

Original Research

Exploring Risk Factors for Early Pregnancy Loss: A Retrospective Hysteroscopy Study in a Single Institution

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Abstract

Background: To explore the risk factors for early pregnancy loss and to study the relationship between early pregnancy loss and intrauterine adhesion (IUA) confirmed by hysteroscopy. **Methods:** A retrospective study was conducted on 226 early pregnancy loss and 51 early pregnancy patients who received medical management combined with hysteroscopy at a regional institution from March 2020 to February 2021. The uterine cavity's shape was evaluated by hysteroscopy 6 hours after treatment with medicine. Risk factors included maternal age, gestational weeks, gravidity, parity, number of prior early pregnancy losses, number of prior induced abortions, mean sac diameter (MSD) and IUA. **Results:** Our results showed that the prevalence of IUA increased significantly in early pregnancy loss cases (31.42%) compared with early pregnancy cases (9.8%) ($p < 0.01$). Multivariate logistic regression analysis showed that maternal age (odds ratio (OR): 1.195, 95% confidence interval (95% CI): 1.077–1.326), gestational weeks (OR: 2.919, 95% CI: 2.028–4.201) and IUA (OR: 8.631, 95% CI: 2.455–30.336) were positively associated with early pregnancy loss, while MSD (OR: 0.943, 95% CI: 0.899–0.990) and parity (OR: 0.194, 95% CI: 0.088–0.428) were inversely associated with early pregnancy loss. **Conclusions:** Maternal age, gestational weeks and, IUA were the risk factors for early pregnancy loss. Special attention is to be given to cases of combined IUA when managing early pregnancy loss.

Keywords: early pregnancy loss; hysteroscopy; intrauterine adhesion; risk factors

1. Introduction

Early pregnancy loss is a common event in the first trimester of pregnancy, occurring in 10%–20% of confirmed pregnancies [1–3]. Approximately 50%–60% of all cases of early pregnancy loss are associated with fetal chromosomal abnormalities [1,4–6]. However, the common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age and prior early pregnancy loss [1,6]. Other maternal etiologies include antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables [7–11].

Intrauterine adhesion (IUA) is a condition characterized by the formation of bands of fibrous tissue within the uterine cavity, which partially or completely replace the endometrial lining. This occurs due to injury to the basal layer of the endometrium [12–14]. Hysteroscopy is a precise diagnostic method for identifying IUA [15]. Based on hysteroscopic assessment, IUA can be classified into different types such as isthmic, marginal, central, or severe [16]. While approximately one in five women encounter

IUA after early pregnancy loss terminated by uterine aspiration [17–19], the prevalence of IUA in patients terminated by medical treatment is rarely reported. In turn, endometrial scarring can hinder embryo implantation or halt its development [20]. Given the acceptance of reproductive freedom, IUA resulting from early pregnancy loss should not be overlooked. How to reduce the incidence of early pregnancy loss is the common goal of clinicians.

This study aimed to explore the risk factors of early pregnancy loss by comparing with early termination of pregnancy. In this study, hysteroscopy was innovatively used to diagnose IUA during abortion, so IUA is analyzed as a possible risk factor, which perhaps further provide help for the prevention and treatment of early pregnancy loss.

2. Materials and Methods

2.1 Study Design

This is a retrospective study of patients who were diagnosed with early pregnancy loss and early pregnancy, admitted to our hospital, and received treatment with medication combined with hysteroscopy between March 2020



Table 1. Characteristics of participants at Baseline.

