# Optimal waiting period for fresh embryo transfer after hysteroscopic adhesiolysis: a retrospective cohort study

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**Abstract**

**Background:** Very few studies have been conducted regarding the optimal time interval between hysteroscopic adhesiolysis and the embryo transfer (ET). Investigation of this optimal time may be helpful for assisted reproductive technology. Therefore, we investigated effects of the interval between hysteroscopic adhesiolysis and ET upon *in vitro* fertilization (IVF) cycle outcomes.

**Methods:** Patients were recruited between January 2014 and September 2017 at the Reproductive Hospital Affiliated to Shandong University. Patients who were diagnosed with intra-uterine adhesion (IUA) and underwent hysteroscopic adhesiolysis before fresh IVF-ET or intra-cytoplasmic sperm injection cycles were classified into three groups according to the interval between hysteroscopic adhesiolysis and ET: less than 90 days (Group 1), 90 to 180 days (Group 2), and greater than 180 days (Group 3). Baseline characteristics, controlled ovarian stimulation (COS) response, and pregnancy outcomes after ET were compared. Analysis of variance or non-parametric tests were used to test numerical data. The Pearson's Chi-squared test was used to test categorical data.

**Results:** A total of 312 patients were recruited as follows: 112 in Group 1, 137 in Group 2, and 63 in Group 3. There were no differences in baseline and COS characteristics among the three groups. The live-birth rate in Group 2 (40.1%) was significantly higher than that in Group 1 (17.9%; $\chi^2 = 14.545$, $P < 0.001$). There were no significant differences in the rates of biochemical, ongoing, and clinical pregnancy, and biochemical and clinical pregnancy abortion, as well as stillbirth among the groups. In the mild IUA patients, the live-birth rate was significantly higher in Group 2 (42.6%) compared with Group 1 (22%; $\chi^2 = 8.413$, $P = 0.004$). In the moderate IUA patients, Group 2 (35.7%) had a higher frequency of live births than Group 1 (6.7%; $\chi^2 = 8.187$, $P = 0.004$).

**Conclusions:** The optimal waiting period for fresh ET after hysteroscopic adhesiolysis was 90 to 180 days in the current study.

**Keywords:** Asherman syndrome; Hysteroscopy; *In vitro* fertilization

## Introduction

Intra-uterine adhesions (IUAs; Asherman syndrome) are composed of fibrotic tissue, which may result in the adherence of opposing surfaces, producing dense or filmy adhesion bands that can lead to partial or complete closure of the uterine cavity. It is possible that after injury to the endometrium, fibrosis may follow with the potential of adhesion formation.[1-3] Clinical features of IUA include menstrual abnormalities (usually amenorrhea or hypomenorrhea), infertility, recurrent spontaneous abortion, and repeated failure of embryo implantation.[4,5]

Implantation remains the rate-limiting step for the success of *in vitro* fertilization (IVF) treatment, with approximately two thirds of implantation failures resulting from inadequate uterine receptivity.[6] In endometrial fibrosis, the lack of sufficient normal endometrial tissue to support implantation and defective vascularization of the residual endometrial tissue will reduce uterine receptivity.[1,7] Therefore, the treatment of IUA may significantly improve endometrial receptivity.

Hysteroscopic surgery is the primary treatment for IUA, but there is lack of an effective method to prevent the recurrence of IUA.[2,5,8-11] A previous study showed a variation in endometrial recovery time following different hysteroscopic surgeries, and that the wounds from adhesiolysis healed within 2 months.[12] Therefore, we believe that the recovery time after surgery is too long to result in recurrence of IUA, or the time is too short to affect the embryo transfer (ET).[12]

In 2016, the relationship between the time point for the start of fresh IVF-ET cycles after hysteroscopic polypectomy and the outcome of pregnancy was studied by

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Pereira *et al*.[13] Their study suggested that the elapsed timeframe between hysteroscopic polypectomy and the start of fresh IVF-ET cycles does not affect cycle outcomes.

