



Effect of endometrial injury on pregnancy outcomes in infertile women undergoing intrauterine insemination

İntrauterin inseminasyon uygulanan infertil kadınlarda endometrial hasarın gebelik sonuçlarına etkisi

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Abstract

Objective: One of the most common treatments for infertility is intrauterine insemination (II). The objective of this study was to determine the effect of endometrial injury on pregnancy outcomes in unexplained infertility in women undergoing II.

Materials and Methods: In this randomized clinical trial, 122 women with unexplained infertility who were referred to Shariati Hospital from 2018 to 2020 were enrolled. They underwent ovulation induction using letrozole and gonadotropins. On day 9 of stimulation, they were randomly assigned to two similar groups of the same size. The first group underwent endometrial local injury by pipelle endometrial sampling, and the second group (control group) received no intervention. Only 1 II cycle was performed for each patient. Patients with negative pregnancy outcomes were followed up for 3 months. Endometrial thickness, dominant follicle count, chemical and clinical pregnancy rate, miscarriage rate, and spontaneous pregnancy rate after the II cycle were compared between the two groups.

Results: Endometrial thickness, dominant follicle count, chemical and clinical pregnancy rate, and miscarriage rate in the same II cycle were not different between the two groups ($p>0.05$). However, the spontaneous pregnancy rate after the II cycle was significantly higher in the endometrial injury group ($p=0.02$).

Conclusion: Endometrial injury increases pregnancy rates in later cycles but not in the same II cycle.

Keywords: Endometrium, infertility, intrauterine insemination, pregnancy outcome

Öz

Amaç: İnfertilitenin en yaygın tedavi yöntemlerinden biri intrauterin inseminasyondur (İİ). Bu çalışmanın amacı, İİ uygulanan kadınlarda açıklanamayan infertilitede endometrial hasarın gebelik sonuçlarına etkisini belirlemektir.

Gereç ve Yöntemler: Bu randomize klinik çalışmaya, 2018'den 2020'ye kadar Shariati Hastanesi'ne sevk edilen, açıklanamayan infertilitesi olan 122 kadın dahil edildi. Letrozol ve gonadotropinler kullanılarak ovülasyon indüksiyonu uygulandı. Hastalar stimülasyonun 9. gününde, aynı büyüklükteki iki benzer gruba rastgele atandılar. Birinci grupta pipelle endometrial örnekleme yoluyla endometriyal lokal hasar oluşturuldu, ikinci gruba (kontrol grubu) ise herhangi bir müdahale yapılmadı. Her hastaya sadece 1 İİ siklusu uygulandı. Gebelik sonuçları olumsuz olan hastalar 3 ay süreyle takip edildi. İki grup arasında endometrial kalınlık, baskın folikül sayısı, kimyasal ve klinik gebelik oranı, düşük oranı İİ siklusu sonrası spontan gebelik oranı karşılaştırıldı.

Bulgular: Endometrial kalınlık, baskın folikül sayısı, kimyasal ve klinik gebelik oranı ve aynı İİ siklusunda düşük oranı açısından iki grup arasında fark yoktu ($p>0,05$). Ancak İİ siklusu sonrası spontan gebelik oranı endometriyal hasarlanma grubunda anlamlı olarak daha yüksekti ($p=0,02$).

Sonuç: Endometriyal hasarlanma sonraki sikluslarda gebelik oranlarını artırmaktadır ancak aynı İİ siklusunda bu durum söz konusu değildir.

Anahtar Kelimeler: Endometriyum, infertilite, intrauterin inseminasyon, gebelik sonucu

PRECIS: Endometrial injury increases spontaneous pregnancy rates after the first intrauterine insemination cycle.

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Introduction

Infertility is defined as not attaining pregnancy for a year without using contraceptive methods. Infertility treatment is performed according to the cause of infertility. Of course, sometimes the cause of infertility is unclear. One of the possible treatments is intrauterine insemination (IUI)^(1,2).

