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ASSISTED REPRODUCTION TECHNOLOGIES

Effect of endometrial mechanical stimulation in an unselected population undergoing in vitro fertilization: futility analysis of a double-blind randomized controlled trial

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Abstract

Purpose Implantation failure is a major limiting factor of successful in vitro fertilization (IVF). The objective of this study was to determine if endometrial mechanical stimulation (EMS) by endometrial biopsy in the luteal phase of the cycle prior to embryo transfer (ET) improves clinical outcomes in an unselected subfertile population.

Methods Double-blind, randomized controlled trial of EMS versus sham biopsy and odds of clinical pregnancy after IVF and embryo transfer. Secondary outcomes included spontaneous miscarriage and live birth.

Results One hundred women enrolled and were randomized from 2013 to 2017. Enrollment was terminated after futility analysis showed no difference in clinical pregnancy between EMS versus control, 47.2% vs 61.7% (OR 0.55, 95% CI 0.25–1.23, $p = 0.15$). There were no significant differences between women who underwent EMS and those who did not in terms of positive pregnancy test 54.7% vs 63.8% (OR 0.69, 95% CI 0.31–1.53, $p = 0.36$), miscarriage 7.5% vs 2.1% (OR 3.76 95% CI 0.41–34.85, $p = 0.22$), or live birth 43.4% vs 61.7% (OR 0.48 95% CI 0.21–1.06, $p = 0.07$).

Conclusions EMS in the luteal phase of the cycle preceding embryo transfer does not improve clinical outcomes in an unselected subfertile population and may result in a lower live birth rate. We caution the routine use of EMS in an unselected population.

Keywords Endometrial mechanical stimulation · Endometrial injury · Endometrial scratch · Embryo transfer · In vitro fertilization · Assisted reproductive technology

Introduction

Embryo implantation failure is a major limiting factor of successful IVF [1]. Implantation is a complex process requiring precise molecular interactions between the embryo and endometrium [2]. Efforts to improve implantation have focused largely on embryonic factors [3]. Little is known to improve endometrial receptivity [4].

Intentional mechanical damage to the endometrium induced via biopsy or curettage, otherwise known as endometrial "scratch" or EMS, has been proposed as a tool to improve endometrial receptivity [5, 6]. Suggested mechanisms induced by local injury to the endometrium and subsequent healing include inflammation and neoangiogenesis resulting in the upregulation of cytokines, adhesion molecules, and growth factors necessary for embryo implantation as well as improved stromal cell decidualization [6, 7].

Previous work suggests EMS may improve implantation and pregnancy rates in women with recurrent implantation failure (RIF) or prior failed cycles [3, 8–11]. Subsequently, some providers have extended EMS to the general subfertile population. However, heterogeneity in study design, small

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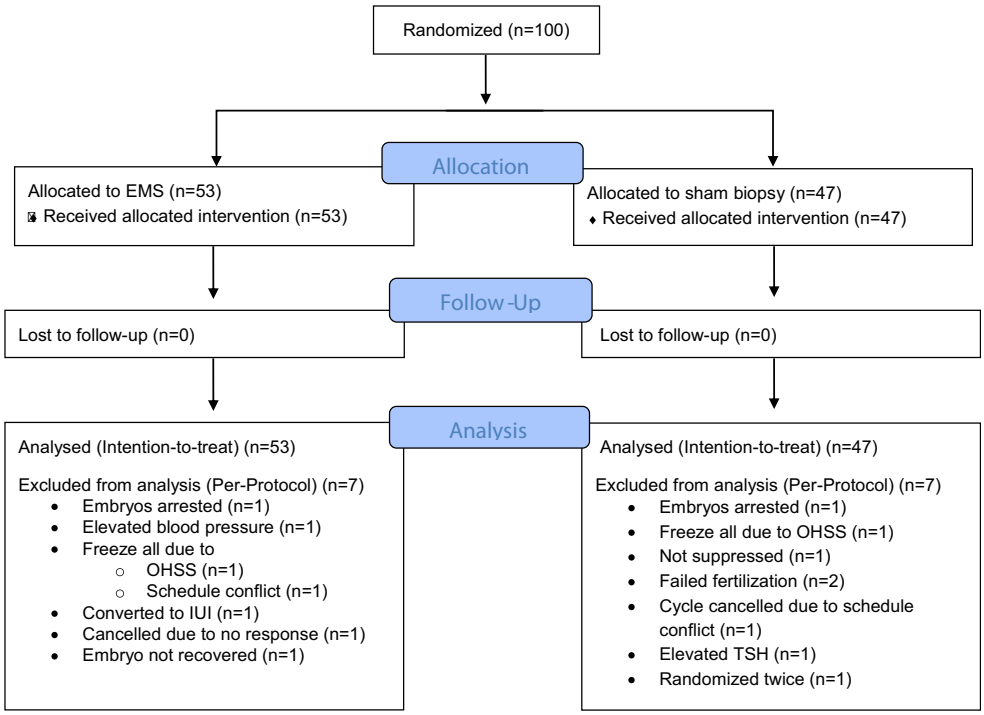

