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Placenta retention is associated with threatened abortion at the early stage of pregnancy

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Abstract

Introduction: Retained placenta (RP) is an obstetric issue complicating around 3% of normal deliveries. Previous studies identified various risk factors for RP. In clinical experience, women with a history of threatened abortion (TA) often are noted to have a higher risk of RP. Yet, limited research has been performed in this area.

Aim: To explore the association between RP and TA.

Material and methods: A retrospective cohort study including 219 women with viable pregnancies who had TA and 219 women who had not experienced TA with no evidence of subchorionic hematoma (SCH) between January 2019 and January 2021 were included. Demographic information and adverse pregnancy outcomes were compared. Women who had TA were further divided into two groups: SCH group and non-SCH group, and their demographic information and adverse pregnancy outcomes were also compared. χ^2 tests or Mann-Whitney *U*-tests were used for categorical/continuous variables respectively.

Results: The incidence of RP among women with TA was 25/219, compared to 10/219 in the control group (aOR = 2.33, 95% CI: 1.05–5.13, $p = 0.04$). Women had TA were at a higher risk of postpartum hemorrhage (aOR = 3.73, 95% CI: 1.68–8.27, $p = 0.001$). In addition, women with SCH were less likely to develop placenta previa ($p = 0.04$). However, when adjusted for confounders, the difference was not significant (aOR = 0.16, 95% CI: 0.02–1.26, $p = 0.08$).

Conclusions: We found that threatened abortion is associated with a higher risk of retained placenta as well as postpartum hemorrhage. Therefore, active management at the third stage of labor was recommended among women with a history of threatened abortion.

Key words: postpartum hemorrhage, subchorionic hematoma, threatened abortion, retained placenta.

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Introduction

Retained placenta (RP) is an obstetric issue complicating around 3% of normal deliveries worldwide [1]. RP is defined as the failure of expulsion of placenta within 30 min of vaginal deliveries [2]. It is one of the major contributors to blood loss after delivery and represents the most common reason for blood transfusion postpartum [3]. In addition, the presence of RP often requires manual or operative removal of placenta, which adversely adds a significant risk to postpartum endometritis and possibly exacerbates blood loss [3, 4]. To date, various risk factors have been identified to be associated with RP, such as prior history of RP, preterm delivery, grand multiple pregnancy, previous history of dilation and curettage (D&C) and *in vitro* fertilization (IVF) conception [1]. Some studies have identified that prolonged oxytocin use could potentially be another modifiable risk factor, and oxytocin exposure during labor may be positively related to RP [5]. Other epidemiological factors, such as maternal age, epidural anesthesia have also been noted to be of higher relevance [6, 7].

Threatened abortion (TA) is defined as any vaginal bleeding or abdominal cramping at the early stage of pregnancy [8]. It is a common condition and is seen in around one quarter of pregnancies [9, 10]. Many studies have associated TA with a higher risk of preterm delivery, cesarean section (C-section), and preterm premature rupture of membranes (PPROM) [10–12]. In recent years, it has been noticed that among women suffering from TA, the incidence of placenta retention is higher. However, limited data have explored the association between RP and TA. Wijesiriwardana *et al.* reported an association between TA and RP, but no significant difference was found after adjusting for confounders [13].

Aim

This study aimed to assess the hypothesis of increased incidence of placenta retention among women who suffered from TA during early pregnancy. Given that RP is associated with a high risk of mortality and morbidity at the obstetric unit, it is of utmost significance to explore its underlying mechanism as well as risk factors. We hope that it could shed light into the mechanism of RP and TA and thus help with better management in the clinical setting.

Material and methods

This is a retrospective cohort study evaluating women with a history of TA at the early stage of pregnancy and admitted to the Guangzhou Women and Children's Hospital during the period from January 2019 to January 2021. The minimal effective sample size was calculated. The data were collected from electronic medical records and included 438 pregnant women. Half of them (219) were characterized as women with a history of vaginal bleeding or lower abdominal pain before 14 weeks of pregnancy (TA group). Another half are blank controls. All of them were offered an ultrasound scan as part of medical assessment. The inclusion criteria were women with livable birth either from vaginal or cesarean section (C-section) at the same institution. Cases with abnormal uterine cavity findings or uterine malformation detected by the pre-pregnancy ultrasound (uterine fibroids, endometrial polyps, uterine septum) were excluded, so were those who had invasive procedures (chorionic villus sampling or amniocentesis) during pregnancy. All multiple pregnancies were also ruled out from this study, and so were those who had intractable pregnancy outcomes.

