Does the time interval between hysteroscopic polypectomy and start of in vitro fertilization affect outcomes?

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Objective: To investigate whether the time interval between hysteroscopic polypectomy and the start of IVF-ET cycles affect IVF cycle outcomes.
Design: Retrospective cohort.
Setting: Academic center.
Patient(s): All patients diagnosed with endometrial polyps undergoing hysteroscopic polypectomy before fresh IVF-ET.
Intervention(s): Hysteroscopic polypectomy.
Main Outcome Measure(s): Patients were divided into three groups based on the time interval between hysteroscopic polypectomy and the start of a fresh IVF-ET cycle. Group 1 consisted of patients who underwent IVF-ET after their next menses, group 2 after two or three menstrual cycles, and group 3 after more than three menstrual cycles. Demographics, baseline IVF characteristics, controlled ovarian stimulation response, and pregnancy outcomes after ET were compared among the groups.
Result(s): A total of 487 patients met inclusion criteria: 241 in group 1 (49.5%), 172 in group 2 (35.3%), and 74 in group 3 (15.2%). There were no differences in the baseline characteristics of the three groups. Ovarian stimulation outcomes, specifically total stimulation days, total gonadotropins administered, and number of oocytes retrieved, were similar between groups. There were no differences in the mean number of embryos transferred. The overall pregnancy outcomes were similar for groups 1, 2, and 3: implantation rate (42.4%, 41.2%, and 42.1%, respectively), clinical pregnancy rate (48.5%, 48.3%, and 48.6%), spontaneous miscarriage rate (4.56%, 4.65%, and 4.05%), and live birth rate (44.0, 43.6%, and 44.6%).
Conclusion(s): Because waiting for two or more menstrual cycles after hysteroscopic polypectomy does not necessarily yield superior outcomes, patients can undergo ovarian stimulation after their next menses without affecting IVF-ET outcomes. (Fertil Steril® 2016;105:539–44. ©2016 by American Society for Reproductive Medicine.)
Key Words: Endometrial polyps, hysteroscopy, polypectomy, in vitro fertilization, timing

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Endometrial polyps are benign localized lesions of the endometrium that are commonly seen in women of reproductive age (1). Endometrial polyps, as well as other intrauterine lesions, such as leiomyomata or septae, can affect implantation of a healthy embryo (2–4) and are implicated in the pathogenesis of subfertility and early pregnancy loss, though the association is controversial (5, 6). Although isolated uterine-associated infertility can be found in 2%–3% of infertile women (7), intrauterine lesions may be found in ~40%–50% of subfertile or infertile women (5–7). Previous observational studies have suggested that resection of endometrial polyps can help to increase natural conception rates as well as increase pregnancy rates with the use of assisted reproduction (8–13). Although current evidence suggests that endometrial polyp resection is beneficial before pursuing assisted reproduction, there

Received September 11, 2015; revised October 18, 2015; accepted October 27, 2015; published online November 18, 2015.
N.P. has nothing to disclose. S.A. has nothing to disclose. J.L.E. has nothing to disclose. J.P.L. has nothing to disclose. R.T.E. has nothing to disclose. P.H.C. has nothing to disclose. Z.R. has nothing to disclose.
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Fertility and Sterility® Vol. 105, No. 2, February 2016 0015-0282/$36.00
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http://dx.doi.org/10.1016/j.fertnstert.2015.10.028

are almost no data regarding the optimal time interval between polyp resection and start of assisted reproduction treatment (14). In this context, we sought to investigate whether the time interval between hysteroscopic polypectomy and the start of in vitro fertilization–embryo transfer (IVF-ET) cycles affect IVF cycle outcomes.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