Thus far, very few studies have been conducted regarding the optimal time interval between hysteroscopic adhesiolysis and ET. This time interval may be related to the severity and extent of IUA, and investigation of the effects of different time intervals may define more optimal conditions for assisted reproductive technology (ART). In this study, we investigated whether the interval between hysteroscopic adhesiolysis and ET affects IVF cycle outcomes.

## Methods

### Ethics approval

This retrospective cohort study was approved by the Institutional Review Board of the Reproductive Hospital Affiliated to Shandong University (No. 2018-29). All participants had given their informed consent.

### Study design

The inclusion criteria were as follows: (1) women aged 26 to 44 years; (2) women diagnosed with IUAs by hysteroscopy undergoing hysteroscopic adhesiolysis before fresh IVF-ET or intra-cytoplasmic sperm injection (ICSI)-ET cycles; (3) had undergone the first fresh ET cycle after surgery; and (4) the surgery was performed between January 2014 and September 2017 in our hospital. The exclusion criteria were as follows: (1) patients with oocyte donor treatment cycles, (2) a history of hysteroscopic adhesiolysis before this surgery, and (3) presence of other comorbidities that prevented matching (eg, chromosomal abnormalities).

Diagnostic hysteroscopy and vaginal ultrasonography were performed routinely on all patients before surgery.[1,14] The surgery was performed by several experienced hysteroscopic surgeons. When needed, laparoscopy was also performed to inspect for tubal patency or pelvic inflammation. The severity and extent of IUA were scored according to classification systems of the American Fertility Society (AFS), the European Society for Gastrointestinal Endoscopy (ESGE), and the Chinese IUA scoring system.[15-17]

To prevent recurrence of IUAs, doctors often inserted an intra-uterine device (IUD) or Foley balloon into the uterine cavity, administered patients with estrogen supplementation to enhance endometrial proliferation, and performed second-look office hysteroscopy. All patients were monitored and managed according to the standard clinical protocol used by the hospital after hysteroscopic adhesiolysis.[18] No patients were lost for follow-up. All patients were classified into three groups according to the interval between the surgery and the fresh ET: Group 1 was less than 90 days; Group 2 was 90 to 180 days, and Group 3 was more than 180 days. Patients were further classified into several subgroups according to the AFS scores to identify the relationship between severity of IUA and subsequent pregnancy outcomes of fresh ET cycles.

### Main outcomes of all the included patients

Recorded baseline characteristics included age, body mass index (BMI), hormone levels on days 1 to 3 of the menstrual period (basal follicle-stimulating hormone [FSH], luteinizing hormone [LH], progesterone [P], and estradiol [E2]). We also recorded pre-operative endometrial thickness, the indication for IVF (male factor, tubal factor, or other), and the type of infertility (primary or secondary). Recorded controlled ovarian stimulation (COS) characteristics were as follows: total dosage and startup dosage of gonadotropin (Gn), protocol type, total number of mature oocytes (>14 mm), peak endometrial thickness, number of embryos transferred, and days to ET. The primary outcome was live-birth rate, which was defined as delivery of any viable infant at 28 weeks or more of gestation during the first fresh ET.[19] Other outcomes included the rates of biochemical pregnancy, clinical pregnancy, and ongoing pregnancy, and also included clinical miscarriage (MR), stillbirth, and biochemical MR.[20] Other characteristics included the surgical procedure (hysteroscopic electrotomy or cold knife) and severity classification (by the AFS, ESGE, and Chinese IUA scoring systems).

### Statistical analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used for data analysis. Quantitative data are expressed as mean ± standard deviation and percentage. Numerical data included age, BMI, basal E2, P, FSH, and LH, and pre-operative endometrial thickness, startup dosage of Gn, total dosage of Gn, total number of mature oocytes, and peak endometrial thickness. Categorical data included the indication for IVF, type of infertility, protocol type, number of embryos transferred, days to ET, surgical procedure, severity classification, and pregnancy outcomes. Analysis of variance or non-parametric tests were used to test numerical data. The Pearson's Chi-squared test was used to test categorical data. A $P < 0.05$ was considered statistically significant. Adjusted odds ratio (OR) and 95% confidence intervals (95% CI) were estimated using logistic regression. Inclusion of the data into the two-category models eliminated confounders when there were differences between the groups ($P < 0.1$) in baseline characteristics.