The control group was comprised of 219 women who delivered at the same institution with no history of vaginal bleeding or lower abdominal pain during early pregnancy. All the control cases had routine ultrasound scan over the same time scale as the women in the TA group. No presence of hematoma should be detected before 14 weeks of gestation. Women in the control group were matched with the study group based on maternal age, maternal body amss index (BMI), and parity. The study protocol was approved by the Committee on the Ethics of Human Research of Guangzhou Women and Children's Hospital.

Definition and data collection

Data regarding patient demographics, pregnancy and delivery-related parameters were extracted from electronic medical records. Gestational age was determined based on the last maternal menstrual period unless the first ultrasound examination (measurement of crown-rump length) found a disparity of more than 7 days. A subchorionic hematoma or intrauterine hematoma was defined as a hypoechoic crescent-shaped adjacent to the gestational sac between the myometrium and chorionic membrane detected by ultrasound. An adverse pregnancy outcome was defined as any serious complications of pregnancy requiring medical intervention to either the expectant mother or the newborn infant, such as treatment or delivery, or admission or treatment of the newborn infant. These adverse outcomes include placenta abruption (PA); early postpartum hemorrhage (PPH); retained placenta; placenta previa (PP); gestational diabetes mellitus (GDM); hypothyroidism; hyperthyroidism; pregnancy-associated hypertension, including preeclampsia and eclampsia; intra-uterine retardation (IUGR); premature rupture of membranes (PROM); and preterm labor (PTL).

Statistical analysis

All the continuous variables data were presented as median (interquartile range) and compared with Mann-Whitney *U*-test. All the categorical data of adverse pregnancy outcomes in the symptomatic and control groups, were presented as the number of exposed cases (percentage out of total number) and compared by Pearson χ^2 test. $P < 0.05$ was considered statistically significant. Odds ratio (OR), adjusted odds ratio (aOR) and confidence interval (CIs) for significant pregnancy outcomes were also established. Statistical analysis was performed with IBM SPSS Statistics for MacBook, version 25 (IBM Corp., Armonk, N.Y., USA).

Results

An overall of 219 women had an ultrasound scan after presenting with symptoms of TA before 14 weeks of preg-

nancy. These were matched to 219 control cases for maternal age, and BMI. In Table I, baseline demographic characteristics were compared and listed, such as maternal age, BMI, parity and previous history of dilation and curettage (D&C), IVF, gestational age of the onset of symptoms and delivery. The median maternal ages were 32 (20–45) and 31 (23–44) years old in the TA and control group respectively, while the median BMIs were 21 (16–32) and 21 (16–31) kg/m^2. No significant differences were found in the distribution of age (p = 0.12) and BMI between these groups (p = 0.82). Furthermore, 53.0% women in the study group were primigravid compared with 50.7% in the control group. There was no significant difference of the parity distribution between the two groups (p = 0.23). The median gestational age (interquartile range) at the time of the ultrasound examination was 70 days (31–173) in the TA group and 84 days (35–97) in the control group, and they were not statistically different (p = 0.79). A significant difference between gestational age at delivery was noted (p = 0.01) between the TA and control group. While 18 women in the TA group (8.2%) were conceived through IVF, the rate of IVF was not significantly different compared to the control group (n = 10, p = 0.12). Additionally, women in the TA group were more likely to have a history of D&C (p = 0.01).

Women with symptoms of TA were subdivided into those who did or did not have intrauterine subchorionic hematoma (SCH) at ultrasound scan. One hundred and three women presenting with TA had evidence of SCH on initial ultrasound examination. Apart from gestational age at the date of ultrasound scan (p < 0.05), no significant differences in baseline demographic characteristics between the group of women with SCH and those without SCH were noted, including maternal age, BMI, parity, IVF, previous history of D&C.

Table II shows comparison of results of various adverse pregnancy outcomes between the TA and control group, SCH and non-SCH group. The incidence of obstetric complications including GDM and pregnancy-associated hypertension, as well as pregnancy-related thyroid conditions were similar between the study and control groups. Additionally, the rate of PPROM in the study group was not significantly different compared to the control cases, and so were IUGR, placenta previa and PTL. However, the incidence of postpartum (p = 0.001) along with RP (p = 0.008) was significantly higher in the TA group compared to the control group. Among women who had symptoms of TA, women with SCH were more likely to suffer from placenta previa compared to the control group (p = 0.04).