The Weill Cornell Medical College Institutional Review Board approved the study protocol. All patients diagnosed with endometrial polyps undergoing hysteroscopic polypectomy before fresh IVF-ET cycles from January 2010 to June 2013 were analyzed for potential inclusion. Endometrial polyps were diagnosed with the use of criteria described by Pérez-Medina et al. (13). A polyp was usually suspected when a hyperechoic endometrial mass with regular contours occupied the uterine cavity either partially or fully (13, 15). Two-dimensional measurements of the polyp were performed, with the mean of these measurements recorded as the definitive measurement (16). Two-dimensional transvaginal ultrasonography, in experienced hands, can detect endometrial polyps accurately (17). All of the hysteroscopic polypectomies (1) were performed in the operating room in the follicular phase of the menstrual cycle. After cervical dilatation to 8 mm, a 22-F monopolar resectoscope with 1.5% glycine as the distention media was used. An automated Stryker fluid management system was also used. Patients did not receive intrauterine balloons or postoperative estrogens after the hysteroscopic polypectomies. All endometrial polyps were confirmed histologically. Exclusion criteria included IVF cycles cancelled before ET, frozen-thawed embryo cycles, donor oocyte cycles, and patients with recurrent IVF failure.

Clinical and Laboratory Protocols

Controlled ovarian stimulation (COS) was carried out to maximize follicular response while minimizing the risk of ovarian hyperstimulation syndrome. COS, hCG trigger, oocyte retrieval, embryo culture, and ET were performed per our standard protocols (18). Gonadotropin doses were based on patient age, weight, antral follicle count, and previous response to stimulation, if any. After initiating COS with the use of gonadotropins (Follistim, Merck; Gonal-F, EMD-Serono; and/or Menopur, Ferring Pharmaceuticals), ovulation was suppressed with the use of 0.25 mg ganirelix acetate (Merck) or cetrotide (EMD-Serono).

hCG was used as the ovulation trigger based on a previously described sliding-scale protocol (15, 18). In general, the hCG trigger was given when two lead follicles attained a mean diameter $\geq$17 mm. Oocyte retrieval was performed under conscious sedation with the use of transvaginal ultrasound guidance 35–37 hours after hCG administration. Intramuscular progesterone was started the day after oocyte retrieval. Choice of insemination or intracytoplasmic sperm injection was based on the male partner's semen analysis. Embryos were cultured with the use of in-house culture media, and embryo transfers were performed with the use of Wallace catheters (Smiths Medical) at $\sim$1 cm below the uterine depth identified at a prior trial transfer.

Outcome Variables

Demographic characteristics recorded included age, gravidity, parity, and body mass index (BMI; kg/m^2). Baseline IVF characteristics recorded were FSH (mIU/mL) and E_2 (pg/mL) level at cycle start. COS parameters recorded were as follows: protocol type (GnRH antagonist vs. GnRH agonist), total days of ovarian stimulation, total dosage of gonadotropins administered (IU), peak E_2 level (pg/mL), peak endometrial stripe (mm), total number of oocytes retrieved, total number of mature oocytes, and mean number of embryos transferred (19). Pregnancy outcomes after ET were also recorded. Implantation rate was defined as the mean number of gestational sacs seen with the use of transvaginal ultrasonography divided by the number of embryos transferred for each patient. Clinical pregnancy rate was defined as the number of intrauterine gestations with fetal cardiac activity per IVF-ET cycle. A biochemical pregnancy was defined as positive hCG level without a gestational sac. Any pregnancy loss after visualization of an intrauterine gestation was considered to be a spontaneous miscarriage, and any birth after 24 weeks of gestation was considered to be a live birth.

Statistical Analyses

All statistical analyses were performed with the use of Stata version 13 (Statacorp). Continuous variables were checked for normality and expressed as mean $\pm$ SD. Categoric variables were expressed as n (%). By study design, patients were assigned to three groups based on the time interval between hysteroscopic polypectomy and the start of a fresh IVF-ET cycle: Group 1 consisted of patients who underwent IVF-ET after their next menses, group 2 after two or three menstrual cycles, and group 3 after more than three menstrual cycles. A sample size of 73 patients was estimated assuming an α error of 5% and a power of 80% to detect a 15% difference in clinical pregnancy rate (14). Analysis of variance and chi-square tests were used to compare means and percentages of recorded parameters among the three groups. Statistical significance was set at $P<.05$.

