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Effect of Chronic Endometritis Treatment on The Outcome of ICSI in Patients with Repeated Implantation Failure

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ABSTRACT

Background: Repeated implantation failure has been one of the concerns in ICSI in recent years. It's linked to maternal or embryonic influences. One of the maternal factors is chronic endometritis (CE) which may affect the outcome of ICSI and so, its treatment may improve the results of ICSI.

Objectives: To evaluate the effect of chronic endometritis treatment on the outcome of ICSI in repeated implantation failure (RIF).

Methods: This is a prospective study conducted at the International Islamic Center for Population Studies and Research, Al-Azhar University on 120 patients with RIF. Patients were scheduled for hysteroscopic endometrial biopsy with histopathological examination. If there was no evidence of CE, the patients were scheduled for ICSI directly (Group A). Patients with CE received antibiotics and endometrial biopsy was done in the next cycle. According to the result of the second biopsy, patients were divided into 2 groups: - Patients with cured CE (Group B) and patients with persistent CE (Group C). We compared the chemical pregnancy rate, clinical pregnancy rate, and the miscarriage rate in study groups.

Results: Patients with cured chronic endometritis had a significant higher chemical and clinical pregnancy rate compared with patients with persistent chronic endometritis (43.5% vs. 17.9% and 39.1% vs. 10.7% respectively). The miscarriage rate was higher in patients with persistent CE than other groups but with no significant difference.

Conclusion: Treatment of chronic endometritis improved the outcome of ICSI regarding the chemical and clinical pregnancy rate.

Keywords: Chronic endometritis, Intra Cytoplasmic Sperm Injection, Infertility, Implantation failure, Repeated implantation failure.

INTRODUCTION

Failure to conceive after two or three rounds of embryo transfer is known as RIF [1]. Either maternal factors or embryonic reasons can lead to implantation failure. Uterine anatomic anomalies, thrombophilia, non-receptive endometrium, and immunological variables are examples of maternal factors [2].

While uterine abnormalities are thought to play a significant role in the likelihood of conceiving using ICSI, some modest intrauterine lesions may go unnoticed in traditional infertility studies based on ultrasound and hysterosalpingography (HSG). One of these anomalies is chronic endometritis (CE), a chronic infectious condition characterised by a persistent inflammation of the endometrium that may not be picked up by HSG and ultrasonography. It is yet unknown how common it is in the general population [3].

It has recently been demonstrated that women with intrauterine diseases, such as endometrial hyperplasia and submucosal uterine fibroids, are more likely to develop CE. Subtle symptoms including leukorrhea, pelvic pain, and dysfunctional uterine haemorrhage can all be signs of chronic endometritis. It is frequently disregarded in clinical practice as a result. By directly visualising mucosal edema, localised or diffuse endometrial hyperemia, and micropolyps (<1 mm), office hysteroscopy can aid in the diagnosis of CE [4]. Nonetheless, endometrial biopsy and histopathological examination are the gold standards for diagnosing CE; the histologic diagnostic flag in this case is the presence of endometrial stromal plasma cells [5].

Although the precise effect of CE on reproduction is still up for debate, a number of research indicate that reproductive results may suffer as a result. This might be caused by an aberrant invasion of plasma cells and other inflammatory cells, which would change the endometrial receptivity. Furthermore, there is ongoing debate on the efficacy of CE therapy in cases of implantation failure [6].

So, in this study we tried to investigate the effect of CE treatment on the outcome of ICSI in patients with RIF.

PATIENTS AND METHODS

This study included 120 infertile women diagnosed with RIF with the following inclusion criteria: Patients with RIF (at least two previous failed ICSI attempts). Age of patients ranging from 20 years to 37 years.

Exclusion criteria: Patients with a fibroid > 4 cm, multiple intramural fibroids, the presence of a sub-mucous fibroid, history of pelvic surgery as: myomectomy, hydrosalpinx, tubal obstruction or any tubal abnormality. Also, patients with chronic specific endometritis as: T.B endometritis and patients with general disease or medication that could potentially affect fertility were excluded.

