History of hysteroscopic adhesiolysis treated intrauterine adhesions and subsequent risk of adverse obstetrical outcome: a matched cohort study of Chinese pregnant women

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Abstract

Objective: To examine whether women with a history of hysteroscopic adhesiolysis (HA)-treated intrauterine adhesions (IUAs) were at higher risk of adverse obstetrical outcomes in subsequent pregnancies. **Design:** Retrospective cohort study. **Setting:** A tertiary-care hospital in Shanghai, China. **Population:** 114,142 pregnant women who were issued an antenatal card and received routine antenatal care in Shanghai First Maternity and Infant Hospital between January 2016 and October 2021. **Methods:** From the cohort of 114,142 pregnant women, women with history of HA-treated IUAs before this pregnancy (N=780) were compared with 4 women with no history of IUAs (N=3010) matched on propensity score, maternal age and parity, mode of conception, pre-pregnancy BMI and prior history of abortion. **Main outcome measures:** Pregnancy complications, placental abnormalities, postpartum hemorrhage and adverse birth outcomes. **Results :** Compared with women with no history of IUAs, women with a history of HA-treated IUAs were at higher risks of preeclampsia (RR=1.69, 95% CI, 1.23, 2.33), placenta accreta spectrum (RR=4.72, 95% CI, 3.9, 5.73) and previa (RR=4.23, 95% CI, 2.85, 6.30), postpartum hemorrhage (RR=2.86, 95% CI, 1.94, 4.23), preterm premature rupture of membranes (RR=3.02, 95% CI, 1.97, 4.64) and iatrogenic preterm birth (RR=2.86, 95% CI, 2.14, 3.81) . Those women were also more likely to receive cervical cerclage (RR=5.63, 95% CI, 3.95, 8.02) during pregnancy and hemostatic therapies after delivery (RR=2.17, 95% CI, 1.75, 2.69). Moreover, we observed that the RRs of those adverse obstetrical outcomes increased with the increasing number of hysteroscopic surgeries. **Conclusion:** Our findings suggest that pregnant women with a history of HA-treated IUAs, especially those with a history of repeat HAs, are at higher risk of adverse obstetrical outcomes. **Key words:** hysteroscopic adhesiolysis, obstetrical outcomes, propensity score matching, cohort study

Introduction

Intrauterine adhesions (IUAs) characterized by partial or complete obliteration of the uterine cavity and/or cervical canal are considered one of the main reproductive system diseases [1-3]. They are caused by intrauterine operation-related trauma to a gravid uterine cavity or nongravid endometrium or intrauterine infection[4-6]. IUAs may cause one or more clinical symptoms, such as menstrual disturbances, periodic abdominal pain or recurrent pregnancy loss, and have a debilitating impact on the quality of life in childbearing-age women [4,5,7].

Hysteroscopic adhesiolysis (HA), which aims to restore regular menstruation and a normal uterine cavity, is the gold standard for diagnosing and treating IUAs in women with fertility requirements [8-10]. The menstrual pattern outcomes and reproductive performance, including conception rate, miscarriage rate and live birth rate, following HA management of IUAs have been frequently described, and most studies have reported relatively favorable outcomes [11-21]. However, only a few studies have focused on obstetric outcomes, and the sample sizes of the existing studies were relatively small [15,22-25].

In this study, using a large retrospective cohort of pregnant Chinese women, we compared the rates of pregnancy complications, placental abnormalities, postpartum hemorrhage (PPH) and adverse birth outcomes in pregnant women with a history of HA-treated IUAs and pregnant women with no history of IUAs and examined whether women with a history of HA-treated IUAs were at higher risk of adverse obstetric outcomes in subsequent pregnancies.

Methods

Study design

A retrospective cohort study was conducted at the Shanghai First Maternity and Infant Hospital, which is one of the largest prenatal care providers in Shanghai, China, with more than 20,000 births per year. A total of 114,142 pregnant women who were issued an antenatal card and received routine antenatal care from January 2016 to October 2021 were identified as potential participants. Women with incomplete medical records, a history of chronic diseases, severe autoimmune diseases, tuberculosis and cancer before this pregnancy and multiple pregnancies were excluded. Additionally, women with early pregnancy loss (pregnancy loss before 12 weeks of gestation) were excluded because some pregnant women experience early pregnancy loss before registering so that it is inaccurate to estimate the early miscarriage rate through our registering medical records. The flowchart of participant enrollment is presented in**Figure 1** . This study was approved by the Institutional Review Board of the Shanghai First Maternity and Infant Hospital.

