Association Between First-Trimester Intrauterine Hematoma and Twin Pregnancy Outcomes: A Retrospective Cohort Study

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Title page

Association between first-trimester intrauterine hematoma and twin pregnancy outcomes: A retrospective cohort study

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Abstract:

Background: In recent years, we have found that first-trimester intrauterine hematoma in twin pregnancy has become increasingly common. The majority of studies on intrauterine hematoma have excluded twin pregnancies, while others did not differentiate between singleton and twin pregnancies. The associations in twin pregnancy are not clear. Therefore, the primary objective of our study was to examine the associations between first-trimester intrauterine hematoma and pregnancy outcomes in twin pregnancy.

Material and methods:1020 twin pregnancies in women who underwent a routine examination from January 2014 to December 2018 were enrolled. According to the presence or absence of intrauterine hematoma, we compared the baseline data and pregnancy outcomes between two groups. Multivariable logistic regression analysis was used to adjust for possible confounding factors.

Results: A total of 209 patients (21.3%) developed intrauterine hematoma in the first trimester. First-trimester intrauterine hematoma was significantly associated with increased odds of miscarriage (adjusted odds ratio 14.27, 95% CI 8.25-24.70) and the vanishing twin syndrome (adjusted odds ratio

3.26, 95% CI 1.11-4.61). However, It did not have increased odds of adverse pregnancy outcomes after 20 Weeks of Gestation .In the final regression model analysis, the associations of hematoma with previous miscarriage history, accepted assisted conception, accompanying vaginal bleeding and miscarriage and vanishing twin syndrome were no longer significant. No association was found between hematoma size or the presence of vaginal bleeding and the risk of pregnancy loss or the vanishing twin syndrome before 20 weeks of gestation (P>0.05).

Conclusion: In women with twin pregnancies, the presence of intrauterine hematoma in the first trimester was associated with one or both fetal losses before 20 weeks of gestation. However, chorionicity in twins, the conception method, the intrauterine hematoma size and the presence of vaginal bleeding were not independently associated with pregnancy loss.

Keywords: intrauterine hematoma, twin gestation, first trimester, miscarriage, vanishing twin syndrome.

Background

First-trimester intrauterine hematoma is a common phenomenon observed during routine obstetric ultrasonography. A total of 62.9% of hematomas occur during the first trimester and usually disappear within three months after detection[1]. Evidence suggests that intrauterine hematomas in singleton pregnancies are associated with an increased risk of adverse outcomes[2-4]; however, these results are based on a singleton pregnancies.

With the development and application of assisted reproductive techniques, the incidence of twin pregnancy is increasing. It has been reported that assisted reproductive techniques contributed to 16.4% of all multiple-birth infants, and approximately 30.4% of assisted reproductive techniques conceived infants were twins in 2016[5]. In recent years, we have found that first-trimester intrauterine hematoma in twin pregnancy has become increasingly common. Twin pregnancy is associated with a higher incidence of maternal-fetal complications and more adverse pregnancy outcomes, such as early miscarriage, premature birth, preeclampsia, prenatal bleeding, postpartum bleeding, intrauterine growth restriction and stillbirth, than singleton pregnancy[6]. However, it has not been reported whether the effect of intrauterine hematoma in early pregnancy on the outcome in twin pregnancy is the same as that in singleton pregnancy. At present, the majority of studies on intrauterine hematoma have excluded twin pregnancies, while others did not differentiate between singleton and twin pregnancies. The associations in twin pregnancy are not clear. Therefore, the primary objective of our study was to examine the associations between first-trimester intrauterine hematoma and pregnancy outcomes in twin pregnancy. We also assessed the risk factors in women with twin pregnancy.

