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Original Research Article

Endometrial Injury and Fertility Increase in Patients with Recurrent Failed Assisted Reproduction Attempts

Athanasios Chasiotis[1*], Antonios Makrygiannakis[2], Sophia Kalantaridou[3], Nikolaos Vrachnis[4]

[1]Obstetric and Gynecologic Department, General Hospital of Limassol, Limassol, Cyprus

[2]Obstetric & Gynecologic Department, University Hospital of Heraklion, Heraklion, Crete, Greece

[3]Obstetric and Gynecologic Department, University Hospital Attikon, Athens, Greece

[4]Obstetric and Gynecologic Department, University Hospital Aretaieio, Athens, Greece

***Corresponding Author's Email: chasiotis.thanos@gmail.com**
Tel.: 0035725801401 / 0035799640754

Abstract

The aim of this systematic review is the collection and presentation of all scientific data to date, regarding the effectiveness of the intrauterine injury in cases of repeated failed attempts of conception, through in vitro fertilization. A systematic review of studies evaluating the association between intrauterine injury and increased fertility in women with recurrent failed IVF attempts was performed, in the databases Medline, PubMed, Embase, Google Scholar and Cochrane Central Registry, with regard to information about the fertility potential of these women. The data of the studies analyzed in the present study, indicate that there is a significant correlation between endometrial injury and increased fertility in women with repeated failed IVF attempts. Hysteroscopy with endometrial tissue damage, or the use of a suction pipette catheter during the menstrual cycle that precedes the ovarian stimulation for a subsequent IVF / ICSI, can highly improve the implantation and clinical pregnancy rates in women with failed IVF attempts. The application of local endometrial injury at the cycle preceding the ovarian stimulation for IVF/ICSI, especially during the luteal phase, seems to enhance the endometrial receptivity to the implanted fetus. The endometrial injury may induce changes in the endometrium that are thought to be able to improve the outcomes of the assisted reproduction efforts. Future RCTs are required in order to establish the integration of this therapeutic approach in ART protocols.

Keywords: Conception, Endometrial injury, Infertility, In vitro fertilization, Pregnancy, Repeated implantation failure

INTRODUCTION

The Assisted Reproductive Techniques (ART) implement treatments and procedures that involve the management of human oocytes and sperm, or embryos, with the ultimate goal of conceiving and achieving a clinical pregnancy (Balen, 2014). The most well-known ART approaches include the In Vitro Fertilization (IVF) and the Intracytoplasmic Sperm Injection (ICSI) (Balen, 2014). These techniques are widely used to treat infertility, but their success rates remain generally low. In fact, less than 30% of ART cycles result in a live birth (Balen, 2014). A crucial condition for the success of the above mentioned methods is the implantation of the fetus, which depends on two factors: the quality of the fetus and the receptivity of the endometrium. It is noticed that even transfers of good quality embryos can lead to failure, due to non-implantation (Sadeghi, 2012).

The cumulative possibility of achieving a pregnancy seems to increase after the second and third ART attempt, however from that point and onwards the success rates tend to decrease. The Recurrent Implantation Failure (RIF) is an unclear clinical entity (Bashiri, Halper and Orvieto, 2018). The majority of the scientific community defines RIF as the consecutive failure of two to six cycles of assisted reproduction. The absence of implantation can be partly attributed to the environment of the endometrium and is therefore proposed the physical injury as a strategy to improve its receptivity (Bashiri, Halper and Orvieto, 2018). The results from the first published study about this intervention indicate that can be achieved higher rates of

implantation (27.7% vs 14.2%, P value <0.001), clinical pregnancy (66.7% vs 30.3%, P value <0.001) and live embryo births (48.9% vs 23.6%, P value = 0.016).

