1-1-2022

# Does Endometrial Scratching Increase Live Birth Rates for Women Undergoing IVF?

Caitlyn Kratzer
*Philadelphia College of Osteopathic Medicine*

# Does Endometrial Scratching Increase Live Birth Rates for Women Undergoing IVF?

Caitlin Kratzer, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 17, 2021

## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not "Endometrial Scratching Increases Live Birth Rates for Women Undergoing IVF?"

**STUDY DESIGN:** A systematic review of three randomized control trials (RCTs) published between 2010 and 2017.

**DATA SOURCES:** All three RCTs were discovered using PubMed. Studies were published in English in peer-reviewed journals and selected based on applicability to the clinical question.

**OUTCOMES MEASURED:** In all three articles, the main outcome that will be reviewed is live birth rate. This was measured by the number of live births per embryos transferred divided by the total number of participants in each corresponding group. Outcomes were described as a percentage.

**RESULTS:** In the RCT conducted by Olesen et al., there was found to be a risk ratio (RR) of 1.29 (95% CI, 0.89-1.86; $p = 0.176$) and NNT of fifteen which is in favor of a small treatment effect for increasing live birth rate with ES in women receiving IVF. Data from RCT by Lensen et al., uncovered an odds ratio of 1.00 (95% CI, 0.78-1.27; $p = 0.97$) indicating there is no higher or lower risk odds of an increase in live birth rate with or without ES. Lastly, Rodriguez et al. revealed a RR of 1.128 (95% CI, 0.92-1.39), NNT of seventeen, and $p = 0.286$ supporting that the studies' statistics are not significant.

**CONCLUSION:** The studies did not find statistical significance in ES increasing live birth rates for women receiving IVF. The treatment effect in each intervention group was small compared to the control group. The results of this review are conclusive and show that ES does not increase live birth rate for women receiving IVF. Additional research and studies should be completed using standardized ES procedures and quality embryos.



**KEY WORDS:** endometrial scratching; birth rates

**INTRODUCTION:**

There are several factors that contribute to infertility, however failure to reach pregnancy when undergoing in vitro fertilization (IVF) is likely due to lack of embryo implantation. The current success rate of IVF remains modest at a 25-30% live birth rate per initiated cycle.[1] Only 30% of all embryos in IVF complete apposition, adhesion, invasion, and implantation to the endometrium.[2] This statistic supports that infertility occurs in the majority of women undergoing IVF, making infertility a common condition that healthcare providers including physician assistants will encounter. According to the Center for Disease Control, 12% of women aged 15-44 years in the United States have difficulty getting pregnant or carrying a pregnancy to term.[3] It is known that the minimal requirements needed to achieve an intrauterine pregnancy includes healthy oocytes, and adequate number of motile sperm, patent and functional fallopian tubes, and the ability to complete sperm deposition. Infertility is a complex medical condition comprised of various etiologies that potentially alter the previously stated requirements. Up to 15% of couples in the United States have an unknown causes of infertility.[3] Treatments for infertility are individualized for each patient depending on etiology, duration, age of female, and patient preferences. Examples of lifestyle modifications that are suggested to improve fertility include smoking cessation, abstinence from alcohol, reducing caffeine intake, and maintaining a BMI of 20-25 $kg/m^2$.[4] Reversible causes of infertility are typically treated with medical or surgical therapies. Irreversible causes of infertility may be treated with assisted reproductive therapies such as IVF, gamete donation, or a gestational carrier.[4] IVF is commonly one of the last therapies suggested after a patient completes trials of an estrogen modulator such as Clomid to improve ovulation, hormone injections, and intrauterine insemination.

Endometrial scratching (ES) has been proposed as a technique to increase implantation rate and live birth rates in women undergoing IVF. This technique was an incidental finding from other studies where it was observed that women in IVF with repeated endometrial biopsies had higher pregnancy rates.[5] The exact mechanism of ES is unclear however there are three suggested theories supporting the procedure. It is proposed that ES delays endometrial maturation which allows the embryo and endometrium to synchronize, provokes an acute endometrial inflammatory process that enhances new vascularization and implantation, and modifies gene expression to be more favorable.[2]