Variable	Group A (n = 226)	Group B (n = 51)	Statistics	p-value
Maternal age, Mean $\pm$ SD	31.19 $\pm$ 4.83	29.78 $\pm$ 5.64	$t = 1.82$	0.0694
Gestational weeks, median (IQR)	10 (9, 11)	7 (7, 8)	$Z = 7.723$	<0.0001
Gravidity, median (IQR)	2 (1, 3)	2 (1, 4)	$Z = 0.021$	0.9833
Parity, median (IQR)	0 (0, 1)	1 (0, 1)	$Z = 4.028$	<0.0001
Number of prior early pregnancy losses, median (IQR)	0 (0, 1)	0 (0, 0)	$Z = 3.372$	<0.0001
Number of prior Previous induced abortions, median (IQR)	0 (0, 1)	0 (0, 1)	$Z = 0.087$	0.9304
MSD, Mean $\pm$ SD	24.19 $\pm$ 9.83	20.92 $\pm$ 9.57	$t = 2.16$	0.0317
IUA, n (%)	71 (31.42%)	5 (9.80%)	$\chi^2 = 9.7620$	0.0018

Note: Group A, early pregnancy loss group; Group B, early pregnancy termination group; MSD, mean sac diameter; SD, standard deviation; IQR, interquartile range; IUA, intrauterine adhesion; Z, Wilcoxon rank-sum test; t, t test.

and February 2021. The study protocols were approved by the Ethics Committee of the first affiliated Hospital of Chongqing Medical (approval number 058/2020), and informed consent was obtained from all participants. Eligible participants included healthy women aged 18 or older, diagnosed with a nonviable intrauterine pregnancy between 6 and 12 completed weeks of gestation through ultrasound examination (GE VOLUSON E8, GE Healthcare, Chicago, IL, USA) (early pregnancy loss group), or diagnosed with a viable intrauterine pregnancy between 6 and 12 completed weeks of gestation through ultrasound examination who requiring induced abortion monitored by (or under) hysteroscopy (early pregnancy termination group). Women diagnosed with cornual pregnancy, cesarean scar pregnancy, and cervical pregnancy were excluded from the study. General data were collected. The participants received therapeutic schedule as follows: (1) early pregnancy loss patients received pretreatment with estradiol valerate and/or mifepristone, followed by carboprost methylate suppositories vaginally; or carboprost methylate suppositories vaginally alone; early pregnancy patients received carboprost methylate suppositories vaginally alone; (2) hysteroscopy (Stryker, Kalamazoo, MI, USA) evaluate the expulsion complete or not and the shape of the uterine cavity 6 hours after treatment with medicines; (3) if residual gestational tissue existed, uterine aspiration was performed (conventional electric suction abortion procedure); (4) hysteroscopy reevaluation until there is no residual pregnancy tissue in the uterine cavity (repeat steps 3 and 4); (5) if IUA was found, hysteroscopic adhesiolysis was performed. The trial was completed by 226 early pregnancy loss participants and 51 early pregnancy participants.

We calculated the prevalence of IUA in the two groups, analyzed and compared the maternal age, gestational weeks, mean sac diameter (MSD), gravidity, parity, number of prior early pregnancy losses, number of prior induced abortions, and whether there was IUA in the two groups.

2.2 Statistical Analyses

Data analyses were performed with SAS version 9.14 (SAS Institute, Cary, NC, USA). We compared the characteristics of participants using the Wilcoxon rank-sum test and t-test, calculated the percentage (with 95% confidence interval (95% CI)) of women in each treatment group who had IUA, and compared the results using the Chi-squared Test. The risk factors were analyzed by logistic regression model.

3. Results

From March 2020 to February 2021, we assessed 226 early pregnancy loss participants and 51 early pregnancy participants for eligibility (Table 1). All cases had completed the process without perforation, infection, or other complications. There were 8 cases of early pregnancy loss and 5 cases of early pregnancy underwent emergency uterine aspiration followed by hysteroscopy due to massive bleeding and incomplete expulsion after 6 hours of treatment with medicine. 264 participants had been observed 6 hours after management with medicine and were then examined by hysteroscopy. Complete expulsion occurred in 93 of 226 women (41.15%) in early pregnancy loss cases, and in 5 of 51 women (9.8%) in early pregnancy cases (Fig. 1).