Endometrial injury is defined as the intentional cause of endometrial tissue damage and it is performed in order to improve the reproductive capacity of women who try to conceive. The most common interventions are the intrauterine injury (scratching) using a suction pipette, as well as with hysteroscopy. As part of an ART cycle, intrauterine injury occurs some time before embryo transfer and is now a routine task, with or without ultrasound guidance (Günther et al., 2020). A pipette (or equivalent device) is inserted through the external cervical orifice and it is being forwarded until it reaches the fundus of the uterus, while a sample of the endometrium is obtained by suction and rotation of the above mentioned device into the endometrial cavity. The movements that are applied to receive the specimen seem to lead to some disruption of the continuity of the endometrium (or to its injury). Hysteroscopy with tissue damage is another technique used to disrupt the endometrium.

The underlying mechanism by which the endometrial injury can improve the endometrial receptivity is not fully understood. However, some mechanisms of action have been proposed. The first hypothesis suggests that this local injury on the proliferating endometrium induces its peeling, a process that it is normally noticed during the preparation of the uterus for pregnancy. It is therefore considered to favor the implantation of the developing embryo (Günther et al., 2020). A second hypothesis is that the endometrial injury induces a local immune response, involving cell mobilization at the site in need of healing. This process is associated with a significant increase in the secretion of cytokines, interleukins, growth factors, macrophages and dendritic cells, which are beneficial factors for embryo implantation (Günther et al., 2020).

Moreover, intrauterine injury can increase the amount of NK cells in the endometrium, restoring their population to normal levels (Seshadri and Sunkara, 2013). Cytokines, growth factors, and natural killer cells induce angiogenesis at the sites of the lesion, providing adequate blood flow to the tissues, thereby preventing the rejection of the fetus. A third hypothesis is related to the observation that ovarian stimulation during ART leads to abnormal endometrial maturation. This condition, at the time of the embryo transfer, makes the endometrial environment unfavorable for implantation. The above mentioned hypothesis argues that the endometrial injury leads to a better synchronization between the endometrium and the transferred fetus (Seshadri and Sunkara, 2013).

Three approaches have been used to enhance the uterine susceptibility by intrauterine injury and therefore to increase pregnancy rates after IVF and embryo transfer:

1. Local stimulation of the endometrium that causes decidualization, which in turn increases the chance of implantation of the transferred embryo (Huang et al., 2011).
2. The healing and repair process following a successful endometrial injury, resulting in a significant increase in macrophages, dendritic cells, and proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), macrophages-1B (MIP-1B), which in turn has a positive effect on implantation (Gnainsky et al., 2010). In particular, TNF-α and MIP-1B were found in high concentrations during the implantation window, highlighting the inflammatory effect on the endometrium - receptor (Zhong et al., 2020).
3. Ovarian stimulation during IVF treatment has been associated with high estrogen levels, leading to premature increase in progesterone levels. Compared to the embryonic stage, the endometrium is already at an advanced stage of differentiation, which makes implantation difficult (Fatemi and Popovic-Todorovic, 2013). Intrauterine injury during the previous menstrual cycle can suppress its proliferation and thus optimize the synchronization between the endometrium and the embryo to be transferred (Huang et al., 2011).

METHOD

Type of research: This is a systematic review of the bibliography.

Material and method

The research was conducted in scientific databases, especially in Medline, PubMed, Embase, Google Scholar and the Cochrane Central Registry of Controlled Trials. The main terms by which the relevant literature was researched are the following: Endometrial injury, in vitro fertilization, repeated implantation failure, infertility. The articles were categorized based on the date of their publication in each database, whereas there was no time limit, as this is a relatively new approach. The first result is placed in June 2003 and the last article, bearing in mind the time of the conduction of this systematic review, was published in September 2020.

