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# Local endometrial injury in women with failed IVF undergoing a repeat cycle: A randomized controlled trial

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ABSTRACT

*Objective:* To evaluate the effectiveness of local endometrial injury in women undergoing *in vitro* fertilization (IVF) with at least one previous unsuccessful attempt.
*Study design:* Randomized controlled trial. Recruited women were randomized into two groups. In group A (pipelle group), women underwent pipelle biopsy twice in the luteal phase in the cycle prior to IVF. In group B (control), women did not undergo any intervention prior to IVF. The primary outcome was clinical pregnancy rate. The secondary outcomes included live birth, miscarriage, multiple pregnancy and preterm delivery rates.
*Results:* One hundred and eleven women were included in the study with 55 in the pipelle group and 56 in the control arm. The baseline clinical characteristics were similar in both groups. The clinical pregnancy rates were not significantly different between pipelle and control group (34.09% *vs.* 27.65%; Odds ratio, OR 1.35, 95% confidence interval, CI 0.55–3.30). The live birth (31.81% *vs.* 25.53%; OR 1.36, 95% CI 0.55–3.39), multiple pregnancy (33.33% *vs.* 61.54%; OR 0.31, 95% CI 0.07–1.47), miscarriage (6.66% *vs.* 7.69%; OR 0.86, 95% CI 0.05–15.23) and preterm delivery rates (35.71% *vs.* 66.66%; OR 0.28, 95% CI 0.05–1.4) were also not significantly different between the two groups.
*Conclusion:* Current study did not find any improvement in IVF success rates following endometrial injury in woman undergoing IVF after previous failed attempt.



## Introduction

Embryo implantation remains the rate limiting step for success in *in vitro* fertilization (IVF) cycle. Even after euploid embryos are transferred following pre implantation genetic screening (PGS), the reported implantation rates are between 67 and 75% [1]. In vivo, "the cross talk" between developing embryo and endometrium through interleukins (IL), growth and immunosuppressive factors facilitates the process of implantation, but *in vitro* culture conditions during IVF preclude any such interactions [2]. These various autocrine and paracrine factors have been shown to help in implantation by inducing favorable endometrial gene expressions [3].

Local endometrial injury or scratching is defined as an intentional damage to the endometrium in women undergoing IVF [4]. This injury can be achieved by pipelle biopsy or by curetting and can be performed in an outpatient clinic with minimal analgesia.

It has been hypothesized the endometrial injury and subsequent healing is associated with increased secretions of cytokines, IL and growth factors which favor implantation process [5]. It is hypothesized that controlled ovarian hyperstimulation (COH) during IVF leads to endometrial advancement [6]. The local endometrial injury performed in the preceding cycle may retard endometrial maturation resulting in better synchronicity between transferred embryo and endometrium [7].

Initial prospective study published by Barash et al., found two fold increase in live birth rate following endometrial injury compared to no intervention in women with one or more previous failed IVF [8]. Subsequently few smaller randomized trials were published which included women with previous IVF failures and

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they reported possible benefit of endometrial injury prior to IVF cycle [9,10]. In contrast, recent studies did not find benefit of endometrial injury in women with previous IVF failures [11,12]. A systematic review which included only women with unexplained recurrent implantation failure (RIF) suggested improved pregnancy rates following local endometrial injury after pooling results from four randomized and three non-randomized trials [13]. The recent Cochrane update found improved live birth and clinical pregnancy rates following endometrial injury in women with more than two previous embryo transfers [14]. However, there have been continuing concerns regarding quality of studies included in many of these systematic reviews [15].

We planned a randomized controlled trial to evaluate the role of local endometrial injury in women with at least one previous unsuccessful IVF.

