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Original Research Article

Pregnancy Rates Increasing by Endometrial Scratching

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Conflict of interest: Nil

Abstract

Objective: The aim of this study was to examine the effect of endometrial scratching in women with unexplained infertility.

Method: A randomized controlled study was conducted in Hi Tech Medical College, Rourkela and a private practice setting. A total of 105 couples with unexplained infertility were randomly allocated into two groups: group A comprised 54 women who underwent endometrial scratching in the luteal phase of a spontaneous menstrual cycle; and group B included 51 women who underwent a placebo procedure. The main outcome measured was cumulative clinical pregnancy rate after 6 months and miscarriage rate.

Results: Clinical pregnancy rate was significantly higher in the women experiencing endometrial biopsy than in the control group (25.9% and 9.8%, respectively, P = 0.04). There was no significant difference in miscarriage rate between pregnant women in the endometrial injury group and pregnant women in the control group (12.5% and 16.5%, respectively, P = 0.79).

Conclusion: Endometrial scratching may improve clinical pregnancy rates in couples with unexplained infertility. Adequately powered studies are mandated to confirm or refute the findings.

Keywords: Biopsy, Endometrium, Infertility, Scratching, Unexplained.

Introduction

Unexplained infertility (UI) is a term used to describe infertile couples in whom standard investigations, including semen analysis, tests of ovulation and tubal patency, have failed to detect any gross abnormality [1]. It is a diagnosis of exclusion. Almost 30–40% of infertile couples would suffer from this type of subfertility [2]. Currently, the exact cause of UI is not known. A diversity of causes had been hypothesized to explain the condition. Cervical, uterine, ovulatory, peritoneal, immunological, endocrinological, genetic defects and reproductive physiology disturbances had been continuously suggested as potential causative factors [3–7]. However, none of these causes was solely able to explain all cases of reproductive failure. Empirically, interventions for managing unexplained infertility had been widely practiced. These interventions include expectant management, intrauterine insemination (IUI) with ovarian stimulation and in vitro fertilization (IVF) [8,9].

Recently, endometrial scratching has been suggested to boost embryo implantation

following recurrent implantation failure after IVF [10,11]. Researchers suggested that endometrial scratching could have a favorable endometrial healing effect on the implantation process. This favorable healing effect may trigger the release of biochemical mediators that could enhance implantation [10,12]. Since an impairment of endometrial receptivity may be a cause of subfertility in a group of couples diagnosed with unexplained infertility, [13–15] endometrial injury may help a group of couples with unexplained infertility.

The aim of this study was to examine the effect of endometrial scratching in women with unexplained infertility undergoing expectant management in a randomized controlled setting.

Methods

Study Design:

This was a randomized prospective study conducted in Hi Tech Medical College, Rourkela within a year.

Methodology:

Patients were randomly divided into two groups: group A and group B. Group A was the interventional group (n = 54) and group B was the control group (n = 51). Randomization and follow up randomization were carried out through a computer generated allocation sequence. Allocation was through a nurse picking up a sealed opaque consecutively numbered envelope.

hough the clinicians were not blinded for patients' allocation. Women were followed up for 6 months after randomization. A pregnancy test was performed a few days after a missed period. Clinical pregnancy was confirmed by the presence of an intrauterine gestational sac on ultrasonography, with a fetal heartbeat 2 or 3 weeks later. Endometrial scratching was performed for women in the interventional group (group A) on an outpatient setting.

The procedure was conducted at the luteal phase on days 21–26 of the spontaneous menstrual cycle. Endometrial samples were obtained using a biopsy catheter. After introduction of the pipelle into the uterine cavity, it was rotated 360 degrees and moved up and down four times after withdrawing the piston [10]. A similar placebo procedure using uterine sound was conducted at the luteal phase on days 21–26 of spontaneous menstrual cycles for women in the control group (group B).

The sound was manipulated in the uterine cavity as similar to the technique used for scratching with the pipelle. All women received 75 mg diclofenac once orally or rectally (30 min prior to the procedure), and 100 mg doxycycline orally twice daily for 5 days after the procedure. Non-hormonal contraception was advised to the patients in both groups in that cycle. Couples in both groups were asked to phone a contact person whenever there was a missed period. Couples were advised to practice sexual intercourse according to their convenience for the next 6 months.

The primary outcome was cumulative clinical pregnancy rate per woman after 6 months. Secondary outcomes included multiple pregnancy rate and miscarriage rate. Clinical pregnancy was confirmed by the presence of an intrauterine gestational sac by transvaginal ultrasound, with fetal heartbeats, 2–3 weeks following a positive pregnancy test. Miscarriage rate was defined as all women in whom pregnancy did not continue after a positive pregnancy test in serum and before 24 weeks' gestation.

Sample Size:

120 couples diagnosed with unexplained infertility among those attending the Hi Tech Medical College, Rourkela, were approached, and asked to participate in the study. Of these, 105 couples agreed to participate: 35 patients from MUH and 70 patients from the private setting.

Inclusion criteria:

women aged between 20 and 39 years with at least 1 year of infertility, regular menstruation with the length of the cycle between 22 and 34 days and ovulation confirmed by appropriately timed mid-luteal progesterone, fertile semen variables (according to World Health Organization criteria 1999), and bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography).

Statistical analysis: spss version 16 was used for statistical analysis. Results are expressed in the form of mean SD for numerical variables and percentages for categorical data. Fisher's exact test was used to compare proportions. The Student's t-test was used to compare means. Statistical significance was set at $P < 0.05$. We adopted an intention-to-treat analysis strategy

Results

From 120 couples approached, 105 agreed to participate. Of these, 98 continued the study and seven withdrew from the study after randomization without receiving their allocated intervention or placebo: three from group A and four from group B. Five patients dropped out and were lost to follow up after receiving their allocated intervention from group A compared to three patients from group B.