Exposed pregnancies

Women who had been hysteroscopically diagnosed with IUAs and underwent hysteroscopic adhesiolysis before this pregnancy were categorized as exposed pregnancies. Adhesion were only divided by scissors through hysteroscope without energy source. Other data regarding hysteroscopic surgery, such as date of surgery, number of surgeries and time interval from surgery to conception, were extracted via manual review of the electronic medical record.

Matched control pregnancies

Women with no history of IUAs were categorized as unexposed control personnel. To control for potential confounders, we matched each exposed pregnancy with four women with no history of IUAs based on propensity scores generated by maternal age and parity, mode of conception, pre-pregnancy body mass index (BMI) and prior history of abortion. In propensity score matching (PSM), the nearest neighbor matching algorithm with a caliper width of 0.2 of the standard deviation of the logit score was used. Women with a history of other hysteroscopic operations, with amenorrhea/oligomenorrhea and with intrauterine adhesions indicated by ultrasound but not received hysteroscopic surgery were further excluded from the matched controls (N=43).

Outcomes

The obstetric outcomes of interest were pregnancy complications, placental abnormalities, PPH and adverse birth outcomes. Pregnancy complications were extracted from medical records and mainly included gestational diabetes mellitus (GDM), gestational hypertension (GH), preeclampsia (PE) and intrahepatic cholestasis of pregnancy (ICP). GDM was diagnosed based on a standard 75 g oral glucose tolerance test (OGTT) according to the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [26]. GH and PE were diagnosed according to the guidelines for the diagnosis and management of hypertensive disorders in pregnancy [27]. ICP was diagnosed according to the guidelines of the Chinese Medical Association of Obstetrics and Gynecology [28].

Placental abnormalities and PPH were also extracted from the medical records. Placental abnormalities comprised low-lying placenta, placenta previa and placenta accreta spectrum, including placenta accrete/increta/percreta. PPH was defined as blood loss [?] 500 ml for vaginal delivery or blood loss [?] 1000 mL for cesarean section. This definition was based on guidelines from the Chinese Society of Obstetrics and Gynecology and Chinese Medical Association[29]. Additionally, hemostatic therapies that referred women re-

ceiving Bakri balloon tamponade (BBT) or surgical management (vascular ligation and uterine compression sutures) for preventing PPH were also extracted.

Adverse birth outcomes, including preterm birth (PTB), cervical insufficiency, small for gestational age (SGA) and macrosomia, were extracted from medical records or newborn birth records. PTB was defined as a live birth before 37 completed weeks of gestation in accordance with the World Health Organization (WHO) definitions[30]. Then, PTB was categorized into three clinical subtypes: spontaneous PTB, preterm premature rupture of membranes (PPROM) and iatrogenic preterm birth. Iatrogenic PTB was defined as either induction or cesarean section before the onset of labor[31,32]. Additionally, the cervical cerclage rate, which is based on the indication of a history of abortion with painless cervical dilation or progressive shortening of the cervical lenth in this pregnancy in the second trimester, was also extracted and reflected cervical insufficiency to some extent [33]. SGA was defined as newborns with birth weight below the 10th percentile for gestational age.

Statistical analysis

SAS version 9.4 (SAS Institute Inc) was used for all statistical analyses. Differences were considered statistically significant when a 2-sided $P < 0.05$. The general demographic characteristics of the participating women are presented as percentages (%), and the distributions of the characteristics were compared between women with a history of HA-treated IUAs and matched women with no history of IUAs.

Log-binomial models using generalized estimating equations methods to account for the paired nature of the matched sample were conducted to estimate the relative risks (RRs) and 95% confidence intervals by comparing the proportions of pregnancy complications, placental abnormalities, PPH or adverse birth outcomes in exposed and matched control pregnancies. The final model included the matched cohorts for analyses of each pregnancy complication, placental abnormality, PPH and adverse birth outcome, respectively, with no additional adjustment. Women with no history of IUAs served as the reference.

