

Original Article

Optimal Interval of Time from Operative Hysteroscopy to Embryo Transfer in an In Vitro Fertilization Cycle

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ABSTRACT **Study Objective:** Data are limited regarding optimal timing between operative hysteroscopy and embryo transfer (ET). This study aimed to assess whether the time interval from operative hysteroscopy to ET affects implantation and clinical pregnancy rates.

Design: Retrospective cohort study (Canadian Task Force classification II-2).

Setting: Private academic center.

Patients: All patients who had operative hysteroscopy followed by a day 5 ET from 2012 to 2017.

Intervention: Interval of time from operative hysteroscopy to ET.

Measurements and Main Results: The interval of time from hysteroscopy to ET was calculated, and linear regression analyses were performed to assess the impact on clinical outcome. A subanalysis of patients who underwent subsequent single, euploid, frozen ET(s) was performed. A total of 318 patients were included. Indications for hysteroscopy included polypectomy (n = 205), myomectomy (n = 36), lysis of adhesions (n = 46), septum resection (n = 19), and retained products of conception (n = 12). The mean interval of time from hysteroscopy to ET was 138.4 ± 162.7 days (range, 20–1390). There was no significant difference in mean interval of time between procedure and subsequent ET when comparing patients who achieved and did not achieve implantation. Patients stratified by interval of time from operative hysteroscopy to ET had similar clinical outcomes. The time interval from hysteroscopy had no impact on odds of implantation (odds ratio [OR], 1.001; 95% confidence interval [CI], .999–1.002; p = .49), ongoing pregnancy (OR, 1.001; 95% CI, .999–1.002; p = .42), or early pregnancy loss (OR, .997; 95% CI, .994–1.000; p = .07) (adjusted for oocyte age, recipient age, endometrial thickness, use of preimplantation genetic testing, use of donor egg, fresh vs frozen ET, ET count). Similar results were observed in the subanalysis restricted to euploid single frozen ETs from autologous cycles.

Conclusion: The time interval from operative hysteroscopy to subsequent ET does not impact the likelihood of successful clinical outcome. Patients who have undergone operative hysteroscopy do not need to delay fertility treatment. Journal of Minimally Invasive Gynecology (2018) 00, 1–6 © 2018 AAGL. All rights reserved.

Keywords: Assisted reproductive technologies; Endometrium; Wound healing; Implantation; Pregnancy; Live birth

Intracavitary uterine pathology such as polyps, submucous myomas, and septae may impair embryo implantation and/or ongoing pregnancy. Operative hysteroscopy is performed before in vitro fertilization to correct intracavitary

uterine pathology, with the goal of maximizing the chances of a successful pregnancy and live birth [1–4]. Infertile patients have been reported to have pregnancy rates as high as 41.6% after hysteroscopic myomectomy and 51.4% after hysteroscopic polypectomy [5,6], whereas patients suffering from recurrent miscarriage who underwent uterine septum resection had term pregnancy rates of up to 75% [7].

Limited data exist on the optimal timing from operative hysteroscopy to embryo transfer (ET). It is unclear whether there is a need to delay subsequent transfer cycles postoperatively to optimize reproductive outcome. Delaying in vitro fertilization cycles can be detrimental to success rates, especially in women of advanced age. Prior studies suggest no difference in implantation and/or clinical pregnancy rates based

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on interval of time between a hysteroscopic procedure and ET but were restricted to polypectomies or uterine septum resections and were limited by small sample size and the lack of inclusion of cases involving frozen embryo transfer within 1 to 2 months after hysteroscopy [8–10]. The interval of time from other types of hysteroscopic procedures (i.e., myomec-tomy, lysis of adhesions, and evacuation of retained products of conception [POCs]) to ET requires further evaluation. Therefore, the objective of this study was to evaluate the effect of time interval from operative hysteroscopy to subsequent ET on implantation and clinical pregnancy rate.

Methods

Study Design and Patient Population

This single-center, retrospective cohort analysis included all patients who underwent operative hysteroscopy followed by transfer of a fresh or vitrified-warmed blastocyst from 2012 to 2017. Patients were identified via the study site's electronic medical records database. ET cycles involved fresh or vitrified-thawed blastocysts derived from autologous or donor oocytes. The interval of time (number of days) between operative hysteroscopy and subsequent ET was noted. Patients were segregated into 4 groups based on the interval of time between operative hysteroscopy and ET (group 1, ET performed within 30 days; group 2, ET performed within 30–60 days; group 3, ET performed within 60–90 days; group 4, ET performed after 90 days).