## Results

During the study period, 1369 patients in our institution were diagnosed with IUA and underwent hysteroscopic adhesiolysis before fresh IVF-ET or ICSI cycles. Of these patients, 312 patients met the inclusion criteria and were grouped as follows: 112 (35.9%) in Group 1, 137 (43.9%) in Group 2, and 63 (20.2%) in Group 3 [Figure 1].

Clinical characteristics of the 312 women are shown in Table 1. There were no significant differences among the three groups in terms of age: the mean age of Groups 1, 2, and 3 were 34.7 ± 5.0, 33.6 ± 5.4, and 33.4 ± 4.8 years, respectively. Recorded baseline characteristics of BMI, hormone levels on days 1 to 3 of the menstrual period (basal FSH, LH, P, and E2), pre-operative endometrial

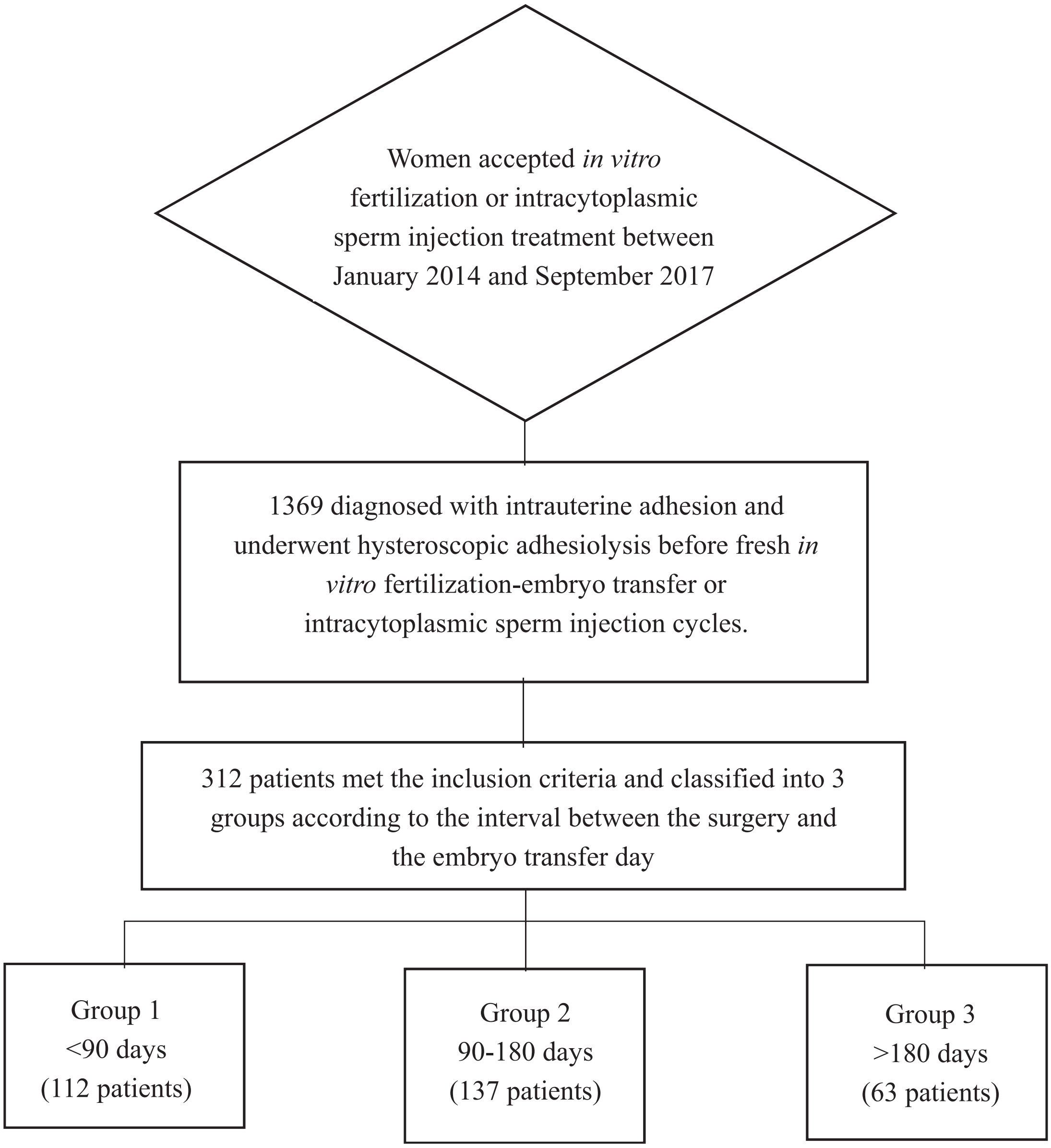


**Figure 1:** Flowchart of this study on the optimal waiting period for fresh embryo transfer after hysteroscopic adhesiolysis.

thickness, indication for IVF (male factor, tubal factor, or other), and type of infertility (primary or secondary) showed no significant differences among the groups.

The COS characteristics were compared among the three groups. No significant differences were observed for the peak endometrial thickness among the three groups. The peak endometrial thicknesses were $0.89 \pm 0.22$ mm, $0.89 \pm 0.19$ mm, and $0.90 \pm 0.20$ mm in Groups 1, 2, and 3, respectively. There were no statistical differences in mean age, total dosage and startup dosage of gonadotropin (Gn), protocol type, total number of mature oocytes (>14 mm), number of embryos transferred, and days of ET. The results are shown in Table 2.

We further compared the main outcomes of the IVF/ICSI treatment cycles undertaken by the three groups. After adjusting the "long protocol" of ovary stimulation and total dosage of Gn by logistic regression analysis, live-birth rate showed a significant change in three groups (OR = 0.676, 95% CI 0.477–0.960; $P = 0.029$), and the frequency of live births after fresh-ET in Group 2 (40.1%) was significantly higher than that in Group 1 (17.9%; $\chi^2 = 14.545$, $P < 0.001$). There were no significant between-group differences in the incidence of biochemical pregnancy, clinical, and ongoing pregnancy, clinical pregnancy abortion, biochemical pregnancy abortion, and stillbirth [Table 3].