In a secondary analysis, women with a history of HA-treated IUAs were further divided into three subgroups: women who received one surgery, two surgeries and more than three surgeries before this pregnancy. RRs and 95% CIs for the associations between the number of surgeries and risk of adverse obstetrical outcomes were estimated by unadjusted log-binomial analysis using generalized estimating equations with women with no history of IUAs serving as the reference. P-values for trend were estimated by including the number of hysteroscopic surgeries as continuous variables in the log-binomial models.

Based on the time intervals from the last hysteroscopic surgery to the date of conception, all women with a history of HA-treated IUAs were further divided into two subgroups: [?] 3 months and > 3 months since the date of the last hysteroscopic surgery. The associations of the time intervals with pregnancy complications, placental abnormalities, PPH or adverse birth outcomes were further examined. The estimated RRs and 95% CIs were reported with women with no history of IUAs serving as the reference.

Finally, to investigate whether the associations of history of HA-treated IUAs with risk of adverse obstetric outcomes differed according to maternal age (< 35, [?] 35), mode of conception (natural conception, conceived through ART) and maternal parity (nulliparous, multiparous), stratified analyses were conducted and the RRs and 95 % CIs were calculated in each subgroup.

Results

Demographic characteristics of the participants

After exclusion, a total of 98, 386 pregnant women were included. Among the 98386 included women, 780 had a history of HA management of IUAs before this pregnancy, and 97, 606 had no history of IUAs. As shown in**Table 1** , the two groups differed in maternal age and parity, prior history of abortion, mode of conception and pre-pregnancy BMI. However, these differences were eliminated by the PSM procedure. After matching, 780 exposed pregnancies and 3010 matched control pregnancies were included in the final analysis.

Association between history of HA-treated IUAs and risk of adverse obstetric outcomes

As shown in **Table 2** , the incidences of GDM (20.3% vs. 18.3%, P =0.19), GH (3.7% vs. 4.1%, P=0.61) and ICP (1.2% vs. 1.0%, P < 0.75) were generally similar between women with a history of HA-treated IUAs and women with no history of IUAs. However, the incidence of PE (5.9% vs. 3.5%, P < 0.01) in women with a history of HA-treated IUAs was significantly higher than that in women with no history of IUAs. Women with a history of HA-treated IUAs were at higher risk of PE, and the adjusted RR was 1.69 (RR=1.69, 95% CI, 1.23, 2.33).

For placental abnormalities, the incidences of placenta previa (5.8% vs. 1.4%, P < 0.01) and placenta accreta spectrum (25.0% vs. 5.3%, P < 0.01) were significantly higher in women with a history of HA-treated IUAs than in women with no history of IUAs. A history of HA-treated IUAs was associated with an increased risk of placenta previa (RR=4.23, 95% CI, 2.85, 6.30) and placenta accreta spectrum (RR=4.72, 95% CI, 3.90, 5.73). As placental abnormality is a known risk factor for PPH, we further examined the associations of a history of HA-treated IUAs with PPH. As shown in **Table 2** , women with a history of HA-treated IUAs were at higher risk of PPH (RR=2.86, 95% CI, 1.94, 4.23), and those women were also more likely to receive hemostatic therapies (RR=2.17, 95% CI, 1.75, 2.69).

Regarding adverse birth outcomes, a history of HA-treated IUAs was significantly associated with an increased risk of PTB. Women with a history of HA-treated IUAs were more likely to receive cervical cerclage (RR=5.63, 95% CI, 3.95, 8.02) and had a higher risk of PPROM and iatrogenic PTB. The adjusted RRs were 3.02 (RR=3.02, 95% CI, 1.97, 4.64) for PPROM and 2.86 (RR=2.86, 95% CI, 2.14, 3.81) for iatrogenic PTB. However, no significantly association was found between history of HA-treated IUAs and SGA (RR=0.89, 95% CI, 0.53, 1.49).

