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Hysteroscopic Endometrial Fundal Incision in Oocyte Recipients before Embryo Transfer May Improve Reproductive Outcomes: A Prospective Study

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Abstract

Background: Induced endometrial injury is a technique described that have positive impact on implantation. The aim of this study was to investigate whether hysteroscopic endometrial fundal incision (EFI) in oocyte recipients before embryo transfer increases pregnancy and live birth rates or not.

Materials and Methods: A prospective study was conducted between 2014 and 2019 at an *in vitro* fertilization (IVF) unit in Greece. As part of the protocol, hysteroscopy and EFI were offered to all the egg recipients and the outcomes compared with those from an older cohort from the same Unit not undergoing hysteroscopy.

Results: In total, 332 egg recipients participated in the study; 114 of them underwent EFI prior to embryo transfer. Both groups were similar in terms of age, years of infertility, duration of hormone replacement treatment (HRT) and number of blastocysts transferred. In the EFI group, minor anomalies were detected and treated in 6.1% (n=7) of the participants. Moreover, pregnancy test was positive in 73.7% of the women in the hysteroscopy group compared to 57.8% in the non-hysteroscopy group (P=0.004). Live birth rate was also higher (56.1 vs. 42.2%, P=0.016) in the EFI group compared to the non-hysteroscopy one.

Conclusion: Apart from the obvious benefit of recognizing obscured anomalies, requiring surgical correction, it appears that in oocyte recipients prior to embryo transfer, EFI might improve uterine receptivity and reproductive outcomes.

Keywords: Endometrial Fundal Incision, Endometrial Scratching, Implantation, Oocyte Donation, Recipients

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Introduction

Implantation remains the rate-limiting factor for the success of *in vitro* fertilization (IVF); it comprises a compound process including several cytokines and growth factors, along with a "dialogue" between embryo and endometrium (1). Extended embryo culture, blastocyst selection, assisted hatching and preimplantation genetic screening (PGS) are techniques that mainly focus on the embryo and probably have no impact on implantation itself (2). With regards to the particular mechanism of successful implantation, several aspects still remain unclear (1).

A manipulation suggested to have positive impact on implantation is hysteroscopy alone or combined with induced endometrial injury ("scratching"); scratching has demonstrated favorable effects on implantation rates, mainly in women with recurrent implantation failure (RIF) (3), while no benefit was found in unselected populations of women undergoing IVF (4). The potential mechanisms of positive effect of scratching might be: i. Induction of decidualization, ii. Production of cytokines, growth factors such as leukemia inhibitory growth factor, interleukin-11, heparin-binding endothelial growth factor, macrophages, and dendritic cells and iii. Improvement of synchronization of endometrium and embryo development following endometrial trauma (5, 6).

During hysteroscopy, notable heterogeneity exists with regards to the scratching method, thus the reported improvement in implantation rates differ (7). Moreover, confounding factors related to autologous IVF treatment may complicate the analysis, while the woman's age can adversely affect the embryo quality (8); ovarian

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hyperstimulation is another variable affecting the embryo development and endometrial receptivity (9). To eliminate such bias, ovum donation cycles should be explored, where the quality of the donated blastocysts arisen from young fertile eggs is relatively stable, thus not affecting the probability of pregnancy in the recipients (10).

The aim of the current study was to assess the impact of a novel method described from our group, the endometrial fundal incision (EFI), on recipients of donated oocytes.

Materials and Methods

Population characteristics

This is a prospective study conducted in "Assisting Nature Center Reproduction and Genetics", a private IVF Unit in Thessaloniki, Greece. Patients were recruited from January 2014 to December 2019. In particular, as part of our local protocol, we offered hysteroscopy and scratching to all the egg recipients without extra cost. Then we compared the reproductive outcomes with those from an older cohort of the same IVF Unit not undergoing hysteroscopy. We estimated a ratio of 1:2 in the groups undergoing hysteroscopy or not. Apart from the evaluation of the uterine cavity, women in the hysteroscopy group underwent correction/removal of any underlying pathology (polyps or adhesions or septum or endometritis) and also underwent EFI with endoscopic scissor. The study protocol was approved by the Institutional Review Board of the IVF Unit (0501201404). Additionally, informed consent was obtained from all the patients in the intervention arm.

