IUGR, IUFD, PPROM, LBW, preeclampsia, neonate gender, anomalies, maternal anemia and postpartum infection, type of delivery.

The following adverse pregnancy outcomes among the two groups were then compared: IUGR (estimated fetal weight by ultrasound examination of <10th percentile or birth weight of <10th percentile for gestational age), gestational hypertension (blood pressure >140/90 mm Hg on at least two occasions >6 hours apart without evidence of chronic hypertension), preeclampsia (criteria for gestational hypertension and significant proteinuria), preterm labor (labor <37 weeks of gestation), PPROM (membrane rupture <37 weeks of gestation), placental abruption (premature separation of a normally implanted placenta), placenta previa (placenta completely or partially covering the internal os), low lying placenta (placenta edge

actually does not reach the internal os but is in close proximity to it) and Cesarean delivery.

The outcomes were established and analyzed with SPSS 13. Univariate and multivariable logistic regression analyses were used to evaluate the association among the two groups with regards to specific pregnancy outcomes. Patients without first-trimester vaginal bleeding were used as the control group. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 600 records with complete antenatal, birth, and pediatric outcome were available for review. The control group consisted of 450 (75%) patients and the bleeding group consisted of 150 patients (25%).

The demographic characteristics of the two groups are summarized in Table 1. Statistically significant differences were noted among the groups for age and parity and previous recurrent miscarriage. In case group, 18% had low-lying placenta in sonography.

All subjects who were included in this investigation had a viable pregnancy confirmed by ultrasound examination at the time of trial enrolment. Compared with the control group, patients with vaginal bleeding were significantly more likely to have a spontaneous loss (42.7%).

Demographic characteristics of neonates are shown in Table 2. After an adjustment was made for the potential confounding factors that included gestational age at delivery, a statistically significant difference was noted in mean birth weight among the two groups**:** control, 3123.45 g ± 591.4; case group, 2866.25 ± 130.3 g ($P < 0.001$). The mean gestational age at delivery for patients in control group and vaginal bleeding group was 38.07 ± 3.2 weeks and 35.71 ± 4.3 weeks, respectively ($P = 0.001$).

Table 2. Demographic characteristic of neonate*

Outcome	Control	Case	*P* value
Anomaly	8(1.7%)	2(2.3%)	0.742
Apgar score†	9	8	0.633
Male	214(47.87%)	50(58.1%)	0.081
Female	233(52.12%)	36(41.86%)	0.081

*Data are given as number (percent) unless specified otherwise.
†Mean.

The obstetric outcomes for patients with first-trimester bleeding compared with patients without bleeding are described in Table 3. No significant difference in the incidence of IUGR ($P= 0.808$), preeclampsia ($P= 0.121$), gender ($P= 0.081$), type of delivery ($P= 0.453$), IUFD ($P= 0.474$) or placenta previa between the control group and subjects with first-trimester vaginal spotting was noted.

Statistically significant differences were noted in these complications: preterm delivery, 14.7% in controls compared with 52.9% in case group ($P < 0.001$, relative risk 3.6, 95% confidence interval 2.4-4.8); PPROM, 6.4% compared with 27.5%, ($P < 0.001$, relative risk 4.2, 95% confidence interval 2.6-6.9); placental abruption, 5.7% compared with 1.5% ($P= 0.015$, relative risk 3.6, 95% confidence interval 1.2-11.3); LBW, 14.9% compared with 7.1% ($P= 0.016$, relative risk 2.1, 95% confidence interval 1.1-3.8); and low lying placenta, 1.1% compared with 18.2%, respectively, were significantly more common in patients with vaginal bleeding compared with control patients.

Table 1. Demographic characteristics of the two study groups*

Characteristic	Controls (n = 450)	Cases (n = 150)	*P* value
Age (years)	26.5±4.52	27.13±4.76	0.014
Low lying placenta†	5(1.1%)	16(18.2%)	0.001
Birth weight (g)	3123.45±591.4	2866.25±523.3	0.001
Gestational age at birth (wk)	38.07±3.2	35.71±4.3	0.001
Previous recurrent miscarriage†	3(0.7%)	9(6%)	0.205
Gravid	2 ±1.1	2.17 ±1.3	0.145

*Data are given as mean ± SD unless specified otherwise.
† Number (percent).

Table 3. Obstetric complications by amount of vaginal bleeding

Outcome	Controls (n=450)	Cases (n=150)	*P* value	Adjusted OR (95% CI)
IUGR	18 (4%)	3 (3.4%)	0.088	
LBW	32 (7.1%)	13 (14.9%)	0.016	2.1
Preterm delivery	66 (14.7%)	46 (52.9%)	0.001	3.6
IUFD	6 (1.3%)	14 (14.1%)	0.747	
Preeclampsia	44 (9.8%)	4 (4.6%)	0.121	
Anemia	139 (30.8%)	34 (22.7%)	0.054	
PPROM	29 (6.4%)	24 (27.5%)	0.001	4.2
Placental abruption	7 (1.5%)	5 (5.7%)	0.015	3.6
Placenta previa	3 (0.6%)	1 (0.6%)	1	
Cesarean delivery	237 (52.7%)	42 (42.8%)	0.453	

Abbreviations: IUGR, intrauterine growth restriction; LBW, low birth weight; IUFD, intrauterine fetal distress; PPROM, preterm premature rupture of membranes.

DISCUSSION

These data show that threatened miscarriage is not only associated with miscarriage but also with adverse pregnancy outcome. Results from this study confirm findings from other authors, that threatened abortion is associated with an increased risk of certain pregnancy-related complications, namely placental abruption, preterm labour, delivery of low birth weight infants and PPROM (15, 16). Generally, high incidence of abortion and complications in threatened miscarriage indicate the necessity of proper programming in care and also educating high risk women. A potential limitation of this study is that the severity of vaginal bleeding was based on a subjective description by the patient. However, the ultimate assessment of vaginal bleeding is based on patient report. Therefore, we believe the results of this study can be applied to clinical practice.