Fig. 1 CONSORT flow diagram

numbers, lack of defined intervention, and inclusion criteria limit the significance and generalizability of prior studies [12]. Moreover, there is limited, and conflicting evidence of the role of EMS in the general subfertile population undergoing IVF [13, 14].

The purpose of this study was to determine if EMS by endometrial biopsy in the luteal phase of the cycle prior to embryo transfer improves the likelihood of clinical pregnancy in an unselected subfertile population. We hypothesized that EMS would result in improved likelihood of clinical pregnancy in an unselected population.

Materials and methods

Study design and participants

Washington University Institutional Review Board (IRB) approved this protocol (IRB ID#201211094). This prospective, double-blind, randomized controlled trial was conducted at a single academic institution. Subjects were enrolled from September 2013 to July 2017. Written informed consent was obtained from each subject prior to randomization. Inclusion criteria were women 18–43 years of age undergoing a fresh or frozen embryo transfer. Women with an abnormal endometrial cavity evaluation or those undergoing third party reproduction cycles were excluded. Subjects planning to undergo IVF and an embryo transfer were screened for inclusion and approached for enrollment.

Randomization and blinding

A computer generated block randomization model was utilized for the randomization schema. Successfully recruited subjects were randomized via consecutively numbered sealed opaque envelopes to the intervention arm (EMS) or to the control arm (sham biopsy) at the time of consent. Both the patient and the clinician performing the embryo transfer were blinded to the randomization arm. The clinician performing EMS or sham biopsy was not blinded.

Description of the intervention

In subjects randomized to the intervention arm, EMS was performed via a standardized technique using an endometrial biopsy pipelle catheter (Endocell™ Trumbull, CT). The cervix was cleansed with betadine, and the pipelle catheter was inserted through the cervix to the fundus. The plunger was then withdrawn to create suction. The sheath was rotated and the pipelle was gently moved up and down three to four times, up to two passes to ensure adequate endometrial tissue was obtained.

Subjects in the control arm underwent a sham biopsy via a standardized technique. The cervix was cleansed with betadine. The biopsy pipelle was then inserted into the posterior fornix and plunger withdrawn. The pipelle was then gently moved up and down behind the cervix three to four times. The pipelle was specifically not inserted into the cervix or uterus. Providers were instructed not to use a tenaculum with either approach.

Table 1 Demographic and clinical characteristics of study participants

Variables	Intervention ($n = 53$)	Control ($n = 47$)	p value
Age (years): mean (SD)	33.57 (3.92)	33.89 (3.61)	0.66
BMI (kg/m^2): mean (SD)	28.3 (7.4)	28.8 (6.3)	0.68
Protocol (%)			0.05
FET	1 (2.2)	6 (12.8)[a]	
Antagonist	5 (9.4	8 (17)	
Long agonist	42 (79.2)	32 (68.1)	
Flare	5 (9.4)	1 (2.1)	
Cycle number			0.21
1	39 (73.6)	27 (57.4)	
2	8 (15.1)	13 (27.7)	
≥ 3	6 (11.3)	7 (14.9)	
Diagnosis (%)			0.65
Unexplained	11 (20.8)	12 (25.5)	
Ovulatory dysfunction	8 (15.1)	7 (14.9)	
Tubal factor	6 (11.3)	5 (10.6)	
Male factor	13 (24.5)	11 (23.4)	
PCOS	11 (20.8)	6 (12.8)	
Recurrent pregnancy loss	0	1 (2.1)	
Endometriosis	2 (3.8)	5 (10.6)	
Diminished ovarian reserve	2 (3.8)	0	
Prior live birth (%)			0.55
Yes	14 (26.4)	10 (21.3)	
No	29 (73.6)	37 (78.7)	

[a] Two underwent PGT-A

If patients were on oral contraceptive pills for their IVF cycle, the procedure was scheduled anytime during the last 7 days or up until 1 day after their pills were discontinued of the cycle prior to embryo transfer. If patients were not on oral contraceptive pills, patients were instructed to check for a luteinizing hormone surge and the procedure was scheduled for 7–13 days following in the cycle prior to embryo transfer.