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Patients who satisfied the inclusion criteria underwent an office hysteroscopy with an endometrial sample during the follicular phase of the menstrual cycle (days 6–12) and were sent for histological investigation.

If there were no evidence of CE, the patients were scheduled for ICSI directly (Group A). Patients diagnosed with CE received antibiotic therapy (doxycycline 200 mg/day, 1 g/day ciprofloxacin and metronidazole) for 14 days and repeated hysteroscopic endometrial biopsy was done in the next menstrual cycle. According to the result of the second biopsy, patients were divided into 2 other groups: - Patients with cured CE (Group B) and patients with persistent CE (Group C).

The study outcomes were:

- Chemical pregnancy rate: Serum HCG levels were tested 14 days after ET.
- Serum HCG >5 IU/l was classified as a chemical pregnancy.
- Clinical pregnancy rate: It was detected when B-mode ultrasonography showed a gestational sac 5 weeks after ET.
- Miscarriage rate: Based on the number of losses before 20 weeks of pregnancy among the overall number of pregnancies.

Ethical approval:

Menoufia Medical Ethics Committee of the Menoufia Faculty of Medicine gave its approval to this study. All participants gave written consent after receiving all information. The Helsinki Declaration was observed throughout the study's duration.

Statistical analysis

The programme SPSS v.22 was used to analyse the data. Quantitative data were presented as mean ± SD and were compared by one-way ANOVA test. Qualitative data were presented as frequency and percentage and were compared by Chi-Square test. All of these tests were deemed statistically significant if the P value was less than 0.05.

RESULTS

There was no statistically significant difference between the groups regarding age, BMI, number of infertility years and number of previous failed ICSI trials **(Table 1).**

Table (1): General characteristics of the studied groups

Variable	Group A (n = 45)	Group B (n = 47)	Group C (n = 28)	P value (ANOVA)
Age (mean ± SD)	30.22 ± 3.4	30.21 ± 3.3	30.14 ± 3.6	0.9
BMI (mean ± SD)	23.24 ±2.4	23.26 ±2.3	22.93 ±2.6	0.8
Infertility Duration (mean ± SD; Years)	8.47 ± 2.6	8.47 ± 2.5	8.61 ± 3.02	0.97
ICSI Failures (mean ± SD)	2.38 ± 0.6	2.40 ± 0.5	2.43 ± 0.63	0.8

Regarding chemical pregnancy rate: There was a significant higher chemical pregnancy rate in Groups A and B compared with Group C. Regarding clinical pregnancy rate: There was a significant higher clinical pregnancy rate in Groups A and B compared with Group C (**Table 2 and Fig. 1)**.

Regarding miscarriage rate: There was a higher miscarriage rate in Group C (10.7%) but it was not statistically significant (**Table 2 and Fig. 2)**.

Table (2): Comparison between the groups regarding the chemical pregnancy rate, the clinical pregnancy rate, and the miscarriage rate

Outcome	Group A (n = 45)	Group B (n = 47)	Group C (n = 28)	*P* value (χ^2)
Chemical Pregnancy, n (%)	18 (40)	20 (43.5)	5 (17.9)	**0.07**
Clinical Pregnancy, n (%)	17 (37.8)	18 (39.1)	3 (10.7)$^{*\#}$	**0.02**
Miscarriage, n (%)	3 (6.7)	3 (6.5)	3 (10.7)	0.8