Additional criteria that were initially set during the research were the English language (all articles under study were written in English), while no other specific filters were set regarding patients' age, journal category, or text availability. Unpublished results were excluded. From the above databases we kept only the articles that were retrieved through Pubmed, as there was an overlap with the few articles that emerged from the other databases. The initial selection was based on whether the studies involved endometrial injury in women undergoing IVF treatment. The criteria for entering the

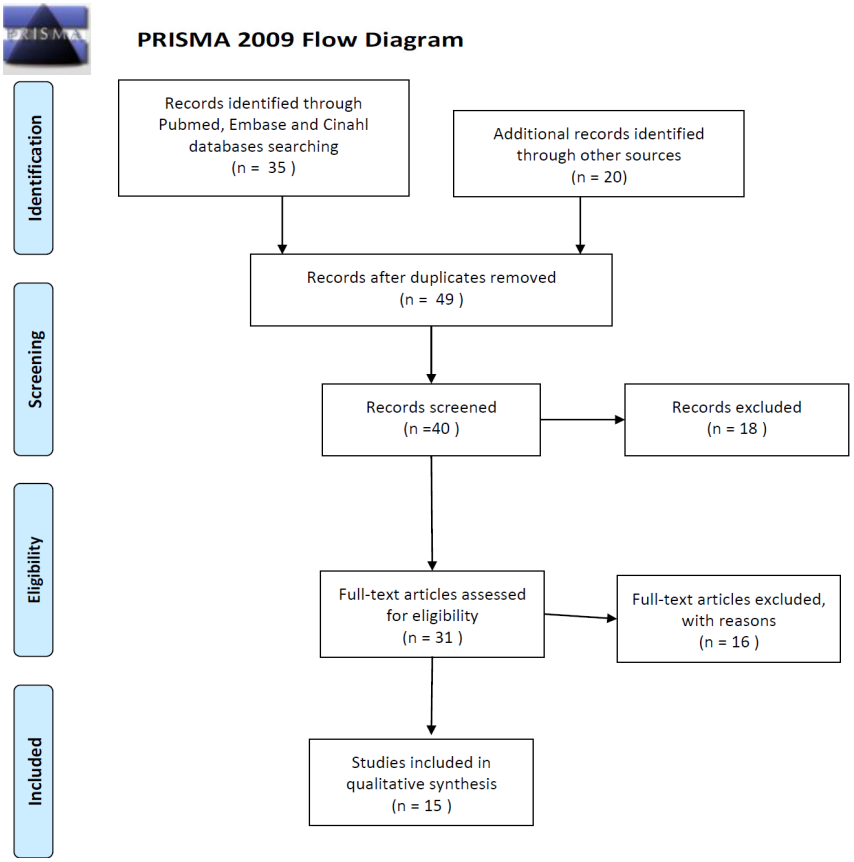

Figure 1. Flow diagram

studies were randomized, while non-randomized studies were included.

Regarding the Pubmed articles, we studied and included in our review 15, which seems, based on title and abstract, to reply to the following questions:

In which cases of women with fertility problems this approach is implemented?

What is the impact of this method to the rates of clinical pregnancies?

Criteria for Entry and Exclusion of Studies

The entry criteria based on which the articles of the present study were selected are the following:

- The selected articles are research studies.
- The language of the publication is English.

The research excluded reviews and in vitro studies in experimental animal models.

In addition, after a second and more detailed evaluation of the articles, it was decided to include those that respond to the following questions:

- Endometrial injury does increase the rate of successful fetal implantation in women undergoing IVF?
- Which women are candidates for endometrial injury?

Qualitative analysis of studies

The qualitative analysis of the studies was performed according to the Newcastle-Ottawa scale, which was formed by the universities of Newcastle and Ottawa. This scale was designed to evaluate the quality of non-randomized studies and includes 3 distinct levels of evaluation: the selection of the study sample, the comparability between the study groups and the verification of the outcome of the study group under study. Figure 1.

Data Export

The exported data relate to the following parameters:

General features: authors, time, location and duration.

Study design: cohort study, prospective study and case control.

Characteristics of the population: sampling method, age, origin, number of participants.

Number of failed attempts that have been preceded.

