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ORIGINAL ARTICLE

Fecundability in couples with idiopathic primary infertility after endometrial scratching: a retrospective cohort study

Spontaneous pregnancy rate in couples with idiopathic primary infertility

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ABSTRACT

Objective. This study aimed to investigate the effect of endometrial injury on spontaneous pregnancy rate (fecundability) in patients with long-term idiopathic primary infertility.

Materials and Methods. 153 women with primary infertility for two or more years were checked. Those in whom a cause could be identified or women with a BMI of > 30 were excluded from the study. Ninety-three women with idiopathic primary infertility who underwent office hysteroscopy in the last 6 months were included in the study provided they received counseling about office hysteroscopy with endometrial scratching and underwent the procedure. Five women were found to have ostial polyps <7 mm in size and had these polyps removed by scissors; three cases were found to have mild to moderate Asherman's syndrome and that treated immediately by adhesiolysis using a cold knife, all excluded from the study and the remaining 85 women that had a normal, healthy endometrial cavities and scratching done were included in our study.

Results. Endometrial injury resulted in 39 (45.88 %) spontaneous pregnancies in the first 6 months after the endometrial injury, which were confirmed by transvaginal ultrasound visualization of the fetal heart at 7 weeks of gestation. Six of the 39 pregnancies resulted in an early miscarriage.

Conclusions. The results of this study showed that endometrial injury by office hysteroscopy may have a positive effect on the spontaneous pregnancy rate (fecundability) in long-term idiopathic primary infertility.

Key words

Infertility, fecundability, and Pregnancy rate.

Introduction

Several steps need to take place for pregnancy to occur naturally: 1) a healthy sperm that travels and fertilizes an ovum; 2) a healthy ovum that is released and is ready to be fertilized; and 3) a healthy receptive endometrial cavity in which the fertilized ovum can be implanted, and that is capable of maintaining the implanted ovum. Any defect in one of the three steps above affects the chances of pregnancy. In approximately 60% of couples, a specific cause can be found, and they are diagnosed with some form of male and/or female infertility [1]. However, in the remaining couples, a specific cause cannot be determined, and they are thus diagnosed with unexplained infertility.

In fertility clinics, idiopathic primary infertility is commonly diagnosed. Although there is a chance for a natural pregnancy to occur in couples diagnosed with idiopathic infertility, the duration of infertility, as well as the age of the female, are important factors to consider when calculating the rate of natural pregnancy in such couples. The longer the duration, the less likely it is for the couple to conceive on their own. One previous study showed that the natural conception rate (fecundity rate) leading to ongoing pregnancy is 24.5% after 12 months in couples with idiopathic or mild infertility, with estimated rates ranging from 22 to 35%, depending on the female age and duration of infertility [2]. Often, however, couples with unexplained infertility choose to undergo treatment rather than wait for a natural pregnancy to occur. However, owing to uncertainty about the specific medical cause of infertility, many couples undergo empirical treatments that can involve significant physical, psychological, and financial burdens.

Many couples with idiopathic infertility undergo in vitro fertilization (IVF); however, successful implantation of the embryo remains the major limiting factor. As implantation failure is the most difficult condition that fertility specialists experience, several approaches, and interventions have been used to overcome this issue in the field of assisted reproductive technologies aiming to increase the implantation rate especially in recurrent implantation failure (RIF) by measuring the potential endometrial biomarkers and underlying biological signaling as one of the proposed factors of RIF is a Disturbance of the endometrial immune microenvironment [28, 29] , and endometrial injury is one of these interventions. Scratching was first reported in 1907 by Loeb [3], who described the rapid proliferation of decidual cells after injury to the endometrium in the uterus of guinea pigs. In 2003, Barash et al. studied endometrial injury and its positive effects on implantation rates. They showed that endometrial biopsies on days 8, 12, 21, and 26 of the menstrual cycle were associated with a higher pregnancy rate after IVF treatment. According to the authors, endometrial injury exerts a positive effect on endometrial receptivity via the release of growth factors and cytokines during the healing process [4].

This study aimed to evaluate the effect of endometrial injury on spontaneous pregnancy rate after six months in long-term unexplained primary infertility.

Ethical consideration

All procedures performed in this study involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethical committee approval was obtained from the Hashemite University, *Zarqa*, *Jordan*. (No.6/7/2021/2022).

