
Timing of endometrial scratching for women undergoing ICSI: A randomized clinical trial

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Abstract

Aim: To determine the optimum time for endometrial scratching in patients with unexplained primary infertility undergoing ICSI-ET cycles after one or more implantation failure.

Methods: A randomized clinical trial was conducted at fertility care unit, Mansoura University Hospital and 2 private fertility centers, Egypt, from November 2016 till June 2018. Eligible participants [142] had unexplained primary infertility, were prepared and scheduled to obligate for ICSI cycles. Patients were randomly allocated into two equal groups using computer-generated tables and sealed opaque envelopes. Endometrial scratching was done either just after oocyte retrieval in (group 1) or mid-luteal in the cycle before induction (group 2). Patients, investigators, and data analysts were not masked to group assignment. The primary outcome measure was implantation rate while the clinical pregnancy rate was settled as the secondary outcome measure.

Results: one hundred forty two clients were included (71 in each group). Baseline characteristics did not differ between both groups as regard the age, BMI, duration of infertility and basic laboratory investigations ($p > 0.05$). The mean estimated day of triggering (14.2 ± 2.1 in G1 vs 13.6 ± 2.2 in G2) together with the mean follicular size (19.3 ± 0.8 in G1 vs 18.5 ± 1.8 in G2) showed also no statistical significance (p values 0.690 and 0.751 respectively). Again, the mean estimated number of ova retrieved (7.4 ± 2.1 in G1 vs 7.1 ± 1.3 in G2) and zygote transferred (2 in each group) presented no significant differences together with the chemical pregnancy rates (54 in G1 vs 52 in G2, $p > 0.05$). On the other hand, IR and CPR are found significantly higher in group 1 compared to group 2, (IR 53.5% vs, 40.8%; whilst CPR 49.3% vs 35.2%, $p < 0.05$).

Conclusion: retrieval day endometrial scratching seemed to improve clinical pregnancy and implantation rates than does mid-luteal endometrial scratching in patients with unexplained infertility.

Keywords: Endometrial Scratch, retrieval day, IVF/ICSI cycles.

INTRODUCTION

Embryos' implantation within the endometrial cavity is actually a critical step in assisted reproductive techniques (ART). Previous researches have suggested that intentional endometrial damage, scratching, might increase the probability of pregnancy in women undergoing ART especially in those who had repeated failed im-

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2019

plantation in spite of good quality embryos transfer [1]. For a genetically normal blastocyst to implant successfully, it should hatch, appose, adhere, penetrate, and then finally invade a well-synchronized endometrium prepared by estrogens and progesterone [2, 3]. For this synchronization to occur, a number of locally acting molecules, namely, growth factors, cytokines, matrix metalloproteinase, adhesion molecules, extracellular matrix components, should be present in sufficient amounts and endometrial scratching (ES) is supposed to enhance the presence of these molecules [2-5]. The usual timing to perform ES was commonly thought to be one week before starting IVF, ICSI treatment in cases of repeated implantation failure with no available evidence supporting its use for those going through first IVF/ICSI cycles as it perhaps do more harm than a good effect [3]. Some authors demonstrated a significant doubling of the implantation rate (IR), clinical pregnancy rate (CPR) and live birth rates in patients who underwent ES in the cycle immediately preceding the IVF cycle [1, 3, 6, and 7]. Consequently, multiple studies have been performed to investigate the effect of ES in those undergoing ART cycles, but the method of scratching, the population being scratched and the study quality varies widely from locality to another [8-10]. Moreover, some stated that there is no consensus on the optimal timing and the number of procedure(s) required for the endometrial injury to exert its maximal benefits [11]. Due to this heterogeneity in design and variability in quality, it remains unclear for whom this treatment could be beneficial and for whom it will be jobless [9]. Therefore, the aim of the present study was to compare the usefulness and the safety of retrieval day versus mid-luteal ES on reproductive outcomes for women undergoing ICSI cycles with unexplained infertility hoping to clear out some disparity put around this maneuver.

