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Endometrial pipelle scratching may decrease abortion rates rather than increasing pregnancy rates in intrauterine insemination cycles

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ABSTRACT

To assess the efficacy of endometrial pipelle scratching (EPS) preceding intrauterine insemination (IUI) cycles. A total of 348 patients with unexplained infertility were enrolled into the study. 117 women with EPS were compared with 231 women without EPS and IUI. Livebirth and pregnancy rates and abortion rates were the primary outcomes. There were no difference in age, duration of infertility, basal hormone and total gonadotropin dose used throughout the cycle and endometrial thickness. In terms of pregnancy outcomes, pregnancy and livebirth rates in EPS group were17.1% and 15.7% respectively, while pregnancy and livebirth rates in Non EPS group were 23.8% and 16% respectively. Spontaneous abortion rate in EPS group was significantly lower than Non EPS group (1.7% vs. 7.8%) which was statistically significant (p = 0.021). EPS did not improve pregnancy and livebirth rates. However, abortion rates were significantly lower in EPS patients. EPS may not have any impact on the embryonic implantation but may improve the proper development of implanted embryos by modulating the local factors.

1. Introduction

IUI is an inexpesive and easily performed, common assisted reproductive technique. Pregnancy outcomes of IUI in the literature ranges from 4% to 24% per cycle (Papillon-Smith et al., 2015). IUI is often the preferred firstline treatment in; unexplained, cervical factor and mild to moderate male factor infertility (Veltman-Verhulst et al., 2016). Clinical pregnancy rates may be influenced by the method of ovarian stimulation, type and duration of infertility, sperm parameters and ovarian stimulation response, female age and endometrial scratching (Luco et al., 2014).

It is the implantation of the embryos that remains to be solved in the modern era of ART and it seems that there

is still a long way to go to understand the implantation process. It is assumed that almost ¾ embryos failed to implant during implantation period (Afsoon et al., 2014). The attractive mechanisms between embryos and the receptive endometrium are two key factors for succesful implantation to occur (Diedrich et al., 2007)

Endometrial scratching, also named as trauma, injury or biopsy, is a simple and microinvasive procedure which can be applied in outpatient conditions. Endometrial scratching can also be applied by hysteroscopy. The mechanism of action of endometrial injury may be hypothetised as; a) endometrial decidualization b) healing which leads to the immune reaction and c) endometrial maturation to improve the synchrony (Jeffrey and Goldberg, 2018).

Animal studies revealed that endometrial trauma provoke the receptivity and decidualization of the endometrium (Finn and Martin, 1972). Scratching th endometrium in either follicular phase or in luteal phase was positively correlated with the increase in the pregnancy rates in IVF (Barash et al., 2008). The luteal phase endometrial scratching carries a risk to damage the developing ealy pregnancy thus scratching in the follicular phase seems much more acceptable (Jeffrey and Goldberg, 2018). Scratching of the endometrium become a controversial issue in ART practive since some report that endometrial injury was associated with increased pregnancy rates (Zhou et al., 2008) while others prove that this procedure may have negative impact on the clinical outcomes (Karimzade et al., 2010). Endometrial scratching during IUI cycles is not extensively studied compared to IVF (Gnainsky et al., 2010; Goel et al., 2017; Senocak et al., 2017).

This study aims to present the impact of endometrial injury in the follicular phase of previous menstrual cycle on the clinical outcomes of IUI cycles in couples with unexplained infertility and mild male subfertility.

2. Materials and methods

This is a retrospective case control study conducted at the fertility clinic of Maternity Hospital, Samsun Training and Research Hospital, Turkey. 117 IUI patient files including EPS were driven from the archives and included in Group 1 while 231 IUI patient files without EPS were included in Group 2 as controls between January 2014 and June 2017. EPS for better clinical outcome were offered to IUI couples and the ones preferred EPS before IUI were compared with the ones refused to have EPS. All participated couples in both groups had basal fertility evaluations including tubal patency test, transvaginal ultrasound examination, semen analysis, a battery of basal hormonal evaluation and serological tests. Written informed consent for each patient were taken and recorded. This study was approved by the institutional review board of Medicana Samsun International Hospital by a grant number of 1997/08.03.2019.

Files not covering the basal evaluations were not included in the study. For obtaining homogenuity in both groups, only unexplained infertiliy and mild male subfertility cases were enrolled into the study.Thus IUI performed due to other factors were also excluded from the study. EPS and Non EPS applied IUI patients performed 42 hours after hCG administration were excluded from the study.