Residual gestational tissue and shape of the uterine cavity were evaluated by hysteroscopy. If complete expulsion occurred, there was no sac in the uterine cavity (Fig. 2A); instead, the sac was still in the uterine cavity (Fig. 2B), in which event uterine aspiration was performed under hysteroscopy. When the residual gestational tissue was removed, the shape of the uterine cavity could be visually evaluated as either normal (Fig. 2C), with a band of scar adhesion tissue found in the middle of the uterine cavity (central IUA) (Fig. 2D), or with scar adhesion tissue found on the wall of the uterine cavity (marginal IUA) (Fig. 2E). Extensive firm adhesions with agglutination of the uterine walls or in which at least one tuba ostium area was occluded were also diagnosed as IUA.

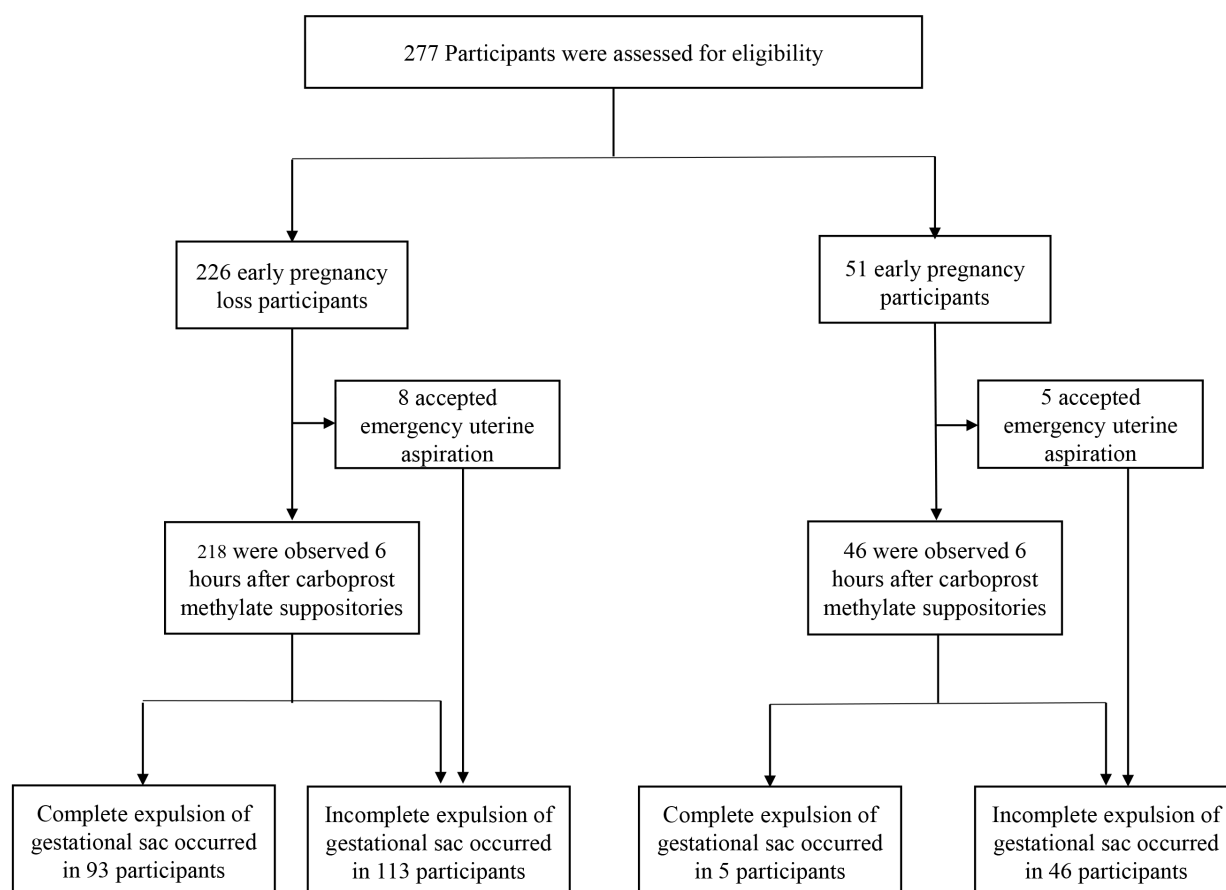


Fig. 1. Enrollment and Analysis.