RESULTS

A total of 741 patients underwent hysteroscopies during the study period. Of the 609 patients who underwent hysteroscopic polypectomy, 487 (80%) underwent IVF treatment and 122 (20%) did not. The 487 patients who met inclusion criteria were grouped as follows: 241 (49.5%) in group 1, 172 (35.3%) in group 2, and 74 (15.2%) in group 3. Supplemental Figure 1 (available online at www.fertstert.org) summarizes the selection of the study cohort.

Table 1 compares the demographic and baseline IVF characteristics of patients undergoing fresh IVF-ET cycles after hysteroscopic polypectomy, stratified by number of menstrual cycles. The mean ages of patients in groups 1, 2, and 3 were 34.7 $\pm$ 4.91 years, 34.3 $\pm$ 4.79 years, and 34.9 $\pm$ 3.91 years, respectively. Similarly to mean age, there was no statistical difference in mean gravidity, parity, or BMI of

TABLE 1

Baseline characteristics of patients undergoing IVF cycles after hysteroscopic polypectomy, stratified by number of menstrual cycles after surgery (n = 487).

Parameter	IVF after next menses (n = 241)	IVF after 2 or 3 menstrual cycles (n = 172)	IVF after >3 menstrual cycles (n = 74)	*P* value
Age (y)	34.7 ± 4.91	34.3 ± 4.79	34.9 ± 3.91	.58
Gravidity	0.85 ± 0.23	0.87 ± 0.21	0.81 ± 0.28	.18
Parity	0.58 ± 0.27	0.55 ± 0.21	0.62 ± 0.28	.13
BMI (kg/m^2)	23.5 ± 6.05	23.6 ± 6.31	23.4 ± 4.62	.97
Basal FSH (mIU/mL)	4.98 ± 3.16	5.31 ± 3.19	5.33 ± 2.99	.50
Basal E_2 (pg/mL)	55.1 ± 9.65	54.2 ± 7.47	55.4 ± 8.68	.49

Note: Data are presented as mean ± SD. BMI = body mass index.

Pereira. Time between polypectomy and IVF. Fertil Steril 2016.

the three groups composing the study cohort. Furthermore, there was no difference in the basal FSH level or basal E_2 level at IVF start. Table 2 compares COS parameters between the groups. The overall mean stimulation days were 9.88 ± 2.13, 9.66 ± 2.04, and 9.61 ± 2.67, and peak endometrial stripes were 9.96 ± 2.25, 10.2 ± 2.32, and 10.5 ± 2.51 in groups 1, 2, and 3, respectively. In addition, there were no differences in the type of COS protocol, total gonadotropins administered, or peak E_2 level.

Table 3 compares the outcomes of IVF-ET cycles of patients undergoing IVF cycles after hysteroscopic polypectomy, stratified by number of menstrual cycles. The mean numbers of embryos transferred were similar among the groups. There was no difference in implantation rates (42.4%, 41.2%, 42.1%; *P*=.98), clinical pregnancy rates (48.5%, 48.3%, 48.6%; *P*=.99), spontaneous miscarriage rates (4.56%, 4.65%, 4.05%; *P*=.98), or live birth rates (44.0, 43.6%, 44.6%; *P*=.99) when comparing the three groups. No second-trimester pregnancy losses were noted in any group. Figure 1 summarizes the aforementioned pregnancy outcomes of the study cohort.

DISCUSSION

Endometrial polyps are benign lesions of the endometrium that contain glands and stroma (4, 5). They may occur as single or multiple lesions, can be sessile or pedunculated, and may range in size from millimeters to centimeters (4, 20). Because most endometrial polyps are asymptomatic, their true incidence remains unknown (1, 20). Some observational studies have estimated that endometrial polyps can be detected in up to 24% of symptomatic women (21, 22). The prevalence of endometrial polyps is thought to be higher in infertile women (1, 22). Endometrial polyps were found in ~32% of 1,000 patients undergoing hysteroscopic evaluation of the uterine cavity before IVF in one large prospective study (23). Although these data suggest a causal association between polyps and infertility (20), the association has been confirmed in only one randomized controlled trial to date (13).

