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ORIGINAL ARTICLE

The impact of accurately timed mid-luteal endometrial injury in nulligravid women undergoing their first or second embryo transfer

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Abstract

Introduction Endometrial injury or 'scratch' preceding an assisted reproductive therapy (ART) cycle has recently been shown not to improve livebirth rates among women undergoing ART. The objective of this study was to compare pregnancy outcomes in nulliparous women who underwent an accurately timed mid-luteal scratch biopsy prior to ART with those who did not.

Methods This was a prospective cohort study. Women were recruited between October 2016 and February 2018 inclusive. Women who met the inclusion criteria and who did not undergo an endometrial scratch in the study period were used as a comparison group. Patients underwent a cycle of ART in the menstrual cycle following endometrial scratch.

Results Ninety-eight women were eligible for participation in the study. There were no differences in rates of implantation (35.7% ($n = 20/56$) vs. 35.4% ($n = 17/48$); $p = 1.00$), clinical pregnancy (40.0% ($n = 20/50$) vs. 39.5% ($n = 17/43$); $p = 1.00$) or live birth (34.0% ($n = 17/50$) vs. 25.6% ($n = 11/43$); $p = 0.50$) per embryo transfer between those who underwent a scratch and those who did not.

Conclusion Endometrial scratch is a simple, inexpensive and low-risk procedure. However, in this relatively small cohort study, no differences in rates of implantation, clinical pregnancy or live birth in women with primary infertility were determined between those who underwent a scratch and those who did not.

Keywords Endometrial scratch · Endometrium · Pregnancy · Unexplained infertility

Introduction

Embryo implantation is a critical step in the reproductive process and requires a receptive endometrium, a normal functional embryo and a synchronized dialogue between maternal and embryonic tissues [12]. Endometrial receptivity is mediated by complex and coordinated hormonal, cytokine and chemokine signalling pathways that facilitate embryo adhesion during the window of implantation and subsequent endometrial remodelling or 'decidualization' in preparation for pregnancy [3]. Embryo-derived trophoblast cells invade endometrium, initiating a robust pro-inflammatory response reminiscent of 'wound repair' [15].

With the advent of improved embryo characterization and selection techniques in assisted reproductive therapy (ART), including developmental morphokinetics and preimplantation genetic testing [11], there is an acute parallel need for a greater understanding of the endometrial factors that mediate receptivity and embryo implantation.

Implantation failure is being increasingly recognized as a critical factor in infertility and early miscarriage, particularly in couples with idiopathic or unexplained infertility. Persistently modest success rates achieved with in vitro fertilization (IVF) [7], despite marked advances in embryology, likely reflect the fundamental contribution of the maternal endometrium to implantation success.

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Endometrial injury or 'scratch' during the mid-luteal phase preceding an ART cycle has previously been reported to improve embryo implantation rates in women with implantation failure [9]. Biological mechanisms by which endometrial injury has been proposed to improve receptivity include increased local secretion of cytokines and growth factors [4] and enhanced decidualization [18]. Delayed endometrial maturation post-wounding is also proposed to improve subsequent synchronization of endometrial receptivity with embryo implantation, referred to as the 'backwards development theory' [18]. However, a recent multicentre randomized controlled trial of 1364 unselected participants undergoing ART found that endometrial scratch between day 3 of the cycle preceding embryo transfer and day 3 of the embryo transfer cycle did not result in a higher rate of livebirth compared to no intervention among women undergoing IVF ([6]). Two recent systematic reviews and meta-analyses concluded that there was no difference in livebirth in women who underwent a scratch in the cycle prior to their first ART cycle. However, important clinical and statistical heterogeneity, in particular endometrial scratch timing, was still encountered making it impossible to draw firm conclusions [14, 16]. Due to significant heterogeneity in patient characteristics, menstrual cycle stage at the time of endometrial scratch and the mode of injury, further standardized work is required in this area.

Clinical questions yet to be answered regarding endometrial injury include the optimal timing of the biopsy, the mode of injury and whether it should be applied to all patients undergoing ART or solely those with recurrent implantation failure.