Operative Procedures

Hysteroscopies were performed by 1 of 13 physicians in a private reproductive endocrinology and infertility practice. All surgeons had advanced endoscopic training. Targeted resection was performed using a Gynecare Versapoint bipolar electrosurgery system or a TCRis resectoscope (Olympus Surgery Technologies Europe GmbH, Hamburg, Germany). Sharp curettage was not performed.

All surgeons have a uniform practice to perform ET within 1 to 2 cycles after operative hysteroscopy, if possible. Timing of transfers performed further from the procedure was based on patient preference regarding when to commence fertility treatment and other logistical factors.

Stimulation Protocol

Controlled ovarian hyperstimulation for in vitro fertilization was performed as previously described [11]. Final oocyte maturation was induced using recombinant human chorionic gonadotropin (hCG, Ovidrel; EMD Serono, Rockland, MA) alone or with 40 IU leuprolide acetate (Lupron; AbbVie Laboratories, Chicago, IL) when at least 2 mature follicles (≥ 18 mm) were present. In high-responding patients at risk of ovarian hyperstimulation syndrome, this was combined with 1000 IU hCG (Novarel; Ferring Pharmaceuticals, Parsippany, NJ).

Vaginal oocyte retrieval (VOR) under transvaginal ultrasound guidance was performed 36 hours after oocyte maturation was triggered.

Laboratory Procedures

Laboratory procedures included in vitro fertilization, embryo culture, trophoctoderm biopsy, embryo cryopreservation, and warming. Oocytes were evaluated for maturity after VOR. For cases in which preimplantation genetic testing was planned, intracytoplasmic sperm injection was used to fertilize metaphase II oocytes.

Developing embryos underwent laser-assisted hatching on day 3, and trophoctoderm biopsy was performed between days 5 and 7 of blastocyst development, as previously described [11]. To identify euploid embryos, molecular techniques included quantitative polymerase chain reaction, array comparative genomic hybridization, or targeted next-generation sequencing. Patients using preimplantation genetic testing were encouraged to undergo freeze-all cycles to ensure comprehensive embryo genetic screening results before ET. Vitrification and warming of cryopreserved blastocysts was performed using the modified Cryotop method, which was previously described [11].

Endometrial Preparation and ET

Endometrial preparation for fresh ET was performed with 50 mg intramuscular progesterone (Progesterone injection; Watson Pharma Inc., Parsippany, NJ) administered daily, beginning 2 days after VOR. Fresh ET occurred 5 or 6 days after VOR. In preparation for the transfer of vitrified-warmed embryos in patients using autologous or donor oocytes, patients underwent synthetic hormonal preparation of their endometria before ET. Suppression of the hypothalamic-pituitary-ovarian axis was performed in certain cases using oral contraceptive pills for a minimum of 14 days, followed by down-regulation with daily-administered leuprolide acetate (Lupron; AbbVie Laboratories) before menses. Patients then took oral estradiol (Estrace; Teva Pharmaceuticals, Sellersville, PA) 2 mg twice daily for 1 week and then 2 mg 3 times daily.

Transvaginal ultrasound was performed weekly to assess the endometrium, to ensure a thickness of at least 7 mm before transfer. Warming and transfer of the embryo was performed after 5 days of progesterone supplementation. In the case of fresh transfer of donor oocyte-derived blastocysts, 2 days after hCG was administered to the oocyte donor to trigger oocyte maturation, leuprolide acetate was discontinued and daily progesterone supplementation was initiated.

Patients underwent blastocyst transfer under transabdominal ultrasound guidance. The number of embryos transferred was determined based on an individualized risk-to-benefit analysis according to demographic and prognostic factors, after a detailed physician–patient discussion. Patients who used preimplantation genetic testing were strongly encouraged to undergo elective single ET.

Outcome Variables

Baseline characteristics included patient age, body mass index, oocyte age, anti-müllerian hormone level, basal antral follicle count, and endometrial thickness. Cycle characteristics included fresh versus vitrified-warmed blastocyst, whether preimplantation genetic testing was performed, donor versus autologous oocyte, and number of blastocysts transferred. Pregnancy outcomes evaluated were pregnancy rate (positive hCG), implantation (gestational sac visualized on transvaginal ultrasound), ongoing pregnancy (intrauterine gestation with fetal cardiac activity), and early pregnancy loss (loss of pregnancy after intrauterine pregnancy was visualized).