## Materials & methods

### *Study design and participants*

This randomized controlled trial was conducted in Reproductive Medicine Unit of a university level hospital between April 2008 and April 2015. Eligible women were invited to participate in the trial, and those who were willing, were recruited for the study after taking a written informed consent. The trial was approved by Institutional Review Board and was registered under Clinical Trial Registry (CTRI/2013/003564). The current study included those women who were undergoing IVF with at least one previous failed cycle with minimum of two good quality embryos (cleavage or blastocyst stage) transferred in an earlier attempt. Women with (i) age $\leq$38 years; or (ii) body mass index (BMI) $\leq$29 kg/m$^{2;}$ or (iii) Follicle Stimulating Hormone level of $<$10 mIU/ml were included. Women with (i) Previous poor response $<$3 oocytes retrieved in previous cycle; or (ii) Local endometrial pathology; or (iii) Uterine malformations; or (iv) Severe endometriosis; or (v) Gross adenomyosis; or (vi) Those with systemic disease such as autoimmune disorders were excluded.

### *Randomization and blinding*

For randomization, computer generated sequence was generated in blocks of ten by department of Biostatistics. Eligible women entering the trial were randomly allocated during luteal phase of preceding cycle to either group A or B by opening consecutively

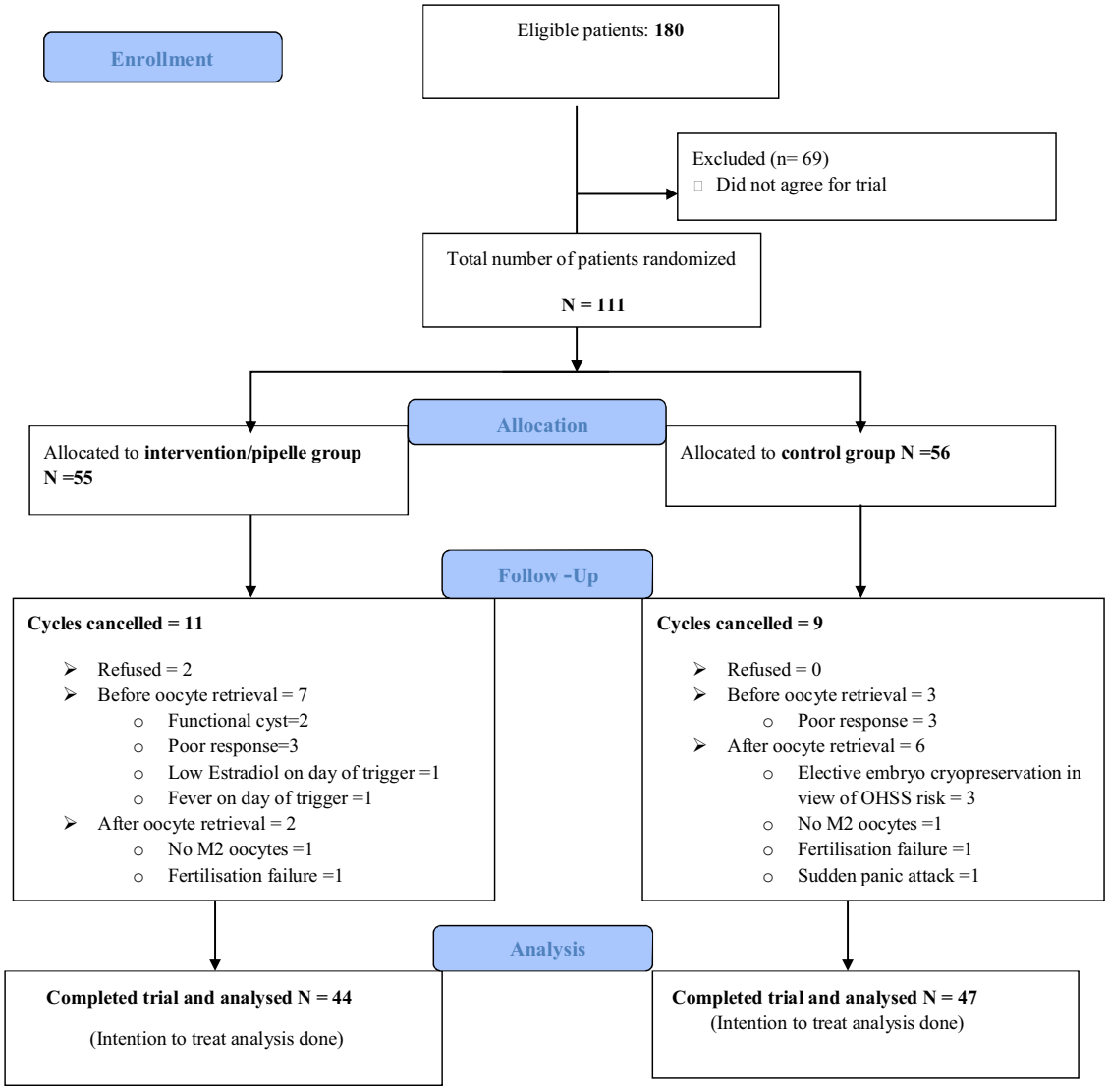


**Fig. 1.** CONSORT flow diagram.

numbered sealed opaque envelops. In group A, in addition to standard IVF protocol, women underwent pipelle biopsy twice within forty eight hours in the luteal phase prior to starting controlled ovarian hyperstimulation (COH). In group B, standard IVF protocol was followed with no additional procedure in the cycle prior to COH. Since no additional intervention was performed in control group, patient and clinician were not blinded.

*IVF protocols*

