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Effect of endometrial injury on in vitro fertilization pregnancy rates: a randomized, multicentre study

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Abstract

Purpose To determine if endometrial injury prior to the first or second in vitro fertilization (IVF) cycle affects clinical pregnancy rates.

Methods This study was a randomized, multicentre, controlled study performed at three Canadian outpatient fertility clinics. Patients undergoing their first or second IVF cycle were randomized to a single endometrial injury 5–10 days prior to the start of gonadotropins in an IVF cycle compared to no injury. The primary outcome was clinical pregnancy rate. Secondary outcomes were live birth rates, implantation rate, endometrial thickness, number of oocytes retrieved and the rate of embryo cryopreservation.

Results Fifty-one women were randomized (25 in the endometrial injury group and 26 in the control group); however, the study was terminated prematurely due to slow recruitment (target 332 patients). Groups were similar at baseline for: age, duration of infertility, BMI, day 3 FSH, and the number having first IVF cycle. The groups were similar for gonadotropin dose, endometrial thickness, number of oocytes retrieved, and embryo cryopreservation rate. The clinical pregnancy rate in the endometrial injury group was 52% (13/25) and 46% (12/26) in the control group ($p=0.45$). Live birth rate in the endometrial injury group was 52% (13/25) and 35% (9/26) in the control group ($p=0.17$). The implantation rate was also similar (58% vs. 45%, $p=0.17$).

Conclusions This study did not detect a difference in implantation, clinical pregnancy or live birth rates; however, the lack of difference in this study may be because it was underpowered.

Clinical trials registrations gov: NCT01983423

Keywords Endometrium · Local injury · IVF outcomes · Implantation

Introduction

Luteal endometrial injury in the cycle preceding IVF was initially described in patients with recurrent implantation failure [1]. Subsequent studies have also shown conflicting results [2–16]. These studies often included patients who had failed at least two or three embryo transfers, although some studies included patients who had only failed one IVF cycle. Two meta-analyzes showed an increase in clinical pregnancy rates [17, 18]. Live birth was only analyzed in one meta-analysis; an increase in live birth was seen only in the observational studies and not in the RCT [17].

One theory for recurrent failed implantation is impaired endometrial receptivity. Endometrial injury is theorized to promote implantation through an increase in inflammatory mediators [3, 19] Failed IVF cycles may be the result of an implantation issue, an embryo issue, or both. The benefits of

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endometrial injury on patients without a history of implantation failed are unclear, and the studies on luteal endometrial injury in this setting have shown conflicting results [20–24]

The objective of our study was to evaluate the effect of luteal endometrial injury in patients undergoing their first or second cycle of IVF.

Materials and methods

Study design and participants

Participants were recruited from May 2013 to May 2015 from three Canadian fertility clinics. The inclusion criteria included: women undergoing their first or second IVF cycle with or without ICSI; age 18–39 years; BMI 18–35 kg/m^2; evaluation of uterine cavity (hysterosalpingogram, sonohysterogram, hysteroscopy) performed in the preceding 24 months; early follicular phase (day 2 or 3) serum FSH evaluated in the preceding 6 months; use of a long GnRH agonist or GnRH antagonist protocol; and documented LH surge 9–11 days before enrolment for patients not pretreated with the oral contraceptive pill or use of the OCP for ≥ 10 days at the time of enrollment. Patients were excluded if they had previously enrolled in this study; had prior early follicular phase FSH level ≥ 12 IU/L; previous poor ovarian response (defined as prior IVF cycle canceled for poor response or ≤ 4 oocytes retrieved); IVF for preimplantation genetic diagnosis or fertility preservation, diabetes mellitus or uncontrolled thyroid disease; abnormal uterine cavity; untreated hydrosalpinx; any contraindication to endometrial biopsy, or if they had office hysteroscopy or other uterine procedure planned or performed during the cycle preceding IVF stimulation; or planned on using surgically retrieved sperm.

Potential participants were identified in the cycle preceding their IVF stimulation. Participants who met the inclusion and exclusion criteria signed informed consent and scheduled for an enrollment visit. This study was approved by The University of British Columbia Clinical Research Ethics Board, Vancouver BC, Canada (#H12-01484) and the Mount Sinai Hospital Research Ethics Board, Toronto ON, Canada (#12-0068-A). The study was registered with Clinicaltrials.gov (NCT01983423).

Randomization and blinding

All patients attended an enrollment visit 5–10 days before FSH initiation. Upon enrollment in the study, patients were immediately randomized to endometrial injury or control groups in a 1:1 ratio, stratified by the study center. The SAS System for Windows was used to generate randomization numbers that were accessed electronically using an encrypted web-based randomization system. The treatment allocation was not blinded.