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Student's *t* tests and χ^2 tests were used to compare baseline demographics and cycle characteristics between study groups. A χ^2 analysis was used to compare clinical outcomes among study groups, categorized according to the interval of time between hysteroscopy and subsequent ET. Linear regression analyses were performed to assess the impact of time between hysteroscopy and subsequent ET on clinical outcome. Univariate and multivariate analyses were performed adjusting for oocyte age, recipient age, endometrial thickness, whether preimplantation genetic screening was performed, donor egg used, fresh versus frozen cycle, and number of embryos transferred. To assess the impact of time interval on ETs using a uniform protocol, a subanalysis was performed that included only patients who underwent transfer of single, euploid, vitrified-thawed blastocysts.

Results

A total of 318 patients underwent operative hysteroscopy followed by a subsequent ET. Indications for hysteroscopy included polypectomy (*n* = 205), myomectomy (*n* = 36), lysis of adhesions (*n* = 46), septum resection

(*n* = 19), and retained POCs (*n* = 12). The mean interval of time from hysteroscopy to ET was 138.4 ± 162.7 days (range, 20–1390). Demographic and cycle characteristics are shown in Table 1. Age and anti-müllerian hormone level followed a normal distribution by Shapiro-Wilk test.

In patients with successful implantation versus no implantation, there was no significant difference in mean interval of time between hysteroscopy and subsequent ET (Table 1). Rates of implantation, clinical pregnancy, ongoing pregnancy, and early pregnancy loss were similar among each of the 4 time interval groups (Table 2). In a univariate analysis the interval of time between hysteroscopy and subsequent ET did not impact implantation (odds ratio [OR], 1.0; 95% confidence interval [CI], .99–1.002; *p* = .49), clinical pregnancy (OR, 1.001; 95% CI, .99–1.002; *p* = .46), or early pregnancy loss (OR, .99; 95% CI, .99–1.002; *p* = .15). When controlling for oocyte age, recipient age, endometrial thickness at transfer, whether preimplantation genetic testing was performed, whether donor or autologous oocytes were used, and the number of embryos transferred, the interval of time from hysteroscopy to ET had no impact on odds of implantation (OR, 1.001; 95% CI, .999–1.002; *p* = .49), ongoing pregnancy (OR, 1.001; 95% CI, .999–1.002; *p* = .42), or early pregnancy loss (OR, .997; 95% CI, .994–1.000; *p* = .07).

In the subanalysis restricted to euploid single frozen ETs from autologous cycles (*n* = 96), similar results were observed. The mean interval of time from hysteroscopy to ET in this subgroup was 159 ± 186.57 days (range, 20–1309). Baseline characteristics and the distribution of patients in each time interval group were similar to that of all patients (Table 3). In a univariate analysis no significant difference was found in odds of implantation (OR, 1.00; 95% CI, .998–1.003; *p* = .71), ongoing pregnancy (OR, 1.001; 95% CI, .998–1.003; *p* = .61), or early pregnancy loss (OR, .995; 95% CI, .988–1.002; *p* = .15) based on time from hysteroscopy to ET. Results were consistent when adjusting for oocyte age, recipient age, endometrial thickness, and the day of embryo development at time of trophectoderm biopsy.

Table 1

Main demographics and cycle characteristics compared among implantation vs no implantation

	Implantation (<i>n</i> = 152)	No implantation (<i>n</i> = 166)	<i>p</i> (95% CI)
Age, yr	38.1 ± 4.7	39.2 ± 4.6	<.05 (.078–2.122)
Oocyte age, yr	35.3 ± 5.0	36.1 ± 5.4	NS
Anti-müllerian hormone level, ng/mL	2.9 ± 2.9	2.7 ± 2.7	NS
Basal antral follicle count	9.1 ± 6.4	9.2 ± 7.3	NS
Endometrial thickness, mm	9.3 ± 2.2	9.1 ± 2.4	NS
Proportion of fresh vs frozen blastocysts	36.4 (55/151)	48.2 (79/164)	<.05 (.112–.124)
Proportion of ETs involving screened, euploid embryos	46.7 (71/152)	31.3 (52/166)	<.005 (.100–.208)
Proportion of ETs derived from donor oocytes	16.4 (25/152)	15.7 (26/166)	NS
Mean no. of blastocysts transferred	1.4 ± .6	1.4 ± .6	NS
Mean interval of time between procedure and ET, days	145.0 ± 175.1	132.3 ± 150.7	NS

Values are mean ± standard deviation or percentage (*n*/*N*). NS = not significant.