Statistics

A 20% effect size was determined to be clinically significant based on prior findings [9]. Sample size calculation determined 100 subjects were required in each arm using a power of 0.8 and two-sided alpha of 0.05 while accounting for a 5% drop-out or lost to follow up rate. Four years into the study 100 women were randomized. Due to challenges with

Table 2 Cycle level characteristics

Variables	Intervention ($n = 53$)	Control ($n = 47$)	p value
Peak estradiol (pg/mL), mean (SD)	2744 ± 973	2682 ± 1020	0.78
Total gonadotropin (U, mean (SD)	2879 ± 1389	2673 ± 956	0.47
Days of stimulation, median (IQR)	10 (6–12)	9 (7–14)	0.18
AMH (ng/mL), mean (SD)	4.29 ± 2.84	3.67 ± 2.48	0.32
Antral follicle count, median (IQR)	34 (22–45)	30 (22–35)	0.21
Day of embryo transfer (%)			0.93
3	20	17	
5	26	23	
Average number of embryos transferred[a]	1.9	2.1	0.63

[a] Average out of subjects who had an embryo transfer

Table 3 Comparison of outcomes between groups with intention-to-treat analysis

Variables	Intervention, $n = 53$ (%)	Control, $n = 47$ (%)	OR	95% CI	p value
Pregnancy test	29 (54.7)	29 (61.7)	0.75	0.31–1.53	0.48
Clinical Pregnancy	25 (47.2)	28 (59.6)	0.61	0.27–1.34	0.22
Miscarriage rate	4 (7.5)	1 (2.1)	3.76	0.41–34.85	0.22
Live birth	23 (43.4)	28 (59.6)	0.52	0.24–1.15	0.12

adequate recruitment, a futility analysis was conducted outside of the planned analysis for the primary outcome using the O'Brien-Fleming approach to determine if study enrollment could be stopped.

Data analysis included both an intention-to-treat and per-protocol approach. Appropriate bivariate statistics were used followed by multivariable logistic regression models to control for potential confounders within subgroup analyses. A p value < 0.05 was considered statistically significant. Analyses were performed in SAS version 9.4 and SPSS version 19.0.

Results

One hundred subjects were recruited and enrolled between September 2013 and July 2017 (Fig. 1). Fifty-three subjects were randomized to the intervention arm, and 47 to the control group. No patients were lost to follow up. Fourteen subjects ultimately did not undergo embryo transfer, seven in each group. One patient was excluded after being randomized twice. The decision boundaries for the O'Brien-Fleming analysis were to accept the null and stop the study if the z test statistic was $-0.92 < z < 0.92$. The z test statistic resulted as $z = 0.15$ and was within pre-set stopping boundaries. Baseline characteristics were similar amongst the two groups (Table 1). Cycle level factors were similar between the two groups (Table 2). Baseline characteristics and cycle level factors were representative of the general IVF population in our clinic.

Using an intention-to-treat approach, there were no statistically significant differences between the two groups when comparing EMS versus the control group in terms of positive pregnancy test 54.7% versus 63.8% (odds ratio (OR) 0.69, 95% confidence interval (CI) 0.31–1.53, $p = 0.36$), clinical pregnancy 47.2% versus 61.7% (OR 0.55, 95% CI 0.25–1.23, $p = 0.15$), miscarriage 7.5% versus 2.1% (OR 3.76 95% CI 0.41–34.85, $p = 0.22$), or live birth 43.4% versus 61.7% (OR 0.48 95% CI 0.21–1.06, $p = 0.07$) (Table 3). Implantation rate was calculated using chi-square for equality of proportions and was noted to be lower in the EMS group, but not statistically significantly different than the control group, 33% vs 47% ($p = 0.09$). Analysis with a per-protocol approach including only patients that underwent an embryo transfer yielded similar results when comparing EMS versus sham biopsy in terms on clinical pregnancy, miscarriage and live birth rate (Table 4).