The objective of this longitudinal study was to compare pregnancy outcomes in women with primary infertility undergoing an accurately timed mid-luteal endometrial scratch prior to ART with outcomes in women who did not have the procedure.

Materials and methods

Study design and patient recruitment

This prospective cohort study was approved by the medical research and ethics committee at the National Maternity Hospital, Dublin. Women undergoing ART (IVF, ICSI or FET) were recruited at Merrion Fertility Clinic, Dublin, between October 2016 and February 2018 inclusive. The study protocol comprised a transvaginal ultrasonographic assessment of the endometrium by a single trained researcher and endometrial scratch. All participants provided written, informed consent.

Inclusion criteria included age < 38 years, no previous pregnancy (including previous biochemical pregnancy, miscarriage or ectopic pregnancy), regular menstrual cycles (25–35 days), no steroid hormone use within the preceding 3 months, and a normal transvaginal ultrasound scan. Fertility aetiologies (endometriosis, male factor, tubal and unexplained infertility) defined by Zegers-Hochschild et al. [17] were included. Women with recurrent implantation failure (RIF) defined as failure to achieve pregnancy after three consecutive transfers of good-quality embryos [7] were included. Exclusion criteria included smoking, systemic disease and body mass index (BMI) ≥ 30 kg/m^2. Women who met the inclusion criteria but did not undergo an endometrial scratch in the study period were included as a comparison group.

Sample collection

Endometrial tissue was biopsied using a pipelle de Cornier endometrial sampler (*Pipelle*®) by a single trained operator using the manufacturer's instructions. The sampler was inserted through the cervical os and advanced gently to the uterine fundus to a depth of 7 cm. The inner catheter of the device was withdrawn to create suction and then rotated three times in the same direction prior to withdrawal. Samples were taken at a defined stage of the menstrual cycle—mid-luteal, LH+7. Sampling was timed accurately with urinary luteinizing hormone (LH) testing (One Step®, Home Health UK, Herts, UK), assessed by the patient twice daily from day 9 of the menstrual cycle. Matched peripheral blood was collected for serum progesterone hormone assessment. Menstrual cycle stage was confirmed by endometrial scratch biopsy and histological and morphological criteria as assessed by the Department of Histopathology, National Maternity Hospital, Dublin. Patients were followed prospectively and underwent ART treatment in the menstrual cycle following biopsy.

ART cycles

In fresh embryo transfer cycles, patients underwent ovarian stimulation using protocols with a combination of GnRH agonist/GnRH antagonist and recombinant FSH (Gonal F, Merck Serono (Ireland) Limited/Puregon, MSD Ireland (Human Health) Limited) or HMG (Menopur, Ferring Pharmaceuticals Ireland Limited). After oocyte fertilization, embryo quality was assessed by an experienced embryologist on days 3 and 5. Embryo transfer was performed either on day 3 or day 5, depending on embryo quality. Blastocysts were graded as top, good or fair quality according to a modified Garner scale [1]. No more than two embryos were transferred on day 3 or day 5. Surplus suitable blastocysts were cryopreserved. After embryo transfer, patients received luteal-phase support with 90 mg of vaginal progesterone daily (Crinone 8% *w/v*, Merck Serono (Ireland) Limited). Serum β-hCG level was measured 16 days following oocyte retrieval, and an ultrasound scan was performed 2 weeks later if β-hCG levels confirmed pregnancy.

In frozen embryo transfer (FET) cycles, oral estradiol hemihydrate at 2 mg three times per day (Fematab; BGP