Table 2

ET outcomes according to interval from operative hysteroscopy					
	<30 days (n = 27)	30–59 days (n = 88)	60–89 days (n = 70)	≥90 days (n = 133)	p
Pregnancy rate	63.0 (17/27)	61.4 (54/88)	60.0 (42/70)	55.6 (74/133)	NS
Implantation rate	44.4 (12/27)	51.1 (45/88)	47.1 (33/70)	46.6 (62/133)	NS
Ongoing pregnancy rate	44.4 (12/27)	45.5 (40/88)	38.6 (27/70)	44.4 (59/133)	NS
Early pregnancy loss rate	18.5 (5/27)	15.9 (14/88)	21.4 (15/70)	11.3 (15/133)	NS

Values are percentage (n/N). NS = not significant.

Table 3

Baseline characteristics and outcomes for euploid single ETs	
Parameter	Value (n = 96)
Age, yr	37.65 ± 3.11
Oocyte age, yr	37.06 ± 3.06
Anti-müllerian hormone level, ng/mL	2.79 ± 2.68
Basal antral follicle count	9.94 ± 6.14
Endometrial thickness, mm	9.00 ± 2.00
Implantation rate	60.4 (58/96)
Ongoing pregnancy rate	55.2 (53/96)
Early pregnancy loss rate	22.0 (15/68)

Values are mean ± standard deviation or percentage (n/N).

A subanalysis of outcomes according to procedure type was performed, which is shown in Appendix [Tables A1](#) and [A2](#). For polypectomies, outcomes were similar when comparing groups according to time interval: <30 days, 30 to 59 days, 60 to 89 days, and ≥90 days ([Table 4](#)). Other procedure types had small numbers to draw conclusions regarding impact of time interval from operative hysteroscopy to ET ([Tables A1](#) and [A2](#)).

Discussion

The study demonstrated that the interval of time from operative hysteroscopy to subsequent ET does not appear to influence the likelihood of a successful clinical outcome. These results are consistent with other studies that have

demonstrated no difference in pregnancy outcome based on the interval of time from hysteroscopic polypectomy or uterine septum resection to ET [8,10]. This study is the first to evaluate the interval of time between a variety of operative hysteroscopic procedures and ET while also evaluating the shortest durations as compared with prior studies [9]. Although only a small proportion of study patients underwent ET within 3 weeks after hysteroscopy, the data are reassuring because implantation and pregnancy rates were not negatively impacted by a rapid return to reproductive treatment.

It is reasonable that many practitioners have advised patients to delay ET after an operative hysteroscopy, because a delayed ET would allow time for the uterine lining to heal and replenish to optimize pregnancy outcomes. Emerging evidence demonstrates, however, that endometrial injury may increase receptivity and successful implantation. Local injury of the endometrium has been found to induce an inflammatory response that may enhance embryo implantation [12]. Biopsy-induced endometrial injury is being actively investigated as a potential treatment strategy to improve implantation rates in patients with recurrent implantation failure [13,14].

There is debate as to whether minimal local endometrial injury is deleterious, insignificant, or beneficial, but it is well established that a greater degree of harm may diminish fertility outcomes because of scarring. The development of synechiae after intrauterine procedures can prevent successful implantation and development of a clinical pregnancy [15,16].

If recent endometrial injury is beneficial for implantation, we might expect to see increased implantation rates

Table 4

ET outcomes according to interval from hysteroscopic polypectomy						
	All (n = 205)	<30 days (n = 22)	30–59 days (n = 66)	60–89 days (n = 41)	≥90 days (n = 76)	p
Implantation	50.2	45.5	54.5	46.3	50.0	NS
Ongoing pregnancy	44.9	45.5	48.5	36.6	46.1	NS
Early pregnancy loss	27.0	28.6	25.6	37.5	22.2	NS

Values are percents. NS = not significant.

within 2 months from a procedure, with a decrease thereafter because of the development of scarring. Alternatively, an increase in implantation rates may be expected after 2 to 3 months from the procedure when wound healing is complete. Our study did find a trend toward increased pregnancy rates with ET more proximal to the hysteroscopic procedure, although this trend was not statistically significant. No clear trend was found in implantation rate, ongoing pregnancy rate, or early pregnancy loss rate. Our findings suggest that tissue healing and remodeling after operative hysteroscopy neither positively nor negatively impacts endometrial receptivity.

The greatest strength of this study was the ability to evaluate the interval of time from a variety of hysteroscopic procedures to ET, making it 1 of the first to include myomectomies, lysis of adhesions, and retained POCs. This allowed for the assessment of varying degrees of endometrial injury. Second, only blastocyst transfers were included. Third, the study was able to perform a subanalysis using 1 uniform protocol of single, euploid, vitrified-thawed blastocyst transfers to control for the confounding effects of embryonic aneuploidy, number of embryos transferred, and the hormonal impact on the endometrial environment on ET outcome.