IUI is a common method for achieving pregnancy in infertile women and is performed multiple times. Each IUI cycle begins with the female patient receiving letrozole and gonadotropins to stimulate ovulation. Follicular development is monitored by sonography, and human chorionic gonadotropin (hCG) is injected to induce the egg, after it reaches 18 mm in diameter. At 24-36 h after hCG injection, semen is placed into the uterus with an intrauterine catheter. If the first IUI cycle is not successful, another cycle is repeated after 1 month. The number of cycles is usually 3 to 6. The IUI success rate is 15-17% per cycle, which increases with each repetitive cycle^(1,2).

For patients who could not get pregnant with IUI treatment, in vitro fertilization (IVF) or microinjection is considered to be the next strategy, which is costly and has more complications. Therefore, increasing the success of IUI can be effective in reducing the cost and infertility problems in infertile couples^(1,2). In previous studies, the effect of endometrial injury on different methods of treatment has been examined. Some studies have shown that the use of endometrial injury increases pregnancy rates; however, other studies did not show an increase in pregnancy rates. Our focus in this study is the effect of endometrial scraping on IUI, which requires more research according to prior studies. The goal of this study was to examine the effect of local endometrial injury by pipelle endometrial sampling on pregnancy rates in infertile women who received IUI. This study helps increase the effectiveness of IUI; therefore, the use of costly and time-consuming methods, such as IVF, is reduced.

Materials and Methods

This study is a prospective randomized clinical trial and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.1569). This study was registered in the Iranian Registry of Clinical Trials (no: IRCT20160224026750N2). All participants provided informed consent before entering the study. Each patient was assigned a specific code to keep the data private and the patient's information confidential. Allocation concealment was performed accordingly, and all the stages of this study complied with the Declaration of Helsinki.

Study samples were infertile women aged 18-35 years undergoing IUI at Shariati Hospital from 2018 to 2020. Medical information was collected through interviews, examinations, and test results. Inclusion criteria were unexplained infertility, infertility duration of 2 to 6 years, body mass index (BMI) of 30 kg/m², regular menses, normal hysterosalpingography, normal pap smear, normal uterine cavity, follicle stimulating hormone

(FSH) level of 10 mIU/mL on the 3rd day of the cycle, normal thyroid-stimulating hormone and prolactin levels, and anti-Mullerian hormone level of more than 1 µg/L.

Exclusion criteria were age over 35 years, uterine myoma, ovarian cyst, uterine cavity abnormalities, endometrial polyp, blockage of fallopian tube, infertility due to male factor, receiving other treatments other than IUI in the last 3 months, and history of diabetes and heart or pulmonary disease.

All male individuals had normal parameters for semen analyses (sperm concentration of more than 15x10⁶ per mL, normal morphology of more than 4%, and progressive motility of more than 32%) based on the World Health Organization⁽³⁾.

Sample size analysis was performed based on Abdelhamid⁽⁴⁾ ($\alpha=0.05$, $\beta=0.2$). The sample size was measured to be 122, and they all met the criteria. None of the patients dropped out for any reason. Transvaginal ultrasound was performed on the 3rd day of menstruation for all women. For ovarian stimulation, letrozole oral intake (Iranian hormone, Iran, 2.5 mg per day) was started on the 3rd day of the cycle for 5 days for all patients. In addition, recombinant FSH (Gonal-F, Merck Sermo, Switzerland, 75 IU) was injected on the 4th and 6th day of the menstrual cycle for all patients.

Endometrial thickness and follicular development were monitored using transvaginal ultrasound on day 9 of the menstrual cycle. On the 9th day of the cycle, patients were randomly divided into two groups of 61 patients. Patients in the first group underwent local endometrial injury in the posterior uterine wall by pipelle endometrial sampling on day 9 of the cycle. In the second group (control group), no intervention was performed.

When at least one follicle reached 18 mm in each patient, 5000 IU of hCG (Choragon, Ferring, Swiss) was injected for ovulation induction in all patients. After 24 h, 0.5 mL of prepared sperm was placed into the uterus using an intrauterine catheter for all patients. After IUI, all patients took 400 mg progesterone suppositories (Cyclogest, Actover, Britain) daily for 2 weeks to support the luteal phase.