RESULTS AND DISCUSSION

The analyzed data of Olesen et al., (Denmark, 2019),

Table 1. Characteristics of the studies selected for the systematic review

Researchers, country of conduct, year	Research purpose	Sample - Sampling	Main results
van Hoogenhuijze et al., Netherlands, 2020	Determining the effect of intrauterine injury on the likelihood of live birth in the following IVF / ICSI cycle, in women with a failed IVF / ICSI	946 women starting a new IVF / ICSI cycle after a failed attempt. They were divided into an intervention group (n = 472) who underwent intrauterine injury and a control group (n = 474) who did not undergo any additional intervention	4.6% more live births were observed in the intervention group, with a probable certainty ranging between –0.7% and + 9.9%.
Izquierdo Rodriguez et al., Spain 2020	Determining the outcome of endometrial injury in patients undergoing IVF cycles with donor eggs, in order to ensure greater homogeneity in fetal quality and endometrial preparation.	333 patients starting a new IVF cycle with a donor egg. 161 patients who underwent endometrial injury (group A) and 172 patients who did not undergo endometrial injury.	Clinical pregnancy rates were 104/161 (64.6%) in group A and 102/172 (59.3%) in group B (RR 1.09, 95% (CI) (0.92-1.29) • p = 0.378). Ongoing pregnancies, miscarriages, multiple pregnancies and live birth rates were also comparable. No significant complications were identified after intrauterine injury, while pregnancy complications were comparable.
Olesen et al., Denmark 2019	Investigate the influence of intrauterine injury during the luteal phase before ovarian stimulation on the increase in clinical pregnancy rates in women with one or more previous implant failures.	304 patients scheduled for IVF / ICSI. The intervention group (n = 151) underwent endometrial injury during the luteal phase before the controlled ovarian stimulation, while no intervention was taken place in the control group (n = 153)	There was no overall significant improvement in clinical pregnancy rates between groups (CI 0.86-1.55). However, subgroup analyzes, revealed that women with three or more previous implant failures had a significant increase in the clinical pregnancy rate (CI 1.05-2.83) after the intervention.
Lensen et al., New Zeland, 2019	Investigate whether endometrial injury after endometrial biopsy increases the chance of a live birth in women undergoing IVF.	1364 women undergoing IVF (fresh or frozen embryo transfer)	The incidence of live births was 180/690 (26.1%) in the intervention group and 176/674 (26.1%) in the control group (CI 95% 0.78-1.27). There were no significant differences between groups, concerning rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy or miscarriage.
Ashrafi et al, Japan, 2017	Determining the effect of endometrial injury on pregnancy rates in women with previous intrauterine insemination failure.	169 women with a history of failed IUI, 2 or more times.	No significant beneficial effect of intrauterine injury on fertility outcome was observed in women with recurrent clinical pregnancy failure. There were also no adverse effects due to the endometrial injury. Further studies are needed in a larger sample of the population.
Reljic et al, Slovenia, 2017	The investigation of the most important prognostic factors for achieving pregnancy after IVF in women with a history of repeated unsuccessful IVF attempts.	429 IVF / ICSI cycles performed in women> 40 years of age were studied, after at least 3 failed IVF / ICSI attempts.	These results suggest that hysteroscopy with endometrial tissue damage prior to ovarian stimulation during IVF / ICSI, may improve implantation and clinical pregnancy rates in women with recurrent failed attempts. However, more studies are needed to confirm this contribution.