Stratified analysis was then performed to examine subjects undergoing their first IVF cycle versus those with a prior failed cycle. With an intention-to-treat approach, there were no significant differences noted in any of the outcome variables amongst patients undergoing their first IVF cycle (Table 5). After controlling for age, BMI and prior live birth EMS was not associated with likelihood of clinical pregnancy (OR 0.47, 95% CI 0.17–1.35, $p = 0.16$) or live birth (OR 0.39, 95% CI 0.91–1.06, $p = 0.08$). For patients with a prior failed cycle, an intention-to-treat analysis revealed no significant differences between groups in any of the outcome measures (Table 6). After controlling for age, BMI and prior live birth EMS was not associated with likelihood of clinical pregnancy (OR 0.33 95% CI 0.06–1.67, $p = 0.18$).

Sensitivity analysis was performed to restrict to subjects undergoing a fresh embryo transfer. There were no significant differences between the two groups when comparing EMS versus the control group in terms of positive pregnancy test 55.8% versus 58.5% (OR 0.89, 95% CI 0.39–2.04, $p = 0.79$), clinical pregnancy 48.1% versus 56.1% (OR 0.73, 95% CI 0.32–1.65, $p = 0.44$), miscarriage 7.7% versus 2.4% (OR 3.33, 95% CI 0.36–31.03, $p = 0.38$), or live birth 44.2% versus 56.1% (OR 0.62, 95% CI 0.27–1.42, $p = 0.26$).

Table 4 Comparison of outcomes between groups with per-protocol analysis (subjects who had an embryo transfer)

Variables	Intervention, $n = 46$ (%)	Control, $n = 40$ (%)	OR	95% CI	p value
Pregnancy test	29 (63.0)	29 (72.5)	0.65	0.26–1.62	0.35
Clinical pregnancy	25 (54.3)	28 (70.0)	0.51	0.21–1.24	0.14
Miscarriage	4 (8.7)	1 (2.4)	3.81	0.41–35.56	0.21
Live birth	23 (50.0)	28 (70.7)	0.43	0.18–1.04	0.06

Table 5 Comparison of outcomes between groups in subjects undergoing their first IVF cycle

Variables	Intervention, $n = 39$(%)	Control, $n = 27$(%)	OR	95% CI	p value
Pregnancy test	24 (61.5)	19 (70.4)	0.67	0.24–1.92	0.46
Clinical pregnancy	21 (53.8)	19 (70.4)	0.49	0.17–1.39	0.18
Miscarriage	4 (10.3)	0	–	–	0.14
Live birth	19 (48.7)	19 (70.4)	0.4	0.14–1.13	0.08

Comment

The effect of EMS on endometrial receptivity has been studied for over a decade. It has been suggested that local endometrial injury in the cycle prior to ovarian stimulation in IVF facilitates cytokines, growth factors, and upregulation of gene expression related to enhanced endometrial receptivity that may improve embryo implantation but evidence is lacking [6, 15]. Additional findings suggest that controlled ovarian stimulation performed during assisted reproductive technology abnormally advances the endometrial maturation, and thus EMS performed in the cycle preceding IVF may lead to better synchronicity between the endometrium and transferred embryo [16, 17]. Our findings demonstrate no improvement in clinical outcomes in terms of clinical pregnancy, spontaneous miscarriage rate or live birth rate with EMS in an unselected subfertile population undergoing IVF.

The first study to investigate EMS and clinical pregnancy with IVF was conducted in 2003 by Barash et al. This initial prospective, non-randomized controlled trial of women with one or more previous failed IVF cycles demonstrated a two-fold increase in live birth rates following endometrial injury compared to the control group [18]. Subsequent randomized controlled trials in women with recurrent implantation failure (RIF) also demonstrated improved implantation, clinical pregnancy, and live birth rates; however, these studies were limited by lack of a well-defined primary outcome [9, 19, 20]. One study was terminated early after noting a 20.3% improvement in clinical pregnancy in an unselected subfertile population after EMS via Pipelle biopsy in the luteal phase prior to transfer [20]. Early termination after and unplanned interim analysis may have resulted in an overestimation of the effect of treatment and ultimately an underpowered study. Recent systematic reviews and meta-analyses concluded that EMS in the cycle prior to IVF may improve IVF success, but as noted above, many of the studies included have been criticized due to lack of standardized inclusion criteria, heterogeneity and timing of the intervention, poorly defined primary outcomes, limited live birth outcomes, and overall lack of power to draw reliable conclusions [3, 8, 11, 12].

