

Comparing the effects of endometrial injury with hysteroscopy or Pipelle cannula on fertility outcome

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Abstract. – OBJECTIVE: To compare the effects of mechanical endometrial injury performed with hysteroscopy or Pipelle cannula on fertility outcome in patients with implantation failure.

PATIENTS AND METHODS: Sixty patients with a history of two or more failed ICSI despite the transfer of high-quality embryos were equally divided into three groups: Group A – injury with hysteroscopy (n=20), Group B – injury with Pipelle cannula (n=20), Group C – no injury (n=20). Patients in group A underwent endometrial injury with monopolar needle forceps between days 10-12 of the proliferative phase in the preceding cycle before ovarian stimulation. Patients in group B underwent endometrial injury with Pipelle cannula between days 22-24 of the mid-luteal phase in the preceding cycle. Patients in group C had no injuries. Beta-hCG, clinical pregnancy, live birth and miscarriage rates were analyzed among the groups.

RESULTS: There were no significant differences in terms of positive pregnancy test, clinical pregnancy and live birth rates between hysteroscopy and Pipelle groups. Compared to the control group, both clinical pregnancy and live birth rates were found to be significantly higher in patients who underwent endometrial injury with hysteroscopy or Pipelle cannula. Miscarriage rates in the control group were significantly higher than those in the Pipelle or hysteroscopic injury.

CONCLUSIONS: Endometrial injuries performed in the follicular phase with hysteroscopic monopolar forceps or in the secretory phase with Pipelle cannula increase pregnancy and live birth.

Key Words:

Endometrial injury, Hysteroscopy, Pipelle cannula, Clinical pregnancy, Live birth, Miscarriage.

of the cycle increased pregnancy rates nearly twice. Many studies followed this pioneering work, but the results were inconsistent. While some of the studies reported the positive effects of injury on fertility outcome, others stated that the results were not sufficient to put endometrial injury into routine use²⁻⁴. The main reason for the incompatibility between the studies was that patient groups were not well selected, the injury used method was different in each study, and the number of injuries was not standard¹⁻⁵. Some studies^{3,5} reported positive results by doing repetitive injuries, while others reported similar results with a single injury. Studies²⁻⁴ reporting a positive effect of injury on fertility were mostly conducted in patient groups with recurrent implantation failure. On the other hand, studies²⁻⁵ reporting the ineffectiveness of injury consisted of patients in their first IVF/ICSI trial.

Most of studies³⁻⁵ preferred outpatient treatment with Pipelle cannula. In addition to those who made injuries in the first or second phase of the cycle, there were studies that made injuries in both cycle phases¹⁻⁵. The number of studies⁶⁻⁸ using hysteroscopy as the method of injury was very low. However, the results of hysteroscopic injury on pregnancy rates were more homogeneous. This success was attributed to the injury caused by seeing the cavity during hysteroscopy. The effects of mechanical injury made with hysteroscopy or Pipelle on fertility outcome have not been compared. This study was, therefore, planned to compare the effects of hysteroscopy-guided needle forceps injury and mechanical endometrial injury with Pipelle cannula on fertility outcome in patients with implantation failure.

Introduction

In a semi-randomized study conducted by Barash et al¹ in 2003, it was reported that mechanical endometrial injury of the endometrium on different days

Patients and Methods

The sample size of the study was calculated with the G*Power 3.1 program. The total mean of

two groups was calculated with the Mann-Whitney test with the effect size of 0.50%, power of 80% and maximum acceptable type 1 error of 5%. That calculation indicated a sample size of 60 women with a 95% confidence interval. Therefore, a total of 60 infertile women with failed IVF/ICSI cycles were included in the study. Participants were selected among infertile patients who applied to Istanbul IVF-Center between 2018-2021. The groups consisted of patients with at least two or more implantation failure. Inclusion criteria were: two or more history of failed IVF/ICSI, being younger than 37 years of age, FSH levels <10 IU/L, normal endometrial cavity on SIS, HSG or 3D USG. To summarize, a group of 60 patients who showed a good response to hormonal stimulation were equally randomized into three groups: group A – injury with hysteroscopy (n=20), group B – injury with Pipelle cannula (n=20), group C – no injury or sham (n=20). Patients in group A underwent endometrial injury with monopolar needle forceps between days 10-12 of the proliferative phase in the preceding cycle before ovarian stimulation. Patients in group B underwent endometrial injury with Pipelle cannula between days 22-24 of the mid-luteal phase in the preceding cycle before ovarian stimulation. In the control group (sham), the fundus was reached by passing the Pipelle cannula through the cervical canal, but no injury was made. Rigid hysteroscopy with a length of 25 cm, a sheath thickness of 5 mm and a 30-degree lens was used. By using monopolar electric energy with needle forceps, mechanical injury was made to the areas up to the distance between the tubal ostia, fundus and posterior wall of corpus. Against any adhesion risk, the injury depth tried to be kept at the sub endometrium level. In the Pipelle group, after the catheter was passed through the cervix and the fundus was reached, the piston was pulled back and the sheath was moved forward and backward. More information about injury details can be found somewhere else^{1,6-8}.

