

## Case Report

# Successful Pregnancy Following Endometrial Injury Induced in the Luteal Phase in a Patient with Previous 14 Failed ICSI Cycles

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Received: January 31, 2017; Accepted: March 17, 2017; Published: March 27, 2017

## Abstract

In spite of the great advance in IVF technology, embryo transfer remains the main step in IVF/ICSI cycle success. Many procedures have been proposed to improve the endometrial receptivity and hence implantation, to embryo transfers. One of these procedures is endometrial injury induced in the preceding cycle to the IVF/ICSI cycle, however, there is a great debate regarding the effectiveness of this procedure. We present a case that achieved pregnancy with successful outcome in the 15<sup>th</sup> ICSI cycle after endometrial injury induced in the preceding cycle.

## Introduction

Repeated IVF/ICSI failure is a distressing condition for both the infertile couple and the treating physician. There is no evidence regarding the limit number of IVF/ICSI cycles to be tried before counseling patients about stop trying and think about other options like adoption. Options like adoption that may not be accepted in some communities including the area where this case is reported.

Implantation failure remains a challenge to IVF/ICSI success. There is no single technique that has been agreed by professionals to be recommended in cases with Repeated Implantation Failure (RIF). One of the techniques that raised great debate is to perform endometrial injury in the cycle preceding the IVF cycle.

## Case Report

The couple was present at Minia IVF unit following 14 failed ICS cycles between 2003 and 2013. The primary etiology for their infertility was male factor (non-obstructive azospermia) except for 2 cycles in which failed fertilization occurred, all other cycles' failures were recorded due to failed implantation of good quality (grade A) embryos. (Male partner is azospermic).

The wife had complete infertility work-up and was found to have normal hormonal profile. She had been tested for ovarian reserve (Antral Follicle Count (AFC) and Anti-Müllerian Hormone (AMH)). The AFC was 12 and AMH was 1.2 ng/ml. That was considered a good reserve considering her age at time of presentation (41 years). The patient had previously had negative tests for antiphospholipid antibodies, auto antibodies screen, antithrombin III, factor V Leiden, factor II prothrombin gene mutation, activated protein C resistance. She had a normal Natural Killer (NK) Cell assay and she had a normal thyroid function and was negative for thyroid antibodies. The couple had a normal karyotype. The wife underwent hysteroscopic evaluation of the uterine cavity in the follicular phase and pelvic blood flow studies at a midcycle and results were normal.

In the last 3 ICSI trials, the patient had been empirically treated with folic acid 5mg, low dose aspirin 80mg, low molecular weight

heparin 4500 IU, Thyroxin 50mcg, Prednisolone 5 mg on daily bases from the day of Embryo Transfer (ET) onwards. Unfortunately, she had a negative pregnancy test in all these trials.

The couple was counseled regarding endometrial injury. They were informed that the procedure is still under evaluation and that there is no strong evidence regarding the possible benefit. The couple agreed to do the procedure and gave a written informed consent. Endometrial sampling was done on day 21 of the non-transfer cycle at the outpatient clinic using Pipelle Endosampler catheter (Med Gyn Endosampler, Med Gyn products, Inc.USA). The catheter was introduced easily through the cervical canal. Scratching of the fundus and posterior wall of the uterine cavity was performed three times. No antibiotics were prescribed to patients after the procedure. In the next cycle, patient started gonadotropin stimulation on day 2 of menstruation at a dose of 450IU daily. Folliculometry was performed using transvaginal ultrasound starting on day six of stimulation GnRH antagonist was started when a leading follicle reached 14 mm and continued daily till the day of hCG. When a leading follicle is 18 mm hCG 10,000 unit was given intramuscularly and ovum pick up was performed 36 hours later under sedation. The last folliculometry scan revealed 14 follilces > 17 mm. A total of 12 mature oocytes (metaphase II) were collected under ultrasound guide. Insemination was done using fresh sperms obtained by TESE (Testicular Sperm Extraction). Successful fertilization occurred in 8 oocytes. Four grade A embryos (2 x 14 cells, 2x 12 cells) were transferred on day 4 after oocyte pickup with a Wallace catheter (Smith Medical International Ltd, Hythe, Kent, UK). Progesterone support of luteal phase was commenced on the day of ET with 800 mg micronized progesterone vaginally. A positive serum HCG pregnancy test was obtained 14 days after ET. The first ultrasound scan performed two weeks after the pregnancy test confirmed the presence of a single gestational sac. A second scan one week later confirmed the presence of fetal heart. The patient had a normal anomaly scan at 20 weeks and progressed to 38 weeks with no complications. She delivered by caesarean section at gave birth to a health male baby weighing 3.2 kg.

## Discussion

Repeated Implantation Failure (RIF) is a challenging problem in IVF / ICSI patients leading to patients and doctors' frustration. Over the last two decades, there have been many attempts to improve implantation and hence pregnancy rates in this group of patients. One of the procedures that aroused great debate is endometrial injury induced in the preceding cycle to IVF/ICSI cycle. The exact mechanism by which this procedure works is still unclear. However, the most accepted theories are inducing decidualization of the endometrium, initiating an inflammatory reaction mediated with cytokines, interleukins, growth factors, macrophages and dendritic cells which are beneficial to implantation and synchronization between the endometrium and the transferred embryos through retarding endometrial maturation [1-3].

There is no consensus regarding the optimal time to perform the procedure. However, it is suggested that endometrial injury performed in the luteal phase is likely to induce more decidualization. There is no consensus also regarding the optimal number of endometrial injuries. In the current case, endometrial injury was performed once. This was in line with most of the previous studies [4-8]. In the studies done by Gnainsky et al., 2010 [3] and Narvekar et al., 2010 [9] two or more endometrial injuries were performed. Endometrial injury was induced by many ways including Novak curette, Pipelle biopsy catheter.

There is marked inconsistency in the results of the different studies evaluating the procedure in patients with RIF. The most recent Cochrane review included 1129 patients from 14 studies and came with the conclusion that there is a moderate quality evidence that endometrial injury induced between day 7 of the previous cycle and day 7 of the embryo transfer cycle is associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous embryo transfers [10].

In this case we present, our patient had previously 14 failed ICSI cycles. In 12 cycles, good quality embryos had been transferred. In the last 3 cycles, she received empirical treatment with low molecular weight heparin, Thyroxin, Prednisolone. However, the results were also negative for pregnancy. In the last successful cycle the only added procedure was the endometrial injury we performed in the luteal phase of the preceding cycle. We suppose that the procedure improved the endometrial receptivity in this lady which was the cause behind her pregnancy in spite of being 41 years on the day of ET. Induction of endometrial injury in the luteal phase of the preceding cycle to IVF/ICSI cycle in patients with RIF is a simple procedure with a potential benefit and insignificant side effects. We recommend its use in all patients with RIF.

Evaluation of embryos was based on grading

Embryos were classified according to Veeck's grading as follow:

**Grade 1:** embryos with blastomeres of equal size and no cytoplasmic fragmentations;

**Grade 2:** embryos with blastomeres of equal size with cytoplasmic fragmentations equal to 15% of the total embryo volume;

**Grade 3:** uneven blastomeres with no fragmentations;

**Grade 4:** uneven blastomeres with gross fragmentation ( $\geq 20\%$  fragments).

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