Demographic features and baseline clinical characteristics of participants were collected from the files and recorded to a database program for statistical analysis.

Ovarian stimulation, IUI luteal phase support and pregnancy confirmation by B-hCG test

All participating women had a diagnosis of unexplained infertility. Recombinant gonadotropin 75 IU (Gonal-f, Merck Serono, Switzerland) SC daily was started on day 3 of menstrual cycle and patients were monitored for follicular response. Patients were called on day 7 and day 10 for follicular monitorization. Gonadotropin stimulation continued until the leading follicle reached 17mm and a single dose of recombinant hCG 250 microgram (Ovitrelle, Merck Serono, Switzerland) injected subcutaneously 36 hours before IUI. IUI was performed under outpatient conditions in Maternity Hospital. A sterile speculum was used to visualize the uterine cervix and cervix was cleansed with isotonic solution. An IUI soft catheter (Cook catheter, Tekservis Medical, Turkey) was inserted through the cervical canal and prepared sperm was injected through the catheter in 60 seconds. A 5 more second was spent for catheter removal. Oral progesteron 100 mg (Progestan tablet, Koçak Farma, Istanbul, Turkey) thrice a day was started as luteal support. A blood test for B-hCG were recommended 15 days after IUI procedure to evaluate the pregnancy outcome.

Sperm preparation for IUI

The semen sample for insemination was analyzed for conventional semen parameters (volume, sperm count, and motility). Semen samples were collected by masturbation into a sterile semen jar in sperm giving room located in the IVF center and processed in the IVF laboratory according to the principles of discontinuous density gradient centrifugation. Semen sample was handled 2 hours before IUI procedure for preparation. Sperm findings after preparation for IUI were recorded. Then prepared sperm in an injector was handled by the patient to keep the body temperature until sample is inseminated by the following physician. A sterile soft IUI catheter was given to the patient to overcome inconvenience that may result from the absence of catheter in maternity hospital.

Sperm is incubated in CO_2 incubator for liquification for 30 minutes in order to get rid of prostaglandin-rich seminal and prostatic secretions. Then sperm is cultured by G1 medium (Vitrolife, Denmark) and sperm is

evaluated under Macler counting system and findings were recorded.Sperm was prepared by continuos density gradient centrifugation and flushed thereafter. Following the washing step, the obtained pellet was suspended in 0.5 mL G1 medium and loaded to an insulin injector .The loaded injector and a catheter for insemination were given to the partner of the patient to be used in insemination procedure.

Endometrial Pipelle Scratching (EPS)

Mechanical endometrial trauma or scratching were performed in the follicular or proliferative phase of menstrual cycle preceeding the IUI. 12 times scratching were performed to induce the acute ingflammatory reaction on the ndometrium. Pipelle (Pipelle de Cornier, Prodimed, France) was preferred to perform endometrial scratching.

Statistical analysis

Descriptive statistics for continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), and nominal variables were expressed as the number and percentage (%). Differences in mean values for each group were evaluated using the Student's t-test, and differences in median values were evaluated using the Mann–Whitney U-test. Categorical data were compared using the Chi-square distribution, with p-values of ≤0.05 considered as statistically significant. Statistical analysis was performed using SPSS for Windows version 22 software (SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 348 patients presented with primary infertility due to unexplained infertility and mild male subfertility were enrolled. 117 patients whom applied EPS were included in group 1 and 231 patients whom did not applied EPS were included in Group 2 for comparisons. Each couple has one cycle of IUI.

Table 1. Baseline characteristics and serum hormone levels of participants. Numerical data presented as mean (SD) or median (25th to 75th percentile).

	EPS (n=117)	Non EPS (n=231)	p values
Age (years)	29.33 ± 6.05	30.33 ± 5.22	0.084
Infertility duration (years)	7.39 ± 4.96	6.23 ± 4.17	0.059
BMI ((kg/m2)	24 (19-28)	23 (19-27)	0.322
Type of infertility Primary Secondary	 78 (66.5%) 39 (33.5%)	 144 (62.5%) 87 (37.5%)	0.728
Basal FSH (mIU/mL)	6.75 (4.0-17.09)	6.50 (3.41-13.14)	0.205
Basal LH (mIU/mL)	4.50 (2.84-12.65)	4.75 (2.31-13.14)	0.135
Basal E2(ng/m)	36.95 (15.05-55.45	35.34 (11.30-51.92)	0.995
Basal Prolactin (ng/mL)	12.75 (6.14-34.30)	13.20 (4.55-34.55)	0.758
Basal TSH (uIU/mL)	1.27 (0.47-2.28)	1.42 (0.71-2.39)	0.438
Endometrial thickness (mm)	8.5 (5-12)	9 (6-12)	0.101
Total gonadotropin dose used	750 (450-1250)	750 (450-1250)	0.304

When the groups were compared in terms of demographic characteristics and baseline hormone levels, there were no difference in age, duration of infertility, basal hormone and total Gonadotropin dose used throughout the cycle and endometrial thickness. Baseline characteristics and hormonal parameters are presented in Table 1.