Inclusion and exclusion criteria

Oocyte recipients were eligible for the study if: i. Their age ranged between 30 and 50 years, ii. Frozen blastocysts were transferred, iii. Absence of submucosal fibromas or polyps in ultrasonography, iv. Endometrial thickness >7 mm and blood progesterone levels <1.5 pg/ml the day before progesterone supplementation during hormone replacement treatment (HRT) preparation and v. EFI was performed with the use of endoscopic scissor only, without use of electrocautery method. Exclusion criteria were: i. Women who had undergone hysteroscopy within 6 months prior to donor oocyte recipient treatment, ii. Women who had undergone any uterine surgery in the past, and iii. Free fluid in endometrial cavity during HRT preparation.

Hormone replacement treatment protocol

All frozen embryo transfers were carried out following the same hormone endometrial preparation protocol; starting on day 2 of the cycle, if ultrasound revealed quiet ovaries and hormone levels were basal [estradiol (E2) <80 pg/ml and progesterone <1.5 ng/ml], the woman could undergo HRT. Estrogen supplementation was administered in the form of 17-b estradiol (estradiol valerate) for 10-20 days before progesterone one. In particular, according to the local protocol, we started (day 2 of the cycle) with 2 mg (1×1), then 4 mg (1×2) until day 5, 6 mg (1×3) for the next 3 days until day 8 and then 8 mg (2×2) onwards until the pregnancy test. Between days 10 and 11 we assessed: i. The endometrial thickness by ultrasound and ii. Blood levels of progesterone, luteinizing hormone (LH) and E2. If endometrial thickness was less than 7 mm, the therapy was continued for 3 more days. Once optimal endometrial thickness was achieved (>7 mm), daily progesterone was offered and embryo transfer scheduled 6 days later. The levels of beta human chorionic gonadotropin (β-hCG) were checked 9 days after embryo transfer or 14 days after the initiation of progesterone supplementation.

Hysteroscopic procedure

All the recipients underwent routine evaluation during their early follicular phase, 1-3 months before the start of a new HRT cycle. Moreover, women planned for hysteroscopy started taking contraceptive pill on day 3 (drospirenone and ethinylestradiol or chlormadinone and ethinylestradiol), in order to achieve better cavity visualization. Following vaginoscopic approach, a hysteroscopy was performed between days 6 and 13 of menstrual cycle. Routine analgesia for sedation was administered. A rigid hysteroscope (4.8 mm hysteroscope; continuous flow; 30° forward oblique view) using 0.9 normal saline was used. After adequate distension of the uterine cavity, systematic inspection was performed. Two senior reproductive medicine consultants (R.N. and E.P.) performed all the hysteroscopic procedures. EFI was performed by using endoscopic scissor 2 mm. The EFI was performed in a single straight line directed from one fallopian ostium to the other; as far as the depth of incision is concerned, incision was continued within the connective tissue until the appearance of the first vessels.

Reproductive outcomes

The primary outcomes were pregnancy and live birth rates; the pregnancy rate was defined as the proportion of women with a positive quantitative serum human chorionic gonadotropin test above 10 mIU/ml, 9 days after blastocyst transfer. First trimester miscarriage rate was defined as the proportion of women with pregnancy loss before 12 weeks of gestation. Live birth was defined as the delivery of a live fetus beyond 24 weeks of gestation.