Patients and methods

A prospective randomized clinical trial involving patients undergoing intra-cytoplasmic sperm injection/embryo transfer [ICSI-ET] treatment for unexplained primary infertility at fertility care unite Mansoura University Hospitals, Mansoura, Egypt and 2 private fertility centers, between November 1, 2016 and June, 30, 2018. Our research was reg-

istered as a randomized clinical trial with a clinical trial identifier [NCT03470298] and also approved by local ethical committee, institutional research board [IRB number R/16.11.11] therefore been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 as revised in 1983 and its later amendments. During the study period, the whole cohort interviewed and enrolled was 270 cycles of women coming for treatment of unexplained infertility, 128 of which were excluded. The sample size was calculated using Graph Pad Inset software version 3.01. Seventy-one patient in each group were required to give the study a power of 80% and α of 0.05. All patients were verbally consented and then each participant gave a written consent before inclusion after receiving detailed written and verbal information about the research. Participation was voluntary and can be withdrawn by the patient at any time with no disadvantages. Included patients were those prepared for fresh ICSI-ET cycle with previous failed ICSI cycle(s), known to be good responders to previous ovulation induction protocol(s), aged less than or equal to 30 years. Our included patients were diagnosed also to have unexplained infertility as evidenced by both partners complete basic investigations, namely semen analysis, mid-luteal progesterone, patent tubes as verified by HSG or previous laparoscopy. We excluded patients having intramural or sub-mucous myoma distorting the endometrial cavity, Asherman's syndrome, those with evident tubal pathology as hydrosalpinx or peritubal adhesions and patients beyond 30 years or those having disturbed hormonal profile. Those with their husbands having abnormal seminogram not fulfilling WHO criteria 2010 [12] were also excluded. From these recruited females, 142 were eligible and divided into two equal groups. Endometrial scratching was done either just after oval retrieval in (group 1) or mid-luteal in the cycle before induction (group 2). The authors selected ICSI cycle protocol that has been previously published by Ghanem et al 2009 [13] where they used antagonist protocol in all cases of both groups. Ovarian stimulation was started on the second or third day of menstruation by daily use of two ampoules Fostimon 75 mg and one ampoule Merional 75 mg [IBSA institute Biochimique SA Laugano 3, Suisse, manufactured in Switzerland] given subcutaneously. Then the antagonist, Cetrotide 0.25 mg, [Cetorelix, IBSA institute Biochimique SA Lau-

gano 3, Suisse, manufactured in Switzerland] was started when the leading follicle reached 14 mm and stopped when it reached 18 mm or more where hCG 10000 IU injection was given to trigger ovulation [IBSA institute Biochimique SA Laugano 3, Suisse, manufactured in Switzerland]. Folliculometry was carried out at the beginning from the sixth day of starting Fostimon then daily or every other day until three or more mature follicles reached 18 mm or more. Egg retrieval was scheduled 35-36 hours later. All patients were followed up by the same sonographer to measure the size of the growing follicles before using Citrotide or hCG and during egg retrieval. The oocyte retrieval was performed by the transvaginal route under ultrasound guidance while the patient under mindful sedation. Endometrial scratching using IUD sheath was done for group 1 patients just after egg retrieval without use of any septic solution part from normal saline; meanwhile it was done for group 2 patients on the day 21 in the cycle before induction under asepsis using povidone-iodine. The same gynecologist carried out the procedure in a systematic manner for patients in both groups by moving from below upwards with scratching the anterior then the posterior wall followed by the left lateral and the right lateral uterine walls and lastly the fundus. The morphology of each aspirated oocyte was then noted after denudation with hyaluronidase. Semen samples were obtained by masturbation on the day of oval retrieval and then processed within one hour of ejaculation to prevent damage from leukocytes and other cells present. To separate the motile sperms from the semen samples, the swim up method was used [14]. On the day of ovum retrieval, intracytoplasmic sperm injection and fertilization was performed for all cases. All metaphases II (MII) were injected by ICSI 3-4 hours post retrieval. All zygotes were cultured individually in 50 µl droplets of P-1 medium, supplemented with 10% Synthetic Serum Substitute (Irvine Scientific, Santa Ana, CA). After 44-46 hours, embryos were moved to complete blastocyst medium (Irvine Scientific, Santa Ana, CA). The newly formed embryos were evaluated by the embryologist and classified according to Veeck's grading [15]: Grade 1 were pre-embryos with blastomeres of equal size and no cytoplasmic fragmentations, Grade 2; pre-embryos with blastomeres of equal size with cytoplasmic fragmenta-