Methods

Study population

We performed a retrospective analysis of mothers who had two gestational sacs on first trimester ultrasound at Guangzhou Women and Children Medical Center from January 2014 to December 2018. These women underwent ultrasound scans at 5 0/7-13 6/7weeks and underwent routine examination at our medical center. Gestational age was calculated based on last menstrual period or first-trimester ultrasound scan per standard guideline[7]. For the women with assisted reproductive techniques, the gestational week was calculated according to the time of embryo implantation. A twin pregnancy was defined as the presence of two gestational sacs. Viability was confirmed by the presence of fetal cardiac activity on transvaginal ultrasound at 6 to 7 weeks of gestational age.We excluded pregnancies with fetal or placental abnormalities , hematoma found after the operation , or underwent elective termination of pregnancy . The patients were divided into the adverse pregnancy (AP) and normal pregnancy (NP) groups according to the presence or absence of intrauterine hemorrhage.

Data collection

We reviewed computerized medical records for each woman to obtain demographic ,clinical information and their ultrasound report .Patient demographic data were collected, including maternal age, parity, and abortion history. The gestational age at first detection of intrauterine hematoma, the chorionicity of twins, conception methods and pregnancy results were reviewed in medical records. The volumes of the hematoma were estimated by measuring the maximum transverse, anteroposterior, and longitudinal diameters and multiplying these values by the constant 0.52, as was suggested by Campbel[8]. A correction factor of 0.52 was used to correct for the crescent shape of the hematoma. All measurements were performed with GE Voluson E8 system (GE Healthcare, Milwaukee, WI, USA) by experienced physicians.

Maternal and neonatal outcomes were recorded as pregnancy outcomes. The outcomes included spontaneous abortion, vanishing twin syndrome(the heart of one stopped beating before 14weeks),preterm delivery at less than 34 weeks of gestation, postpartum hemorrhage, preeclampsia, and low birth weight (selective intrauterine growth restriction or twin-to-twin transfusion syndrome were excluded),Stillbirth (fetal demise at 20 weeks of gestational age or older) and Fetal distress .

Statistical analysis

Quantitative characteristics are described as the mean ± standard deviation. A t-test was used for comparison between the AP and NP groups. Qualitative characteristics were described by number (percentage), and the chi-square test was used for comparison between the AP and NP groups.We correlated three groups of intrauterine hematoma size using the Kruskal-Wallis test or chi-square test .The associations between intrauterine hematoma and pregnancy loss were estimated using logistic regression analyses.Initially,unadjusted analyses estimated crude odds ratios and95% confidence intervals (CI) (model 1). Multivariable logistic regression analysis was used to adjust for possible confounding. We carried out data analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC); P levels were significant at less than 0.05.

Result

Of 1200 consecutive women with twins gestation seen during the study period, 1020 were recruited. We excluded patients with fetal or placental abnormalities (n=11), hematoma found after the operation(n=6) , underwent elective termination of pregnancy(n=8) or lost to follow-up(n=12).A total of 983 women who presented for prenatal examination before 14 weeks of gestation with twin pregnancy over the course of the study period were ultimately included in this analysis. Among them, 209 patients (21.3%) developed intrauterine hematoma in the first trimester (AP group), while 774 patients (78.7%) did not (NP group)(Figure 1). Regarding the baseline characteristics of these women, there were no differences in maternal age, chorionicity in twins or the gestational week at first ultrasound scan between the two groups (Table 1). Women with a previous miscarriage history and those who underwent assisted conception were likely to develop intrauterine hematoma. Pregnant women with intrauterine hematoma were more likely to experience vaginal bleeding ($p<0.001$) (Table 1). However, in the final regression model analysis, the associations with previous miscarriage history, assisted conception, accompanying vaginal bleeding and miscarriage and the vanishing twin syndrome were no longer significant (Table 2, Table 3).

We compared the pregnancy outcomes between the two groups. In the AP group, 63 patients (30.1%) had miscarriages, and twenty-six patients (12.4%) had vanishing twin syndrome. In the NP group, there were 50 cases (6.5%) of miscarriage, and 36 cases (4.7%) of vanishing twin syndrome. There were

significant differences between the two groups (P<0.001) (Table 4). Our logistic regression analyses showed that first-trimester intrauterine hematoma was significantly associated with increased odds of extreme miscarriage (adjusted odds ratio 14.27, 95% CI 8.25-24.70) and vanishing twin syndrome (adjusted odds ratio 3.26, 95% CI 1.11-4.61) (Tables II and III). However, unlike the NP group, the AP group did not have increased odds of stillbirth, preeclampsia, preterm labor (<34 weeks), low birth weight , postpartum hemorrhage or fetal distress (Table 4).

