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ORIGINAL ARTICLE

Local endometrial scratching under ultrasound-guidance after failed intrauterine insemination and cycle outcome: A randomized controlled trial

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KEYWORDS

Intrauterine insemination;
Endometrial scratch;
Pregnancy rate

Abstract *Background:* Interaction between the embryo and endometrium plus endometrial receptivity is considered as two strong issues affecting the implantation outcome. *Purpose:* To investigate the effect of local endometrial scratching on pregnancy rate after failed previous intra uterine insemination. *Study design:* A prospective, randomized, control trial. *Setting:* At Cytogenetic and Endoscopy Unit, Zagazig University Hospital. Patients and methods: A total of 226 women either with unexplained or with mild male factor infertility were divided randomly into approximately two groups: in study group, 114 women and in control group, 112 women. For both groups, folliculometry was started at cycle day 7 additionally and at the same setting; endometrial scratching was done only for the study group. *Outcome results:* Biochemical and clinical pregnancy rates. *Results:* The biochemical and clinical pregnancy rates were significantly higher in the endometrial scratching group compared to the control group [27/106 (25.5%) vs. 15/106 (14.1%) $p = 0.03$ and 24/106 (22.6%) vs. 12/106 (11.3%); $p = 0.02$] respectively. Also, ongoing pregnancy rate was statistically significantly different between both groups [22/106 (20.7%) vs. 11/106 (10.4%); $p = 0.03$]. *Conclusion:* Endometrial scratching is useful in increasing pregnancy rates after failed previous intra uterine insemination trials when it is performed in the mid proliferative phase.

1. Introduction

Unexplained infertility is supposed when there are no detectable particular causes of infertility on a routine evaluation (1). Evidence demonstrating that about 75% of human pregnancies not succeed almost immediately after conception incriminates that implantation failure may be a possible cause of unexplained infertility (2). Implantation process still remains a limiting step in ART outcome. Implantation is defined as the adhesion or fixation of good blastocyst to receptive endometrium throughout a specific period which is called the window of implantation (3). During this window, there is a perfect dialog between the embryo and the endometrium.

A receptive uterus includes the endometrial cellular changes and modulated appearance of different cytokines, prostaglan-

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dins, growth and transcription factors (4). Currently, implantation failure is the most important barrier in human fertility and mostly is attributed to the failure of the uterus to gain receptivity. Uterine fibroid, hydrosalpinx, endometriosis, endometrial polyp and polycystic ovary syndrome are possible causes of repeated implantation failure (RIF) (5).

Recently to improve implantation, endometrial scratching has attracted many attentions and has rapidly become included into clinical practice. It has been revealed that mechanical manipulation of the endometrium can improve receptivity by modulating gene expression of factors needed for implantation like laminin alpha 4, integrin alpha 6, matrix metalloproteinase 1 (6) and glycodelin A (7). Acute regenerative process after endometrial scratching could slow down the disproportionate endometrial development which is often associated with ovarian stimulation cycles therefore, restoring embryonic-endometrial synchrony and helping implantation (8). Another promising mechanism by which endometrial scratching may increase uterine receptivity is through local increase production of growth factors and pro inflammatory cytokines (9,10).

Animal studies have demonstrated that scratching of the endometrium provoke the decidualization and so, enhance the endometrial receptivity (11). In human there are conflicting results in this regard; Barash et al. (12) demonstrated that performing multiple endometrial biopsies at different times of the IVF cycle is associated with higher pregnancy rate. Additionally, Zhou et al. (8) demonstrated that inducing local endometrium injury in Controlled Ovarian Stimulation (COS) cycles is associated with a higher pregnancy rate. However, Karimzade et al. (13) have shown that local endometrial injury on the day of ova pickup disturbs the receptive endometrium and has a negative effect on implantation rate in IVF cycles. A Cochrane Library systematic review was published in 2015 in which moderate-quality evidence shows that endometrial injury done between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle is associated with an improvement in clinical pregnancy and live birth rates in women with more than two previous embryo transfers cycles (14).

The aim of the study was to assess the effect of local endometrial scratching on incidence of clinical pregnancy rate after failed one IUI trial.

2. Patients and methods

This was a prospective, randomized, control trial designed to assess the effect of endometrial scratching on improving the reproductive outcome in stimulated IUI cycles. Patients who were selected to share in this work gave their written informed consent before starting. After approval of the local ethics committee, the study was performed between March 2013 and May 2015 at the Cytogenetic and Endoscopy Unit, Zagazig University Hospital, Egypt.

2.1. Patient recruitment and treatment

This study was conducted on referred women either those with unexplained or those with mild male factor infertility and after failed previous one IUI trial. Sample size was calculated based on the primary outcome of improving pregnancy rate after endometrial scratching. Two sided significant level is 95% with a power of 80% and the ratio of study to control group was 1:1. According to 36% pregnancy rate in the study group and 18% pregnancy rate in the control group as reported by Abdelhamid (15), a minimum of 106 patients were needed in each group. As there is an expecting proportion of subjects who may be dropped out before the end of the study, 10% of subjects were added; therefore, a total of 233 patients were screened regarding eligibility for the study. They fulfilled the following inclusion criteria: female age 19–37 years with normal basal hormonal profile [FSH, LH] 3–10 mIU/ml and 1.8–8.5 mIU/ml respectively, normal uterine cavity as assessed by HSG, patents both tubes and normal semen analysis. However, mild male factor infertility was defined when there was 2 or more semen analysis with 1 or more items below the 5th centile as defined by the WHO, 2010 (16). Exclusion criteria were patients with unilateral tubal patency, a history of ovarian hyper stimulation syndrome (OHSS), diminished ovarian response, endometriosis or multiple female factor. Unexplained infertility was diagnosed when there is a confirmed tubal patency, normal semen analysis according to WHO criteria, and ovulatory cycles based on ultrasonic follicle tracking and mid-luteal progesterone levels (17).

2.2. Ovarian stimulation and scratching

Before starting 7 patients were excluded from the study because they reject to participate in the study. Thus, the remaining 226 women were subjected to complete history taking and clinical examination. To exclude residual ovarian cyst, basal transvaginal pelvic ultrasonography (TVS) is mandatory for all patients. Controlled ovarian stimulation was done by combined sequential protocol CC/hMG; Clomiphene Citrate 100 mg daily starting from day 2 of the menstrual cycle and continued for 5 days. On the day following the fifth day of CC therapy, Human Menopausal Gonadotropin (hMG) (Menogon, Ferring) was starting in the form of 75 IU/day IM injection. At the same sitting of starting the COS, patients were divided randomly by using random table (computer), software Open Epi version 3.21 into two approximately groups: in study group (scratching group) 114 women in whom ovarian stimulation, scratching, folliculometry and insemination were done while in the control (non- scratching group) 112 women were subjected to ovarian stimulation, folliculometry and insemination. Patients were allocated to either group by the randomization stated while allocation concealment concentrated on preventing selection and confusing biases. In the study group, endometrial scratching was planned on day 7 of the same cycle, while in the control group, classic IUI was planned without endometrial scratching.

2.3. Endometrial scratching

Scratching was done by using the embryo mucus aspiration catheter (Rocket medical) which is a small, flexible catheter that can be used to scratch the lining endometrium gently after cutting the tip of the catheter sheath obliquely.

The procedure of the endometrial scratch was performed as follows:

1. Prepare the patient in the Lithotomy position.
2. Speculum is gently inserted into the vagina to expose the cervix which is cleaned with sterile gauze.

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