Statistical analysis

The values of the continuous variables are expressed herein as mean (SD) and absolute (%) frequencies, when applicable. The between-group differences were compared by using the independent samples t test. Categorical variables were statistically analyzed by using Pearson's $\chi 2$ test and Fisher's exact test. Statistical significance was defined as $P<0.05$. SPSS v25.0 (IBM Corp., Armonk, NY, USA) used for data analysis.

Results

Among 342 women initially screened, 10 were excluded from the final analysis as, one become spontaneous

pregnant, one abandoned the treatment and eight women had already known uterine pathology. Therefore, a total of 332 recipients that underwent frozen embryo transfer were included. Moreover, 114 recipients underwent hysteroscopy and 218 were chosen from the older cohort of our Unit.

The age of the women included in the study ranged from 35 to 50 years; no significant differences were found in the age, duration of infertility, duration of HRT, number of blastocysts transferred and peak endometrial thickness between the two groups (Table 1). The mean duration of infertility in the whole sample was 6.4 years. All the women underwent embryo transfer with two blastocysts except from 10 cases that preferred single blastocyst transfer to avoid twins. The mean blastulation rate was 59.4%; 60.4% in EFI-group and 58.3% in control group (P=0.77).

Minor anomalies were detected and treated in 6.1% (n=7) of the participants in the hysteroscopy group; one woman was diagnosed with U1a (T shape uterus), three with U2a (partial septate, arcuate uterus), two with U2b (septate uterus) and one with several adhesions. All these women, including those with minor uterine abnormalities (n=7) and those with normal cavity (n=107) underwent EFI.

Regarding main outcomes, the pregnancy test was positive in 73.7% (n=84) in the hysteroscopy group compared to 57.8% (n=126) in the non-hysteroscopy group (P=0.004). Moreover, live birth rate was significantly higher in the hysteroscopy group (56.1%, n=64), as compared to 42.2% (n=92) in the non-hysteroscopy one (P=0.016, Table 2, Fig.1).

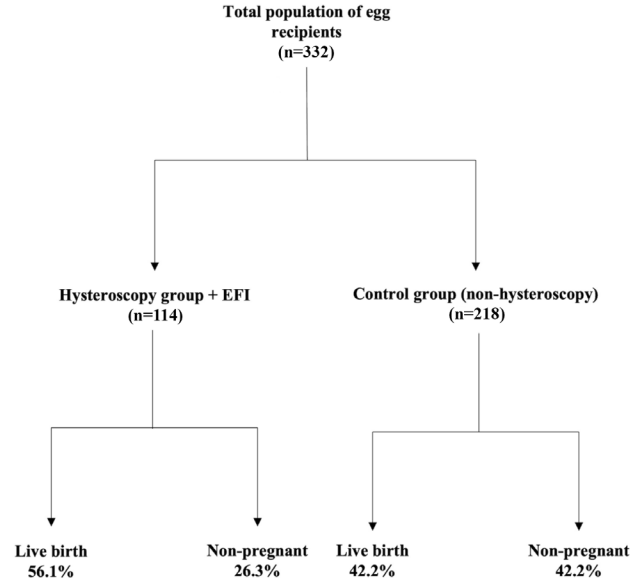

Fig.1: Flow chart of the study. EFI; Endometrial fundal incision.

In a subgroup analysis, we excluded the seven cases diagnosed with uterine abnormalities and found that both pregnancy and live birth rates remained higher in the hysteroscopy group (74.8 vs. 57.8%, P=0.003 and 54.2 vs. 42.2%, P=0.04, respectively).

Of note, there were 2 (1.8%) minor complications related to the hysteroscopy: one during cervical dilatation where false route was taken and corrected under ultrasound guidance and one during operative procedure; moderate bleeding continued after septum resection and patient was offered 6-hours of close monitoring. Both were diagnosed at the time of surgery.