Endometrial injury

For patient randomized to the endometrial injury group, an endometrial injury was performed immediately using a Pipelle catheter introduced into the uterine cavity. The inner core was withdrawn creating a suction pressure into the hollow core of the cavity which allowed acquisition of endometrial tissue upon rotation within the cavity. This was performed within the office setting without anesthesia. The endometrial sampling was considered adequate if endometrial tissue is deemed adequate for histological assessment by a local pathologist. The endometrial injury was performed between 5–10 days prior to the start of gonadotropin stimulation for controlled ovarian stimulation (Fig. 1). Those in the control group received the usual care without an endometrial injury.

Controlled ovarian hyperstimulation for IVF

Subjects began gonadotropin stimulation within 5–10 days of enrolment per routine procedure at their study center. Study procedures were designed to be flexible to accommodate the range of standard fertility practices used at the various study centers. FSH stimulation with or without LH activity was conducted per study center protocol and

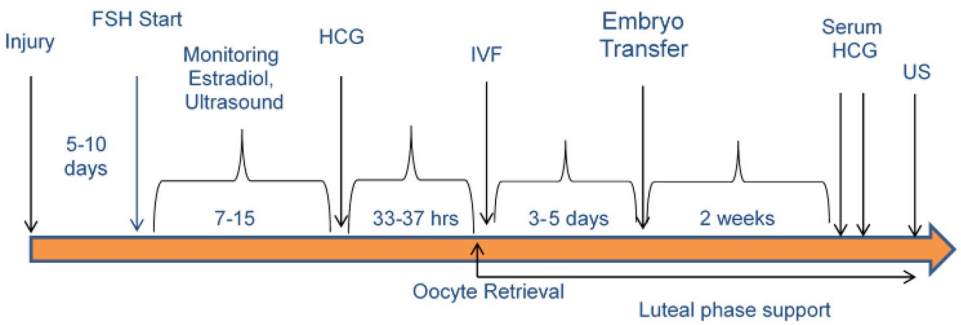

Fig. 1 Timeline for endometrial injury in IVF cycle

either GnRH agonist or antagonist cycles could be used. Figure 1 outlines the study procedures following the start of FSH. Ovarian response was monitored by serial transvaginal ultrasound measurements of follicular diameters, and serum estradiol monitoring. Initial gonadotropin dose and dose adjustments were based on study center protocol. Ultrasound guided oocyte retrieval occurred 36 h after trigger injection. Embryo transfer was performed 3–5 days after oocyte retrieval. Luteal support with progesterone was initiated after oocyte retrieval and continued for at least 17 days depending on initial pregnancy test results.

Outcome measures

The primary outcome was clinical pregnancy rate. Pregnancy status was evaluated on the basis of two sequential hCG blood tests early in pregnancy approximately 2 weeks after the embryo transfer and if positive an ultrasound was booked to confirm viability at approximately 7 weeks gestation. Clinical pregnancy was defined as documented fetal heartbeat approximately 5 weeks after implantation. The clinical pregnancy rate is the number of pregnancies expressed per 100 randomized women. Implantation rate was the number of gestational sacs visualized on ultrasound divided by the total number of embryos transferred. Live birth rate was defined as the number of live births per 100 women randomized (initiated) cycles. A live birth delivery included deliveries that resulted in at least one live birth.

Sample size calculation

The 2008 Canadian ART Registry (CARTR) shows a clinical pregnancy rate of 38% for IVF cycles in Canada. This was used to estimate a 40% clinical pregnancy rate for the control group. A 15% increase in clinical pregnancy rate would be clinically meaningful. The sample size calculation was performed using a one-sided Chi-square test with continuity correction and an alpha of 0.05 assuming a clinical pregnancy rate of 40% in the control group and 55% in the intervention group. A total of 332 subjects (166 in each group) are required to provide an 80% power to detect a clinically meaningful, 15% absolute increase in clinical pregnancy rate.

Statistical analysis

The analysis was performed based on intention-to-treat and per protocol principles for the primary outcome. A one-sided Fisher's exact test was used for differences in clinical pregnancy rate between intervention and control groups. Secondary outcomes and cycle characteristics were analyzed based on intention-to-treat (ITT) principles also using either one-sided Fisher's exact test or Mann–Whitney *U* test where appropriate. Statistical program for the social sciences (SPSS Inc., Version 24) was used for statistical analysis.