Associations between the number of hysteroscopic surgeries and the risk of adverse obstetric outcomes

To some extent, the number of hysteroscopic surgeries a woman underwent reflected their severity of IUAs. We additionally examined the potential impacts of the number of hysteroscopic surgeries on obstetrical outcomes. Among the 780 women with a history of HA-treated IUAs, 371, 315 and 94 underwent 1, 2 and [?] 3 hysteroscopic procedures before this pregnancy, respectively. There were graded relationships between the number of hysteroscopic surgeries and the risk of PE (**Figure 2A**), placenta previa (**Figure 2B**), placenta accreta spectrum (**Figure 2C**), PPH (**Figure 2D**) and iatrogenic preterm birth (**Figure 2H**) .The monotonic increases in RRs were observed with an increasing number of hysteroscopic surgeries (p-value for trend ¡0.01). Additionally, women who underwent more surgeries were more likely to receive o receive hemostatic therapies (**Figure 2E**) and cervical cerclage (**Figure 2F**).

Associations between the time interval from complete hysteroscopic surgery to the date of conception and risk of adverse obstetric outcomes

The time interval from complete hysteroscopic surgery to the date of conception may impact obstetrical outcomes, and we further examined the associations of this time interval with adverse obstetrical outcomes. Among the 780 women with a history of HA management of IUAs, 229 completed hysteroscopic surgery within 3 months before the date of conception, and 551 completed hysteroscopic surgery more than 3 months after conception. As shown in **Table 3** , the RRs of PE, placenta previa, placenta accreta spectrum, PPH, PPROM and iatrogenic PTB were generally similar (overlapping 95% CIs) among women who completed hysteroscopic surgery within 3 months before and more than 3 months before the date of conception. Additionally, this time interval also did not affect the likelihood of receiving cervical cerclage or hemostatic therapies.

Stratified analysis

Results of stratified analysis were shown in **Table S1-3** . The associations of history of HA-treated IUAs with adverse obstetric outcomes were generally similar across different subgroups of maternal age (confidence intervals of subgroups overlap) (**Table S1**). Similarly, mode of conception (**Table S2**) and maternal parity

(**Table S3**) also did not modify the associations of history of HA-treated IUAs with adverse obstetric outcomes

Discussion

This matched cohort study of pregnant Chinese women provided a comprehensive assessment of the associations between a history of HA-treated IUAs and obstetric outcomes in subsequent pregnancies. We observed that women with a history of HA-treated IUAs were at higher risk of PE, placenta accreta spectrum and previa, PPH and PTB. Those women were also more likely to receive cervical cerclage during pregnancy and hemostatic therapies after delivery. Moreover, we observed that the RRs of adverse obstetric outcomes increased with the increasing number of hysteroscopic surgeries. To our knowledge, this is one of the largest studies to report such associations.

PE, characterized by a multiorgan disorder, occurs in pregnancy with a clinical syndrome of hypertension and multiorgan hypoperfusion. In this study, we observed a significantly higher incidence of PE among women with a history of HA-treated IUAs than among women with no such exposure. PE are rarely mentioned in previous literature. Two previous studies compared the incidence of pregnancy-induced hypertension (GH, PE, eclampsia and HELLP syndrome) between women with a history of HA-treated IUAs and women with no such exposure. However, neither of these studies reported any significant difference in the incidence of pregnancy-induced hypertension between the two groups[23,24]. The development of PE is thought to be associated with abnormal placentation and placental hypoxia and/or ischemia[34]. Patients with previous IUAs usually experience endometrial trauma damaging the decidua basalis, insufficient or defective maturation of the endometrium and decidualization[35]. Impaired endometrial function and the abnormal adherence of the blastocyst to the decidualized endometrium have been shown to be involved in the pathogenesis of PE [36-38]. Additionally, patients with IUAs often have a prior history of recurrent spontaneous abortions (RSA), which may have shared risk factors and etiology with PE.