Two weeks after IUI, β -hCG levels was measured to evaluate chemical pregnancy. If chemical pregnancy was positive, patients continued taking progesterone until 8th week of pregnancy. If β -hCG test was negative, patients were followed up for 3 months to determine if they naturally got pregnant or not. Clinical pregnancy test was performed 2 weeks after positive chemical pregnancy test by observing pregnancy sac in transvaginal ultrasound. In this study, the IUI cycle was performed only once for each patient.

In both groups, the patients were similar in terms of age (Figure 1), BMI, infertility duration (Figure 2), FSH in 3rd day of cycle, and polycystic ovary ($p>0.05$) and it is shown in Table 1. Data regarding the two groups, including endometrial thickness, dominant follicle count, chemical pregnancy rate, clinical pregnancy rate, spontaneous pregnancy rate, and abortion rate, were gathered and compared.

Statistical Analysis

Comparison of the groups was performed using independent sample t-test, Fisher’s Exact test, and chi-square test. Data analysis was performed using IBM SPSS 13 and significance level was less than 0.05.

Results

The ovulation induction outcomes are shown in Table 2. After ovulation induction, there were no statistically significant differences in endometrial thickness (Figure 3) and the number of dominant follicles between the two groups ($p>0.05$).

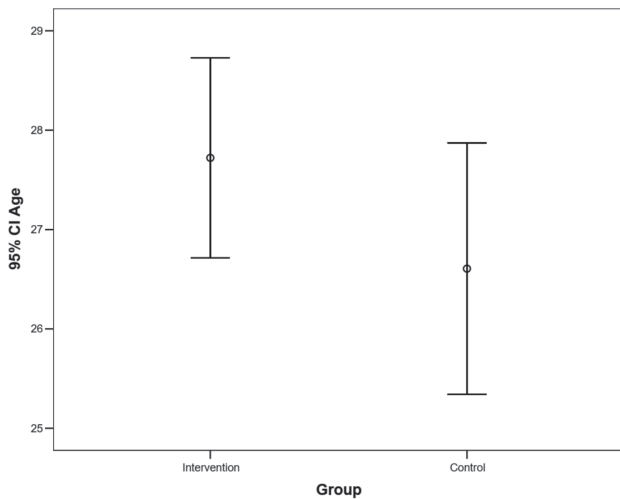


Figure 1. Age of infertile women who received IUI in two groups of endometrial injury and control

IUI: Intrauterine insemination, CI: Confidence interval

The pregnancy outcomes are shown in Table 3. The chemical pregnancy rate, clinical pregnancy rate, and abortion rate were not significantly different between the two groups ($p>0.05$). However, the spontaneous pregnancy rate after the IUI cycle in the endometrial injury group was significantly higher than that in the control group ($p=0.02$). The total pregnancy rate (clinical pregnancy plus spontaneous pregnancy) in the endometrial injury group was also significantly higher than that in the control group ($p<0.01$) due to higher spontaneous pregnancy rate in that group.

It is worth mentioning that multiple pregnancies did not occur in any patient.

Discussion

IUI is a non-invasive and cheap method compared with other fertility assistance methods, and it is widely used in infertile couples. The main obstacle in infertility treatments is the failure of embryo implantation during treatment cycles. The percentage of embryo implantation in these cycles is 15%. During the process of healing the endometrial injury, cytokines and growth factors are secreted from immune cells, which improve embryo implantation. Endometrial injury by biopsy increases endometrial blood flow and strengthens the endometrial immune system. Therefore, it can affect endometrial tissue thickness and future pregnancy outcomes^(1,2).

Some studies suggest that the effect of endometrial injury persists for a long time, even up to 6 months^(5,6). These findings may explain the high spontaneous pregnancy rate for 3 months after endometrial injury in our study. Due to the author’s personal difficulties and lack of time, we could not follow-up the patients for more than 3 months.