Products Ireland Limited) or transdermal E2 (Estradot 50mcg) was commenced on day 1 of the cycle for endometrial preparation. An ultrasound scan was performed after approximately 12 days, and embryo transfer was scheduled when the endometrium was defined as optimal (≥ 7 mm with types 1, 2 or 3 endometrial pattern [5]). Where the endometrium was deemed sub-optimal, the oestrogen dose was increased and the patient was re-scanned 3 to 4 days later. If the endometrial thickness was sub-optimal at this stage, the cycle was cancelled. Progesterone supplementation was introduced 5 days prior to the day of planned embryo transfer. A natural cycle was used in some women who had ovulatory cycles and if medicated approaches had proven unsuccessful, poorly tolerated or were not optimal. In these natural cycles, an ultrasound scan was performed on day 10 of the menstrual cycle and luteinizing hormone (LH) urinary kit testing was commenced once daily when the lead follicle measured or was anticipated to be ≥ 14 mm. A natural cycle was modified by the addition of a hCG trigger of 5000 IU to time ovulation once a follicle of 17 mm was observed or anticipated in the presence of an adequate endometrium.

ART cycle outcomes

ART cycle outcomes were defined as follows: positive pregnancy test (positive beta human chorionic gonadotropin (β-hCG) test) per embryo transfer; implantation rate (number of gestational sacs in utero per number of embryos transferred); clinical pregnancy rate (ultrasonographic visualization of one or more gestational sacs or ectopic pregnancy per embryo transfer); and live birth rate per embryo transfer [17]. Outcomes were analysed separately for all ART cycles, for women who had fresh cycles only, for women who had no previous embryo transfer and for women with unexplained infertility.

Data analysis

Statistical analysis was performed using SPSS version 23.0 software. For comparison of clinical characteristics, parametric tests (independent samples *t* tests and two-way analysis of variance (ANOVA)) and non-parametric tests (Chi-square with Fisher's exact tests and Mann-Whitney *U* test) were used to assess differences between the groups. A p value of < 0.05 was considered statistically significant.

Results

Patient and cycle characteristics

Ninety-eight women were eligible to participate in the study. Of this cohort, 55 women (56.1%, $n = 55/98$) underwent a scratch in the cycle preceding the planned ART cycle. Of these 55 patients, five (9.1%, $n = 5/55$) women did not undergo an embryo transfer in the subsequent cycle and were excluded. Forty-three women (43.9%, $n = 43/98$) did not have an endometrial scratch but underwent a fresh cycle of ART in the subsequent menstrual cycle (Fig. 1).

Patient characteristics of the two groups are outlined in Table 1. All women were nulliparous. There were no significant differences in age, body mass index (BMI), duration of infertility, serum Anti-Müllerian Hormone (AMH) levels or menstrual cycle length. More women in the scratch group had a diagnosis of unexplained infertility (58.0% ($n = 29/50$) vs. 27.9% ($n = 12/43$); $p = 0.006$) and had undergone a previous unsuccessful ART cycle (40.0% ($n = 20/50$) vs. 11.6% ($n = 5/43$); $p = 0.001$). Only two women in the entire cohort (both in the 'no scratch' arm) met the definition of recurrent implantation

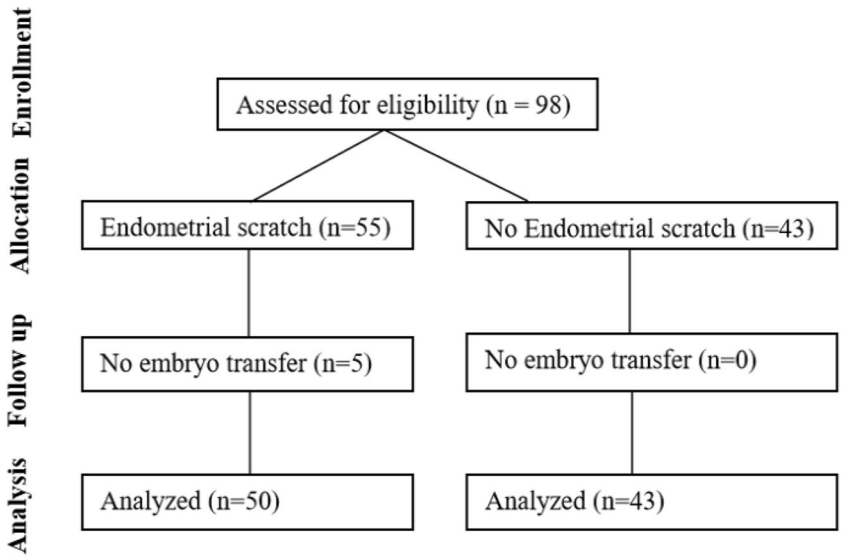

Fig. 1 Eligibility and enrollment to study

Table 1 Patient demographics comparing women who underwent endometrial scratch ($n = 50$) and women who did not ($n = 43$)