Crude odds ratio and 95% confidence interval were calculated and shown in Table III. A multivariate logistic regression was performed to examine the association of early pregnancy TA with livable deliveries while controlling for the effects of potential confounders: postpartum hemorrhage, gestational age at delivery, retained placenta, spontaneous delivery or caesarean section. The adjusted odds ratios with 95% CI were presented in Table III. TA was found to be independently associated with RP (aOR = 2.33, 95% CI: 1.05–5.13, p = 0.04) as well as PPH (aOR = 3.73, 95% CI: 1.68–8.27, p = 0.001). Women with SCH were less likely to develop placenta previa (OR = 0.20, 95% CI: 1.26–5.75,

Table I. Maternal baseline demographic characteristics in the study (TA group) and control groups

Characteristic	Threatened abortion (TA group) (n = 219)	Control group (n = 219)	P-value	SCH group (n = 143)	Non-SCH group (n = 76)	P-value
Maternal age	32 (20–45)	31 (23–44)	0.12	32 (23–44)	33 (20–45)	0.12
Maternal BMI	21.3 (16–32)	21.2 (16–31)	0.82	21.1 (16–30)	21.6 (17–32)	0.07
Parity:			0.227			0.07
0	116 (53.0)	111 (50.7)		70 (49.0)	46 (60.5)	
1	92 (42.0)	87 (39.7)		64 (44.8)	28 (36.8)	
2	10 (4.6)	20 (9.1)		8 (5.6)	2 (2.6)	
	1 (0.5)	1 (0.5)		1 (0.7)	0 (0)	
Previous D&C:			0.01			0.37
0	152 (69.4)	172 (78.5)		101 (70.6)	51 (67.1)	
1	48 (21.9)	39 (17.8)		31 (21.7)	17 (22.4)	
2	14 (6.4)	5 (2.3)		9 (6.3)	5 (6.6)	
3	3 (1.4)	3 (1.4)		1 (0.7)	2 (2.6)	
4	2 (0.9)	0 (0)		1 (0.7)	1 (1.3)	
In vitro fertilization	18 (8.2)	10 (4.6)	0.12	13 (9.1)	5 (6.6)	0.52
Gestational age at TA [days]	70 (31–173)	84 (35–97)	0.16	77 (35–173)	57 (31–145)	0.000
Gestational age at delivery [days]	273 (210–290)	274 (218–290)	0.01	272 (210–290)	274 (239–285)	0.16
C-section	99 (45%)	74 (34%)	0.009	66 (46%)	33 (43%)	1.00

All continuous variables are presented as median (interquartile range). All categorical variables are expressed as proportions (n %) unless otherwise specified. BMI – body mass index, D&C – dilation and curettage, TA – threatened abortion, C-section – Cesarean section.

Table II. Adverse pregnancy outcome among symptomatic and asymptomatic groups and associations with retained placenta

Adverse outcome	TA group, *n* (%)	Control group, *n* (%)	*P*-value	SCH group, *n* (%)	Non-SCH group, *n* (%)	*P*-value
Placental abruption	7 (3.2)	3 (1.4)	0.201	6 (4.2)	1 (1.3)	0.25
PPH	28 (12.8)	9 (4.1)	0.001	18 (12.6)	10 (13.2)	0.91
Retained placenta	25 (11.4)	10 (4.6)	0.008	14 (9.8)	11 (14.5)	0.30
Placenta previa	7 (3.2)	5 (2.3)	0.56	2 (1.4)	5 (6.6)	0.04
GDM	49 (22.4)	49 (22.4)	1.00	29 (20.3)	20 (26.3)	0.31
Pregnancy-induced hypertension	19 (8.7)	17 (7.8)	0.73	13 (9.1)	6 (7.9)	0.77
Hypothyroidism	5 (2.3)	6 (2.7)	0.76	5 (3.5)	0 (0)	0.10
Hyperthyroidism	2 (0.9)	2 (0.9)	1.00	2 (1.4)	0 (0)	0.30
IUGR	7 (3.2)	4 (1.8)	0.36	6 (4.2)	1 (1.3)	0.25
Preterm rupture of membrane	43 (19.6)	43 (19.6)	1.00	29 (20.3)	14 (18.4)	0.74
Preterm labor	15 (6.8)	16 (7.3)	0.85	9 (6.3)	6 (7.9]	0.39

PPH – postpartum hemorrhage, GDM – gestational diabetes mellitus, IUGR – intrauterine growth retardation.

