

Impact of mechanical endometrial injury on clinical pregnancy rates in women with clomiphene-resistant polycystic ovary syndrome

Endometrial injury in PCOS

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Abstract

Aim: In this study, it was aimed to evaluate the effect of mechanical endometrial injury before letrozole treatment on clinical pregnancy rates in patients with clomiphene-resistant polycystic ovary syndrome (PCOS).

Material and Methods: Thirty women with PCOS who could not achieve ovulation despite 150 mg of clomiphene citrate (CC) daily were included in the study. Patients in the PCOS group were equally divided into two groups before letrozole treatment (n=15). Group 1: Endometrial injury was performed with a pipelle cannula in the midluteal phase, and letrozole treatment was started in the next cycle. Group 2: In this group of patients endometrial injury was not performed. Letrozole treatment was started in these patients in the next cycle. Twenty patients with unexplained infertility were taken as a control.

Results: Beta hCG was found positive in 4 of 15 patients with endometrial injury in the PCOS group (26.6%). Beta hCG was found positive in 3 of 15 CR-PCOS cases who did not undergo injury (20%). Although beta hCG positivity was higher in the injury group, the difference was not significant ($p=0.34$). Clinical pregnancy was detected in 3 cases (20%) in patients with injury in the PCOS group. Similarly, clinical pregnancy was detected in 3 of the patients without injury (20%). In the control group, beta hCG positivity and clinical pregnancy rate were detected in 2 out of 10 patients with mechanical endometrial injury (20%).

Discussion: Mechanical endometrial injury before letrozole treatment does not increase clinical pregnancy rates both in women with clomiphene-resistant PCOS and unexplained infertility.

Keywords

Clomiphene-Resistant, PCOS, Unexplained Infertility, Mechanical Endometrial Injury, Clinical Pregnancy

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder with subfertility metabolic and hormonal disorders, affecting approximately 10% of women of reproductive age [1,2]. Systemic inflammation can lead to additional morbidities such as insulin resistance and endothelial dysfunction. Due to the high androgen synthesis and anovulation, a large proportion of PCOS cases suffer from subfertility. An increase in insulin levels causes hyperandrogenemia by stimulating LH-mediated IGF and androgen synthesis in follicles [3,4]. Endometrial decidualization is impaired due to hyperinsulinemia and increased androgen levels due to insulin resistance. In addition, hypoandrogenemia leads to subfertility by decreasing the expression of endometrial receptivity genes. Receptivity is further impaired, as increased insulin impairs hepatic degradation of androgens and decreases IGFBP synthesis in the endometrial stroma [5-7].

First-line treatment in subfertile PCOS patients is ovulation stimulation with clomiphene citrate (CC). Patients who do not ovulate despite six months of CC therapy are diagnosed with CC-resistant PCOS. In patients who do not respond to CC treatment, second-line treatment is the use of aromatase inhibitor (AI). In cases where pregnancy cannot be achieved with AI, the third step approach is ovarian drilling or ART. Ovulatory dysfunction and hyperandrogenemia are the two mechanisms most frequently accused of decreased fertility in subfertile PCOS patients [1-3]. However, in the last decade, disruption in endometrial receptivity genes due to androgen elevation has also been suggested as a cause of subfertility [4]. The fact that high testosterone levels reduce homeobox gene expression indicates the role of the endometrium in decreasing fertility [4-6].

Mechanical endometrial injury is a widely used method of increasing pregnancy rates in patients with a history of recurrent implantation failure. It has been reported that mechanical injury performed with a pipelle cannula or accompanied by hysteroscopy in patients with two or more failed IVF/ICSI attempts increases endometrial receptivity and leads to an increase in pregnancy rates [8,9]. There are no studies investigating the effect of endometrial injury before starting AI treatment in clomiphene citrate-resistant PCOS cases. This study was planned to investigate the effect of mechanical endometrial injury in the cycle before starting AI treatment on clinical pregnancy rates in patients with CC resistant PCOS.