The primary outcome measures were the percentage of biochemical pregnancy, clinical pregnancy, miscarriage, and live birth and the results obtained compared among the three groups. A positive beta-hCG test in blood samples 12 days after embryo transfer was accepted as biochemical pregnancy. Clinical pregnancy was defined as evidence of a gestational sac, confirmed by ultrasound examination. Live birth was defined as delivery of a live fetus after 24 completed weeks of gestational age. Patients with abnormal endo-

metrial cavity, submucous fibroids, endometrial polyp, intrauterine synechia, endometrioma or hydrosalpinx causing implantation defects were excluded from the study. Patients who were transferred from diagnostic hysteroscopy to operative hysteroscopy were not included in the study. In addition to those who responded poorly to ovulation stimulation, patients over 37 years of age were also excluded from the study. All procedures performed in this study were in accordance with the ethical standards of international research committee and local approval was obtained from the Istanbul IFV-Center. All patients recruited for the study were fully counseled and signed written informed consent.

Participants in each group were treated according to a standard antagonist protocol with individually dosed recombinant FSH starting on day 2-3 of the menstrual cycle. 0.25 µg gonadotrophin-releasing hormone antagonist was started on the 5th or 6th day of stimulation. When at least three follicles reached 16-17 mm in diameter, maturation of follicles was induced with recombinant hCG. Oocyte pick-up was performed 36 hours after hCG application. Ovarian follicles were aspirated using a single-lumen, 17-gauge needle guided by trans-vaginal ultrasonography. Intracytoplasmic sperm injection was performed using the sperm on the day of oocyte retrieval. Embryos were assessed and selected based on the morphologic criteria. Two fresh embryo transfers were performed on the third day of development under ultrasound guidance. Luteal phase support was provided with vaginally administered progesterone.

Statistical Analysis

The baseline characteristics of the three groups of participants including injury with hysteroscopy, injury with Pipelle cannula and non-injury groups were compared using ANOVA and Chi-square tests. Comparison of quantitative variables between the three groups was done using Student's *t*-test for independent samples. For comparing categorical data, Chi-square test was performed. Statistical analyses were performed using Excel software and SPSS version 21.0 statistical software (IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered as statistically significant.

Results

The mean age, BMI, basal FSH and LH levels of the patients in all three groups, and the number

Table I. Comparison of the clinical pregnancy, miscarriage and live birth rates of groups.

	B-hCG positivity	Clinical pregnancy	Miscarriage	Live birth
1-Hysteroscopic injury (n=20)	8 (40%)	8 (40%)	1/8 (12.5%)	7 (35%)
2-Pipelle injury (n=20)	7 (35%)	7 (35%)	1/7 (14.2%)	6 (30%)
3-Control (no-injury; n=20)	4 (20%)	4 (20%)	1/4 (25%)	3 (15%)
	p-value			
1 vs. 2	0.06	0.44	0.56	0.60
1 vs. 3	0.01	0.02	0.02	0.01
2 vs. 3	0.03	0.04	0.03	0.01

of unsuccessful attempts were found to be similar. There was a history of two failed IVF/ICSI attempts in 67% of patients in the hysteroscopic injury group, 70% of patients in the Pipelle group, and 69% of patients in the control group. There was no significant difference between the groups in terms of failed attempts. Likewise, no significant difference between the groups in terms of the total number of oocytes collected, the number of MII oocytes or 2 PN zygotes, and the number of transferred embryos. Similarly, there was no difference between the groups in terms of total rFSH dose, induction time, estradiol levels on the day of hCG and endometrial thickness. Endometrial scratching was successfully performed on all patients in the hysteroscopic injury and Pipelle groups. There were no complications in both groups except pain and vaginal bleeding in the form of spots after the injury procedure. Pain improved spontaneously in some patients and with analgesics in others. IVF indications of each group were classified as tubal, male, or ovulatory factor, unexplained infertility or mixed causes and their incidence were found to be similar in each group.

Positive Beta-hCG, clinical pregnancy and live birth rates were found to be similar between hysteroscopy and Pipelle groups. Although there was a slight increase in both clinical pregnancy (40% vs. 35%, $p < 0.44$) and live birth rates (35% vs. 30%, $p < 0.60$) in the hysteroscopy group the difference was not significant. On the other hand, positive Beta-hCG, clinical pregnancy and live birth rates were found to be significantly higher in both hysteroscopy and Pipelle groups when compared with the control group. Whether it was done hysteroscopically or with Pipelle, the injury had a positive effect on reproductive outcome. Miscarriage rates were found to be similar in the hysteroscopy and Pipelle groups. In the control group, the miscarriage rates were significantly higher than both the Pipelle and hysteroscopy groups. The clinical pregnancy, abortion and live

birth percentages and comparisons of the groups are presented in Table I.