When the groups were compared in terms of pregnancy outcomes, pregnancy and live birth rates in EPS group were 17.1% and 15.7% respectively, while pregnancy and livebirth rates in Non-EPS group were 23.8% and 16% respectively. Though no statistical significance observed between the groups in terms of live birth and pregnancy rates, number of patients conceived in Non-EPS group was found higher. Spontaneous abortion rate in EPS group was significantly lower than Non-EPS group (1.7% vs. 7.8%) and the difference between the groups was statistically significant (p = 0.021). Pregnancy outcomes are presented in Table 2.

Table 2. Pregnancy outcomes for EPS versus Non-EPS IUI cycles.

	EPS (n=117)	Non EPS (n=231)	p values
Positive β-hCG test	20 (17.1%)	55 (23.8%)	0.150
Pregnacy rate	20 (17.1%)	55 (23.8%)	0.150
Live birth	18 (15.4%)	37 (16.0%)	0.879
Spontaneous abortion	2 (1.7%)	18 (7.8%)	0.021*

4. Discussion

This study aimed to show the beneficial effect of EPS in the follicular phase of previous menstrual cycle on the clinical outcomes of IUI cycles in couples with unexplained infertility and mild male subfertility. It was found that EPS was not associated with increased pregnancy rates in IUI cycles instead the number of pregnancies were lower than Non-EPS patients though not raised statistical significance. The results of this study showed that a microinvasive outpatient procedure, EPS, may have beneficial effect on the proper implantation of the embryos since the abortion rates were significantly lower in EPS group.

Endometrial scratching has long been used in many ways in the clinical practice of ART and is one of the most controversial issues in infertility practice. Simon et al investigated more than 300 publications on the use of endometrial scratching and nearly all papers were found low or poor quality (Simon and Bellver, 2014). Levin et al. (2017) retrospectively evaluated 1810 IVF cycles in which 415 cycles were with endometrial pipelle scratching while 1395 cycles were matched as controls. After completing the matching process, they compared 238 ES cycles with 238 NonES cycles and concluded that mechanical endometrial trauma has nothing to do

with improved implantation and pregnancy rates (Levin et al., 2017). A metaanalysis of 14 randomised controlled trials conducted by Nastri et al. (2015) concluded that endometrial scratching in the luteal phase of previous menstrual cycle or early follicular phase of fresh IVF cycles improves the clinical outcomes (Wise 2013; Nastri et al., 2015). Though it is widely used in IVF practice, there is a very low tendency to use endometrial scratching in ovulation induction or IUI cycles (Lensen et al., 2016). A Cochrane review of nine RCTs with 1512 patients in 2016 conducted by Lensen et al revealed that the quality of evidence fort he use of ES in IUI cycles are low or very low (Lensen et al., 2016). Vitagliano et al. (2018) reproted an update review in 2017 and by their rigorus effort, studies not peer reviewed and with poor quality were excluded and eligible 8 RCTs including 1871 cycles were enrolled into their systematic review. They concluded that ES significantly improves the clinical pregnancy rates without increasing ectopic, miscarriage and multiple pregnancy rates (Vitagliano et al., 2018). Goel et al. (2017) al found significantly high pregnancy rates in thier RCT. They assesded 284 IUI cases and eligible 144 patients were randomised into two groups equally without any dropouts and found 31.9% pregnancy rate in ES group compared to 16.7% pregnancy rate of nonES controls and concluded that ES is beneficial, cost effective and simple method that can be attached in IUI cycles (Goel et al., 2017). Radhakrishan et al., in their randomised case control study evaluated the impact of ES on the clinical outcomes in 240 patients and concluded that ES, by increasing the levels of IL-6 and adhesion molecules like E-Cadherin, may increase the clinical pregnancy rates in IUI cycles (Radhakrishnan, 2015). Gupta et al. (2015) evaluated 64 couples fort he efficiency of ES in their RCT and randomised patients equally and 32 women with 78 IUI cycles with ES were compared with 32 women with non ES. They concluded that ES has better pregnacy and ongoing pregnancy rates (Gupta et al., 2015). Şenocak et al. (2017) evaluated 80 women in their RCT and 40 women with ES by Novak curette to the posterior side of the endometrium were enrolled into group 1 while 40 women without ES were included in control group for comparisons. They concluded that though the clinical pregnancy rates and pregnancy rates were higher than controls, the difference did not reach statistical significance and they recomend more RCTs with larger patient populations (Senocak et al., 2017). Contrary to these datas, Zarei et al. (2014) in their RCTs in 144 patients concluded that the use of ES in previous menstrual cycle has nothing to do with the increased chance of pregnancy (Zarei et al., 2014). However, they add their limitations and problems in design in their study and inconvenience of their patients with their protocol. Kriplani et al. (2016) arranged a RCT and evaluated 124 women and 62 women with ES in IUI cycles were compared with 62 cycles without ES and concluded that though pregnancy rate in ES group is higher, it did not reach a statistical significance and they also recommended larger scale RCTs to document the impact of ES during IUI cycles (Kriplani et al., 2016). In this study, pregnancy rates were slightly lower than Non-EPS patients but abortion rates were found significantly lower in EPS patients which may be explained by the beneficial effect of local mediators on the implanted embryos rather than implantation of embryo itself. This outcome was not reported in the published articles on endometrial scratching in IUI cycles and should be taken into consideration.