To analyze the effect of the severity of IUAs on the outcome, we compared the rate of severity classification among the three groups. We used three scoring methods to scale the severity, including AFS, ESGE, and the Chinese IUA scoring system. There were no significant differences found [Table 4]. Moreover, we analyzed the effect of different surgical procedures on the outcome, including

**Table 1: Baseline characteristics of patients who underwent hysteroscopic adhesiolysis.**

| Characteristic | Group 1 ($n=112$) | Group 2 ($n=137$) | Group 3 ($n=63$) | $F$ or $\chi^2$ | $P$ |
|---|---|---|---|---|---|
| Age (years) | 34.7 ± 5.0 | 33.6 ± 5.4 | 33.4 ± 4.8 | 1.740* | 0.177 |
| BMI (kg/m$^2$) | 23.83 ± 3.28 | 24.22 ± 3.60 | 25.46 ± 4.84 | 3.722* | 0.156 |
| Basal E2 (pg/mL) | 63.38 ± 96.75 | 50.83 ± 55.96† | 47.03 ± 45.97‡ | 1.344* | 0.262 |
| Basal P (ng/mL) | 15.02 ± 6.34§ | 15.58 ± 8.53‖ | 16.70 ± 9.37¶ | 0.854* | 0.428 |
| Basal FSH (IU/L) | 7.02 ± 3.02 | 7.06 ± 3.08† | 6.60 ± 2.25‡ | 0.575* | 0.564 |
| Basal LH (IU/L) | 5.25 ± 3.42 | 4.89 ± 3.22† | 4.90 ± 4.01‡ | 0.356* | 0.701 |
| Indication for IVF | | | | | |
| Male factor | 25 (22.3) | 35 (25.5) | 11 (17.5) | 1.624# | 0.444 |
| Tubal factor | 71 (63.4) | 89 (65.0) | 45 (71.4) | 1.215# | 0.545 |
| Combination | 2 (1.8) | 1 (0.7) | 0 | 1.488# | 0.475 |
| Others | 14 (12.5) | 12 (8.8) | 7 (11.1) | 0.936# | 0.626 |
| Pre-operative endometrial thickness (mm) | 7.12 ± 2.46 | 7.52 ± 2.19 | 7.58 ± 2.36 | 1.589* | 0.308 |
| PCOS | 8 (7.1) | 20 (14.6) | 8 (12.7) | 3.460# | 0.177 |
| Type of infertility | | | | 4.077# | 0.130 |
| Primary infertility | 25 (22.3) | 39 (28.5) | 23 (36.5) | | |
| Secondary infertility | 87 (77.7) | 98 (71.5) | 40 (63.5) | | |