Characteristic	Scratch ($n = 50$)	No scratch ($n = 43$)	p value
Age (years)	34.6 (SD 2.1)	34.7 (SD 2.9)	0.85
BMI (kg/m^2)	23.3 (SD 2.7)	23.6 (SD 3.1)	0.62
Duration of infertility (months)	31.8 (SD 18.1)	33.1 (SD 17.3)	0.73
AMH (pmol/L)	18.7 (SD 13.8)	16.7 (SD 10.4)	0.44
Cycle length (days)	29.0 (SD 2.4)	28.8 (SD 1.9)	0.66
Fertility aetiology			
Male factor infertility	13 (26.0%)	18 (41.9%)	0.13
Unexplained infertility	29 (58.0%)	12 (27.9%)	0.006
Endometriosis	7 (14.0%)	12 (27.9%)	0.12
Tubal	1 (2.0%)	1 (2.3%)	1.00
Previous unsuccessful embryo transfers			
None	30 (60.0%)	38 (88.4%)	0.002
One	13 (26.0%)	3 (7.0%)	0.04
Two	7 (14.0%)	0 (0.0%)	0.03
Three	0 (0.0%)	2 (4.6%)	0.24

Values reported are means ± standard deviation in parentheses. All other entries are absolute values and percentages in parentheses

failure [7]. An additional seven (14.0%, $n = 7/50$) women in the scratch group had already had two previous embryo transfers. The majority of women in both groups were undergoing their first or second embryo transfer (90.3%; $n = 84/93$).

ART cycle characteristics are outlined in Table 2. There were fewer fresh cycles performed in the scratch arm of the study (66.0% ($n = 33/50$) vs. 97.7% ($n = 42/43$); $p = 0.0001$). This is consistent with the fact that more of those patients in the scratch group were undergoing their second embryo transfer. There were no other differences between the groups in terms of stimulation protocol, dose of stimulation or endometrial thickness and morphology on ultrasound. The majority (≥ 92%) of embryo transfers were performed at blastocyst stage in both groups (92.0%, $n = 46/50$ vs. 93.0%, $n = 40/43$). Almost 90% in each group had a single embryo transfer (88.0% ($n = 44/50$) vs. 88.4% ($n = 38/43$; $p = 1.00$) and over 90% in each group had at least one top- or good-quality embryo transferred (92.0% ($n = 46/50$) vs. 90.7% ($n = 39/43$); $p = 1.00$).

Table 2 ART cycle characteristics comparing women who underwent endometrial scratch ($n = 50$) and women who did not ($n = 43$)

Variable	Scratch ($n = 50$)	No scratch ($n = 43$)	p value
Fresh cycle	33 (66.0%)	42 (97.7%)	0.0001
Antagonist	9/33 (27.2%)	17/42 (40.4%)	0.33
Recombinant FSH	30/33 (90.1%)	40/42 (95.2%)	0.65
Days of stimulation (gonadotropin)	11.1 (SD 1.8)	10.5 (SD 2.0)	0.13
Total gonadotropin dose (IU)	2690 (SD 1397)	2300 (SD 1463)	0.19
ICSI	19/33 (61.3%)	25/42 (59.5%)	1.00
Frozen embryo transfer (FET) cycle	17/50 (34.0%)	1/43 (2.4%)	0.0001
Hormone Replacement Therapy for FET	15/17 (88.2%)	1/1 (100%)	1.00
Endometrial thickness at OCR/FET schedule	9.8 (SD 1.9)	9.9 (SD 2.3)	0.82
Triple line morphology	50 (100%)	43 (100%)	1.00
Transfer of at least one top quality embryo	17/50 (34.0%)	20/43 (46.5%)	0.14
Transfer of at least one good quality embryo	46/50 (92.0%)	39/43 (90.7%)	1.00
Double embryo transfer	6 (12.0%)	5 (11.6%)	1.00
Day 3 transfer	4 (8.0%)	3 (7.0%)	1.00