Material and Methods

A total of 50 infertile patients, 30 of whom were diagnosed with PCOS and 20 with unexplained infertility, were included in the study. Thirty patients in the PCOS group consisted of clomiphene-resistant cases who did not ovulate despite the use of 150 mg/day CC. The control group consisted of 20 patients who did not have the laboratory and skin manifestations of PCOS and who were diagnosed with unexplained infertility. After the evaluation of ovulatory function, tubal patency and semen analysis, if no etiology was found, the diagnosis of unexplained infertility was made. The study was started after obtaining patient consent and approval from the local ethics committee. PCOS was defined according to the revised Rotterdam criteria,

which require two of the following three manifestations: (i) oligo-anovulation or anovulation (oligomenorrhoea or amenorrhoea); (ii) high concentrations of androgen in the bloodstream (biological hyperandrogenism) and/or clinical signs of androgen surplus (hyperandrogenism); and (iii) polycystic ovaries shown by ultrasonography (more than 12 follicles measuring 2-9 mm on at least one ovary). When CC treatment fails, defined as no ovulation after six months of treatment at an appropriate dose, the patient is regarded as resistant to CC. Induction with letrozole was planned as second-line treatment in PCOS patients in whom the diagnosis of CC resistance was certain. The patients in the PCOS group were equally divided into two groups before letrozole treatment (n=15). Group 1: Endometrial injury was performed with a pipelle cannula in the midluteal phase (LH+7-9) and letrozole treatment was started in the next cycle. Mechanical injury was performed in accordance with previous studies. The Pipelle cannula was introduced through the cervix into the fundus. The piston of the cannula was withdrawn to create negative pressure and suction. Then the catheter was pushed back and forth in the cavity and withdrawn. The procedure was repeated until most of the cavity was injured. Group 2: In this group of patients, the pipelle cannula was passed through the cervix and advanced to the fundus, but no injury was made. Letrozole treatment was started in these patients in the next cycle. Twenty patients with unexplained infertility were taken as a control group and equally divided into two groups. While the injury was applied to 10 of the patients in Group A, the remaining ten patients were not injured (Group B). The patients in Group A were injured with a pipelle cannula 7-9 days after the LH peak. The Pipelle cannula was placed along the cervix of the patients in Group B, but no injury was performed. Women with endometrioma or hydrosalpinx thought to affect implantation were not included in the study.

In the post-injury cycle, patients in the PCOS group were given a letrozole tablet twice a day for 5 days, starting from the 3rd day of the cycle. The patients in the control group were given CC (150 mg/day) three times a day for five days in the post-injury cycle. CC was started between days 2-6 of the cycle. The cycle was monitored with ultrasound examination and mid-luteal serum progesterone levels. Patients in both groups were offered timed intercourse between days 12-18 of the cycle. Primary outcome measures were positive beta hCG rate and clinical pregnancy rates. Clinical pregnancy rate is defined as evidence of a gestational sac, confirmed by ultrasound examination at the 4th week of transfer. Beta hCG values and clinical pregnancy rates of the patients in both groups were recorded and compared both within and between the groups

Statistical analysis

The analysis of collected data was performed using the Statistical Package for Social Sciences software 21.0 for Windows package software (SPSS, Inc., Chicago, IL, USA). The parameters studied in the PCOS and control groups showed normal distributions, which were confirmed by the one sample Kolmogorov-Smirnov test. The Mann-Whitney U test for continuous variables and Pearson's chi square test for categorical variables were used. Data are presented as mean \pm SD. Clinical pregnancy and positive beta-hCG rates were given

as percentages. $P < 0.05$ was used for determining statistical significance.