Values are shown as mean ± standard deviation or $n$ (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. * $F$ value. † $n=133$. ‡ $n=61$. § $n=111$. ‖ $n=131$. ¶ $n=59$. # $\chi^2$ value. BMI: Body mass index; E2: Estrogen; P: Progesterone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; IVF: *In vitro* fertilization; PCOS: Polycystic ovarian syndrome.

**Table 2: Controlled ovarian stimulation characteristics of patients who underwent hysteroscopic adhesiolysis.**

| Parameters | Group 1 ($n=112$) | Group 2 ($n=137$) | Group 3 ($n=63$) | $F$ or $\chi^2$ | $P$ |
|---|---|---|---|---|---|
| Protocol | | | | | |
| Long protocol | 40 (35.7) | 64 (48.2) | 23 (36.5) | 5.524* | 0.063 |
| Short protocol | 43 (38.4) | 43 (31.4) | 23 (36.5) | 1.416* | 0.467 |
| Other protocol | 29 (25.9) | 30 (21.9) | 17 (26.9) | 0.829* | 0.661 |
| Days of embryo transfer | | | | | |
| 2 | 0 | 1 (0.7) | 0 | 1.281* | 0.527 |
| 3 | 70 (62.5) | 96 (70.1) | 43 (68.3) | 1.655* | 0.437 |
| 4 | 1 (0.9) | 1 (0.7) | 2 (3.2) | 2.247* | 0.325 |
| 5 | 41 (36.6) | 39 (28.5) | 18 (28.6) | 2.190* | 0.334 |
| Startup dosage of Gn (IU) | 186.82 ± 56.25‡ | 186.58 ± 62.60 | 204.76 ± 60.49 | 5.376† | 0.068 |
| Total dosage of Gn (IU) | 2085.3 ± 933.2‡ | 2048.2 ± 908.0 | 2247.2 ± 969.8 | 1.108† | 0.559 |
| Total number of mature oocytes (>14 mm) | 7.68 ± 3.81 | 8.12 ± 3.92 | 7.02 ± 3.76 | 1.785† | 0.170 |
| Peak endometrial thickness (cm) | 0.89 ± 0.22 | 0.89 ± 0.19 | 0.90 ± 0.20 | 0.322† | 0.956 |
| Number of embryos transferred | | | | 2.168* | 0.338 |
| One | 56 (50.0) | 56 (40.9) | 27 (42.9) | | |
| Two | 56 (50.0) | 81 (59.1) | 36 (57.1) | | |

Values are shown as mean ± standard deviation or $n$ (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. * $\chi^2$. † $F$. ‡ $n=111$. Gn: Gonadotropin.

hysteroscopic electrotomy and cold knife surgery. There were no significant differences among the three groups [Supplemental Table 1, http://links.lww.com/CM9/A97]. In addition, to provide more precise recommendations regarding ET to patients with different degrees of IUAs, patients were classified into three subgroups according to the AFS scores. We compared only mild and moderate patients because the number of severe patients was too small. In both the mild and moderate groups, significant differences for the live-birth rate at three different time intervals were observed [Tables 5 and 6]. In the mild groups, Group 2 (42.6%) had a higher frequency of live births than Group 1 (22.0%; $\chi^2=8.413$, $P=0.004$). In the moderate groups, Group 2 (35.7%) had a higher frequency of live births than Group 1 (6.7%; $\chi^2=8.187$, $P=0.004$).