The use of assisted reproductive therapies has almost doubled over the past decade, however remains rare when compared to the demand. Preliminary data from the CDC shows that in 2019 there were 330,773 assisted reproductive therapy cycles performed at 448 reporting clinics in the United States that resulted in 77,998 live births.[3] A disadvantage to undergoing IVF is the high cost. Select states have approved insurance mandates that require private insurers to cover at least two assisted reproductive therapy treatment cycles, resulting in a greater use in those states.[3] It is unknown the exact number of healthcare visits per year or cost of IVF with the addition of ES. Of the fertility clinics in the United Kingdom, Australia, and New Zealand that performed ES, it was reported there was an associated cost of up to $500.[1]

## OBJECTIVE:

The objective of this selective EBM review is to determine whether or not "endometrial scratching improves live birth rates in women undergoing IVF?"

## METHODS:

The references analyzed for this systematic review were selected based on their relevance and ability to answer the patient focused question: Does endometrial scratching increase live birth rates for women undergoing IVF? These resources were found on PubMed using keywords "endometrial scratching" and "birth rates". All three studies are randomized control trials (RCTs) that were published in the English language in peer reviewed journals. Inclusion criteria included a publication date of 2017 to the present day. Any study published before 2017 was excluded. A summary of statistics reported in the these three RCTs to measure live birth rate when ES was performed include RR, 95% CI, p-value, and OR. The dichotomous data provided in these studies allowed for NNT to be calculated and used to determine the treatment effect of ES.

Patient population studied in the primary research selected included women receiving IVF. Each study had specific inclusion and exclusion criteria as listed below in Table 1. The intervention examined was ES in women undergoing IVF compared to no ES in women undergoing IVF. The measured outcome was live birth rate amongst these two groups.

## OUTCOMES MEASURED:

The patient oriented outcome this systematic review will focus on is live birth rate which was measured by all three RCTs selected. Live birth rate was measured by the number of live births per embryo transfer divided by the total number of women randomly assigned to that group. Rodriguez et al. defines live birth as the "birth of a live baby beyond the 24 weeks of pregnancy".[2] Olesen et al. study measured additional variables including clinical pregnancy rate,

**Table 1** Demographics and Characteristics of Included Studies

| Study | Type | # Patients | Age (yrs) | Inclusion Criteria | Exclusion Criteria | W/D | Intervention |
|---|---|---|---|---|---|---|---|
| Olesen et al.[5] | RCT | 304 | 18-40 | Females IVF patients with one or more prior implantation failures, regular menses (28-32 days), and BMI 18-32 $kg/m^2$. | Females with congenital uterine abnormalities, fibroids, polyps, or suspected hydrosalpinges or adenomyosis. | 50 | Endometrial scratching using a Pipelle de Cornier in the luteal phase before ovarian stimulation at cycle days 18-22 |
| Lensen et al.[1] | RCT | 1364 | 32-38 | Females planning IVF with their own oocytes (stimulated IVF cycle with planned fresh-embryo transfer or frozen-embryo transfer) | Females not planning embryo transfer, contraindications to Pipelle biopsy, any disruptive intrauterine procedures within 3 months prior to the start of IVF | 242 | Endometrial scratching with 3mm diameter pipelle between day 3 of the cycle preceding the IVF cycle and day 3 of IVF cycle |
| Rodriguez et al.[2] | RCT | 352 | 18-50 | Patients undergoing egg donor IVF treatments with a normal uterine cavity assessed by 2D transvaginal US | Endometrial polyps if polypectomy performed at least 2 months prior, severe male factor of < 2 million sperm per mL, factors interfering with embryo implantation (uterine fibroids, Mullerian malformations, severe adenomyosis), hydrosalpinx, BMI > 35 $kg/m^2$, previous ES or hysteroscopy, and frozen embryo transfers | 19 | Endometrial scratching with endometrial biopsy catheter 5-10 days before menses preceding the transfer cycle |

ongoing pregnancy rate, and miscarriage rate then took it a step further and developed subgroup analyses based on the number of previous failed implantations.[5] In addition to live birth rate (LBR), Lensen et al. study measured clinical pregnancy, ongoing pregnancy, biochemical pregnancy, multiple pregnancy, ectopic pregnancy, and miscarriage per group.[1] The outcomes furthermore measured in Rodriguez et al. study comprised of positive pregnancy test, clinical pregnancy, ongoing pregnancy, early miscarriage, late miscarriage, and multiple pregnancies.[2]