Table 1: Demographic characteristics of the participants

Baseline characteristics of the participants	Hysteroscopy+EFI group (n=114)	Non-hysteroscopy control group (n=218)	P value
Mean age in years	39.7 ± 5.6	40.1 ± 6.1	0.31
Number of patients with history of previous hysteroscopy	3 (2.63)	9 (4.12)	0.34
Mean duration of infertility in years	6.03 ± 1.23	6.86 ± 1.17	0.19
Mean duration of HRT in days	17.48 ± 1.77	17.76 ± 1.16	0.45
Mean number of blastocysts transferred	1.79 ± 0.4	1.79 ± 0.42	0.65
Mean number of blastocysts available for transfer	4.55 ± 1.97	4.56 ± 1.97	0.86
Mean peak endometrial thickness in mm	9.69 ± 1.5	10.13 ± 1.25	0.16

Data are presented as mean ± SD or n (%). For the analyses independent samples t test, Pearson's χ^2 test and Fisher's exact test were employed. EFI; Endometrial fundal incision and HRT; Hormone replacement treatment.

Table 2: Reproductive outcomes in oocyte recipients with or without hysteroscopic endometrial fundal incision

Outcomes	Hysteroscopy+EFI group (n=114)	Non-hysteroscopy control group (n=218)	P value
Positive β-hCG rate per ET	73.7% (n=84)	57.8% (n=126)	0.004
Miscarriage rate <12 weeks	17.5% (n=20)	15.5% (n=34)	0.3
Live birth rate per ET	56.1% (n=64)	42.2% (n=92)	0.016

For the analyses Pearson's χ^2 test and Fisher's exact test were employed. β-hCG; Beta human chorionic gonadotropin, ET; Embryo transfer, and EFI; Endometrial fundal incision.

Discussion

We found that hysteroscopy along with targeted EFI 1-3 months before the embryo transfer in oocyte recipients may improve pregnancy and live birth rates. Moreover, no differences in the miscarriage rates were observed between the two groups.

Hysteroscopy has been proposed as a significant diagnostic tool in the diagnosis of infertility that increases the cost of an IVF cycle (11). Therefore, whether to undergo hysteroscopy or not before the first IVF cycle, still remains an issue, especially in Greece, where assisted reproductive techniques mainly take place in private IVF centers. Of note, in our study the EFI was offered to all the participants free of charge.

Endometrial scratching has been proposed as a simple cost-effective and minimally invasive procedure to improve endometrial receptivity during IVF cycles (12). Nevertheless, data remains inconclusive with regards to reproductive outcomes. The reason that EFI may be beneficial for implantation can be justified by three possible explanations. First, in contrast to the pipelle, where the blinded catheter scratches the posterior or the anterior uterine wall and never the fundus itself, in our technique the injury is directed to the fundus and the surgeon can even control the depth of the injury. Second, in cases with arcuate uterus (type U2a), the scratching is simultaneously therapeutic as it repairs this congenital variation of the uterine fundus considered physiological without impact on implantation in the past. According to data from a retrospective matched-control study, uterine anomalies have a negative impact on both pregnancy and live birth rates and thus, should be treated (13). Third, as we found, up to 6% of minor anomalies can be still identified by hysteroscopy itself, which would have been remained undiagnosed in the non-hysteroscopy group; however, we found that, even after excluding the cases with uterine abnormalities, the pregnancy and live birth rates remained higher in the EFI group.

As already mentioned, the reason that literature remains inconclusive whether scratching is beneficial or not, is that the majority of studies are heterogeneous; most studies investigated the effects of blinded injuries on the uterine cavity. In particular, Jayakrishnan et al. (14) treated the uterine pathology and induced injury with the hysteroscope only. Moreover, in another study, curettage of the fundus and the posterior wall post hysteroscopy was performed (15). Seval et al. (16) performed injury with the use of monopolar needle forcep. Our method is a well described standardized method of endometrial injury of the fundus in the follicular phase.