Results of this study support other evidence that, in some patients, first-trimester vaginal bleeding may indicate underlying placental dysfunction, which may be manifest in later pregnancy by a variety of adverse outcomes that have also been related to placental dysfunction (17). In one study, an increased risk of preeclampsia, preterm delivery, placental abruption, and Cesarean delivery was observed for patients who reported light bleeding, although these risks were low with an OR of < 2.0 (16). For patients who reported heavy vaginal bleeding during the first trimester, they observed increased risks of IUGR, preterm delivery, PPROM, placental abruption, and Cesarean delivery. With the exception of Cesarean delivery (OR, <2.0) these associations appear to be both statistically and clinically significant (16, 18). In our study increased risk of preterm delivery (rr= 3.6), PPROM (rr= 4.2), placental abruption (rr= 3.6) and LBW (rr= 2.1) was occurred.

In 1993, Verma *et al.* reported that pregnancy-induced hypertension was significantly more common in subjects with threatened abortion and a viable pregnancy compared with subjects without vaginal bleeding (6% vs. 4.7%, respectively; $P < 0.05$) (2). However, their study was limited by a total of only 113 subjects. Another study did not find an association between first-trimester vaginal bleeding and gestational hypertension but did find that patients with light bleeding were statistically more likely to have preeclampsia (16). This association carried a low OR of < 2.0. Similarly, we don't find significant association between vaginal bleeding and preeclampsia.

Preterm delivery before 37 week's gestation occurs in 7-11% of pregnancies, but is responsible for 85% deaths of normally formed infants. Despite significant advances in perinatal medicine, the incidence of preterm delivery has remained unchanged. The prediction of preterm delivery from currently available methods is unreliable, therefore, associated risk factors remain an important measure of identifying at-risk pregnancies (19, 20). This is especially evident by the significantly increased rate of early neonatal death rate in infants born from

mother who had presented with a threatened miscarriage, probably secondary to the increased rate of preterm deliveries and placental abruption. The only potential risk factor found to be associated significantly with the risk of preterm delivery in women with a threatened miscarriage was unexplained antepartum haemorrhage rather than other factors, such as smoking or preterm rupture of membranes. In our study, preterm delivery was more common in bleeding group (rr= 3.6).

The association between vaginal bleeding and preterm delivery has also been noted by others (21-23). Both Batzofin *et al.* (4) and Williams *et al.* (7) reported that patients with bleeding had double the risk of preterm delivery compared with patients without bleeding. The study of Williams *et al.* was limited to first trimester bleeding (7); Batzofin *et al.* included patients with bleeding up to 20 weeks (4). Strobino and Pantel-Silverman failed to show an association between preterm delivery before 36 weeks of gestation with light vaginal bleeding in the first or second trimester of pregnancy (24). Another study found that preterm delivery is increased significantly in patients with either light (OR, <2.0) or heavy (OR, 3.0) first-trimester bleeding (16).

Other studies were reported that patients with first-trimester threatened abortion are also at increased risk for placental abruption and IUGR (1, 25). Placental haemorrhage may recur later in pregnancy, which results in placental abruption. In present study placental abruption was significantly more common in case group (rr= 3.6) but no increase risk for IUGR (rr= 0.088) was found.

Haddow *et al.* reported an increased risk for low birth weight (<2500 g) in pregnancies that were complicated by vaginal bleeding (26). Infants of patients with heavy bleeding had nearly a 200 g difference in birth weight compared with control infants after accounting for preterm delivery. In present study risk of LBW was increased (rr = 2.1).

Our findings corroborate other studies that suggested an association between threatened abortion and PPROM (4-6). Although the cause is unclear, it is hypothesized that disruption of the chorionic-amniotic plane by adjacent haemorrhage may make the membranes more susceptible to rupture (4). Alternatively, the prolonged presence of blood may act as a nidus for intrauterine infection. Persistent or recurrent placental haemorrhage could also stimulate subclinical uterine contractions that result in cervical change and eventual ruptured membranes. In our study PPROM was increased in case group (rr = 4.2).

Placenta previa is a common cause of obstetric vaginal bleeding. It is possible that first-trimester bleeding could be a reflection of placenta previa in some patients. Das *et al.* reported an increased risk for a low-lying placenta among patients with threatened abortion but reported no difference in placental location compared with control subjects by 36 weeks of gestation (15). Others have found a higher rate of placenta previa among patients with heavy vaginal bleeding during the first trimester, but this association was not statistically significant (14, 4). Our data showed that placenta previa was not increased in case group but presence of low lying placenta was increased in case group ($P < 0.001$).

Currently, there is no information in the literature regarding threatened abortion and Cesarean delivery. One study suggested that a statistical association is present with threatened abortion and risk for cesarean delivery (4). In present study, Caesarean delivery was not higher in case group ($P < 0.455$).

In conclusion, the current study reports that patients with first-trimester threatened abortion are at increased risk for spontaneous loss and adverse pregnancy outcome. For patients who reported vaginal bleeding during the first trimester, we observed increased risks of LBW, preterm delivery, PPROM, placental abruption, and low lying placenta. These associations appear to be both statistically and clinically significant. Because the overall prognosis is favourable, these results can be used to help reassure patients with threatened abortion during the first trimester. At the same time, physicians should be aware of the adverse outcomes that are associated with first-trimester bleeding and remain alert for signs of these complications.

Conflict of interests

The authors declare that they have no competing interests.

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