Table 1. Demographic characteristics of infertile women who received IUI in two groups of endometrial injury and control

	Endometrial injury group (61 women)		Control group (61 women)		p-value
	Mean	SD	Mean	SD	
Age (year)	27.72	3.93	26.61	4.94	0.17
BMI (kg/m ²)	24.17	2.97	25.15	2.69	0.06
Infertility duration (year)	2.84	2.16	3.44	2.37	0.14
Patients with polycystic ovary	7	0	8	0	0.8
FSH index in day 3 of IUI cycle (mIU/mL)	5.46	2.41	6.31	3.14	0.4

BMI: Body mass index, FSH: Follicle stimulating hormone, IUI: Intrauterine insemination, SD: Standard deviation

Table 2. Ovulation induction outcomes of infertile women who received IUI in two groups of endometrial injury and control

	Endometrial injury group (61 women)		Control group (61 women)		p-value
	Mean	SD	Mean	SD	
Endometrial thickness (mm)	7.93	1.13	7.59	1.3	0.12
Dominant follicle count	1.69	0.62	1.92	0.74	0.15

IUI: Intrauterine insemination, SD: Standard deviation

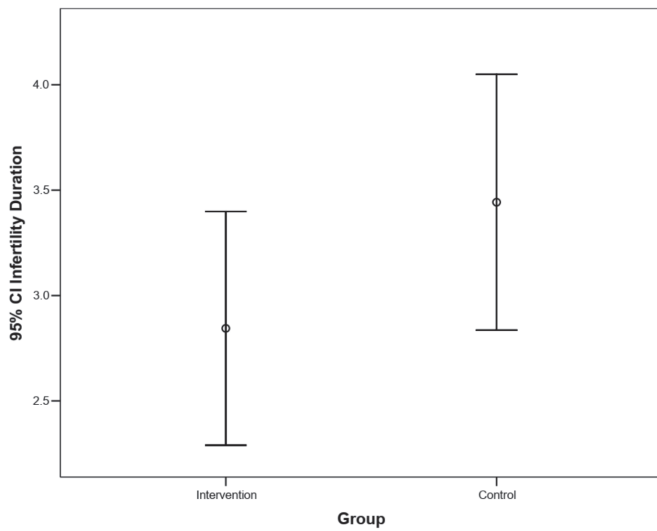


Figure 2. Infertility duration of infertile women who received IUI in two groups of endometrial injury and control

IUI: Intrauterine insemination, CI: Confidence interval

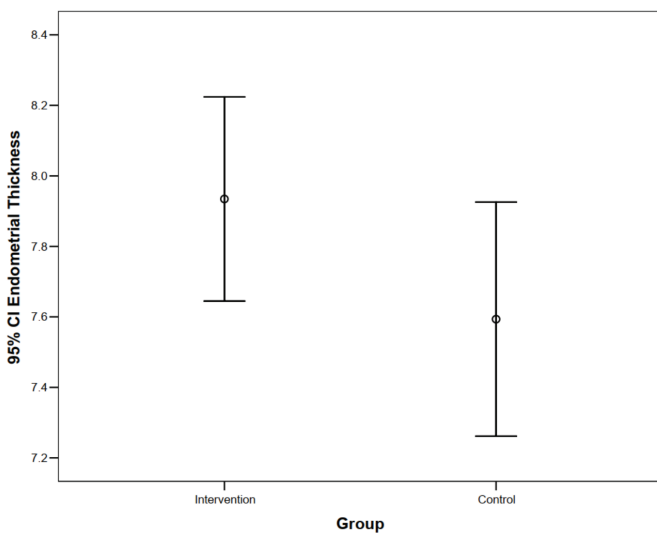


Figure 3. Endometrial thickness of infertile women who received IUI in two groups of endometrial injury and control

IUI: Intrauterine insemination, CI: Confidence interval

Many studies have evaluated the effect of local endometrial injury on pregnancy rates using different treatments. Concerning unexplained infertility, studies have shown that endometrial injury has a positive effect on pregnancy rates in unexplained infertile women^(6,7).

Effect of Endometrial Injury on the Same IUI Cycle

According to previous studies by Abdelhamid⁽⁴⁾, Bahaa Eldin et al.⁽⁸⁾, Wadhwa et al.⁽⁹⁾ and Gupta et al.⁽¹⁰⁾ endometrial sampling performed on the same IUI cycle significantly increases pregnancy rates for that cycle. However, other studies by Maged et al.⁽¹¹⁾, Ashrafi et al.⁽¹²⁾ and Ghuman et al.⁽¹³⁾ did not show a significant increase in pregnancy rates. Our findings suggest that endometrial sampling during the same IUI cycle does not increase pregnancy rates during that cycle.