The placenta accreta spectrum, which refers to abnormal adherence of the placental trophoblast to the uterine myometrium or morbidly adherent placenta, is a major cause of PPH. It includes placenta accreta (directly implanted onto the uterine myometrium), placenta increta (invasion of the trophoblast into the myometrium) and placenta percreta (invasion through the myometrium into the surrounding organs)[39]. Cases of women who developed placenta accreta spectrum and PPH after IUA surgery have been frequently reported[5,40,41]. Additionally, some small studies also reported higher incidences of placenta accreta spectrum and PPH among women with a history of IUAs or a history of HA-treated IUAs[13,17,22,24], which were consistent with our findings. The placenta accreta spectrum results from the absence of the normal decidua basalis and endometrial re-epithelialization in the scar area, so the trophoblast and villous tissue can invade deeply within the myometrium [39,42]. Women with a history of HA endometrial scar repair and loss of the endometrial basal layer may have higher incidences of placenta accreta spectrum. In addition to the placenta accreta spectrum, we also observed a higher incidence of placenta previa. To our knowledge, placenta previa has rarely been reported. Consistent with our study, two retrospective cohort studies conducted in Changsha and Beijing also reported a higher incidence of placenta previa among women with a history of HA-treated IUAs[22,24].

The placenta plays a crucial role in fetal growth and development, and placental abnormalities may impair fetal growth and result in adverse birth outcomes [43,44]. We further examined the impacts of HA-treated IUAs on birth outcomes. Although previous studies did not report any difference in newborn gestational weeks[22,24], we observed a significantly higher incidence of PPROM and iatrogenic PTB among women with a history of HA-treated IUAs, and those women were also more likely to receive cervical cerclage to prevent spontaneous abortion or PTB. Various risk factors have been consistently associated with PTB. Recent studies suggest that bacterial vaginosis and vaginal microbiota disorder also play an important role in the development of PTB, especially PPROM [31, 45-48]. The pathological changes in IUAs are bound to influence the physiology and metabolites in the uterus, which may influence vaginal microbial diversity [49]. Additionally, after the first HA surgery, a copper intrauterine device (Cu-IUD) was often inserted into the uterus to prevent the recurrence of adhesion. However, the use of Cu-IUDs may increase the risk of bacterial vaginosis[50,51], which

may explain the higher risk of PPROM among those women. A history of cervical dilation has been associated with an increased risk of PTB, which may explain why women with more HA surgeries have a higher risk of PTB. Iatrogenic PTB may be attributed to the higher incidence of the placental accreta spectrum, placenta previa and PE in women with a history of HA-treated IUAs, as they are common cause of iatrogenic PTB [52].

Previous studies on newborn birth weight also yielded inconsistent results. In a case-control study, Saeed et al. reported that newborns of women with IUAs had significantly lower birth weights (2.23 ± 0.28 kg) than newborns of women without IUAs (3.13 ± 0.383 kg)[25]. Two other studies did not find any difference in newborn birth weight between women with a history of HA-treated IUAs and women with no such exposure [22,24]. Considering birth weight was highly dependent on gestational age, we compared the differences in SGA rate between the two groups. In our study, we found no significant association between history of HA-treated IUAs and risk of SGA.

Strengths and Limitations

The major strengths of our study are the large sample size and the use of PSM methods to eliminate the potential impacts of maternal age and parity, prior history of abortion, mode of conception and pre-pregnancy BMI. Furthermore, this study first explored the impacts of the number of HA surgeries and the time interval from complete surgery to the date of conception on obstetric outcomes. However, there are some limitations that warrant attention. First, all participants of our study were from one of the largest cities in China, which may limit the generalizability of our findings. Second, due to lack of sufficient untreated pregnancies with IUAs, we could not determine whether the increased risk of adverse obstetric outcomes was attributed to the HA treatment or the disease of IUAs itself. Finally, all data were from medical records, and due to data inaccessibility, we could not obtain the AFS score of each IUA case. However, we used the number of hysteroscopic surgeries a woman underwent to reflect the severity of their IUAs. Scoring of IUA and adjuvant treatment after HA are crucial factors of prognosis and more prospective research are need to be further investigated whether these factors have impact on obstetrical outcomes.

Conclusion

Our findings suggest that pregnant women with a history of HA treatment of IUAs, especially those with a history of repeat HAs, are at higher risk of some adverse obstetric outcomes, and thus, close monitoring of pregnancies of those women is essential to screen for potential pregnancy complications or adverse birth outcomes and implement early prevention and intervention.