The study had a few limitations. First, the sample size of the study was small, and we were unable to stratify patients by the indication for operative hysteroscopy to understand the relative effects of each type of procedure on clinical outcome of subsequent ET. Second, a large proportion of procedures included were polypectomies (65%). Third, only a small sample of patients had an ET less than 30 days after the procedure ($n=27$). Transfers within 2 months from a procedure is an area of interest for further investigation given the recent discussions surrounding the interaction between endometrial injury and implantation rates. Additionally, the study is limited by its retrospective nature. The timing of ET was not randomized and may have been influenced by clinical judgment pertaining to various factors, such as the extent of the procedure.

In conclusion, the interval of time from hysteroscopic procedures to subsequent ET did not modify clinical outcome. Based on this study's findings, patients who have undergone an operative hysteroscopy can be reassured that they do not need to excessively delay their attempt to conceive via ET. A trend toward increased pregnancy rate was found with ET more proximal to the hysteroscopic procedure, which might be substantiated with larger prospective studies powered to detect a difference in these outcomes. It is possible that a minor degree of endometrial injury generates an inflammatory cascade that enhances implantation, whereas deeper injury can cause scarring, thereby impairing implantation. Further research correlating the degree of the injury and the tissue remodeling response with ET outcomes based on interval of time from the injury could help guide clinicians in planning ET after a hysteroscopic procedure. Based on available evidence, however, planning of ET

should be determined according to patient needs and desired timing of conception rather than on the theoretical time believed necessary for endometrial healing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jmig.2018.10.019](https://doi.org/10.1016/j.jmig.2018.10.019).

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Appendix: Subanalysis tables

Table A1

Baseline demographics and cycle characteristics

	Polypectomy (n = 205)	Myomectomy (n = 36)	Lysis of adhesions (n = 46)	Septum (n = 19)	Retained POCs (n = 12)
Average interval from hysteroscopy to ET, days (range)	137 (20–1390)	123 (20–399)	161 (20–829)	113 (29–262)	166 (55–400)
Age at ET, yr	38.9 ± 4.7	39.32 ± 4.56	37.93 ± 4.59	38.0 ± 3.66	36.83 ± 5.58
Oocyte age, yr	36.46 ± 5.08	36.14 ± 4.56	33.74 ± 5.06	35.2 ± 5.01	30.29 ± 5.37
Anti-müllerian hormone level, ng/mL	2.93 ± 2.69	2.07 ± 1.53	2.86 ± 3.30	1.16 ± 1.01	5.03 ± 6.52
Basal antral follicle count	9.53 ± 7.04	9.73 ± 7.20	8.09 ± 6.78	7.5 ± 3.78	7.08 ± 6.27
Endometrial thickness, mm	9.69 ± 2.26	8.85 ± 1.63	7.71 ± 1.57	8.76 ± 2.79	8.17 ± 2.83
Implantation, %	50.2	47.2	37.0	36.8	66.7
Ongoing pregnancy, %	44.9	44.4	32.6	36.8	66.7
Early pregnancy loss, %	27.0	20.0	28.5	30.0	20.0

Values are mean ± standard deviation unless otherwise defined.

Table A2

Outcomes by interval of time according to procedure type

	All	Group A: <30 days	Group B: 30–59 days	Group C: 60–89 days	Group D: ≥90 days
Polyps					
No. of cases	205	22	66	41	76
Implantation	50.2	45.5	54.5	46.3	50.0
Ongoing pregnancy	44.9	45.5	48.5	36.6	46.1
Early pregnancy loss	27.0	28.6	25.6	37.5	22.2
Myomectomy					
No. of cases	36	1	10	7	18
Implantation	47.2	.0	40.0	57.1	50.0
Ongoing pregnancy	44.4	.0	30.0	57.1	50.0
Early pregnancy loss	20.0	n/a	50.0	20.0	0.0
Lysis of adhesions					
No. of cases	46	3	8	14	21
Implantation	37.0	33.3	50.0	35.7	33.3
Ongoing pregnancy	32.6	33.3	50.0	21.4	33.3
Early pregnancy loss	28.5	50.0	.0	50.0	22.2
Septum					
No. of cases	19	1	3	4	11
Implantation	36.8	100.0	.0	50.0	36.4
Ongoing pregnancy	36.8	100.0	.0	50.0	36.4
Early pregnancy loss	30.0	.0	n/a	33.3	33.3
Retained POC					
No. of cases	12	0	1	4	7
Implantation	66.7	n/a	100.0	75.0	57.1
Ongoing pregnancy	66.7	n/a	100.0	75.0	57.1
Early pregnancy loss	20.0	n/a	0.0	25.0	20.0

Values are percents unless otherwise defined. n/a = not applicable.