Results

Mechanical endometrial injury was successfully performed in patients in both groups. Except for mild inguinal pain, cramping and spotting, no serious complications developed. Beta hCG was found positive in 4 of 15 patients with endometrial injury in the PCOS group (26.6%). Beta hCG was found positive in 3 of 15 women with PCOS who did not undergo mechanical endometrial injury (20%). Although beta hCG positivity was higher in the injury group, the difference was not significant ($p = 0.34$). Clinical pregnancy was detected in 3 out of 15 women with endometrial injury in the PCOS group (20%). Similarly, clinical pregnancy was detected in 3 out of 15 patients with PCOS without injury (20%). There was no significant difference between the PCOS groups in terms of CPR ($p = 0.07$).

In the control group, beta hCG positivity was detected in 2 out of 10 patients with mechanical endometrial injury (20%). Likewise, positive pregnancy test rate was detected in 2 out of 10 patients in the non-injured group (20%). The difference between the two groups was recorded as insignificant ($p = 0.50$). In the control group, clinical pregnancy was detected in 2 out of 10 patients with endometrial injury (20%). Similarly, clinical pregnancy was detected in 2 out of 10 patients without endometrial injury (20%). In the control group, CPR was found to be similar in patients with and without endometrial injury.

Discussion

If there is no ovulatory response to clomiphene citrate treatment in infertile PCOS patients, low-dose gonadotropin can be added to CC or aromatase inhibitor therapy can be started. Insulin-sensitizing drugs can be added to increase ovulatory performance and reduce insulin resistance [2]. All these applications provide an effective treatment as long as they are accompanied by lifestyle changes and weight loss. Aromatase inhibitors can also be used as a second line treatment. The aromatase inhibitor letrozole at a dose of 2.5 mg/day can be used as an alternative treatment to induce ovulation in women who have failed to respond to CC. Letrozole can provide a highly effective ovulatory process in CC-resistant PCOS cases [10,11]. However, despite the multiplicity of medical approaches, many PCOS patients have to go to ART. We designed this study to test whether mechanical endometrial injury before letrozole affects pregnancy rates in a CC resistant PCOS population. First, we divided our patients diagnosed with CC-resistant PCOS into two groups. In the first group, we performed mechanical endometrial injury with a pipelle cannula in the midluteal phase of the cycle before starting letrozole and 7-9 days after the LH peak. We recommended timed sexual intercourse for patients after ovulation stimulation with letrozole in the next cycle. We gave letrozole treatment to our CC resistant patients in the second group without causing mechanical injury. We divided the control group patients, consisting of patients diagnosed with unexplained infertility, into two groups and performed endometrial injury in one group and did not perform in the other group. We compared the positive pregnancy test rates

and clinical pregnancy rates in the PCOS and control groups, both within and between groups. In CC-resistant PCOS cases, mechanical endometrial injury before letrozole treatment did not lead to a significant increase in either positive pregnancy test rates or clinical pregnancy test rates. Similarly, mechanical endometrial injury did not significantly change positive pregnancy test rates and clinical pregnancy rates in patients with unexplained infertility. When PCOS and unexplained infertile groups were compared among themselves, clinical pregnancy rates were found to be similar.

In the last decade, the possibility of endometrial receptivity defect has become increasingly important both in PCOS patients and unexplained infertile patients [10,11]. This study, in which we planned to determine whether mechanical endometrial injury affects pregnancy rates by stimulating the expression of both inflammation and receptivity genes in these two patient groups, was investigated for the first time in the literature [8,9]. As a result of our study, we showed that mechanical injury does not have a positive contribution to pregnancy rates.

Conclusion

Despite the limited number of cases, our results are clinically important. As a result of this study, we have once again confirmed the idea that mechanical injury is not a very effective approach except for patients with recurrent implantation failure. It is important to continue treatment by following conventional approaches in both CC-resistant PCOS patients and unexplained infertile patients. It will be possible to make clearer recommendations on this issue thanks to randomized controlled studies to be carried out by increasing the number of cases. As a result, mechanical injury before aromatase inhibitor treatment in CC-resistant PCOS does not positively increase fertility outcomes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with 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. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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