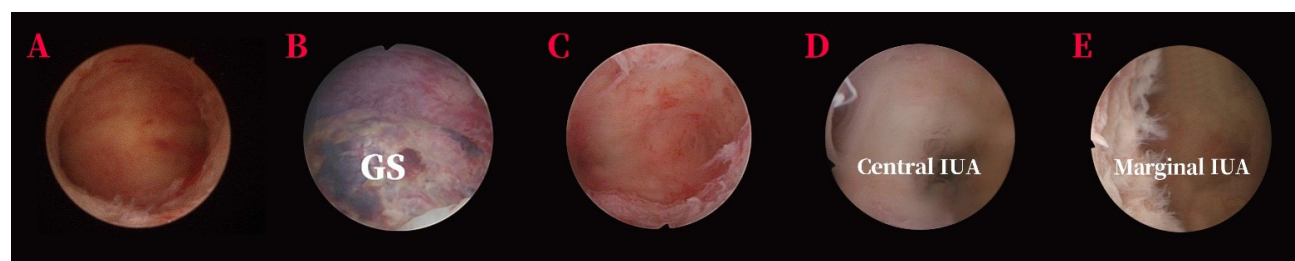


Fig. 2. The shape of the uterine cavity under hysteroscopy after medicine management. (A) The gestational tissue was completely expelled, and the shape of the uterine cavity was normal. (B) The gestational tissue was not expelled. (C) The shape of the uterine cavity was normal after uterine aspiration. (D) Central intrauterine adhesion was found after uterine aspiration. (E) Marginal intrauterine adhesion was found after uterine aspiration. IUA, intrauterine adhesion; GS, gestational sac.

3.1 Comparing the Prevalence of IUA

IUA occurred in 71 of 226 women [31.42%; 95% CI: 25.36–37.48] in the early pregnancy loss group, and in 5 of 51 women in the early pregnancy group (9.8%; 95% CI: 1.65–17.97). The prevalence of IUA in the early pregnancy loss group was significantly higher than that in the early pregnancy group ($\chi^2 = 9.7620$, $p < 0.01$) (Table 2).

3.2 Analysis of the Risk Factors for Early Pregnancy Loss Compared with Early Pregnancy

Univariate logistic regression analysis showed that maternal age, gestational weeks, MSD, parity, number of prior early pregnancy loss and, IUA were meaningful variables associated with early pregnancy loss ($p < 0.1$) (Table 3). Multivariate logistic regression analysis showed that maternal age (odds ratio (OR): 1.195, 95% CI: 1.077–1.326), gestational weeks (OR: 2.919, 95% CI: 2.028–4.201) and, IUA (OR: 8.631, 95% CI: 2.455–30.336) were

Table 2. The prevalence of IUA in the two groups.

Outcome	Early pregnancy loss group (n = 226)	Early pregnancy termination group (n = 51)	Statistic	p-value
	Number (percent)	Number (percent)		
IUA	71 (31.42%)	5 (9.80%)	$\chi^2 = 9.762$	0.0018
95% CI	25.36–37.48	1.65–17.97		

Note: IUA, intrauterine adhesion; 95% CI, 95% confidence interval.

Table 3. The risk factors for early pregnancy loss.

Parameter	Univariate logistical regression analysis			Multivariate logistical regression analysis		
	p-value	OR	95% CI	p-value	OR	95% CI
Maternal Age	0.0708	1.060	0.995–1.129	0.0008	1.195	1.077–1.326
Gestational weeks	<0.0001	2.690	2.027–3.570	<0.0001	2.919	2.028–4.201
Parity	<0.0001	0.369	0.234–0.583	<0.0001	0.194	0.088–0.428
MSD	0.0332	1.038	1.003–1.074	0.0177	0.943	0.899–0.990
IUA Yes vs. No	0.0035	4.214	1.606–11.058	0.0008	8.631	2.455–30.336
Gravidity	0.8399	0.980	0.804–1.194			
Number of prior early pregnancy losses	0.0037	4.379	1.614–11.876			
Number of prior induced abortions	0.3765	0.859	0.614–1.203			

Note: OR, odds ratio; IUA, intrauterine adhesion; MSD, mean sac diameter.

positively associated with early pregnancy loss ($p < 0.05$), while the MSD (OR: 0.943, 95% CI: 0.899–0.990) and parity (OR: 0.194, 95% CI: 0.088–0.428) were inversely associated with early pregnancy loss. Gravidity, number of prior early pregnancy losses and, number of prior induced abortion were not associated with early pregnancy loss (Table 3).