The exact mechanism of endometrial injury is not certain but it is aimed to trigger acute inflammatory reaction and to induce the release of certain cytokines and other inflammatory molecules which mimics the implantation process and crosstalks of embryo and endometrium. Further release of macrophages and other immune cells produce an environment resembling endometrial window (Lensen et al., 2016; Ashrafi et al., 2017). This hypothesis was supported by the increased factors found in the second biopsies of women who had endometrial scratching (Gnainsky et al., 2010). Preferrence of pipelle for endometrial trauma may have additional benefit since gentle scratching triggers inflammatory response without producing any harm to the endometrium. Others like Novak curette or vacuum aspirators may produce harmful endometrial injury than expected beneficial effect (Vitagliano et al., 2018).

Here in this study, pipelle was preferred for endometrial scratching in the follicular phase of menstrual cycle precceding IUI cycle.

In conclusion, EPS did not improve pregnancy and livebirth rates and even pregnancy rates were lower than Non-EPS patients although not raised statistical significance. However, abortion rates were significantly lower in EPS patients. EPS may not have any impact on the embryonic implantation but may improve the proper development of implanted embryos by modulating the local factors. Retrospective nature of this study is a limitation and further prospective randomised studies, especially those evaluating the endometrial factors improving the clinical outcomes or decreasing the abortion rates are warranted. EPS seems beneficial in reducing the abortion rates in IUI cycles of unexplained infertility with mild male subfertility.

REFERENCES

Ashrafi, M., Tehraninejad, E.S., Haghiri, M., Masomi, M., Sadatmahalleh, S.J., Arabipoor, A., 2017. The effect of endometrial scratch injury on pregnancy outcome in women with previous intrauterine insemination failure: A randomized clinical trial. J. Obstet. Gynaecol. Res. 43, 1421-1427.

Barash, A., Dekel, N., Fieldust, S., Segal, I., Schechtman, E., Granot, I., 2003. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. Fertil. Steril. 79, 1317-1322.

Simon C., Bellver J., 2014. Scratching beneath 'The Scratching Case': Systematic reviews and meta-analyses, the back door for evidence-based medicine. Hum Reprod. 8, 1618-1621.

Diedrich, K., Fauser, B.C., Devroey, P., Griesinger, G., 2007. Evian nnual eproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. Hum. Reprod. Update. 13, 365-377.

Levin, D., Hasson, J., Cohen, A., Or, Y., Ata, B., Barzilay, L., Almog, B., 2017. The effect of endometrial injury on implantationand clinical pregnancy rates. Gynecol. Endocrinol. 33, 779–782.

Finn, C.A., Martin, L., 1972. Endocrine control of the timing of endometrial sensitivity to a decidual stimulus. Biol. Reprod. 7, 82-86.

Gnainsky, Y., Granot, I., Aldo, P.B., Barash, A., Or, Y., Schechtman, E., Mor, G., Dekel, N., 2010. Local injury of the endometrium induces an inflammatory response that promotes successful implantation. Fertil. Steril. 94, 2030-2036.