Endometrial polyps are rarely diagnosed before menarche, which suggests that estrogenic stimulation of the endometrium plays a significant role in their development (24). Because polyps contain functional endometrium, they can develop in conditions associated with increased or unopposed E_2 levels, as in the case of ovarian stimulation during IVF (10, 15, 20). Molecular mechanisms, including the overexpression of estrogen and progesterone receptors (25), endometrial aromatase (26, 27), and mutations in the *HMGIC* and *HMGI[Y]* genes (28, 29), also have been implicated in the development of endometrial polyps (20). Polyps may adversely affect fertility by mechanically

TABLE 2

Ovarian stimulation outcomes of patients undergoing IVF cycles after hysteroscopic polypectomy, stratified by number of menstrual cycles (n = 487).

Parameter	IVF after next menses (n = 241)	IVF after 2 or 3 menstrual cycles (n = 172)	IVF after >3 menstrual cycles (n = 74)	*P* value
Protocol				.96
GnRH agonist based	27 (11.2)	19 (11)	9 (12.2)	
GnRH antagonist based	214 (88.8)	153 (89)	65 (87.8)	
Total stimulation (d)	9.88 ± 2.13	9.66 ± 2.04	9.61 ± 2.67	.49
Total gonadotropins administered (IU)	3,118.2 ± 1,950.0	3,023.9 ± 1,477.5	3,056.4 ± 1,610.1	.86
E_2 on day of trigger (pg/mL)	1,518.3 ± 734.6	1,609.4 ± 718.9	1,607.1 ± 754.1	.40
Peak endometrial stripe (mm)	9.96 ± 2.25	10.2 ± 2.32	10.5 ± 2.51	.19
No. of oocytes retrieved	10.9 ± 7.27	10.7 ± 5.93	11.2 ± 6.32	.86
No. of mature oocytes	8.67 ± 6.19	8.45 ± 4.62	8.59 ± 5.49	.92
Embryos transferred	1.93 ± 0.49	1.89 ± 0.73	1.97 ± 0.68	.62

Note: Data are presented as mean ± SD or n (%).

Pereira. Time between polypectomy and IVF. Fertil Steril 2016.

TABLE 3

Pregnancy outcomes of patients undergoing IVF cycles after hysteroscopic polypectomy, stratified by number of menstrual cycles (n = 487).

Parameter	IVF after next menses (n = 241)	IVF after 2 or 3 menstrual cycles (n = 172)	IVF after >3 menstrual cycles (n = 74)	*P* value
Age (y)	34.7 ± 4.91	34.3 ± 4.79	34.9 ± 3.91	.74
Embryos transferred	1.93 ± 0.49	1.89 ± 0.73	1.97 ± 0.68	.62
Implantation rate (%)	42.4	41.2	42.1	.98
Clinical pregnancies	117 (48.5)	83 (48.3)	36 (48.6)	.99
Biochemical pregnancies	21 (8.71)	16 (9.30)	7 (9.46)	.98
Spontaneous miscarriages	11 (4.56)	8 (4.65)	3 (4.05)	.97
Live births	106 (44.0)	75 (43.6)	33 (44.6)	.99