Materials & Methods

Medical records of 153 women with primary infertility for two or more years were checked in August 2022, private or identifying information of all 153 women was seen only by the corresponding author during data collection. Those in whom a cause of infertility could be identified (male factor, female factor and combined factor) or women with a BMI of > 30 were excluded from the study and by this we removed any confounding factor that may affect the results of the study. Data of Ninety-three women with idiopathic primary infertility who underwent office hysteroscopy in the last 6 months were included in the study provided they received counseling about office hysteroscopy with endometrial scratching and underwent the procedure. Five cases were found to have ostial polyps <7 mm in size and had these polyps removed by scissors; three cases were found to have mild to moderate Asherman's syndrome and that treated immediately by adhesiolysis using a cold knife, all excluded from the study and remaining 85 women that had normal, healthy endometrial cavities and scratching done were included in our study. The endometrial injury was done by office hysteroscopy in the late follicular phase (days 8–11).

Statistical Analysis

The data collected from these patients' files were organized using Microsoft Excel and analysed using SPSS v16, which was later written in Microsoft Word.

Results

Eighty-five of a total of 93 women with long-term idiopathic primary infertility underwent endometrial injury by office hysteroscopy at the late follicular phase (days 8–11) and that followed up for 6 months without any further treatment such as ovulation induction with or without intrauterine insemination and only advised to have regular sexual intercourse (at least twice per week).

The age range of the patient group was between 21 and 34 years, with a mean age of 28.26. (Table I)

The BMIs of the group ranged from 19.10 to 30, with a mean BMI of 23.74. (Table I)

The patient group had infertility durations that ranged between 24 and 41 months, with a mean duration of 31 months. (Table I)

A total of 39 women (45.88%) conceived spontaneously within 6 months and were confirmed at 7 weeks of gestation by transvaginal ultrasound visualization of the fetal heart. Six of the 39 pregnancies resulted in an early miscarriage.

The women who conceived ranged in age from 21 to 34 years, with a mean age of 28.26 years (Table II). Women who conceived had BMIs ranging from 19.4 to 30, with a mean of 23.64 (Table II).

The participants who conceived had idiopathic primary infertility durations ranging from 24 to 39 months, with a mean of 30.95. (Table II).

There was no significant difference between the statistics of the total participant group and the group that conceived, and pregnancies occurred across different age groups, BMI levels, and infertility durations. The correlational analysis between conception and age, BMI, and infertility duration did not reveal any significant correlation between the mentioned criteria (Table III-5V), which could be interpreted as endometrial Injury being effective regardless of age, BMI, and infertility duration.

Discussion

In this study, we found that the spontaneous pregnancy rate in the first 6 months in couples with long-term idiopathic primary infertility will increase after endometrial injury by office hysteroscopy. Another finding of our study is that women's age, BMI, or duration of unexplained infertility have no effect on the increase in spontaneous pregnancy rate after endometrial injury.

The exact cause of idiopathic primary infertility is not fully understood. Several theories have been proposed to explain this condition. Ovulatory, cervical, uterine, peritoneal, endocrinological, immunological, and genetic defects have been hypothesized as potential causative factors [5,6,7,8,9], but none of these theories could explain all cases of unexplained infertility.

Several approaches have been proposed to manage couples with idiopathic primary infertility, including IVF, IUI, and controlled ovarian hyperstimulation. [10,11] Implantation failure has been a challenging factor in these treatment options, which is why multiple interventions have been suggested to overcome it and increase the chances of clinical pregnancies. Endometrial scratching is an effective method for enhancing the success of embryo implantation. [12,13, 30]

Barash et al. [4] were the first to investigate the effects of endometrial injury on the chance of conception by endometrial sampling in IVF patients. They found that this resulted in a doubling of the couple's chances of conceiving in the next IVF-embryo ET cycle. Multiple studies have revealed increased implantation, clinical pregnancy, and/or live birth rates [12,13,14,15].

Several hypotheses have been proposed to explain the mechanism by which endometrial injury enhances the chances of a successful clinical pregnancy.

- First, the endometrial injury may increase the implantation rate via sterile inflammation, as the wound healing process may be stimulated by the secretion of many inflammatory mediators such as cytokines, interleukins, growth factors, macrophages, and dendritic cells, which may increase embryo implantation [16].

- Second, endometrial injury may induce structural and functional changes at the molecular level in the stroma and epithelium of the endometrium, which increases the probability of embryo implantation [17,18].

Additionally, it is thought that the injury-induced wound-healing process may help in embryo-endometrial synchronization. Zhou et al. proposed that injury-induced wound healing could slow endometrial development, which could lead to enhanced embryo-endometrial synchronization [17]. Li and Hao suggested that the wound-healing process after a local endometrial injury during the proliferative phase may induce synchronization between endometrial age and embryo age, which is a vital issue for successful embryo implantation [19].