Goel, T., Mahey, R., Bhatla, N., Kalaivani, M., Pant, S., Kriplani, A., 2017. Pregnancy after endometrial scratching in infertile couples undergoing ovulation induction and intrauterine insemination cycles-a randomized controlled trial. J. Assist. Reprod. Genet. 34, 1051-1058.

Malhey, R., Goel T., Gupta, M, R., Mahey, T., Goel, G., Kachhawa, A., Kriplani, A., 2015. To evaluate the pregnancy rate after endometrial scratching in couples with unexplained infertility inovulatıon induction and IUI cycles. Fertil. Steril. 689.

Jacqui, W., 2013. Endometrial Scratching improves IVF pregnancy rate. BMJ. 347, 6007.

Jeffrey, M., Goldberg, M. D., 2018. Endometrial scratching to increase pregnancy rates with intrauterine insemination. Fertil. Steril. 109, 2.

Karimzade, M. A, Oskouian, H., Ahmadi, S., Oskouian, L., 2010. Local injury to the endometrium on the day of oocyte retrieval has a negative impact on implantation in assisted reproductive cycles: A randomized controlled trial. Arch. Gynecol. Obstet. 281, 499-503.

Kriplani, A., Goel, T., Mahey, R., Garima, K., Sharma, J.B., Bhatla, N., 2016. Pregnancy rate after endometrial scratching in couples with unexplained infertility in ovulation induction and IUI Cycles- A randomised controlled trial. Fertil. Steril. 19, 588.

Lensen, S., Sadler, L., and Farquhar, C., 2016. Endometrial scratching for subfertility: Everyone's doing it. Hum. Reprod. 31, 1241–1244.

Lensen, S.F., Manders, M., Nastri, C.O., Gibreel, A., Martins, W.P., Templer, G.E., Farquhar, C., 2016. Endometrial injury for pregnancy following sexual intercourse or intrauterine insemination. Cochrane Database Syst. Rev. CD011424.

Lensen, S., Martins, W., Nastri, C., Sadler L., Farquhar, C., 2016. Pipelle for pregnancy (PIP): Study protocols for three randomised controlled trials. Trials. 17, 216.

Luco, S.M., Agbo, C., Behr, B., Dahan, M.H., 2014. The evaluation of pre and post processing semen analysis parameters at the time of intrauterine insemination in couples diagnosed with male factor infertility and pregnancy rates based on stimulation agent. A retrospective cohort study. Eur. J. Obstet. Gynecol. Reprod. Biol. 179, 159-162.

Nastri, C.O., Lensen, S.F., Gibreel, A., Raine-Fenning, N., Ferriani, R.A., Bhattacharya, S., Martins, W.P., 2015. Endometrial injury in women undergoing assisted reproductive techniques. Cochrane Database Syst. Rev. 22; CD009517.

Papillon-Smith, J., Baker, S.E., Agbo, C., Dahan, M.H., 2015. Pregnancy rates with intrauterine insemination: Comparing 1999 and 2010 World Health Organization semen analysis norms. Reprod. Biomed. Online. 30, 392-400.

Radhakrishnan, G., 2015. Evaluation of endometrial scratching on intrauterine insemination outcome and endometrial receptivity. Fertil. Steril. 104, Supplement, e169.

Senocak, G.C., Yapca, O.E., Borekci, B., 2017. Comparison of pregnancy rates between patients with and without local endometrial scratching before intrauterine insemination. J. Gynecol. Obstet. Hum. Reprod. 46, 687–690.

Vitagliano, A., Noventa, M., Saccone, G., Gizzo, S., Giovannni, S., 2018. Endometrial scratch injury before intrauterine insemination: Is it time to re-evaluate its value? Evidence from a systematic review and meta-analysis of randomized controlled trials. Fertil. Steril. 109, 84-96.e4

Veltman-Verhulst, S.M., Hughes, E., Ayeleke, R.O., Cohlen, B.J., 2016. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst. Rev. 9, CD001838.

Zarei, A., Alborzi, S., Dadras, N., Azadi, G., 2014. The effects of endometrial injury on intrauterine insemination outcome: A randomized clinical trial. Iran J. Reprod. Med. 12, 649–652.

Zhou, L., Li, R., Wang, R., Huang, H.X., Zhong, K., 2008. Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. Fertil. Steril. 89, 1166-1176.