tions equal to 15% of the total embryonic volume; Grade 3; pre-embryos with uneven blastomeres with no fragmentation while Grade 4 are those of uneven blastomeres with gross fragmentation equal to or more than 20%. All selected embryos were transferred on day 3 involving two good quality grade 1 embryos using the tactile technique. The embryos were deposited high up in the cavity 1-2 cm below the uterine fundus by the same catheter (Labotect GmbH, Labor-Technic-Göttingen, Germany) under ultrasound guidance via a senior consultant in all transfers using the maneuver described by Ghanem et al; 2016 [16]. Luteal phase support was initiated in both groups on the day of egg retrieval and involved a daily dose of Prontogest 100 mg IM (Progesterone, Marcy Pharmaceutical industries, Obour city, Egypt) until the day of β -hCG test 14 days after embryo transfer. We compared the number of eggs retrieved, fertilization rate, cycle outcome regarding IR and clinical CPR in both groups. The primary outcome measure was (IR) while (CPR) was considered as the secondary outcome measure. Implantation rate was defined as the number of gestational sacs seen on trans-vaginal sonography divided by the number of embryos transferred meanwhile CPR was defined as ultrasound evidence of fetal heart beating and calculated as the number of patients with clinical pregnancy divided by the number of patients who had embryo transfer.

Statistical analysis

The data were collected, tabulated and statistically analyzed by IBM computer using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean \pm SD and compared between the two groups using independent Student's t test. Categorical data were expressed in number and percent and compared using the χ^2 test. Statistical significance was set at $p < 0.05$.

Results

A total of 270 patients with unexplained infertility were interviewed, screened and enrolled in the study, of them 128 patients were excluded due to failure for fulfilling the inclusion criteria and the rest were divided into two equal groups (figure 1).

Baseline characteristics are shown in Table (1); there were no recorded significant differences be-

tween both groups as regard the age, BMI, duration of infertility, base line investigations namely FSH, LH, prolactin levels as well as mid-luteal progesterone level, $p > 0.05$.

The mean estimated day of triggering (14.2 ± 2.1 in G1 vs 13.6 ± 2.2 in G2) together with the mean follicular size (19.3 ± 0.8 in G1 vs 18.5 ± 1.8 in G2) showed also no statistical significance (p values 0.690 and 0.751 respectively), [table 2]. Again, the mean estimated number of ova retrieved (7.4 ± 2.1 in G1 vs 7.1 ± 1.3 in G2) and zygote transferred (2 in each group), presented no significant differences together with chemical pregnancy rates (54 in G1 versus 52 in G2), $p > 0.05$ [table 2]. On the other hand, IR and CPR are found significantly higher in group 1 compared to group 2, (IR 38 (53%) vs, 29 (40%); CPR 35 (49.2%) vs 25 (35.2%), $p < 0.05$ as shown in table [2].

Discussion

The main findings of the study confirmed endometrial scratching on the oval retrieval day is more effective than if did mid-luteal in managing couples with unexplained infertility. This is indicated by the determination of higher implantation and clinical pregnancy rates in the study group (1).

Indeed implantation failure is considered as a major barrier in human's fertility and is mainly attributed to failure of the uterus to acquire normal receptivity. The term 'implantation failure' is used commonly for women with failure of at least three attempts of high-quality embryo's transfer [17-19]. The treatment of this failure remains a challenge in spite of transfer of good-quality embryos at sometimes [19, 20]. This study focused to examine the effectiveness of ES with IVF/ICSI cycles selecting a clear population; namely those who have had at least one failed implantation keeping in mind both patient burden and healthcare costs.