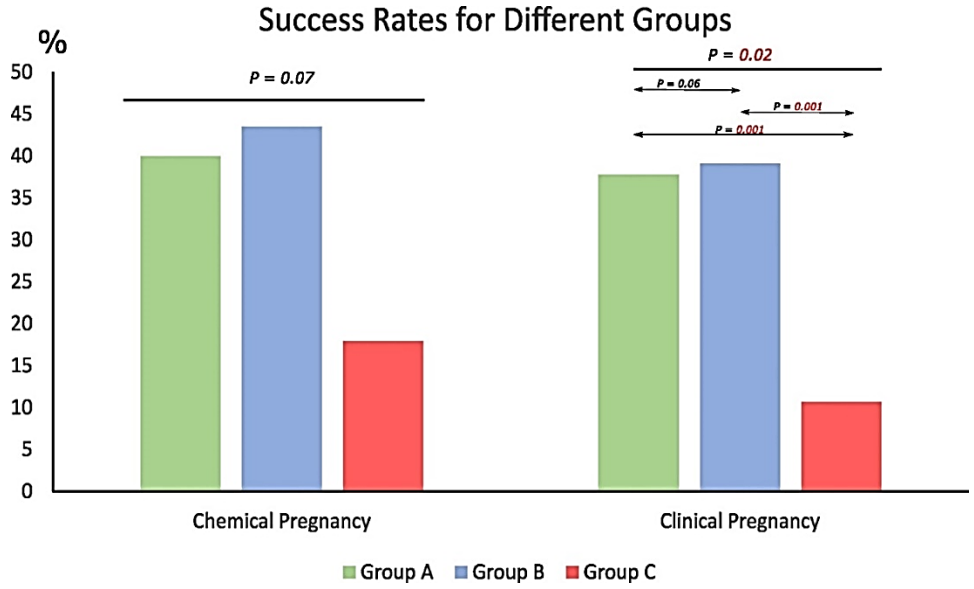

Figure (1): Difference between chemical pregnancy rate and clinical pregnancy rate in study groups.

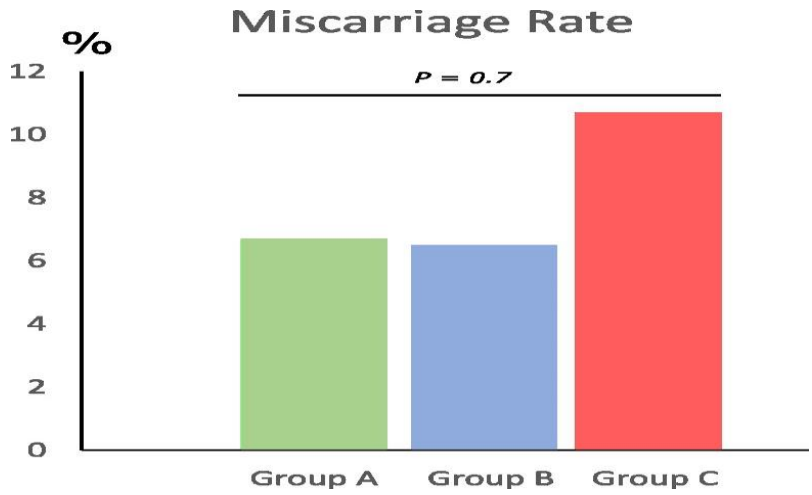

Figure (2): Difference between the groups regarding miscarriage rate.

DISCUSSION

Studying endometrial diseases and how they affect reproduction has gained popularity over the past 20 years. An increasing body of research indicates that CE may lower ICSI success rates and have a deleterious impact on spontaneous fertility [6].

Plasma cells in the endometrial stroma are a hallmark of CE, a chronic inflammatory disease. Due to its poor symptomatology, which includes abnormal uterine bleeding, pelvic pain, dyspareunia, and leucorrhea, CE is often a modest condition that is frequently missed by doctors [7]. The diagnosis of CE is difficult because leukocytes are frequently seen in the endometrium, especially before menstruation, and histological investigation might be deceiving because clinical and ultrasonography exams are frequently non-specific [8].

For these reasons, hysteroscopy can aid in the diagnosis of CE by enabling the identification of certain symptoms including stromal edema, micropolyps, and localised or widespread hyperemia [9].