We performed a subanalysis of the 209 women with intrauterine hematoma. We compared the intrauterine hematoma features between women who did and did not ultimately experience pregnancy loss (one or two embryos) at less than 20 weeks of gestation (Table 5). We found no associations between intrauterine hematoma volume, intrauterine hematoma diameter or vaginal bleeding and pregnancy loss (one or two embryos) before 20 weeks of gestation.

Discussion

In this retrospective cohort study, the incidence of hematoma in twin pregnancies reached 21.3%, which was similar to the incidence of hematoma in singleton pregnancies[9-11]. Moreover, we found that the fetal loss rate in pregnant women with early intrauterine hemorrhage (IUH) was significantly higher, the abortion rate was 13 times higher, and the vanishing twin syndrome rate was 2 times higher than those in women without early IUH. However, first-trimester intrauterine hematoma was not significantly associated with an increased risk of stillbirth, preeclampsia, preterm labor, low birth weight , postpartum hemorrhage or fetal distress in twin gestation.

The effect of hematoma on first trimester pregnancy outcomes has been debated for many years. Many studies have specifically examined the relationship between first-trimester IUH and pregnancy outcomes in singleton pregnancies. Sandor Nagy reported that women presenting with first-trimester IUH had higher risks of pregnancy-induced hypertension (RR 2.1, 95% CI 1.5–2.9), preeclampsia (RR 4.0, 95% CI 2.4–6.7), placental abruption (RR 5.6, 95% CI 2.8–11.1) and small for gestation age neonates (RR 2.4, 95% CI 1.4–4.1) than women without IUH and vaginal bleeding[12]. Tuuli et al reported an increased risk of pregnancy loss in women with subchorionic hematoma (17.6% vs 8.9%) in a meta-analysis in 2011[13]. Recently, Naert reported that first-trimester subchorionic hematoma before 14 weeks of gestation was not independently associated with pregnancy loss before 20 weeks of gestation[14]. It was not associated with adverse pregnancy outcomes in women at more than 20 weeks of gestation[15]. However, the majority of these studies excluded twin pregnancies. In our study,

logistic regression analyses were performed to explore associations between intrauterine hematoma and pregnancy outcomes. To our knowledge, our study is the first to specifically examine the associations between first-trimester intrauterine hematoma and pregnancy outcomes in twin gestations.

We did not find any specific characteristics of twin gestation to be predictive of pregnancy loss or the vanishing twin syndrome when intrauterine hematoma was present. Multivariable logistic regression analysis was used to adjust for possible confounding factors. Maternal age and chorionicity in twins were not predictive factors. This finding was similar to that of McLennan's study, which found that maternal age was not the main factor affecting adverse outcomes in twin pregnancies[16]. Although the intrauterine hematoma group had higher rates of maternal miscarriage history, assisted conception, and vaginal bleeding, we found that these factors were not major contributors to fetal loss in early pregnancy. Stabile et al. reported that in vitro fertilization was not associated with an increased risk of spontaneous abortion[8]. Lucovnik et al. compared outcomes in 2710 twin pregnancies without early bleeding and 275 twin pregnancies with bleeding and found that bleeding was not significantly associated with any adverse perinatal outcome[17]. Eaton et al. found that women with IVF twin gestations, regardless of the presence of first-trimester bleeding, had high live-birth rates, but first-trimester bleeding was associated with an increased risk of low birth weight [18]. Our study results are consistent with those of previous research. However, the durations and sizes of intrauterine hematomas were not described in detail. Repeated vaginal bleeding may cause infection and increase the risk of choroiditis. In our study, we found some cases of intrauterine infection due to repeated vaginal bleeding and premature rupture of membranes in the second trimester of pregnancy. Therefore, repeated vaginal bleeding in twin pregnancy should be given additional attention in clinical practice.