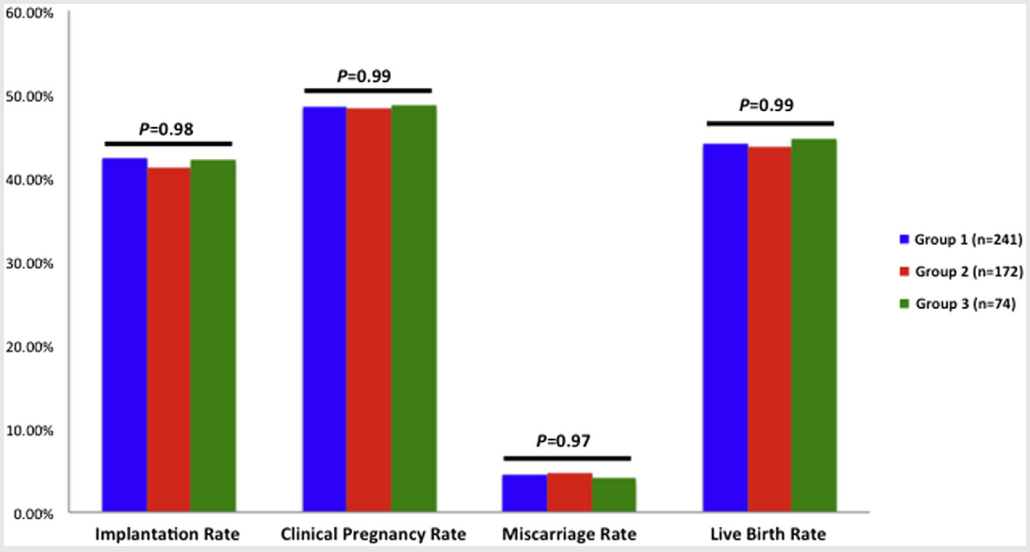
Note: Data are presented as mean ± SD or n (%), unless stated otherwise.

Pereira. Time between polypectomy and IVF. Fertil Steril 2016.

interfering with sperm transportation or as space-occupying lesions impeding embryo implantation (4, 5). The glands and stroma in endometrial polyps are unresponsive to progesterone stimulation, leading to defective implantation at the site of the polyp (20, 30). Endometrial polyps may also induce local inflammatory changes (31, 32) or produce glycodelin (33), a glycoprotein that has been shown to inhibit natural killer cell activity and render the endometrium less receptive to implantation (19). It is also speculated that endometrial polyps decrease messenger RNA levels of HOXA10 and HOXA11, known molecular markers of endometrial receptivity (4, 20).

The natural course of endometrial polyps is still not well understood (22, 34). Although small endometrial polyps (<10 mm) can regress spontaneously in ~25% of cases (35, 36), definitive treatment options are largely surgical (20). In this context, hysteroscopic polypectomy remains the criterion standard for both diagnosis and treatment of endometrial polyps (1, 20). Previous studies have shown that resection of endometrial polyps can improve natural conception rates, particularly in patients with unexplained infertility (3, 5). In one retrospective study of 78 patients by Varasteh et al., a pregnancy rate of 78.3% was noted after polypectomy compared with a pregnancy rate of 42.1% in patients with normal uterine cavities (12). Other studies have reported natural conception rates of 76% (37) and 50% (38) after hysteroscopic polypectomy. Pregnancy rates are also improved in patients undergoing hysteroscopic polypectomy before undergoing intrauterine insemination (IUI) (15, 20). In a prospective randomized study of 215 patients, Pérez-Medina et al. found that those who underwent polypectomy before IUI had an increased pregnancy rate (51.4%) compared with patients who did not (25.4%) (13). These findings were confirmed by another

FIGURE 1



Pregnancy outcomes of IVF-ET cycles of patients undergoing IVF cycles after hysteroscopic polypectomy, stratified by groups (group 1 underwent IVF-ET after their next menses, group 2 after two or three menstrual cycles, and group 3 after more than three menstrual cycles).

Pereira. Time between polypectomy and IVF. Fertil Steril 2016.

independent study, which reported pregnancy rates of 40.7% and 22.3% in patients who, respectively, did and did not undergo polypectomy before IUI (8).

Current evidence supports the resection of endometrial polyps diagnosed before starting fresh IVF-ET cycles (1, 6). However, there is limited evidence regarding the optimal time interval between hysteroscopic polypectomy and initiation of a fresh IVF-ET cycle. In a retrospective study of 60 patients, Eryilmaz et al. compared the ovarian stimulation and pregnancy outcomes of 29 and 31 patients who underwent IVF <6 months and ≥ 6 months, respectively, after hysteroscopic polypectomy (14). They concluded that the IVF outcomes of the study cohort were unrelated to the time interval between the hysteroscopic polypectomy and the initiation of the IVF (14). Consistent with these findings, the COS parameters and pregnancy outcomes of our study cohort undergoing fresh IVF-ET after hysteroscopic polypectomy remained independent from the number of menstrual cycles between polypectomy and IVF cycle start.