The notion of using induced endometrial injury to increase clinical pregnancy rates and live birth rates [19, 20] arises from the fact that the genes responsible for implantation are sometimes 'switched off' during the time when the embryos are supposed to implant. Endometrial injury might 'switch on' these genes with a subsequent tissues' repair associated with release of many

growth factors, hormones, chemicals and cytokines that make the new lining is more receptive to an implanting embryo with a positive crosstalk [22-24]. Endometrial injury was earlier investigated by Barash et al. 2003 [1] in a prospective study and concluded that women assigned to endometrial biopsy in the preceding cycles demonstrated twice more likely to get pregnant as compared to controls with no scratching. Since then a dynamic talk and many researches moved to study this issue but with heterogeneity of methods used and the proper timing. The best time to perform ES is principally thought to be approximately 7-14 days before starting controlled ovarian hyper-stimulation to increase the chance of clinical pregnancy and live birth. Raziel et al., 2007 [25]; reported in a case control study for ICSI patients with higher order implantation failure performed twice on days 21 and 26 an increased implantation and clinical pregnancy and even ongoing pregnancy rates in the intervention group. Moreover; demonstrated endometrial injury on days 11 - 13 and 21 - 24 of the non-transfer cycle or at least 7-14 days before the transfer cycle, during the luteal phase, resulted in improving pregnancy outcomes in women with unexplained repeated implantation failure [2, 26-30]. Our results come permitting the effect of endometrial injury and investigating the impact of timing too. Here, the authors found endometrial scratching done on the oval retrieval day is better and more effective than if done in the previous mid-luteal cycle as proved by higher IR and CPR in group 1 compared to group 2 being 53% vs, 40% and 49.2% vs 35.2% respectively [$p < 0.05$ in table 2]. These results come supporting the advantageous effect of ES, but the new incident is the higher effectivity in those with recent intentional endometrial injury (group 1). This might be explained by the fact that, inflammation process in the first group is still fresh with abundant switched on genes and inflammatory mediators making the endometrium in a good quiescent and cross talk state. An additional advantage of performing ES in the same cycle, according to the authors' opinion, is the patient's convenience, less visit, and no long time until transfer and this gave no chance for drop out cases.

Two recent studies published from our locality [31, 32] and supporting our results where they

did ES in the mid proliferative phase of the same transfer cycles and both found increase in IR and CPR. The latter study used endometrial scratch-suction maneuver and reporting that using suction is more advantageous as it can remove any small polyp or blood clots that may be hazardous for the implanting embryos. In this study, we did not use suction maneuver during ES, a point that in need to be more investigated to clear out whether it adds to scratching or not. In addition, our findings come in agreement with those results proved by some other authors [33-37] who studied the effectiveness and impact of timing of ES on the outcome of unexplained infertility management. Though, they studied the maneuver effectiveness with intrauterine insemination after repeated implantation failure, but their results showed significantly higher CPR in groups that underwent ES in the same stimulation-transfer cycles than those who had the maneuver at the mid-luteal time of the preceding cycle or those without scratch. Again they explained the prior failure to implant was due to poor endometrial receptivity as the sole cause of infertility which probably improved by ES. Moreover; Parsanezhad et al. 2013 [38] studied the role of intentional endometrial injury, induced by pipelle endometrial sampling after controlled ovarian hyper-stimulation performed during the pre-ovulatory days then followed by regularly timed intercourse. They concluded that local endometrial injury could increase pregnancy rate compared to the control group. This also supports the role and effectiveness of ES when become more close to ovulation, like our findings, even when there is no extra maneuver and leaving the pregnancy for natural chances. In addition, the study published by Huang et al 2011 [39], verified results that came supporting our findings despite they used a site-specific hysteroscopic endometrial injury. They concluded that endometrial injury performed during the ongoing IVF cycle, between days 4-7, instead of those received during prior cycles, significantly improves the outcome in patients with repeated implantation failure.