To observe the pregnancy outcomes more intuitively, we prepared a curve of the relationship between the time window and pregnancy outcomes to reflect the change in pregnancy rates. This curve showed a trend toward higher clinical pregnancy and live-birth rates, and also a trend toward a lower miscarriage rate, for Group 2 compared with Groups 1 and 3. The results are shown in Supplementary Figure 1, http://links.lww.com/CM9/A97.

There were no significant between-group differences in age, COS characteristics, and severity classification. We

**Table 3: Pregnancy outcome of patients who underwent hysteroscopic adhesiolysis.**

| Outcomes | Group 1 | Group 2 | Group 3 | *P* | OR (95% CI) | *P** |
|---|---|---|---|---|---|---|
| Clinical pregnancies rate | 57/112 (50.1) | 74/137 (54.0) | 23/63 (36.5) | 0.065 | 1.221 (0.896–1.665) | 0.206 |
| Clinical MR | 13/57 (22.8) | 11/74 (14.9) | 6/23 (26.1) | 0.359 | 1.119 (0.618–2.207) | 0.710 |
| Biochemical pregnancies rate | 63/112 (56.3) | 86/137 (62.8) | 30/63 (47.6) | 0.126 | 1.098 (0.807–1.496) | 0.551 |
| Biochemical MR | 6/63 (9.5) | 12/86 (14.0) | 7/30 (23.3) | 0.199 | 0.627 (0.340–1.157) | 0.136 |
| Live-birth rate | 20/112 (17.9) | 55/137 (40.1) | 16/63 (25.4) | <0.001 | 0.676 (0.477–0.960) | 0.029 |
| Stillbirth rate | 0/112 (0) | 1/137 (0.73) | 1/62 (1.61) | 0.444 | 0.102 (0.006–1.686) | 0.111 |
| Ongoing pregnancies rate | 44/112 (39.3) | 62/137 (45.3) | 16/63 (25.4) | 0.028 | 1.198 (0.868–1.653) | 0.272 |

Data are presented as *n*/*N* (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. * Logistic regression analysis was conducted by adjusting for us of "long protocol" of ovary stimulation and total dosage of gonadotropin. OR: Odds ratio; CI: Confidence interval; MR: Miscarry rate.

**Table 4: Severity classification of patients who underwent hysteroscopic adhesiolysis.**

| Parameters | Group 1 (*n* = 112) | Group 2 (*n* = 137) | Group 3 (*n* = 63) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| AFS | | | | | |
| Mild | 82 (73.2) | 94 (68.6) | 42 (66.7) | 1.005 | 0.605 |
| Moderate | 30 (26.8) | 42 (30.7) | 20 (31.7) | 0.638 | 0.727 |
| Severe | 0 | 1 (0.7) | 1/63 (1.6) | 1.625 | 0.444 |
| Chinese scoring system | | | | | |
| Mild | 7 (6.2) | 13 (9.5) | 8 (12.7) | 2.132 | 0.344 |
| Moderate | 105 (93.8) | 122 (89.1) | 55 (87.3) | 2.429 | 0.297 |
| Severe | 0 | 2 (1.4) | 0 | 2.571 | 0.937 |
| ESGE | | | | | |
| I | 2 (1.8) | 3 (2.2) | 1 (1.6) | 0.101 | 0.937 |
| II | 47 (42.0) | 57 (41.6) | 17 (27.0) | 4.631 | 0.099 |
| III | 27 (24.1) | 46 (33.6) | 26 (41.3) | 5.867 | 0.053 |
| IV | 22 (19.6) | 19 (13.9) | 11 (17.5) | 1.515 | 0.330 |
| Va | 14 (12.5) | 12 (8.8) | 7 (11.1) | 0.936 | 0.626 |
| Vb | 0 | 0 | 1 (1.6) | 3.965 | 0.138 |

Data are presented as *n* (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. AFS: American Fertility Society; ESGE: European Society for Gynecologic Endoscopy.