Age, BMI, the number of years of infertility, and the number of unsuccessful ICSI efforts did not significantly differ between the groups when it came to the preoperative data used in this study to determine if the chosen treatment will primarily influence the postoperative results. In the chosen group in our study, the prevalence of CE was 62%. In a retrospective analysis conducted in 2015 on 106 patients who had recurrent ICSI failure, **Cicinelli *et al.*** [1] discovered that 66% of the patients had CE.

Also, in 2018 in another retrospective study on 95 patients, **Cicinelli *et al.*** [6]**,** found the prevalence was 56.8%**.** In comparison to the 30.3% recorded by **Johnston- MacAnanny *et al.*** [10] in 2010, this rate was nearly twice as high. The new developments in hysteroscopy and histopathology for the identification of CE may account for this disparity.

In our study, we found that there was no significant statistical difference between patients with cured CE and patients with no CE regarding chemical pregnancy rate (43.5% vs. 40%) and clinical pregnancy rate

(39.1% vs. 37.8%). Furthermore, there was no discernible variation in the miscarriage rate (6.5% vs. 6.7%). We concur with **Kitaya *et al.*'s**[11] 2017 prospective research with 420 patients, which sought to ascertain if oral antibiotic therapy enhances the live birth rate in subsequent cycles and to explore the prevalence of CE in infertile women with a history of RIF. The clinical pregnancy rate did not reach a statistically significant level (p value: 0.52) but was greater in the cured RIF/CE group (37.1%) than in the RIF/non-CE group (27.0%). Furthermore, the miscarriage rate (11.6 % vs. 16.4% with P value: 0.5) did not differ significantly [11].

Unlike our study, they compared the outcome in 3 subsequent ET cycles and found that the clinical pregnancy rate and the live birth rate was also higher in cured CE group with a significant difference (P value = 0.032 and 0.037 respectively), but the miscarriage rate did not change much (P value = 0.26) [11].

We also agree with **Agrawal *et al.*** [12] in their prospective study on 78 patients with RIF that aimed to ascertain the prevalence of CE in ART-using infertile women and the impact of antibiotic therapy on the incidence of pregnancy. They discovered that the pregnancy and miscarriage rates in the groups with and without treated CE were, respectively, 66.7% and 25% and 55.7% and 27.5% (p value = 0.41) [12].

In our study, we found that there was a significant statistical difference between patients with cured CE and patients with persistent CE regarding chemical pregnancy rate (43.5% vs. 17.9%) and clinical pregnancy rate (39.1% vs. 10.7%) with P value = 0.001. The miscarriage rate was higher in patients with persistent CE (10.7% vs. 6.5%), but it was not statistically significant (P value = 0.7). We agree with **Cicinelli *et al.*** [1], in their study on 61 patients with RIF in the period from 2009 to 2012. They found that there was a significantly higher chemical pregnancy rate in women with cured CE compared with women with persistent CE (65.2 versus 33.0% with P value = 0.039). There was no discernible variation in the quantity of miscarriages throughout the first trimester [1].

We also agree with **Cicinelli *et al.*** [6], in 2018 in their retrospective study on 95 women with RIF. They discovered a statistically significant difference in the conception rates of women with cured CE and those with chronic CE (Pregnancy rate = 76.3% vs. 20%, P < 0.0001).

Also, in 2021 **Agrawal *et al.*** [12] in their prospective study on 78 patients with RIF concluded that the pregnancy rate was higher in patients with cured CE than patients with persistent CE but it was not statistically significant (66.7% vs. 37.5%, P value = 0.16). Also, like our study, the miscarriage rate was higher in patients with persistent CE than patients with cured CE (33% vs. 25%), but also it was not statistically significant (P value = 0.16) [12].

CONCLUSION

When patients with recurrent implantation failure received CE treatment, the chemical result of ICSI and the clinical pregnancy rate improved.

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