For standard agonist protocol, daily dose of Gonadotrophin releasing hormone (GnRH) agonist, 0.5 mgs subcutaneously (Lupride, Sun pharmaceuticals, Gujarat, India) was started from mid luteal phase of preceding cycle and after 10 days, down regulation was confirmed by hormonal levels and ultrasound. Once downregulation was confirmed, COH was started from day one of menstrual cycle with 150–300 IU of recombinant FSH (Recagon, Organon, Dublin, Ireland) and follicular monitoring done. When at least three follicles >17 mm developed, 5000 IU of Inj. Human Chorionic Gonadotrophin (hCG) (Pregnyl, Organon, Dublin, Ireland) was administered and oocyte retrieval was planned after 35 h post hCG trigger. Between one to three embryos were transferred at either cleavage or blastocyst stage. Micronized progesterone, 400 mgs, twice a day, intravaginally (Naturogest, German remedies, Mumbai, India) along with intramuscular progesterone, 100 mgs (Gestone, Ferring, Mumbai, India) twice weekly, was given for luteal support.

For antagonist protocol, recombinant FSH was used for COH from day two-three of menstrual cycle and multiple dose flexible protocol was followed for antagonist administration. GnRH antagonist, 0.25 mgs (Ganirelix, Organon, Dublin, Ireland) was started once lead follicle size was 14 mm and continued till trigger day.

For flare protocol, GnRH agonist, 1 mgs (Leupride, Sun pharmaceuticals, Gujarat, India) was started from day one of menstrual cycle for three days and subsequently dose was reduced to 0.5 mgs until the day of trigger while COH was simultaneously initiated by day three.

For ultralong protocol, monthly GnRH depot, 3.75 mgs, intramuscular (Leuprolide depot, Sun pharmaceuticals, Gujarat, India) preparation was used three months prior to IVF for pituitary down regulation. As in the case of long agonist protocol, down regulation was confirmed by hormonal assay and ultrasound before initiating COH.

The serum beta hCG level was checked on day 18 after oocyte retrieval. In case of positive pregnancy test (>5 miu/ml), a transvaginal ultrasound was done after two weeks to record presence of intrauterine gestational sac and the numbers.

The pregnancy was followed up and birth details were obtained from hospital records, telephonically and email.