Table III. Multivariate analysis of factors with potential confounding factors between TA and control groups

Adverse outcome	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*P*-value
Time of abortion	0.69 (0.51–0.93)	0.78 (0.52–0.97)	0.03
Gestational age at delivery [days]	1.02 (1.00–1.04)	1.02 (0.99–1.04)	1.02
C-section	1.37 (1.08–1.72)	1.63 (1.08–2.44)	0.02
PPH	3.2 (1.57–7.43)	3.73 (1.68–8.27)	0.001
Retained placenta	2.69 (1.26–5.75)	2.3 (1.05–5.13)	0.04
Placenta previa (SUH vs. non-SUH)	0.20 (1.26–5.75)	0.16 (0.02–1.26)	0.08

Adjusted for: times of abortion, PPH, retained placenta, C-section, gestational age at delivery for the TA and control group. Placenta previa was adjusted for gestational age at the day of TA.

$p = 0.04$). When adjusted for gestational age at TA, the significance between SCH and non-SCH group was no longer significant (OR = 0.16, 95% CI: 0.02–1.26, $p = 0.08$).

Discussion

The failure to separate and expel the placenta is potentially life threatening as it could impair normal uterine contractility and lead to postpartum hemorrhage. The exact mechanism of placenta retention is still poorly understood. In cows, it was found that an oxidative reaction and a destruction of the apoptotic process in the placenta were present in RP [14, 15]. RP, sometimes considered a mild form of placenta accreta spectrum, was postulated to share a similar pathological mechanism with each other, the defective placentation, in which the placenta was inadequately formed in the uterus among humans [16, 17]. Clinically, RP could be categorized into three types: first, the placenta incarceration, which means that the placenta has detached completely but was not able to be delivered spontaneously due to the closure of the cervix. Second, placenta adherens, the placenta is adherent to the uterus, resulting in retroplacental contraction failure, and the placenta detachment failure. Third, focal placenta accreta, the placenta is aggressively attached to the uterine myometrium due to defective decidua. This type of RP cannot be completely separated manually [18, 19].

In this study, the incidence of RP is significantly higher among women with TA compared to the control group (11.4% vs. 4.6%). It is found that women who suffered from TA are at a higher risk of experiencing RP. When adjusted for potential confounders, an association was also noted (aOR = 2.3, 95% CI: 1.05–5.13). An association between TA and RP were first revealed by Hertz and Heisterberg in 1985 [20], as well as a higher incidence of manual removal of placenta among women who suffered from TA [21, 22]. This finding was later on further supported by Wijesiriwardana *et al.,* in which 7627 women with TA were studied, and compared with 31633 controls (OR = 1.40, 95% CI: 1.21–1.62), although the underlying mechanism could not be identified [13]. Accordingly, adhesive scarring between the uterine wall and the placenta at the site of bleeding is thought to be responsible for the high risk of RP among women with TA [17, 19]. However, in our study, symptomatic women with SCH were not significantly associated with RP compared with women without SCH. Therefore, it might indicate that there could be another mechanism underneath as women with SCH should reasonably more likely have localized uterine adhesive injury. It is uncertain whether the exposure of certain medicine during the early stage influenced the pathological state of the placenta. Progesterone, in various forms, is often prescribed to women with TA, although its efficacy remains controversial [8, 23, 24]. The idea of using proges-

terone is to prepare the uterus for embryo implantation, uterine quiescence enhancement and uterine contractions suppression [8]. In this study, all the women in the study group were exposed to progesterone, either oral dydrogesterone or intramuscular progesterone or both. However, the data of medication exposure could not be correctly extracted as the prescription of the medicine is not well guided. Some of the patients may take the medicine till late pregnancy, while others might not take as advised. To date, the effect of progesterone exposure on the pathological placenta implantation has not been studied. It is unclear that whether the exogenous progesterone could play a role in the embryo implantation and placenta formation through regulation of Th1/Th2/Th17 [21].