Results

This study ended after 2 years with 51/332 patients enrolled due to suboptimal enrollment with 25 subjects in the endometrial injury group and 26 in the control group (Fig. 2—Consort 201 flow diagram). All patients randomized to endometrial injury received the intervention. Two patients from each group did not complete an embryo transfer due to either OHSS or cancelation for poor response. The baseline cycle characteristics were similar between the endometrial injury and control groups including the age of women, duration of infertility, BMI, day 3 FSH as shown in Table 1. Most subjects were undergoing their first IVF cycle [86% (44/51)]. No significant differences were detected in the cycle characteristics comparing the endometrial injury group to the control group for endometrial thickness on day of trigger, initial and total FSH doses, number of oocytes retrieved and proportion having a day 5 embryo transfer (Table 2).

There was no significant difference in clinical pregnancy rates between the endometrial injury and control groups based on both ITT [52% (13/25) versus 46% (12/26); $p=0.45$] and per protocol analysis [52% (12/23) versus 50% (12/24); $p=0.48$] (Table 3).

There were no reported side effects or complications from the endometrial injury procedures.

Discussion

Our study did not find an increase in clinical pregnancy or live birth with luteal endometrial injury in the patients undergoing their first or second IVF cycle. We chose to study patients undergoing their first and second IVF cycle, as many studies show pregnancy rates are similar between patient's first and second IVF cycles; however, most of our patients were undergoing their first IVF cycle.

The benefit of endometrial injury has been shown more consistently in patients with failed IVF cycles [18]. It is possible that a subset of patients has suboptimal endometrial receptivity and implantation. This group may become apparent after failing several IVF cycles; therefore, endometrial injury may have a higher potential to improve pregnancy rates in this selected population. The benefit of endometrial injury cannot be assumed to extend to the routine use for all patients undergoing IVF, especially for patients undergoing their first IVF cycle, and needs to be evaluated independently.

The studies on patients undergoing their first IVF cycle have shown conflicting results. One prospective cohort study