The strengths of the present study include its sample size, which is larger than previously published studies (10, 14). The clinical pregnancy rates in this study are higher than the pregnancy rates reported in the Eryilmaz et al. (14) and Lass et al. (10) studies, which were 20.5% and 22.4%, respectively. Whereas our study stratified the time period between polypectomy and IVF cycle start by the number of intervening menstrual cycles, Eryilmaz et al., analyzed a period of 6 months between polypectomy and IVF cycle start. Some studies have suggested higher implantation and pregnancy rates after mild endometrial injury in the menstrual cycle preceding IVF (39, 40). Group 1 in the present study represents such a clinical scenario, but the implantation and pregnancy rates of group 1 were similar to those of groups 2 and 3.

The present study is not without limitations. All hysteroscopic polypectomy cases were performed in the operating room with the use of a monopolar resectoscope. We remain uncertain whether the observed IVF-ET cycle outcomes would remain unchanged if polypectomy were performed in the office setting or with other resection methods, such as bipolar electrode excision (41) or hysteroscopic morcellation (42, 43). Though our analysis of IVF-ET cycle outcomes was stratified according to the number of menstrual cycles between hysteroscopic polypectomy and IVF cycle start, no patient in the study cohort underwent a fresh IVF-ET cycle >5 months (five menstrual cycles) after hysteroscopy. Therefore, it is difficult to predict whether our results hold true beyond the 5-month period. Furthermore, it must be noted that reasons for delaying IVF-ET were largely logistical or personal. Finally, because the study was retrospective in nature, its conclusions should be interpreted with caution and should be subject to larger prospective settings.

CONCLUSION

The data from this study suggest that the time elapsed between hysteroscopic polypectomy and the start of fresh IVF-ET cycles does not affect cycle outcomes. Waiting for two or more menstrual cycles after surgery did not yield superior outcomes. Therefore, patients may undergo ovarian stimulation for fresh IVF-ET cycles after their next menses following hysteroscopic polypectomy without affecting outcomes. This approach may be especially beneficial in patients who require specific timing of IVF cycles owing to logistical or geographic reasons.

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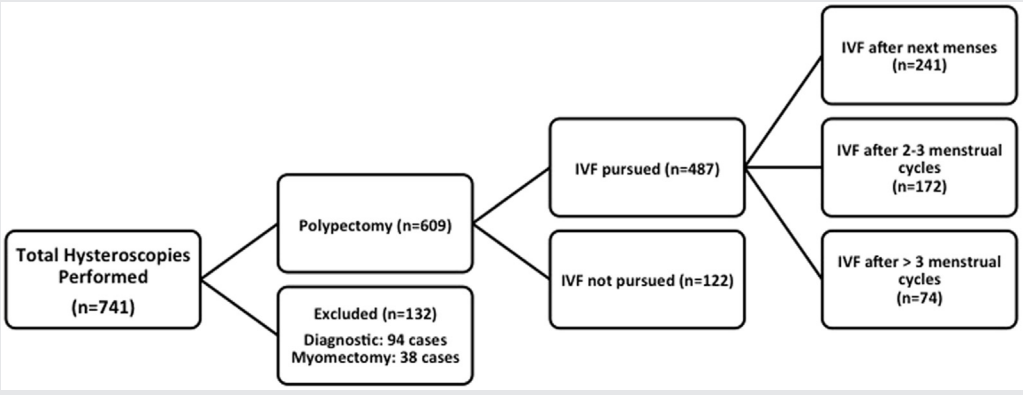
SUPPLEMENTAL FIGURE 1



Selection of the study cohort.

Pereira. Time between polypectomy and IVF. Fertil Steril 2016.