A Cochrane review concluded that endometrial scratching probably does not affect the pregnancy (OR: 1.08; 95% CI: 0.95-1.23) or the live birth (OR: 1.12; 95% CI: 0.98-1.28) rates, but notes that only evidence of moderate certainty exists (17). Furthermore, the same study found that endometrial scratching does not affect the risk of miscarriage (OR: 0.88; 95% CI: 0.68-1.13), which is in accordance to our findings. Furthermore, according to data from a futility analysis of a double-blind randomized controlled trial, endometrial mechanical stimulation with pipelle in the luteal phase of the cycle before embryo transfer does not improve reproductive outcomes in an unselected subfertile population and may result in lower live birth rates (18). This finding is in contrast with our results; it may be attributed to the technique used for scratching. Of note, we performed the EFI in the proliferative phase and according to published data, there is no significant difference in reproductive outcomes between scratching in the proliferative and the luteal phase (19).

Successful implantation is a complex process requiring a combination of three major physiological events to occur: i. A receptive endometrium, ii. An euploid embryo, and iii. The establishment of a proper dialogue between the semiallotypic embryo and maternal endocrinological/ immune system (1, 20). Although several theories on the association of endometrial injury with improved pregnancy rates have been proposed, our study has strengthened the hypothesis that mechanical injury may enhance uterine receptivity. If this occurs via cytokines released or modification of the immune system or release of vascular growth factors, it needs further investigation; according to published data, the concentrations of interleukin- (IL-) 6, IL-8, IL-12 (p70), IL-13, interferon- (IFN-) γ, monocyte chemotactic protein- (MCP-) 1 and vascular endothelial growth factor (VEGF) are increased in women undergoing endometrial scratching (21). Moreover, according to another study, scratching may affect the expression of genes involved in endometrial preparation for implantation or induce the production of cytokines and growth factors to enhance decidual proliferation (22).

To our knowledge, this is the first study in which a standardizing endometrial injury during hysteroscopy takes place in egg donation cycles. The main strength of our study is that the use of egg donation program can minimize the effect of embryo quality in our results. The embryos transferred are of young women with healthy fertile background, ensuring a limited bias regarding the reproductive outcome between the groups. By standardizing the method, with the use of endoscopic scissor and targeting only the fundus, we propose a method that should be easily applied by any reproductive medicine specialist. On the contrary, the main limitation of the study is the lack of randomization; this may be limited by the fact that no differences in the demographic characteristics were identified between the two groups. Moreover, the complete data set was obtained from a single IVF center and the same two senior doctors performed all the EFI procedures, as this could overcome possible inter-observer discrepancies. Another limitation of the study is that in the hysteroscopy group, uterine pathology was

detected in about 6% of the cases, which is in accordance with previously published data (23). We cannot estimate the proportion of cases with endometrial pathology in the non-hysteroscopy group, but it is probably the same since the two cohorts are from the same IVF Unit. Finally, the time interval between the hysteroscopy and the embryo transfer should be also taken into further consideration.

Conclusion

Our study has provided direct evidence to support the hypothesis that hysteroscopy plus EFI one to three months before embryo transfer is beneficial for the implantation in oocyte recipients. Apart from the obvious benefit of hysteroscopy to detect obscured anomalies, a discrete procedure tested the hypothesis that a site-specific mechanical injury during hysteroscopy could improve reproductive outcomes. More longitudinal trials using EFI in selected populations are encouraged to better understand the mechanism of action and further assess the effect of the procedure. Finally, cost-effectiveness analyses on the routine use of hysteroscopy in all egg recipients should be conducted.

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Authors' Contributions

R.N., N.P.; Conceptualization. N.P., I.T.; Methodology. G.M., E.P.; Validation. E.T.; Investigation. T.C.; Resources. R.N.; Data Curation. N.P; Writing-Original Draft Preparation. I.T.; Writing-Review and Editing. A.A.; Visualization. E.P.; Supervision and Project administration. All authors read and approved the final manuscript.

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