*Outcome measures*

The primary outcome was clinical pregnancy rate defined was as evidence of gestational sac on ultrasound. Secondary outcomes

**Table 1**
Baseline comparisons between study groups.

| Variables | Intervention group n = 55 | Control group n = 56 | P value |
|---|---|---|---|
| Age: years- Mean (SD) | 31.35(4.20) | 32.02(3.19) | 0.3 |
| BMI:kg/m$^2$- Mean (SD) | 25.37(4.04) | 24.64(3.17) | 0.2 |
| Total dose: IU –Median(IQR) | 2025(1300–2800) | 2600(1875–3600) | 0.05[a] |
| Number of days of stimulation-Median(IQR) | 10(9–12) | 10(9–12.5) | 0.9[a] |
| Number of oocytes retrieved-Median (IQR) | 9(5–18) | 8(4–11.5) | 0.1[a] |
| Number of embryos transferred (SD) | 2.5(0.66) | 2.4(0.77) | 0.5 |
| ART cycle number- frequency (%) | | | |
| 2nd cycle | 34(50.75) | 33(49.25) | 0.9 |
| 3rd cycle | 16(47.06) | 18(52.94) | |
| 4th cycle | 4(57.14) | 3(42.86) | |
| 5th cycle | 1(50.00) | 1(50.00) | |
| 7th cycle | 0(0) | 1(100) | |
| Indication of infertility (%) | | | |
| Tubal | 10(52.63) | 9(47.37) | 0.8 |
| Anovulation | 7(63.64) | 4(36.36) | |
| Male | 18(43.90) | 23(56.10) | |
| Unexplained | 3(50.00) | 3(50.00) | |
| Endometriosis | 3(37.50) | 5(62.50) | |
| Combined | 14(53.85) | 12(46.15) | |
| Fertilisation Rate | 292/424 (69%) | 308/417 (74%) | 0.1 |
| Protocol- frequency (%) | | | |
| Long | 19(44.19) | 24(55.81) | 0.2 |
| Antagonist | 31(57.41) | 23(42.59) | |
| Short | 5(45.45) | 6(54.55) | |
| Ultralong | 0(0) | 3(100) | |

BMI – body mass index; IQR – inter quartile range; SD – standard deviation; ART – assisted reproductive technology.
[a] Non-parametric tests was used; Missing cases excluded.

were live birth, implantation, multiple pregnancy, miscarriage and preterm delivery rates. No participant women underwent more than one IVF cycle during the study period.

Live birth defined as delivery of live fetus after 24 completed weeks of gestation. Implantation rate was number of sacs seen on ultrasound divided by number of embryos transferred. The miscarriage rate was miscarriages before 24 completed weeks of gestation divided by number of clinical pregnancies. Multiple pregnancy was defined as more than one gestational sac on early ultrasound and pre term delivery was defined as delivery between 24 and 37 completed weeks of gestation.

*Sample size calculation and statistics*

Previous study reported doubling of clinical pregnancy rate following endometrial injury [8]. Assuming a clinical pregnancy rate per initiated cycle of 20% in women with previous unsuccessful IVF attempt, and doubling of clinical pregnancy rate following endometrial injury, the calculated target sample size was 180 (90 patients in each arm) with significance of 0.05 and a power of 80%. Statistical analysis was done using Statistical Program for Social Science (SPSS, Inc., version 17.0, Chicago, IL, USA) using independent sample *t*-test for continuous variables and Chi square for categorical variables taking a *P* value of $<0.05$ as significant. An intension to treat (ITT) was done.

## Results

A total of 180 women were eligible for the trial and 69 refused to participate. Finally, 111 eligible women were recruited and analyzed in the study (Fig. 1). After randomization, pipelle group had 55 women and control group had 56 women. Forty four women in pipelle group and 47 women in the control group completed the study.

The common reasons for recruited women not completing the trial included poor response, presence of ovarian cyst, non-retrieval of oocyte and fertilization failure as illustrated in flow diagram (Fig. 1).

Baseline characteristics like age, body mass index, indication for IVF, protocol used and number of previous IVF attempts did not significantly differ between the two groups (Table 1). The IVF treatment characteristics such as days of stimulation, total dose of gonadotrophins, number of oocytes retrieved, fertilization rate and number of embryos transferred were also not significantly different in the two groups (Table 1).