**Table 5: Pregnancy outcomes of AFS-mild patients who underwent hysteroscopic adhesiolysis.**

| Outcomes | AFS-mild | | | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| | Group 1 (*n* = 82) | Group 2 (*n* = 94) | Group 3 (*n* = 42) | | |
| Clinical PR | 42/82 (51.2) | 54/94 (57.4) | 15/42 (35.7) | 5.491 | 0.064 |
| Clinical MR | 10/42 (23.8) | 10/54 (18.5) | 3/15 (20.0) | 0.408 | 0.815 |
| Biochemical PR | 46/82 (56.1) | 62/94 (66.0) | 21/42 (50.0) | 3.575 | 0.167 |
| Biochemical MR | 4/46 (9.0) | 8/62 (12.9) | 6/21 (28.6) | 4.854 | 0.088 |
| Live-birth rate | 18/82 (22.0) | 40/94 (42.6) | 11/42 (26.2) | 9.310 | 0.010 |
| Stillbirth rate | 0/82 (0) | 1/94 (1.0) | 1/42 (2.0) | 1.771 | 0.412 |
| Ongoing PR | 32/82 (39) | 43/94 (45.7) | 11/42 (26.2) | 4.657 | 0.097 |

Data are presented as *n*/*N* (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. AFS: American Fertility Society; PR: pregnancies rate; MR: miscarry rate.

also eliminated confounders by logistic regression when there were differences ($P < 0.1$) in baseline characteristics between the groups. Thus, the outcome results were likely to be related to the time window between the hysteroscopic adhesiolysis and the ET.

## Discussion

In the present study, we determined the effect of the time window between hysteroscopic adhesiolysis and ET upon the outcomes of IVF/ICSI cycles. We found that the optimal waiting period for ET after hysteroscopic adhesiolysis was 90 to 180 days. Time intervals longer than 3 months should be used for improved ART outcomes.

Intra-uterine adhesions are a consequence of trauma to the endometrium and can lead to partial or complete endometrial dysfunction with impairment of fertility and the menstrual cycle (amenorrhea and hypomenorrhea).[1,14]

Table 6: Pregnancy outcomes of AFS-moderate subgroup patients who underwent hysteroscopic adhesiolysis.

| Outcomes | AFS-moderate Group 1 ($n=30$) | Group 2 ($n=42$) | Group 3 ($n=20$) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Clinical PR | 15/30 (50.0) | 20/42 (47.6) | 7/20 (35) | 1.209 | 0.546 |
| Clinical MR | 3/15 (20.0) | 1/20 (5.0) | 3/7 (42.9) | 5.537 | 0.063 |
| Biochemical PR | 17/30 (56.7) | 24/42 (57.1) | 8/20 (40.0) | 1.807 | 0.405 |
| Biochemical MR | 2/17 (11.8) | 4/24 (16.7) | 1/8 (12.5) | 0.220 | 0.896 |
| Live-birth rate | 2/30 (6.7) | 15/42 (35.7) | 4/20 (20.0) | 8.498 | 0.014 |
| Ongoing PR | 12/30 (40.0) | 19/42 (45.2) | 4/20 (20.0) | 3.734 | 0.155 |

Data are presented as *n*/*N* (%). Group 1: Interval between hysteroscopic adhesiolysis and the embryo transfer day less than 90 days; Group 2: Interval between 90 and 180 days; Group 3: Interval greater than 180 days. AFS: American Fertility Society; PR: Pregnancies rate; MR: Miscarry rate.