In our study, we compiled and analyzed the basic characteristics of hematoma and found that intrauterine hematoma size was not associated with pregnancy loss or the vanishing twin syndrome. There are many reports in the relationship between the size of intrauterine hematoma and the pregnancy outcome; the effect of intrauterine hematoma size on the rate of pregnancy loss varies by study. This may be due to the irregular shapes of uterine hematomas, which makes measurement difficult. Second, different measurement methods were used, resulting in different conclusions. Recently, Howard T et al. compared four methods of measurement and found that subjective hematoma size based on the fraction of the gestational sac size correlated best with first-trimester pregnancy outcome[19]. Since the subjective evaluation method was difficult in twin pregnancies, three

orthogonal hematoma measurements were performed, and the conclusion was the same as that of Mackenzie N et al[14].

It has been reported that in women with normal twin pregnancies, approximately 30% will become singleton pregnancies, and 10% will result in no fetuses[20-22]. The disappearance of gestational sacs or embryos after documented fetal heart activity in multiple pregnancies is known as the vanishing twin phenomenon[23]. And the vanishing twin phenomenon was thought likely to have the association with a chromosomal abnormality[24].We found that the risk of total pregnancy loss was notably higher than the disappearance of one twin if the women presented IUH (30.1% vs 12.4%). The exact reason is not clear. Perhaps the effect of intrauterine hematoma on early gestation is “all or nothing”. It was reported that the vanishing twin phenomenon is associated with preterm delivery , very preterm delivery and small for gestation age neonates and low birth weight infants[25]. However, we did not explore the differences in pregnancy outcomes of pregnancies with a vanishing twin caused by first-trimester intrauterine hematoma, which can be further analyzed in the future.

Our study has some limitations due to its retrospective design. The population was from a single obstetric practice, so the data may be subject to regional limitations. Another limitation of this study is that the sizes of the hematomas may have changed since the ultrasound examinations. In addition, persistent intrauterine hematoma may have an impact on pregnancy outcomes, but the duration of intrauterine hematoma was not specifically evaluated in this study.

Conclusion

In women with twin pregnancy, the presence of intrauterine hematoma in the first trimester is associated with one or both fetal losses before 20 weeks of gestation. In addition, chorionicity in twins, the conception method, the intrauterine hematoma size and the presence of vaginal bleeding were not independently associated with pregnancy loss.

List of abbreviations : Intrauterine hemorrhage (IUH) ;adverse pregnancy (AP) ; normal pregnancy (NP) .

Declarations

Ethical approval

This study was approved by the Guangzhou Women and Children’s Medical Center Institutional Review Board(NO46001 , 2020).

Consent for publication : Not applicable.

Availability of data and materials

Guangzhou Women and Children's Medical Center Institutional Review Board has approved and supported that only researchers of the manuscript will have access to the dataset, so the data used in this study is not available for public view. Still, reasonable requests can be written officially to the medical center and corresponding author.

Disclosure of interests

The authors have no conflicts of interest to report.Completed disclosure of interests forms are available to view online as supporting information.

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Authors' contribution

Jie Zheng: Data collection ; Weidong Li:data statistics and analysis; Wanqing Ji: Data collection, writing—original draft,funding acquisition; Fang Guo: writing—review & editing ; Bo Hou:funding ; Ping He:supervision.All authors read and approved the final manuscript.