4. Discussion

In our retrospective study, IUA, or Asherman's syndrome, as an acquired uterine cavity abnormality, was a risk factor for early pregnancy loss, in line with the published literature [21–23]. IUA is a scar disease in fact, which will cause the embryo implantation failure, or the embryo stops developing. This may be the reason why IUA was positively associated with early pregnancy loss in this study. Hysteroscopy is the gold standard for the diagnosis of IUA [24–26]. In this study, hysteroscopy was used to confirm whether there was residual trophoblast tissue which could then be removed in time; moreover, it was effective in evaluating the shape of the uterine cavity after abortion, as typical adhesions can be observed and simultaneous adhesiolysis can be operated to prevent the aggravation of IUA. However, diagnosing IUA immediately might not be optimal due to the risk of missed diagnosis, as uterine involution might not be complete at this stage. Although all hysteroscopy operations in this study were performed by one senior physician to minimize bias, the actual prevalence of IUA might have been higher than our data suggest. Additionally, early pregnancy patients who needed hysteroscopy termination of pregnancy might have harbored concerns about IUA or insufficient medication efficacy, leading to potential selection bias in the study.

According to the guidelines for transvaginal ultrasonographic diagnosis of early pregnancy loss [1,27], diagnosing early pregnancy loss can be challenging in the gestational weeks due to the requirement of waiting for more than two weeks. As the gestational week increases, the diagnosis of early pregnancy loss becomes easier and more definitive. This may be the reason why gestational weeks was positively associated with early pregnancy loss in this study. Hence, timely diagnosis of early pregnancy loss is often challenging. Maternal age was the risk factor for early pregnancy loss, in line with the published literature [1,6]. Previous early pregnancy loss is considered a risk factor for subsequent occurrences, but this study did not find it to be a significant factor [1,6]. This may be due to sample size limitations.

In clinic, for those patients with risk factors for early pregnancy loss, follow-up and monitoring should be emphasized to facilitate early diagnosis and treatment. For patients experiencing early pregnancy loss and presenting risk factors for IUA, such as a history of recurrent miscarriages, multiple dilation and curettage procedures, multiple pregnancies, or issues like retained products of conception and placenta implantation, it is necessary to consider uterine aspiration under hysteroscopy or hysteroscopy following treatment with medication [28–30]. The goal is to prevent missed diagnosis of IUA and subsequent early pregnancy losses from the same cause.

5. Conclusions

Early pregnancy loss is a common event in the first trimester of pregnancy. The common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age and prior early pregnancy loss.

According to this study, we found that maternal age, gestational weeks and, IUA were risk factors associated with early pregnancy loss. Approximately one in five women encounter IUA after early pregnancy loss terminated by uterine aspiration. In turn, endometrial scarring can hinder embryo implantation or halt its development. IUA resulting from early pregnancy loss should not be overlooked. Combined IUA should be vigilant when managing early pregnancy loss.

Availability of Data and Materials

Data and other materials can be made available by the corresponding author upon a reasonable request.

Author Contributions

CC and XL contributed equally to this work. CC, QZ, XL and ZH contributed to the study concept and design; CC completed Hysteroscopy; CC, XY and YC contributed to the acquisition of the data; BP, YC analyzed and interpreted the data; QZ, CC, XL and XY drafted the manuscript; QZ, CC, BP, YC provided critical revision of the manuscript; QZ, XL and ZH supervised the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the first affiliated Hospital of Chongqing Medical University (approval number 058/2020). Informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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