Table 1. Continue

Siristatidis et al, Greece, 2017	Evaluation of the effect of intrauterine injury on infertile women with recurrent implantation failures undergoing assisted reproduction techniques.	103 infertile women with a history of RIF. 1st group: n = 51 underwent endometrial trauma by hysteroscopy. 2nd group: n = 52, underwent the original protocol without any intervention.	Endometrial injury and the duration of infertility were independent prognostic factors of live births.
Shahrokh-Tehraninejad et al, Iran, 2016	Evaluation of the effect of local endometrial injury on the rates of clinical pregnancies after frozen embryo implantation, in women with recurrent implantation failure.	120 women under the age of 40 with at least 2 IVF cycles, randomly divided into 2 groups. 1st group: n = 60 women who underwent endometrial injury 2nd group: n = 60, women who did not undergo any intervention.	Regarding the clinical pregnancy rate, no significant difference was observed between the interventional and the control group.
Kanazawa et al, Japan, 2016	Evaluation of the efficacy of the intrauterine injury at the cycle before the frozen embryo transfer, in women with recurrent implantation failures.	173 women aged 41 years and younger with repeated failed implantation attempts. 1st group: n = 38 underwent mild endometrial tissue damage 2nd group: n = 35 underwent hysteroscopy 3rd group: n = 90 did not undergo any intervention	The results suggest that endometrial damage has a positive effect on pregnancy.
Kitaya et al, Japan, 2016	Identification of subgroups of patients who appear to benefit from local endometrial injury after repeated implantation failures.	Comparison of clinical parameters between 2 groups of women 1st female population: n = 94, achievement of pregnancy (LEI-CP group) 2nd female population: n = 114 non-pregnancy (LEI-NP group)	The findings suggest that LEI is more effective in improving pregnancy outcome in patients with RIF with non-existent tubal obstruction and especially in patients with polycystic ovarian syndrome. The age of the women, the concentration of basal follicle-stimulating hormones, the number of previous cycles, and the number of embryos / blastocysts transferred in the last three RIF cycles were significantly lower in the LEI-CP group ($p < 0.047$), than in the LEI-NP group.
Singh et al, India, 2015	Evaluation of endometrial injury in improving implantation rates in women undergoing IVF-ET cycles.	60 infertile women. 1st group: n = 30, underwent endometrial injury 2nd group: n = 30, did not undergo any intervention.	Implantation rates are significantly increased after endometrial injury in patients with previous failed IVF. Implantation rates, miscarriages, miscarriage rates and births / live births were compared between the two groups.
Yeung et al, China, 2014	The contribution of intrauterine injury to the improvement of clinical pregnancy rates in infertile women, before ovarian stimulation.	300 women who were intended to undergo IVF were randomly divided into 2 groups (n = 150/group). The women of the 1st group underwent endometrial injury.	There were no significant differences in the study characteristics, as well as in the results between groups.

Table 1. Continue

Hayashi et al, Japan, 2013	Evaluation of the efficacy of endometrial injury before the IVF-ET cycle in patients with recurrent implantation failures.	89 infertile women who were to undergo embryo transfer. 1st group: n = 40, underwent endometrial injury 2nd group: n = 49, did not undergo any intervention	Endometrial injury in the luteal phase of the previous cycle, significantly improved the outcome of IVF-ET in sterile patients with RIF.
Huang et al, Taiwan, 2011	Investigating whether an injury caused by hysteroscopy during a controlled ovarian stimulation cycle, improves the subsequent fetal implantation rates in women with recurrent implantation failure	30 women with an adequate response to controlled ovarian stimulation. 1st group: n = 6, underwent endometrial injury hysteroscopically 2nd group: n = 24, did not undergo any intervention	The study demonstrates that the hysteroscopic endometrial lesion that occurs during the IVF cycle significantly improves fertilization success in patients with recurrent implant failure.
Narvekar et al, India, 2010	Determining whether endometrial damage caused by Pipelle sampling could improve the chances of pregnancy in the subsequent IVF cycle in women who had previously failed IVF.	100 women with previous failed clinical pregnancy attempts, despite good quality embryo transfer. They were divided into 2 groups randomly. The first one underwent endometrial injury twice during the cycle preceding the embryo transfer. The 2nd was the control group.	Endometrial injury during the previous cycle improves the number of live births, clinical pregnancies, and IVF-ET implantation rates in patients with previous unsuccessful IVF cycles.

reveal a significant correlation between endometrial injury and increased fertility rates. Based on their research results in 304 patients with recurrent failed implantations or intrauterine inseminations, they concluded that intrauterine injury during the luteal phase of the previous cycle significantly increases the clinical pregnancy rates in women with three or more previous implant failures. This result seems to coincide with previous reports, in which it was indicated that especially women with repeated implantation failures seem to benefit from endometrial injury. It is important that in this study there were no significant differences in both prenatal and birth data between groups.