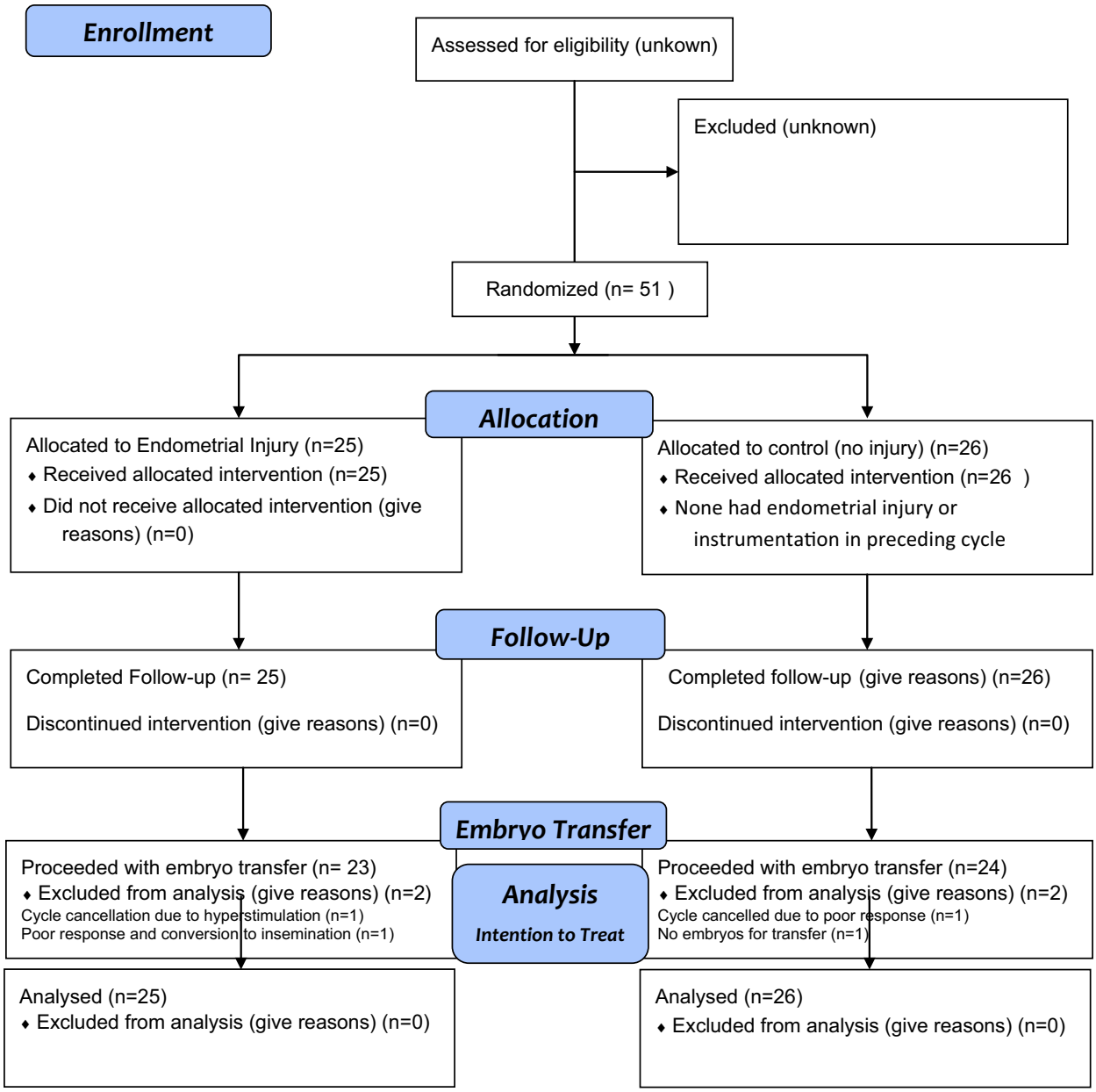

Fig. 2 Consort 2010 flow diagram

Table 1 Baseline characteristics of study participants

Characteristic	Endometrial injury ($n=25$)	Control ($n=26$)
Age in years (range)	33.8 (26–39)	33.4 (27–38)
Duration of infertility (years ± standard deviation)	2.5 ± 2.1	2.4 ± 1.3
BMI (kg/m^2) (mean ± standard deviation)	23.2 ± 3.2	23.5 ± 4.6
Day 3 FSH (IU/L) (mean ± standard deviation)	6.6 ± 2.2	6.5 ± 1.5
First IVF cycle (%)	22 (88)	22 (85)

of 69 patients showed a higher pregnancy rate after endometrial injury [20]. A large RCT of 400 patients showed a higher live birth rate after endometrial injury. However, all the patients (intervention and control) underwent a hysteroscopy in the preceding cycle [22]. Three other RCTs have failed to show a benefit to endometrial injury, although the

Table 2 Cycle characteristics

	Endometrial injury ($n=25$)	Control ($n=26$)	p value
Endometrial thickness (mm)	10.4	10.2	0.72
Initial FSH dose (IU)	241	251	0.42
Total FSH (IU)	2871.5	2989.7	0.76
# oocytes	14.5	12.6	0.39
Day 5 transfer	21/25	21/26	0.5

Table 3 Pregnancy and cycle outcomes

	Endometrial injury $N=25$	Control $N=26$	p value
Clinical pregnancy rate (%)	13/25 (52)	12/26 (46)	0.45
Implantation rate (%)	21/36 (58)	18/40 (45)	0.17
Live birth rate (%)	13/25 (52)	9/26 (35)	0.17
Embryo cryopreservation (%)	17/25 (68)	14/26 (54)	0.39

studies differed slightly from our current study [21, 23, 24]. One study of 100 patients described the study population as good responders, although it was unclear if it was their first IVF cycle [23]. The second study of 142 patients performed two biopsies (in the proliferative and luteal phase in the preceding cycle) [21]. The third RCT included 300 IVF patients, of which 70% were undergoing their first IVF cycle [24]. An open-label, randomized trial of 1360 patients did not find a difference in live birth rates after endometrial biopsy in patients undergoing fresh or frozen embryo transfer or the subgroup analysis of recurrent implantation failure patients [16].

The largest limitation of our study was the low enrollment and sample size. The study was initially powered to include 332 patients; the study was prematurely closed due to slow enrollment. Due to low enrollment, the study may have been underpowered to detect a difference.

Conclusion

Our current study did not detect a benefit of luteal endometrial injury for implantation, clinical pregnancy or live birth in IVF patients. However, the study was underpowered due to low enrollment. In our study, 86% of the patients were undergoing their first IVF cycle. Further larger studies are required to evaluate the benefit of luteal endometrial injury in patients undergoing their first IVF treatment cycle.

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Compliance with ethical standards

Conflict of interest J Hilton: No conflicts to declare except for the study funding. KE Liu: No conflicts to declare except for the study funding. CA Laskin: No conflicts to declare except for the study funding. J Havelock: No conflicts to declare except for the study funding.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by The University of British Columbia Clinical Research Ethics Board, Vancouver BC, Canada (#H12-01484) and the Mount Sinai Hospital Research Ethics Board, Toronto ON, Canada (#12-0068-A).

Informed consent Informed consent was obtained from all individual participants included in the study.

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