The clinical pregnancy rate per embryo transfer was 34.09%(15/44) in pipelle group *versus* 27.65%(13/47) in the control group and this difference was not significantly different (odds ratio, OR 1.35, 95% confidence interval, CI 0.55–3.30; $P=0.5$) (Table 2). The positive pregnancy (OR 1.76, 95% CI 0.76–4.08; $P=0.1$) and live birth rate per transfer (OR 1.36, 95% CI 0.55–3.39; $P=0.5$) also did not differ significantly among pipelle and control group (Table 2).

There was no significant difference in multiple pregnancy (OR 0.31, 95% CI 0.07–1.47; $P=0.1$) and miscarriage rates (OR 0.86, 95% CI 0.05–15.23; $P=0.9$) among the pipelle and no intervention group. The preterm delivery rates did not differ significantly among the two groups (OR 0.28, 95% CI 0.05–1.41; $P=0.1$) (Table 2).

An intention to treat analysis was done and the live birth rate per women randomized did not show any significant difference between the two groups (OR 1.25, 95% CI 0.52–3.02; $P=0.6$) (Table 3). The positive pregnancy (OR 1.53, 95% CI 0.70–3.35; $P=0.2$) and clinical pregnancy rates (OR 1.24, 95% CI 0.53–2.93; $P=0.6$) per woman randomized also did not show any significant differences between the pipelle and control groups (Table 3).

## Comments

The current study did not find any significant differences in clinical pregnancy rates following endometrial injury in preceding cycle among women undergoing IVF after a previous unsuccessful attempt compared to control group. There was no significant difference in live birth, miscarriage, preterm delivery and multiple pregnancy rates between the two groups.

Findings of the current study are in agreement with earlier studies which have evaluated the role of local endometrial injury in women undergoing IVF with previous unsuccessful cycles, and found no significant difference in clinical pregnancy rate in women who had endometrial biopsy in preceding cycle compared to no intervention [11,12]. A randomized trial by Yeung et al., which included 300 infertile women undergoing IVF, reported no significant difference in live birth rates (30.5% *vs.* 30.8%; $P=0.96$) among women who were undergoing first IVF cycle and had endometrial injury induced by pipelle in previous cycle compared to control group who did not have any such intervention [12]. A subgroup analysis revealed significantly lower live birth rates (13.3% *vs.* 32.6%; $P=0.04$) among women undergoing repeat IVF (atleast one prior fresh or frozen transfer) and had endometrial injury *versus* those who did not undergo the intervention. This subgroup was heterogeneous and included subpopulation of women with one to six IVF failures which is similar to current study population. Investigators did not give any possible reason for lower live birth in this subgroup and suggested that potential harm due to endometrial injury cannot be excluded. The earlier published studies have found favorable impact of endometrial injury in women undergoing IVF [9,10]. Karimzade et al. included 115 women with RIF (two to six unsuccessful cycles with at least 10 high grade embryos transferred) in their randomized trial and reported significantly higher clinical pregnancy rates (27.1 *vs.* 8.9%; $P=0.02$) though the authors did not report the live birth rates [9]. Narvekar et al., included women with atleast one IVF failure in their randomized trial and found significantly higher (22.4 *vs.* 9.8; $P=0.04$) live birth rate following endometrial biopsy compared to no intervention [10]. Authors did not mention details regarding number of previous unsuccessful attempts hence proportion of RIF

**Table 2**
Comparison of outcomes between the study groups[a].

| Variables | Intervention group n = 44 (%) | Control group n = 47 (%) | P value | OR | 95% CI |
|---|---|---|---|---|---|
| Live Birth rate | 14(31.81) | 12(25.53) | 0.5 | 1.36 | 0.55–3.39 |
| Clinical pregnancy | 15(34.09) | 13(27.65) | 0.5 | 1.35 | 0.55–3.30 |
| Positive Pregnancy test | 22(50.00) | 17(36.17) | 0.1 | 1.76 | 0.76–4.08 |
| Implantation Rate | 20/110 (18%) | 22/113 (19.5%) | 0.9 | 0.92 | 0.47–1.81 |
| Multiple pregnancy | 5/15(33.33) | 8/13(61.54) | 0.1 | 0.31 | 0.07–1.47 |
| Miscarriage rate | 1/15(6.66) | 1/13(7.69) | 0.9 | 0.86 | 0.05–15.23 |
| Preterm | 5/14(35.71) | 8/12(66.66) | 0.1 | 0.28 | 0.05–1.41 |

[a] Denominators include only those who completed the study.