In a study of 2017, regarding the effect of the most important prognostic factors for achieving pregnancy after IVF in women with a history of repeated unsuccessful IVF attempts (Reljic et al, Slovenia, 2017), 429 IVF / ICSI cycles were studied in women aged > 40 years, after at least 3 failed IVF / ICSI attempts. The results revealed that hysteroscopy with endometrial tissue damage at the cycle that precedes the ovarian stimulation phase during IVF / ICSI, could improve implantation and clinical pregnancy rates in women with multiple failed attempts. In addition, when evaluating the effect of the local endometrial injury on the clinical pregnancy rates after frozen embryo implantation in women with recurrent implantation failure, it was noticed that endometrial injury and the duration of infertility were independent prognostic factors of live births (Siristatidis et al, Greece, 2017). The same conclusions were reached in a recent study by van Hoogenhuijze et al. (Netherlands, 2020), who based on their research results, indicated that couples with a failed IVF / ICSI had a 4.6% (95% CI −0.7% to + 9.9%) higher birth rate after the application of endometrial injury before the second IVF / ICSI. In the same study, a difference of 5.1% (95% CI −1.2% to + 11.4%) was observed even after 12 months, taking into account all IVF / ICSI attempts and pregnancies within this period.

The results of Kanazawa et al, Japan, 2016, suggest that endometrial damage has a positive effect on pregnancy, while Kitaya et al, in a study of 200 women, revealed benefits from local endometrial injury after repeated implantation failures.

In contrast, a study concerning the effect of endometrial injury on pregnancy rates in women with previous intrauterine insemination failure (Ashrafi et al, Japan, 2017), indicated that no significant beneficial effect of endometrial injury on the fertility outcome was observed. There were also no adverse effects due to endometrial injury.

Analyzing the data of their study, Kitaya et al, Japan, 2016,showed that LEI is more effective in improving the outcome of pregnancy in patients with RIF, with non-existent fallopian tube obstruction and especially in

patients with polycystic ovary syndrome, while implantation capacity appears to be significantly increased after endometrial injury in patients with a previously failed IVF attempt.

The evaluation of the efficacy of endometrial injury before the IVF-ET cycle in patients with recurrent implantation failures and in infertile women undergoing embryo transfer, indicated a significant improvement in the outcome of subsequent IVF-ET attempt (Kanazawa et al, Japan, 2016).

In addition, a hysteroscopic endometrial lesion significantly improves fertilization success among patients with recurrent implantation failure, whereas in women who underwent endometrial injury twice during the cycle that precedes the embryo transfer, there was a significant improvement in achievement of clinical pregnancy, as well as in the number of live births, after previous unsuccessful IVF attempts (Narvekar et al, India, 2010).

CONCLUSIONS

The application of local endometrial injury at the cycle preceding the ovarian stimulation for IVF/ICSI, especially during the luteal phase, seems to enhance the endometrial receptivity to the implanted fetus. On the other hand, intervention near the embryo transfer can potentially disrupt the endometrium, having a negative effect on its implantation. These findings inevitably raise the clinical question of whether there is a significant benefit from performing local endometrial injury in the pre-implantation cycle in all women undergoing IVF, or whether it should be limited to women with RIF. Furthermore, tests for subgroup differences between hysteroscopy and endometrial biopsy were statistically significant, which may be due to the larger sample size in studies implementing hysteroscopy, compared to the endometrial biopsy. Indisputably, this simple and inexpensive procedure could reduce the incidence of infertility, with the maximum benefits in terms of economy as well as the emotional well-being of infertile couples. Future RCTs are required, which should additionally consider the expression pathways of molecules and genes caused by single or multiple endometrial lesions, in relation to the phase of the menstrual cycle they are carried out, in order to establish the integration of this therapeutic approach in ART protocols.

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