*Values reported are means ± standard deviation in parentheses. All other entries are absolute values and percentages in parentheses

ART outcomes

All cycles

Overall, no difference was seen in positive pregnancy test rates (48.0% ($n = 24/50$) vs. 51.2% ($n = 22/43$); $p = 0.84$), implantation rates (35.7% ($n = 20/56$) vs. 35.4% ($n = 17/48$); $p = 1.00$), clinical pregnancy rates (40.0% ($n = 20/50$) vs. 39.5% ($n = 17/43$); $p = 1.00$) and live birth rates (34.0% ($n = 17/50$) vs. 25.6% ($n = 11/43$); $p = 0.50$) per embryo transfer between those who underwent a scratch and those who did not.

Fresh cycle only

When data were analysed by fresh cycle only ($n = 75$), again there were no differences in rates of positive pregnancy test (48.5% ($n = 16/33$) vs. 52.4% ($n = 22/42$); $p = 0.82$), implantation (41.7% ($n = 15/36$) vs. 36.2% ($n = 17/47$); $p = 0.65$), clinical pregnancy (45.5% ($n = 15/33$) vs. 40.5% ($n = 17/42$); $p = 0.81$) and live birth (39.4% ($n = 13/33$) vs. 26.2% ($n = 11/42$); $p = 0.32$) per embryo transfer.

No previous embryo transfer

In women who had no previous embryo transfer ($n = 68$), there were no differences in positive pregnancy test (56.7% ($n = 17/30$) vs. 50.0% ($n = 19/38$); $p = 0.63$), implantation (46.9% ($n = 15/32$) vs. 36.6% ($n = 15/41$); $p = 0.47$), clinical pregnancy (50.0% ($n = 15/30$) vs. 39.5% ($n = 15/38$); $p = 0.46$) and live birth (43.3% ($n = 13/30$) vs. 26.3% ($n = 10/38$); $p = 0.20$) per embryo transfer.

Unexplained infertility

When the subgroup of women with unexplained infertility ($n = 41$) was analysed separately, there were no differences in rates of positive pregnancy test (58.6% ($n = 17/29$) vs. 58.3% ($n = 7/12$); $p = 1.00$), implantation (38.2% ($n = 13/34$) vs. 38.5% ($n = 5/13$); $p = 1.00$), clinical pregnancy (44.8% ($n = 13/29$) vs. 41.7% ($n = 5/12$); $p = 1.00$) or live birth (37.9% ($n = 11/29$) vs. 25.0% ($n = 3/12$); $p = 0.49$) per embryo transfer.

No complications were reported in any women who underwent an endometrial scratch. The cohort with recurrent implantation failure (2.2%, $n = 2/93$) was too small to justify separate analysis.

Discussion

This prospective longitudinal study found no differences in implantation rates, clinical pregnancy rates or live birth rates per embryo transfer when endometrial scratch was performed in the mid-luteal phase preceding an ART cycle in women with primary infertility undergoing their first or second embryo transfer. Furthermore, there were no differences in any outcome when analysed separately for women with unexplained infertility or those undergoing only a fresh cycle.

The effect of endometrial scratch has been described in five systematic reviews and meta-analyses to date [2, 8, 9, 14, 16]. Although the initial three meta-analyses suggested benefit, more recent meta-analyses have reported no difference in ongoing pregnancy or live birth rates. However, they have all concluded that well-conducted trials of endometrial scratch in defined patient populations are required due to significant clinical heterogeneity in the studies to date, in particular in relation to timing of endometrial scratch (Table 3).