Regardless of the reason, all these theories have one thing in common: their conclusion that endometrial injury increases the chances of a successful pregnancy. El-Toukhy et al. suggested that hysteroscopy before starting an IVF cycle increased the success rate. Hysteroscopy might improve IVF outcomes despite the inevitable degree of sustained endometrial injury during hysteroscopy [20,21,22].

Endometrial injury can be performed in a variety of ways, one of which is with a small 3 mm wide catheter known as Pipelle®. It is usually considered a low-risk procedure with a low rate of complications. Another alternative method is an injury during diagnostic hysteroscopy. A small optical instrument, measuring only 3 mm in diameter, is used to inspect and evaluate the uterine cavity to detect or rule out potential barriers to implantation as well as to "scratch" the endometrium [23]. Therefore, routine hysteroscopy with endometrial biopsy has been advised as a basic part of the work-up for women with idiopathic infertility [24.25.26,27].

Endometrial injury due to hysteroscopy can be intentionally performed after inspection and photographic documentation. A mucosal lesion is usually created on the posterior wall when an instrument is withdrawn. Huang et al. [22] combined hysteroscopy and site-specific endometrial injury in patients with recurrent implantation failure and reported a 100% ongoing pregnancy rate in the hysteroscopy and LEI groups compared with that in the control group.

The results of our study coincide with those of previous studies, where we found with statistical significance that endometrial injury caused by office hysteroscopy has a positive effect on the rate of spontaneous pregnancy (fecundity) in cases of long-term idiopathic primary infertility whereas other causes of infertility have already been ruled out. This warrants further studies on the same subject, as it could have an impact on the number of patients attempting IVF treatment or other costly treatment methods before attempting endometrial injury.

Study Limitations:

- Our study is retrospective, not an RCT study.

- The sample size is not big enough to draw a solid conclusion.

Conclusion

The study has shown that the spontaneous pregnancy rate (fecundability) in long-term idiopathic primary infertility may increase after the endometrial injury caused by office

hysteroscopy. This positive effect does not seem to be affected by age, BMI, or duration of infertility and stretches across multiple groups with different ages, weights, and durations of infertility. Our findings warrant large RCT studies on the same subject in the future and on unexplained primary infertility specifically, as this type of infertility is common and still one of the most difficult cases to treat. Moreover, it could have an impact on the number of couples attempting IVF treatment or other costly methods of treatment before attempting endometrial Injury.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions:

F.R: Research question, data collection, manuscript editing

B.O and M.B: Manuscript writing, final Editing

A.Q and L.A: Data analysis, manuscript writing

All authors read and approved the final manuscript.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interest.

Ethical approval

Ethical committee approval was obtained from the Hashemite University, Zarqa, Jordan, Ref. Number: IRB (NO. 6/7/2021/2022). patients' consent was obtained as per the hospital policy for the procedure. No private or identifying information is mentioned in the article.

Data Sharing

Data available on request from the authors

Informed consent

N.A

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Table 1

		Age	BMI	Duration of infertility in months
N	Valid	85	85	85
	Missing	0	0	0
Mean		28.26	23.7353	31.00
Median		28.00	23.6000	31.00
Minimum		21	19.10	24
Maximum		34	30.00	41

Table 2

		Age	BMI	Duration of infertility in months	Time to natural pregnancy in months
N	Valid	39	39	39	39
	Missing	0	0	0	0
Mean		28.26	23.6410	30.95	4.36
Minimum		21	19.40	24	3
Maximum		34	30.00	39	6

Table 3: Correlation Between Age and Conception

		Age	women conceived?
Age	Pearson Correlation	1	.001
	Sig. (2-tailed)		.995
	N	85	85
women conceived?	Pearson Correlation	.001	1
	Sig. (2-tailed)	.995	
	N	85	85

Table 4: Correlation Between BMI and Conception

		women conceived?	BMI
women conceived?	Pearson Correlation	1	.028
	Sig. (2-tailed)		.799
	N	85	85
BMI	Pearson Correlation	.028	1
	Sig. (2-tailed)	.799	
	N	85	85

Table 5: Correlation Between Duration of Infertility and Conception

		women conceived?	Duration of infertility in months
women conceived?	Pearson Correlation	1	.011
	Sig. (2-tailed)		.918
	N	85	85
Duration of infertility in months	Pearson Correlation	.011	1
	Sig. (2-tailed)	.918	
	N	85	85