In contrast, more recent randomized controlled trials have failed to detect a clinical benefit from EMS in women with previous failed IVF cycles and in a general subfertile population, which is consistent with the findings in our current study [10, 13, 21]. In an adequately powered randomized control trial by Yeung et al., 300 women in an unselected, subfertile population were randomized to EMS or no EMS via Pipelle biopsy in the luteal phase of the cycle preceding IVF. In this study, 69.7% of women included were undergoing their first IVF cycle, and 30.3% of subjects were undergoing a repeat IVF cycle. When comparing EMS to no EMS, there was no significant difference in ongoing pregnancy rates (26.7% versus 32%), implantation rate (32.8% versus 29.7%), clinical pregnancy (34% versus 38%), miscarriage rates (30.3% versus 18.6%), or live birth rate (26% versus 32%) [13]. Subgroup analysis of women undergoing their first embryo transfer showed no significant difference between groups [13]. In women undergoing repeated cycles Yeung et al. did note a significantly lower ongoing pregnancy rate in the EMS group which was similar to our findings, however the study was not powered for subgroup analysis. Despite the limitations of prior work and lack of evidence for its broader application, EMS has been extended to the general population of women undergoing IVF and advertised to improve implantation rates.

There are some limitations to the current study. It was not powered to make comparisons within the subgroup analyses. Only 33 patients had a prior failed cycle. Of these we noted a 13.5% lower live birth rate in the EMS arm versus the control arm, which is in contrast to prior findings. Additionally, the

Table 6 Comparison of outcomes between groups in subjects with a prior failed cycle

Variables	Intervention, $n = 14$ (%)	Control, $n = 19$ (%)	OR	95% CI	p value
Pregnancy test	5 (35.7)	9 (47.4)	0.62	0.15–2.55	0.5
Clinical pregnancy	4 (28.6)	8 (42.1)	0.55	0.13–2.4	0.42
Miscarriage	0	1 (5.3)	–	–	–
Live birth	4 (28.6)	8 (42.1)	0.55	0.13–2.4	0.42

majority of patients were undergoing their first cycle and a fresh cycle which may limit generalizability. Two patients underwent PGT-A, both of which were in the control arm; one had a negative pregnancy test, and one had a live birth. Similarly, six patients underwent a frozen embryo transfer in the control arm, versus only one in the intervention arm contributing to the near significant difference in protocols between the two groups ($p = 0.05$). Of these, two were the subjects that had PGT-A performed with the aforementioned outcomes, and the other four all had live births. To address this, sensitivity analysis was performed restricting to fresh cycles only and demonstrated no significant differences in clinical outcomes. The difference in live birth rate was less significant when restricted to fresh cycles with an 11.9% difference in live birth favoring the control arm compared to the 18.3% difference noted in the intention-to-treat approach including both fresh and frozen cycles. This difference should be taken into consideration when interpreting our results.

Strengths of this work include the prospective, double-blind, randomized controlled design. The use of a sham biopsy and blinding of the patient and physician performing the embryo transfer served to prevent potential selection and reporting bias. Our intervention and inclusion criteria were well defined. Unlike previous studies, we report live birth. While the difference in positive pregnancy test was less than 10% amongst the two groups, clinical pregnancy and live birth rate were 14.5% and 18.3% lower respectively in the intervention arm, and would suggest that potential harm from EMS must be considered. Although it was an unplanned analysis due to difficulty with recruitment, use of a futility analysis at 50% enrollment enabled us to terminate enrollment early while minimizing the risk of type I error, conserving our overall power and reducing unnecessary exposure and potential risk of the intervention in additional subjects [22, 23]. Subjects were approached in a standardized fashion by a trained research coordinator. Enrollment was slower than anticipated and was largely based on subject's lack of interest in participating as this was not designed as an opt-out intervention. Subjects did not state a specific reason for lack of interest in participating.

It is important to identify strategies for improving embryo implantation for all women undergoing IVF. While work in specific populations of women may demonstrate benefit for EMS, our findings argue against the routine use of EMS prior to ET.

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Compliance with ethical standards

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

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