The baseline characteristics of the two groups, such as age, duration of infertility, type of infertility and body mass index were not statistically different (Table 1). No associated complications were reported among women randomized to undergo endometrial scratching. Histopathology revealed 'secretory endometrium' in the majority of the biopsies (40 samples), while 14 samples showed non-specific endometritis. As both groups had received doxycycline for 5 days after the procedure, no further treatment was provided for any case regardless of the results of the biopsy.

Table 1: Patients' characteristics and the outcomes of the Study

Parameter	Scratching	Placebo	*P*-value
	(*n* = 54)	(*n* = 51)	
Age (years)†	30.56 ± 5.08	31.38 ± 5.17	0.43
Body mass index†	30.1 ± 2.1	31.2 ± 1.5	0.37
Duration of subfertility (months)†	73.4 ± 3.5	77.5 ± 3.6	0.67
Basal FSH (IU/ml)†	7.8 ± 1.2	7.4 ± 1.4	0.23
Type of subfertility‡			
Primary	38 (70.3%)	38 (74.5%)	0.45
Secondary	12 (22.2%)	10 (19.6%)	
Biochemical pregnancy rate‡	16 (29.6%)	6 (11.7%)	0.03*
Cumulative clinical pregnancy rate‡	14 (25.9%)	5 (9.8%)	0.04*
Multiple pregnancy rate‡	1 (7%)	0 (0%)	1
Miscarriage rate‡	2 (12.5%)	1 (16.6)	0.79

Biochemical pregnancy was confirmed in 16/54 women in the interventional group (group A), and in 6/51 women in the control group (group B). The biochemical pregnancy rate was significantly higher in women in group A than in women in group B (29.6% and 11.7%, respectively, P = 0.03). Clinical pregnancy occurred in 14/54 women in the interventional group (group A), and in 5/51 women in the control group (group B). The cumulative clinical pregnancy rate was significantly higher in women in group A than in women in group B (25.9% and 9.8%, respectively, P = 0.04). There was no significant difference in miscarriage rate among women in the two groups (12.5% and 16.6%, respectively, P = 0.79). One pregnancy for a woman in the

endometrial scratching group was twin pregnancy. There were no multiple pregnancies among pregnant women within the control group.

Discussion

Our results showed a beneficial effect of endometrial scratching, in terms of biochemical pregnancy rate and cumulative clinical pregnancy rate, in women with unexplained infertility. The earliest reports for the effectiveness of this procedure came from Barash et al., who reported twofold higher pregnancy rates among women with recurrent implantation failure who underwent endometrial biopsy prior to IVF treatment compared to controls.16 Subsequently, several publications had demonstrated the same favorable effect [10,11,17–20]. Earlier, a number of studies explored the role of the classical dilatation and curettage operation in women with infertility [21–24]. These studies demonstrated a favorable effect of the procedure in subfertile women. Researchers attributed this favorable effect to the diagnostic capability of this procedure and had not examined its potential therapeutic effect.

Endometrial scratching is a simple, minimally invasive, low-cost procedure that may boost biochemical and clinical pregnancy rates in women with unexplained infertility. The questions regarding the underlying mechanism of the procedure action remain unanswered, however some hypotheses have been made to explain its beneficial effect. It was hypothesized that the local injury to the endometrium in a cycle might induce proper decidualization for implantation competency [17,25]. Li and Hao suggested that endometrial injury increases the expression of estradiol receptor in endometrial stroma causing changes in endometrial maturation [17]. Mechanical endometrial stimulation with a microcurette or an oil injection had been known to induce decidual tissue formation in guinea pigs and in mice in a manner similar to the endometrial changes that occur with the initiation of early pregnancy [12,26].

A proper healing effect, implemented through the released cytokines and growth factors after endometrial scratching, might induce the observed favorable effect.27,28 The simple mechanical effect by removing polyps and abnormally thickened endometrium had been also suggested.10 A favorable effect of lipoid injection on fertility outcome in women with unexplained infertility has been mentioned in the literature [29,30]. Authors attributed the effect to the hydrostatic recanalizing effect on tubes. However, a theoretical beneficial effect of lipiodol on endometrium should not be overlooked. Patients with unexplained infertility might not share the same hidden cause of infertility. This may trigger thoughts about which couple with unexplained infertility may be more likely to benefit from this procedure. Plausibly, any factors negatively affecting the endometrium might be overcome through the suggested healing effect of this procedure. More studies on the effect of this procedure may help to refine the exact population who may get benefit from the procedure

Limitation

One of the limitations of our study is that it is a small, randomized study without a priori power calculation. The reason for that was the lack of similar studies about the probable difference of pregnancy rate between the two procedures. Although we opened the door for recruitment of couples after at least 1 year of unexplained infertility, our data showed that the mean duration of infertility within the two groups was 71 months. Epidemiological studies indicated that the chances of spontaneous pregnancy decrease significantly after 4.5 years of infertility [31,32]. This may represent indirect evidence of the beneficial effect of the procedure.

Moreover, the follow-up for patients was limited to 6 months' duration. We do not know whether extending the follow-up duration could have affected the results. More information is needed as regards the timing of the procedure and whether repeating the procedure in women who failed to conceive after undergoing it once may be beneficial or not. Thus, we call for larger randomized study(s) exploring this demonstrated favorable effect in women with unexplained infertility.

Conclusion

In our study, we reported cumulative pregnancy rate per woman rather than per cycle. As far as we are concerned, this was the most appropriate outcome measure for the success of the examined procedure as its mechanism of action has yet to be elucidated. We did not know whether the intervention would work in the index cycle or in the next cycles.

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