For ART, IUAs require clinical management because they are associated with infertility and recurrent pregnancy loss.[8] Approximately 7% of patients present with a primary fertility complaint.[21] Moreover, recurrent implantation failure (RIF), the failure to conceive after three or more IVF or ET cycles, is also associated with IUAs.[22] Altered endometrial thickness and inflammation and can lead to IUAs that affect the outcome of IVF/ICSI.[7,23]

Patients should be encouraged to undergo second-look office hysteroscopy because of the high rate of recurrence of IUA after surgery and its significant effects on subsequent reproductive outcomes; office hysteroscopy can easily and effectively separate new adhesions.[24-26] In our study, all patients were treated with an artificial menstrual cycle for 1 to 2 months after hysteroscopic surgery, to allow recovery of the endometrium. Subsequently, patients underwent second-look hysteroscopy. Some patients had excellent outcomes and were able to start fresh IVF or ICSI cycles. But, if adhesion recurs, patients require reoperation and ART cycles will be delayed.

We examined ART outcomes to determine the optimal time to perform IVF after hysteroscopic adhesiolysis surgery. According to our results, Group 2 with a 90- to 180-day time interval had higher live-birth and ongoing pregnancy rates than the groups with less than 90-day (Group 1) or greater than 180-day (Group 3) time intervals. Furthermore, our first concerned outcome is live-birth rate. The live-birth rate was significantly higher in Group 2 than that in Group 1. The lack of a significant difference between Groups 2 and 3 may reflect the small sample size of Group 3 compared with the other two groups. From the ratio trend, we observed that the clinical miscarriage rate of Group 2 was lower than that of Groups 1 and 3, although the difference was not statistically significant. We propose that the optimal waiting period for ET after hysteroscopic adhesiolysis is 90 to 180 days. One explanation for the differences between Groups 1 and 2 may be that the wounds of adhesiolysis do not fully heal within 3 months. A thick endometrium is more favorable for embryo implantation and development,[7] and endometrium becomes thicker with a longer recovery time.[12,27] Our previous results of second-look surgery also showed that there was a better endometrial recovery and fewer abnormalities at 2 months compared with 1 month post-surgery. The clinical pregnancy rate of Group 3 was lower than that of Group 2, and the miscarriage rate was increased. It is possible explanation that the smaller sample size of Group 3 affected the outcomes. Alternatively, new IUAs may be formed after the second-look office hysteroscopy.

In the current study, patients exhibited IUAs with different degrees of severity. We further investigated whether there was a relationship between the degree of severity of IUAs and the optimal waiting periods for ET with respect to ART outcomes. In the mild and moderate IUA groups, significant differences were observed in the live-birth rate at the three different time intervals. In the mild subgroup, the live-birth rate was significantly higher in Group 2 than that in Group 1. In the moderate subgroup, the live-birth rate was also significantly higher in Group 2 than that in Group 1. This comparison indicates that the optimal waiting period of the moderate group is 90 to 180 days. We propose that the time interval for embryo transplantation after hysteroscopic adhesion separation should be no less than 3 months.

Our study demonstrated the effect of the time window between the hysteroscopic adhesiolysis and the ET upon IVF/ICSI cycle outcomes. The optimal time interval for embryo transplantation after hysteroscopic adhesion separation was 90 to 180 days. Shorter or longer time intervals reduced the pregnancy rate, which has significance for clinical ART. In addition, the severity and extent of IUAs were scored according to different classification systems. We further analyzed the outcomes of patients with different degrees of severity of IUA, to allow us to provide accurate advice to affected patients. However, our study has some limitations. First, this is a retrospective study that may include selection bias and diminish the strength of the current conclusions. There are many confounding factors that affect pregnancy outcomes; hence, we used the multifactor model as a statistical method of correction. Our total sample size was not large. Larger sample sizes are needed to confirm this outcome in a future study. The Group 3 sample size was less than the other two groups and may affect the outcomes. Future studies should examine a larger sample size, in particular for Group 3. Furthermore, new IUAs may form after the second-look office hysteroscopy; this may have affected the outcomes.

In conclusion, the time interval between hysteroscopic adhesion separation and the day of fresh ET affected the outcome of IVF/ICSI with fresh ET cycles. The optimal time interval for ET after hysteroscopic adhesion separation was 90 to 180 days, and the time interval should be no less than 3 months.


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## Conflicts of interest

None.

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