In the literature, data have shown conflicting evidence regarding the association between TA and various late pregnancy outcomes, including preterm delivery, pregnancy-induced hypertension, preeclampsia, and placental abruption [12, 20]. For example, both Wijesiriwardana *et al.* and Weiss *et al.* reported that patients with TA have an increased risk of preterm delivery [10, 13]. However, Strobino and Pantel-Silverman were unable to show an association between preterm birth and TA [25]. Furthermore, in the study done by Weiss *et al.* in 2004, TA was also associated with a higher risk of placental abruption, and intrauterine growth retardation (IUGR) [10]. A higher risk of PPROM was also noted in the same study, although it was only significant among women with heavy bleeding. In our study, we found no significant association between TA and preterm birth, IUGR, and PPROM respectively. The divergence of data could result from different inclusion criteria, incomplete follow-up and difficulty in controlling for baseline variables.

In our study, previous dilation and curettage (D&C) of the uterine wall is associated with a high risk of retained placenta, which is in line with prior publications [1]. It is also found that grand parity is associated with retained placenta, which is unsurprising as an increased risk of pathological implantation over a uterine scar by D&C or C-section may lead to retained placenta or even placenta accrete [16, 25, 26]. However, most of the data in the publications were compromised by a highly heterogenous population of women regarding parity and history of abortion, especially dilation and curettage [27]. In this study, we further evaluated the association between women with TA and without TA when adjusted for such confounders. An association of RP, along with PPH and TA was also noted.

SCH is a common finding on the ultrasound among women with TA. It is suggested to result from a partial shear of the chorionic membranes from the uterine wall, and tear of the spatial artery, causing bleeding. Among women who had viable deliveries, SCH is found to be associated with a higher risk of various adverse pregnancy outcomes and perinatal outcomes [22, 28]. It is hypothesized that SCH signifies an underlying placental dysfunction which subsequently results in pregnancy complications, such as pre-eclampsia, placental abruption, and IUGR [22, 29]. However, several studies had failed to find an association between SCH and adverse pregnancy and perinatal outcomes. Inman *et al.* [30] analyzed 1210 patients with an incidence of 12.5% of SCH and it was found that SCH did not increase the risk of pre-eclampsia, placenta accreta spectrum, and placental abruption or any other adverse pregnancy and perinatal outcomes. Interestingly, we found a trend toward a decreased incidence of placenta previa among women who had SCH during early pregnancy. Noticeably, this association was not seen between symptomatic women with TA and those who did not and was not significant when adjusted for the confounder (gestational age at TA). This finding is inconsistent with the study done by Wijesiriwardana *et al.,* in which a positive association between TA and placenta previa was noticed (aOR = 1.77, 95% CI: 1.09–2.87, $p = 0.017$) [13]. Furthermore, Weiss *et al.* and Mulik *et al.* found a similar phenomenon but no significant association was noted ($p = 0.08$) [10, 11]. Notably, it is thought that the location of the chorion frondosum within the uterine cavity is responsible for this association as an inferior position is more likely to cause bleeding [11, 13]. Das *et al.* reported an increased risk of a low-lying placenta among women with threatened miscarriage but no significant differences in placental location compared with the control group [31]. The adverse result in our study could be due to the limitation of the positive sample. Larger studies are required to clarify this association.

One of the strengths of our study is that we included women who delivered through surgery for the purpose of exposure of all TA patients that may be influenced by RP. The diagnosis of RP, mostly placenta adherens, was made by the surgeon who had to do manual removal to help with the complete expulsion the placenta. We noted that women in the study group were more likely to have C-section, while the difference among symptomatic women with and without hematoma is not significant. This finding is in line with the study done by Wijesiriwardana *et al.* [13]. Another strength of our study is that it is the first, to our knowledge, to study the association between RP and TA with merely livable birth. Third, subgrouping comparison in terms of pregnancy outcome between SCH and non-SCH patients. This allows for increased generalizability to a more diverse population suffering from threatened miscarriage and may aid counseling when SCH is detected.

Admittedly, there are some limitations of the study that need to be acknowledged. First, this study may be limited by a retrospective chart review design, which has an inherent risk of bias and errors in data collection. We could not rule out other factors that could potentially have influenced the results of the study. Second, the rarity of each individual adverse pregnancy outcome in the SCH and non-SCH groups made it difficult to establish a statistically significant association of some parameters.

Conclusions

We present here for the first time a markedly higher incidence of retained placenta among women with threatened abortion during early pregnancy. However, further studies are needed to confirm this association and elucidate its underneath mechanism. Nevertheless, threatened abortion

should be considered as being associated with a higher risk of retained placenta and postpartum hemorrhage. We therefore recommend active management during third stage of labor among women with a history of threatened miscarriage.

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Conflict of interest

The authors declare no conflict of interest.

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