The most recent study reported is a multi-centre, open-label, randomized trial that was conducted between June 2014 and June 2017 in 13 centres across five countries. Endometrial scratching was not associated with any improvement in livebirth rate (26.1% ($n = 180/690$) vs. 26.1% ($n = 176/674$), OR = 1.00 (0.78 to 1.27)). Subgroup analysis did not identify any subpopulations that may benefit from endometrial scratching; there was no evidence of a benefit in women with RIF or undergoing their first ART cycle, undergoing fresh or frozen cycles. Subgroup analysis did not show any impact of the timing of endometrial biopsy on livebirth rate (day 3 of the cycle preceding embryo transfer to day 3 of the embryo transfer cycle) [6].

Strengths of our study include its prospective study design. Endometrial scratch was performed once in the mid-luteal phase by a single operator. Unlike previously published work, the menstrual cycle stage was accurately timed and confirmed using serum progesterone and by histological assessment. While previous work, including the recent multi-centre trial by Lensen et al. [6], showed no effect of the cycle stage at which the biopsy was performed, profound morphological and biochemical changes occur in the endometrium throughout the menstrual cycle and it is important to exclude this as a possible confounding variable. We also limited inclusion to women with primary infertility aged less than 38 years. We excluded any women who had previously conceived, as implantation failure can be associated with an aberrant gene expression profile compared to fertile controls [13]. Additionally, endometrial function is different in multiparous and nulliparous women and pathologies thought to be associated with an altered immune response, such as pre-eclampsia, show very different patterns in multiparous and nulliparous women.

Limitations of our study include the fact that patients were not randomized and the relatively small study sample size. However, it did study the effect of offering a scratch program in a clinical rather than a research setting and is therefore important for general clinical practice. Our study adds to the

Table 3 Systematic reviews and meta-analyses addressing benefit of endometrial scratch prior to ART

Author	Randomized trials	Non-randomized trials	Quality of evidence	Number of patients	Pregnancy rate (RR)	Inclusion criteria	Day of cycle
El-Toukhy [2]	2	6	Variable	193	Clinical pregnancy rate 2.63 (95% CI 1.39–4.96)	Variable	D5 preceding to D7 of IVF cycle
Potdar [9]	2	2	Good	444	Clinical pregnancy rate 2.32 (95% CI 1.72–3.13)	Variable	D7–26 of preceding cycle
Nastri [8]	9	0	Moderate	1496	Ongoing pregnancy rate 1.42 (95% CIC 1.08–1.85)	Variable	D7 preceding to D7 of IVF cycle
Vitagliano [16]	7	0	Not reported	1354	Ongoing pregnancy rate/Livebirth rate 0.99 (95% CI 0.57–1.73)	First embryo transfer cycles. Variable patient and cycle demographics	Follicular or luteal phase (untimed) in preceding cycle
van Hoogenhuijze et al. [14]	2	0	Moderate	227	Livebirth rate 0.95 (95% CI 0.64–1.41)	First embryo transfer cycles. Variable inclusion criteria	7–14 days prior to ovarian stimulation

accumulating data suggesting that, notwithstanding its potential effect on those with RIF, there is certainly unlikely to be a benefit in performing a scratch for those undergoing their first or second embryo transfer. Another limitation of our study is that embryos were not assessed for aneuploidy. However, in the vast majority of patients, only good- and top-quality blastocyst stage embryos were transferred, predominantly as single embryo transfers. Finally, although there was a higher number of FET cycles in the scratch arm of this study, which may impact our study homogeneity, a recent multicentre randomized trial of 2157 ovulatory women reported no difference in live birth rates between fresh and frozen embryo transfer cycles (48.7% and 50.2%, $p = 0.50$) [10].

Endometrial scratch is a simple, inexpensive and low-risk procedure. However, in this relatively small cohort, no differences were found in rates of implantation, clinical pregnancy or ongoing pregnancy rates in women with primary infertility undergoing their first or second embryo transfer. This study adds to the growing evidence of similar results from international RCTs in recent years, and contributes new information by controlling for any possible effect of cycle stage at the time of biopsy or an impact of previous pregnancy.

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Compliance with ethical standards

This prospective cohort study was approved by the medical research and ethics committee at the National Maternity Hospital, Dublin. All participants provided written, informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

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