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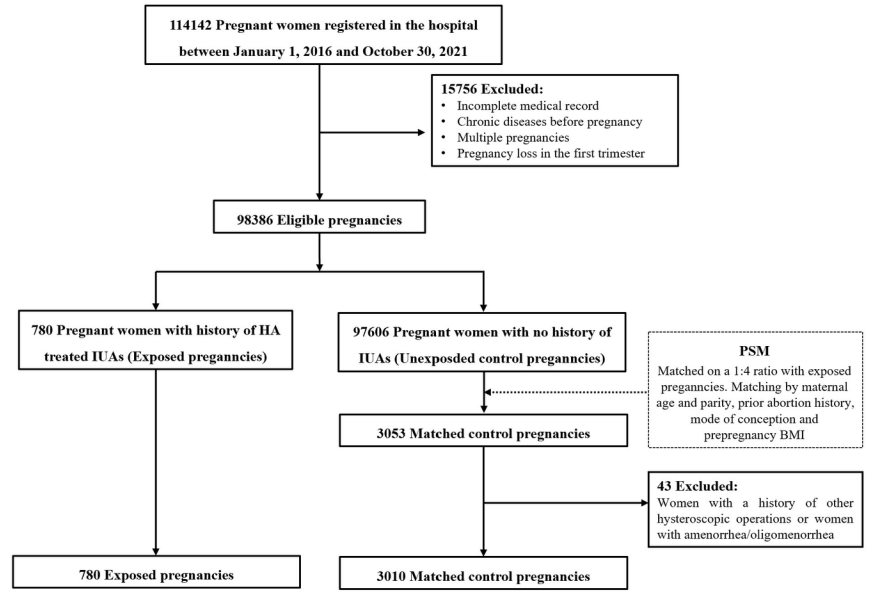
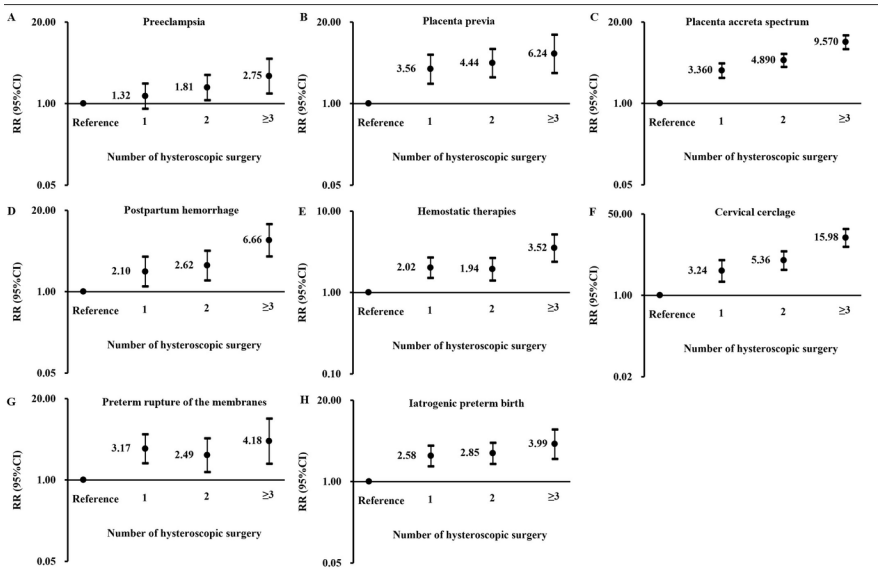
Figure legend

Figure 1:The flowchart of participant enrollment. 780 women with history of HA-treated IUAs before this pregnancy were compared with 3010 women with no history of IUAs matched on propensity score, maternal age and parity, mode of conception, pre-pregnancy BMI and prior history of abortion.

Figure 2:Associations between the number of hysteroscopic surgeries and the risk of adverse obstetric outcomes. Relative risks (RRs) of PE (Figure 2A), placenta previa (Figure 2B), placenta accreta spectrum (Figure 2C), PPH (Figure 2D), hemostatic therapies (Figure 2E), cervical cerclage (Figure 2F), PPROM (Figure 2G) and iatrogenic preterm birth (Figure 2H) associated with the number of hysteroscopic surgeries. All P for trend < 0.01.





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