Effect of local endometrial injury on pregnancy outcomes in ovum donation cycles

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Objective: To evaluate the effect of local endometrial injury (LEI) on clinical outcomes in ovum donation recipients.
Design: Retrospective cohort analysis of ovum donation cycles conducted from 2005 to 2012.
Setting: Two private IVF centers.
Patient(s): Total 737 ovum donation cycles.
Intervention(s): LEI by endometrial "scratch" with the use of a Pipelle catheter.
Main Outcome Measure(s): Clinical pregnancy and live birth rates.
Result(s): No statistically significant differences were found in clinical pregnancy rates and live birth rates in cycles subjected to LEI compared with those without. Combination of LEI with fibroid uterus resulted with significantly higher clinical pregnancy rates compared with LEI in normal uterine anatomy.
Conclusion(s): This is the first study done in ovum recipients who underwent LEI by a "scratch" procedure after failed implantation. Unlike most previous reports, which found improved pregnancy rates with the use of "scratch effect" or "minor endometrial injury" after repeated implantation failures in standard IVF with own eggs, we did not find any changes in implantation rates in a population of egg recipients following this procedure. In view of a possible positive effect of LEI in cycles with a previous four or more failures, prospective randomized controlled studies are warranted to better define the target population who may benefit from this intervention. (Fertil Steril® 2014;102:1048–54. ©2014 by American Society for Reproductive Medicine.)
Key Words: Repeated implantation failure, local endometrial injury, endometrial scratch, ovum donation, uterine factors

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Implantation is a multistep process, in which the embryo attaches to the endometrium and invades the deeper layers. A successful implantation is a vital event in the survival of an early pregnancy, and it depends mainly on two basic factors: embryo quality and endometrial receptivity (1).

Despite enormous research in reproductive medicine and significant advances in treatment protocols and techniques, repeated implantation failure (RIF) remains a major rate-limiting step in the process of assisted reproduction treatment (ART). RIF is defined as failure to achieve pregnancy after two to six IVF cycles over which more than ten good-quality embryos were transferred (2). In common practice, however, RIF is suspected after three or more unsuccessful IVF cycles in which good-quality embryos were transferred (3). Most studies exploring interventions to improve the implantation rates have proposed various management options to influence embryonic factors, such as optimization of culture media, assisted hatching, modifying embryo transfer (ET) techniques, blastocyst transfer, and preimplantation genetic screening. In contrast, surprisingly fewer approaches have been suggested to overcome suboptimal endometrial receptivity, although that factor is estimated to cause up to two-thirds of implantation failures (4). Interventions include hormonal treatment, especially in cases

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of thin endometrium, correction of intrauterine anatomic abnormalities, immunotherapy, and mechanical endometrial stimulation by local injury (3).

The first observation that endometrial injury caused by scratching the progestational guinea pig uterus results in rapid growth of decidualized endometrial cells was reported by Leob in 1907 (5). Later trials in rats demonstrated that uterine injury by oil injection also provokes decidualization (6). These observations led to an assumption that endometrial injury could contribute to a successful implantation and to improved reproductive outcomes in unexplained RIF cases.

One of the first studies that noted increased rates of implantation, clinical pregnancies, and live births following endometrial injury in women with RIF was published by Barash et al. in 2003 (7). Since then, several randomized (8, 9) and nonrandomized (10–12) controlled studies have demonstrated that local endometrial injury (LEI) significantly increases clinical pregnancy and implantation rates in IVF cycles. A meta-analysis by Potgar et al. in 2012, pooling seven controlled studies (four randomized and three nonrandomized) with a total of 2,062 participants, showed that LEI induced in the cycle preceding ovarian stimulation is 70% more likely to result in a clinical pregnancy compared with no intervention (13). A recent Cochrane analysis also reported that endometrial injury performed before the ET cycle improves clinical pregnancy and live birth rates in women undergoing ART, except for endometrial injury on the day of oocyte retrieval, which was found to be associated with significantly reduced ART outcome (14).

The scientific explanation of the underlying mechanisms of endometrial injury is not fully understood. It was proposed that endometrial injury affects the expression of endometrial genes involved in the preparation of the endometrium for embryo implantation expression (15, 16) and induces local inflammatory reaction with increased production of cytokines and growth factors, which in turn promote decidual proliferation (17) or improve the synchronicity in interaction between the endometrium and the embryos (18).

There are numerous confounding variables that complicate the analysis in studies comparing different groups of patients undergoing autologous IVF cycles. One of the major confounders is the woman's age, which can adversely affect embryo quality as well as endometrial functioning. Ovarian hyperstimulation is another variable that can not be controlled for and has possible adverse influence on embryo development and endometrial receptivity (19–21).

Ovum donation cycles provide a unique model for partial elimination of the confounding factors related to autologous IVF treatment. Endometrial preparation in egg recipients is performed by a standard protocol of exogenous hormonal treatment and is less dependent on endogenous ovarian function. In addition, oocyte donors are typically young women with good ovarian reserve, thus embryo quality is expected to be relatively similar in terms of implantation potential. Therefore, the decreased variability of age, ovarian function, and embryo quality in oocyte donation cycles allows for a better exploration of the independent effect of interventions on endometrial receptivity.

To the best of our knowledge, no studies have been published in the professional literature regarding the effects of LEI and pregnancy outcomes in ovum recipients. Therefore, the objective of the present study was to examine the influence of LEI by endometrial scratch with the use of a Pipelle catheter in the cycle before ET on clinical pregnancy and live birth rates a in a large cohort of ovum recipients.

MATERIALS AND METHODS

The cohort study data were collected retrospectively from a computerized database. All oocyte donation cycles performed from June 2005 to October 2012 at two private IVF centers were reviewed.

The local Institutional Review Board approved the study. Given the retrospective nature of the analyses, written informed consent was not required.

Oocyte Donors

Oocyte donors were aged 23–30 years and had proven fertility. All underwent preliminary counseling and filled in a health questionnaire. Screening tests for human immunodeficiency virus, cytomegalovirus, syphilis and hepatitis, and genetic tests for Fragile X and CF were performed. Informed consent was undertaken prior to starting a treatment cycle. The protocol for ovarian stimulation, ovum retrieval, IVF-ICSI, and embryo handing in the laboratory was performed as previously described (22). ET was performed on day 2–6 post egg collection.

Recipients

All recipients underwent general health assessments, implications counseling, and genetic counseling. Welfare of the child forms from their general practitioners were mandatory according to the Human Fertilization and Embryology Authority (HFEA) code of practice. All recipients underwent routine screening tests and assessment of uterine cavity by three-dimensional transvaginal ultrasound, saline solution sonohysterography, and/or diagnostic hysteroscopy. When present, endometrial polyps, intrauterine adhesions, and submucous myomas were removed with the use of operative hysteroscopy. Myomectomy was also performed in cases of myomas distorting the endometrial cavity according to sonographic findings, aquascan examination, or hysteroscopy.

The protocol for recipients' hormonal treatment was maintained as previously described (23). Briefly, recipients received estradiol valerate (EV), initiated with a standard dose of 6 mg daily and increased according to the response. Menstruating women were synchronized with the use of low-dose oral contraceptive pill or GnRH agonist and started EV on day 5 after stopping oral contraception pill or on the desired day after down-regulation.

Endometrial thickness was assessed by serial vaginal scans during the treatment cycle by measuring the maximal distance between the echogenic interfaces of the myometrium and endometrium in the plane through the central longitudinal axis of the uterine body. Endometrial pattern was defined as the type of relative echogenicity of the endometrium