On the other hand there are some studies which have shown minimal [40] or no benefit of injuring the endometrium in the previous cycle in improving implantation or pregnancy rates [6, 41-43]. The possible explanation may be the longer time passed after scratching with limited benefit due to fading

out the effective mediators and cytokines responsible for good endometrial receptivity. Despite this supports our believe for ES to be as close as much to ovulation and transfer days, as indicated by results obtained from group 2 (less IR and CPR) compared to group 1, but further data is required to explain this disparity. Moreover, contrary to our detections; there are few results reporting a negative and at sometimes detrimental effect of endometrial injury on IR and CPR especially when performed in the transfer cycle near to or on the day of oocyte retrieval [44,45]. Was this attributed to persisted blood clots and endometrial fragments that need time to be cleared from the uterus?

Our study may add to facts regarding benefits of endometrial scratching in IVF/ICSI cycles management of infertile couples being a cost-effective, cheap and well-tolerated procedure. In addition, some strength of this study appears from being a prospective randomized controlled trial of good power (80%). However, the main limitations of the study are the small size in each arm and absence of the miscarriage and live birth rates estimation. This stresses the need for further large randomized trials, better to be multi-centric, to verify the findings and improve the statistical power. Another point of discussion is whether the use of povidone-iodine in group 2 during the endometrial scratch could decrease IR and CPR. To our information, no studies have investigated the effect of scrubbing the cervix with povidone-iodine at the preceding mid-luteal day on the embryo transfer and or implantation rate.

Conclusion

Endometrial scratch in the transfer cycle especially on the oval retrieval day can improve endometrial receptivity with subsequent increase in implantation and clinical pregnancy rates than when achieved at mid-luteal day of the previous cycle.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' contribution

Abdelhady Zayed; Protocol development, data collection

Osama Warda; Protocol development and data collection

Ahmed Ragab; Data analysis, manuscript writing.

Yasser Mesbah; Data collection and patient management

Ahmed El-Zayadi; Data collection and analysis

Ahmed Badawy; Data analysis, manuscript writing.

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Tables' legend:

Table [1]: Baseline characteristics of both studied groups together with the results of basic laboratory investigations.

Table [2]: Result of ovulation induction, mean day of triggering, mean follicular size, primary and secondary outcome measures in the two studied groups.

Table 1: Baseline characteristics of both studied groups together with the results of basic laboratory investigations.

	G1 (n=71)	G2 (n=71)	P value
Age (years)	25.4±3.1	26.1±3.1	0.225
Body mass index	25±0.8	25±0.2	1.00
Duration of infertility (years)	3.2±0.3	3.3±0.4	0.094
Baseline lab investigations:			
FSH (mIU/ml)	5.5± 1.3	5.8± 1.02	0.6
LH (mIU/ml)	6.3± 1.5	6.2 ± 1.3	0.41
Mid-luteal progesterone level	20.5± 3.4	19.2± 4.05	0.184
PRL(mIU/ml)	12.56 ± 2.3	12.5 ± 2.8	0.852

Data are presented by mean ± SD, p value was set statistically significant when <0.05. Abbreviations: FSH; follicle stimulating hormone, LH; luteinizing hormone; PRL, prolactin hormone.

Table 2: Result of ovulation induction, mean day of triggering, mean follicular size, primary and secondary outcome measures in the two studied groups.

Characteristics	G1 (n=71)	G2 (n=71)	P value
Mean day of triggering	14.2 ± 2.1	13.6 ± 2.2	0.690
Mean follicular size/mm	19.3 ± 0.8	18.5 ± 1.8	0.751
Number of ova retrieved	7.4+ 2.1	7.1+1.3	0.31
Number of zygote transferred	2	2	000
Chemical pregnancy rate	54 (76.05%)	52 (73.2%)	0.21
Implantation rate	38 (53.5%)	29 (40.8%)	0.01*
Clinical pregnancy rate	35 (49.3%)	25 (35.2%)	0.001*

Values are presented as mean ± SD, number (percentage), p value was set significant when <0.05. (*) significant P value