**Table 3**
Comparison of outcomes variable between the study groups[a].

| Variables | Intervention group n = 55 (%) | Control group n = 56 (%) | P value | OR | 95% CI |
|---|---|---|---|---|---|
| Live Birth rate | 14(25.45) | 12(21.42) | 0.6 | 1.25 | 0.52–3.02 |
| Clinical pregnancy | 15(27.27) | 13(23.21) | 0.6 | 1.24 | 0.53–2.93 |
| Pregnancy test | 22(40.00) | 17(30.35) | 0.2 | 1.53 | 0.70–3.35 |

[a] Denominators include all those who were recruited for the study (Intention to treat analysis).

in this study was unclear. The favorable impact of endometrial injury has been more consistently observed in women with RIF group than women undergoing first IVF cycle or with previous one unsuccessful attempt [9,12,16,17]. The proportion of RIF (≥3 transfers) in current study was low (10/111) and could explain lack of beneficial effect of endometrial injury in the study.

A systematic review evaluated the role of endometrial injury in women with RIF undergoing IVF and included seven trials (four randomized and three non-randomized trials) with 2062 participants [13]. After pooling results from three studies, the live birth rate was found significantly higher in the endometrial injury group (Risk ratio, RR 2.46, 95% CI1.90 −3.18; $P < 0.00001$) compared to control group. The review included both randomized and non-randomized trials. The population of included studies was not similar due to heterogeneity in the definition of RIF and method of endometrial injury employed. Another systematic review published subsequently on similar topic of endometrial injury in RIF found four RCTs but did not perform the meta analysis due to substantial clinical heterogeneity among included studies. The authors suggested insufficient evidence to support endometrial injury in RIF [18].

An updated Cochrane review evaluated endometrial injury in IVF *versus* no intervention or sham procedure and included a total of 14 trials with 2128 participants. Endometrial injury was associated with higher live birth or ongoing pregnancy rate (RR 1.42, 95% CI 1.08–1.85; P = 0.01) compared to control in women with more than previous two embryo transfers and quality of evidence was moderate [14].

Though evolving evidence seems to suggest a possible beneficial role of endometrial injury prior to IVF, especially in women with RIF, it has been challenged due to inclusion of trials with high risk of bias in the reviews [13–15]. The recent trials have reported lower live birth rate following endometrial injury in women with repeat IVF cycles and RIF [11,12]. While investigating and interpreting the role of endometrial injury, there is a need to distinguish different study populations under evaluation such as women undergoing first IVF cycle, those with one IVF failure and women with RIF. The ambiguity surrounding true effect of endometrial injury is likely to continue until results from adequately powered randomized trials are available.

The main limitation of the study was small sample size and premature termination of the trial before the planned sample size could be achieved. Due to premature termination, the *post hoc* calculation showed the study had a power of only 65% to detect the stipulated change in clinical pregnancy rate (RR 2). Further, in light of Cochrane update findings showing smaller effect of same intervention (RR 1.5), the actual power is likely to be even lower [14]. Due to reduced power, possibility of type II error cannot be ruled out. The recruitment for the trial was slow leading to extension of study period beyond estimated time frame. With stronger evidence emerging in favor of endometrial injury [14], it became ethically challenging to continue the trial.

Findings of the current study are too imprecise to reach a conclusion regarding possible benefit or harm following local endometrial injury in women undergoing IVF after previous failed attempt. However, it adds to growing body of evidence and pooling of results from similar studies may help reach more definitive conclusions. There is need to conduct well designed randomized trials with clearly defined study group since the treatment effect appears to be different among various sub population of women undergoing IVF.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Funding

No funding support.

## Condensation

We conducted a randomized controlled trial to evaluate the effectiveness of endometrial injury in women undergoing IVF with previous unsuccessful attempt and found it of no additional benefit.

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