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Figures

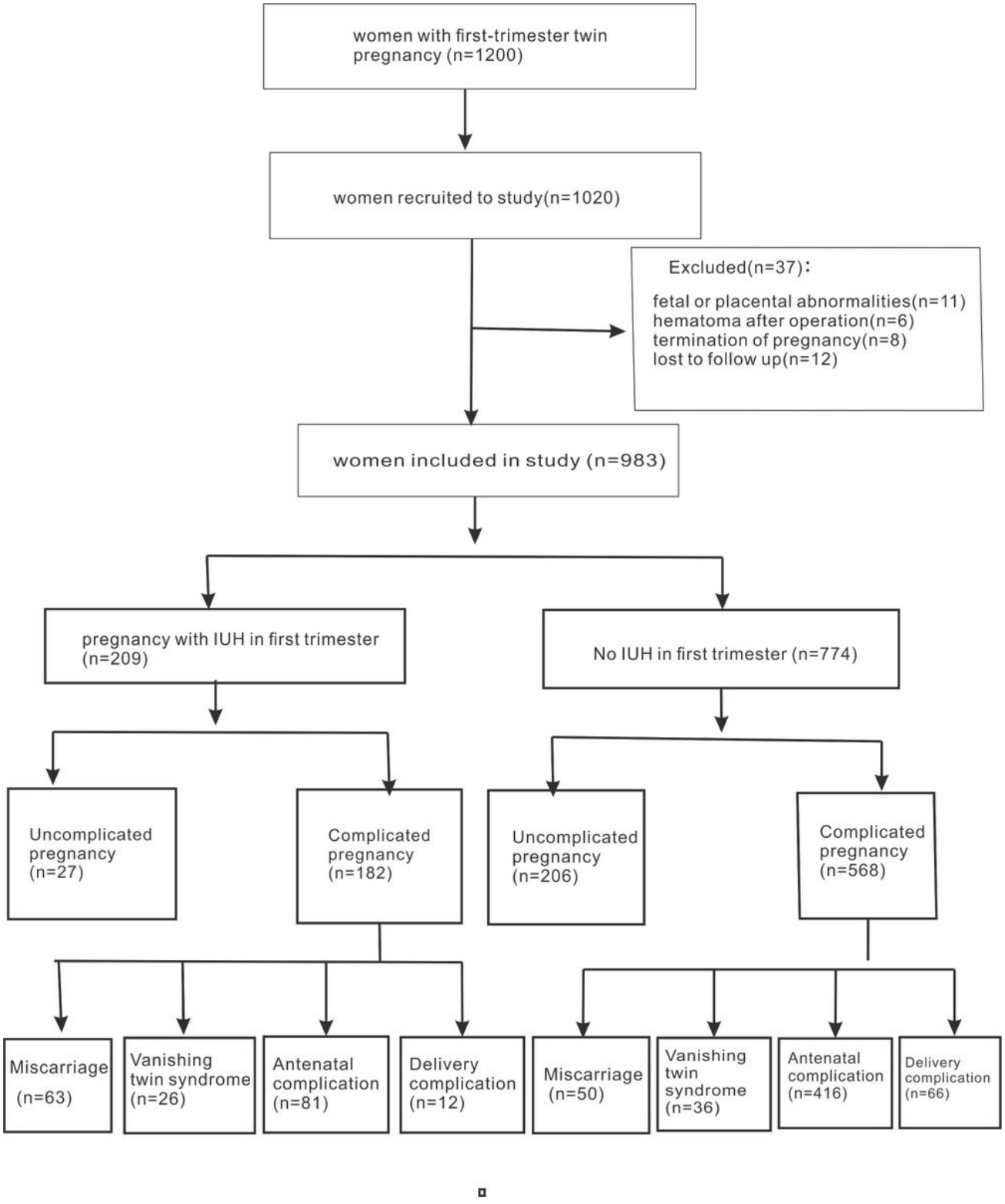

Figure 1

Flowchart showing inclusion in study of women with twin pregnancy , and incidence of pregnant outcomes according to the presence or absence of intrauterine hemorrhage.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableIMaternalcharacteristicsBasedonthePre.doc
- Table2.AdjustedRiskofmiscarriageBefore20Weeks.doc
- Table3.AdjustedRiskofvanishingtwinsyndrome.doc
- Table4Pregnancyoutcomes.doc
- Tablev.doc