Effect of Endometrial Injury After the First IUI Cycle

According to a past study by Maged et al.⁽¹¹⁾ endometrial sampling performed on the first IUI cycle significantly increases pregnancy rates after the first cycle. However, other studies by Wadhwa et al.⁽⁹⁾ and Ghuman et al.⁽¹³⁾ showed no increase in pregnancy rates after the first cycle. Our findings suggest that endometrial sampling increases pregnancy rates after the first cycle.

Studies Conducted on Past Literature

In systematic reviews by Sar-Shalom Nahshon et al.⁽¹⁴⁾ and Bui et al.⁽¹⁵⁾, they concluded that concerning the effect of endometrial injury on IUI, reaching conclusions and comparing the results is difficult due to varied types of enrolled patients, type and time of intervention, and the number of IUI cycles in different studies. Almog et al.⁽¹⁶⁾ conducted a literature search on endometrial injury and found that endometrial injury has a positive impact on implantation and improves the pregnancy rate. However, more research needs to be conducted on patient selection, timing, technique, and number of endometrial biopsies. Their results support our study results. In a systematic review by Vitagliano et al.⁽¹⁷⁾ they concluded that endometrial injury during the follicular phase of the same cycle of IUI improves clinical pregnancy and ongoing pregnancy rates in IUI cycles.

Table 3. Pregnancy outcomes of infertile women who received IUI in two groups of endometrial injury and control

	Endometrial injury group (61 women)		Control group (61 women)		p-value
	Quantity	Percentage	Quantity	Percentage	
Chemical pregnancy rate	15	24.6%	9	14.8%	0.31
Clinical pregnancy rate	14	23%	8	13.1%	0.4
Spontaneous pregnancy rate after IUI cycle	6	9.8%	0	0%	0.02
Miscarriage rate	1	1.6%	1	1.6%	1
Total pregnancy rate (clinical and spontaneous pregnancy)	20	32.8%	8	13.1%	<0.01

IUI: Intrauterine insemination

In some studies, endometrial thickness and dominant follicle count were not different between the control and endometrial injury groups^(9,18,19). However, another study showed higher endometrial thickness and dominant follicle count in the endometrial injury group⁽¹⁰⁾.

In general, some studies show that endometrial injury done by sampling has a positive effect on IUI pregnancy rates^(8-11,14,15,17,19,20), whereas other studies found no change at all^(10,12,13,18,21,22). The designs of past studies differ from one another. Timing of endometrial sampling seems to be important in terms of pregnancy results. In conclusion, more studies with larger sample sizes and more variables need to be conducted on this matter.

Study Limitations

Due to lack of time, the number of IUI cycles performed was a limitation of this study. It is recommended that future studies examine pregnancy rates in multiple consecutive IUI cycles.

Conclusion

Endometrial thickness and dominant follicle count were not significantly different between the control and endometrial injury groups. In the first IUI cycle, endometrial injury during the follicular phase did not change pregnancy rates compared with the control group. However, after the first cycle, endometrial injury increased the spontaneous pregnancy rate compared with the control group. Therefore, endometrial injury does not immediately affect pregnancy in the same cycle; however, it does have a positive effect on pregnancy rates in later cycles. In conclusion, performing endometrial sampling during the follicular phase of the IUI cycle is a simple, practical, and cost-effective procedure that increases the chances of later pregnancy.

Ethics

Ethics Committee Approval: This study is a prospective randomized clinical trial and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.1569).

Informed Consent: All participants provided informed consent before entering the study.

Authorship Contributions

Surgical and Medical Practices: S.H., Concept: S.H., S.M., R.P., Design: S.H., S.M., M.T., Data Collection or Processing: S.H., S.M., R.P., Analysis or Interpretation: S.H., M.T., Literature Search: S.M., R.P., Writing: S.H., S.M., R.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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