Discussion

In the selected patient group, mechanical endometrial injury makes a significant increase in pregnancy rates^{1,2,5}. However, it does not show the same success in patients with their first IVF/ICSI trial or in unexplained infertility^{5,9}. The heterogeneity of patient groups in mechanical injury studies, the differences in the time and method of injury prevent the results from being homogeneous^{1,5,9}. At the beginning of the problems that make the results heterogeneous, some studies have used Pipelle cannula to make mechanical injury, while others have done the injury with hysteroscopy^{1,6,7}. Studies using Pipelle cannula for injury are more numerous than hysteroscopic injury studies. However, despite the numerical scarcity, the results obtained in hysteroscopic injury studies are more homogeneous and most studies show that pregnancy rates increase⁶⁻⁸. Although the results mostly show an increase in pregnancy rates, there are also reports⁵ that injury with Pipelle does not affect fertility outcome.

In the literature, there is no study comparing the injury with Pipelle cannula with hysteroscopic injury. In this study, for the first time, we compared the effects of Pipelle and hysteroscopic injury on fertility outcome in patients with implantation failure. We found that clinical pregnancy and live birth rates significantly increased in both injury groups. Although clinical pregnancy and live birth rates were slightly higher in the hysteroscopy group than in the Pipelle group, the results did not reach statistical significance. In summary, both types of injuries improved pregnancy rates. When we briefly reviewed previous studies on hysteroscopic injury, we found that our results were similar. In the study conducted by Seval et al⁶, patients diagnosed with RIF

and normal endometrium were divided into two groups: in the first group, injury was made with monopolar needle forceps during hysteroscopy, and only diagnostic hysteroscopy was performed in the control group without injury. The implantation, clinical pregnancy and ongoing pregnancy rates of the hysteroscopy-guided electrical energy injury group were found to be significantly higher than the non-injured control group. Narvekar et al⁸ showed to injuries in the patient group, with a previous history of unsuccessful IVF/ICSI at least once: they made the first injury in the follicular phase on the day they performed hysteroscopy and the second one in the secretory phase. Pipelle cannula was used in both injuries. No injury was made to the control group. At the end of the study, implantation, clinical pregnancy, and live birth rates were found to be significantly higher in the injury group than in the control group. However, it is not clear whether the study is a hysteroscopy study since the first injury was performed in the follicular phase accompanied by hysteroscopy, and the second injury was performed in the luteal phase and without hysteroscopy. In the study conducted by Shohayeb and El-Khayat⁷ patients with recurrent implantation failure were divided into two groups. The first group got injury with a Novak curette during hysteroscopy, and the control group only performed hysteroscopy and did not apply injury. Implantation, clinical pregnancy and live birth rates were found to be significantly higher in the injured group compared to the control group. Although these studies are similar in terms of the patient groups they selected, the hysteroscopic injury methods applied are not standard. Considering the differences in the number of injuries and the periods in which the injury was made between the studies, it is understood that the results are of medium quality. However, despite all these differences, all three studies reported an increase in implantation and live birth rates. The common conclusion that we can deduct from the three studies is that hysteroscopy-guided injuries with monopolar forceps or Novak curette increase the pregnancy rate at similar rates⁶⁻⁸. However, in these studies, injury was performed with needle forceps, Pipelle cannula or Novak curette, and a standard method was not applied. We used needle forceps in all cases, we did not make any additional injury. We performed the injury once in the follicular phase in the hysteroscopy group, and once in the secretory phase in the Pipelle group. Our results are compatible with above studies in terms of fertility outcome.

Conclusions

When we compared the groups in terms of miscarriage rates, we encountered a lower percentage in both injury groups compared to the controls. However, due to the low number of abortion cases, we refrain from commenting on the net effect of injury on abortion rates. As a result, although the underlying effect mechanisms are not clear, pregnancy rates may have increased due to the increase in the release of growth factors and inflammation molecules during wound healing in the endometrium after injury^{10,11}. Further studies are needed to elucidate the underlying mechanism of the fertility enhancing effect of injury. Regardless of the underlying mechanism, endometrial injury increases the fertility outcome. Injuries made with both hysteroscopy and Pipelle have a similar and positive effect on pregnancy outcome.

Conflict of Interest

The authors declare that they have no conflict of interests.

Informed Consent

All patients recruited for the study were fully counseled and signed a written informed consent.

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of international research committee and local approval was obtained from the Istanbul IFV-Center.

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