**RESULTS:**

Olesen et al. conducted a randomized controlled trial to compare the live birth rate in women receiving IVF with ES to women receiving IVF without ES.[5] Beginning in February 2014-December 2017, a total of 304 women from four public fertility clinics in Denmark between the ages 18-40 years old who met the inclusion and exclusion criteria listed in Table 1 were selected to participate.[5] Allocation of subjects was concealed and they were randomized into two groups using an internet based randomization list.[5] 151 participants were allocated into the intervention group and 153 participants were allocated into a control group.[5] ES was carried out in the intervention group once in each quadrant of the endometrium using a Pipelle de Cornier while lying in a lithotomy position during the luteal phase before ovarian stimulation at cycle day 18-22.[5] It was not possible to blind subjects in this study as ES is a procedure. Participants designated to the control group received the same IVF treatment as the experimental group however did not undergo ES prior to ovarian stimulation.[5] 27 participants from the experimental group and 23 participants from the control group withdrew from the study however, all were included in an intention to treat analysis regardless of whether they completed the study or not.[5] This systematic review will focus on the objective data measuring live birth

rate determined by the number of live births divided by the total number of participants for each group.

As shown below in Table 2, 31.1% of the subjects in the ES group experienced live births compared to 24.2% in the control group with a measured p-value of 0.176.[5] Women receiving ES with IVF had a 1.285 higher probability of a live birth when compared to the control group (95% CI; 0.89-1.86).[5] Given this dichotomous data, a numbers needed to treat (NNT) of 15 was calculated. This calculation supports that for every 15 patients who receive ES while undergoing IVF, one more patient will have a live birth when compared to women undergoing IVF without ES. Other than a brief period of pain during the ES procedure, this particular study had no reports of uterine infections, bleeding, or additional adverse events.[5]

**Table 2** Olesen et al.[5] Treatment Outcomes

| Study | EER | CER | RR (95% CI) | P-value | RBI | ABI | NNT |
|---|---|---|---|---|---|---|---|
| Olesen et al.[5] | 0.311 | 0.242 | 1.285 (0.89-1.86) | 0.176 | 0.285 | 0.069 | 15 |

Lensen et al. published a study in 2019 that also compared live birth rates in women undergoing IVF with ES and without ES. Participants were recruited from June 2014 – June 2017 from 13 different sites in 5 various countries.[1] In all, 3627 women were assessed for eligibility to participate however due to inclusion and exclusion criteria that is listed in Table 1, the study designated 1364 participants to undergo randomization by an online third party randomization system which ensured concealment.[1] There were two groups within the study including an experimental group comprised of 690 subjects and a control group made up of 674 subjects.[1] The experimental group underwent an ES procedure performed by a clinician with a pipelle approximately 3 mm in diameter between day 3 of cycle preceding IVF cycle and day 3 of the IVF cycle.[1] It was not possible to keep this a blinded study due to the intervention being a

procedure. The patients allocated to the intervention group were instructed to attend the procedure with a full bladder and given pain medication.[1] The control group completed IVF without ES in accordance to the standardized protocols specific to each practicing clinic they attended.[1] The primary objective outcome measured in this study was live birth rate per randomly assigned woman.[1]

Outcomes were analyzed using OR (95% CI; 0.78-1.27) and a p-value of 0.97.[1] As recorded in Table 3, an OR of 1 indicates little to no treatment effect because there is no higher or lower odds of women in the ES group to have a live birth when compared to the control group. Women in the ES group had a 0% increase in live births when compared to the control group.[1] A p-value of 0.97 signifies these results are not statistically significant and the results listed in Table 3.0 had a 97% probability of occurring due to chance.[1] There were a total of 242 women that were lost to follow up or did not complete the study due to procedural difficulties, personal reasons, or became naturally pregnant during the trial.[1] Of the 690 in the intervention group, 14 adverse reactions were reported including excessive pain, dizziness, nausea, and excessive bleeding.[1]

**Table 3** Lensen et al.[1] Reproductive Outcomes

| Study | EER | CER | OR (95% CI) | P-value |
|---|---|---|---|---|
| Lensen et al.[1] | 0.261 | 0.261 | 1.00 (0.78-1.27) | 0.97 |

Rodriguez et al. is a third RCT that investigated improvements in live birth rates for women receiving IVF with ES compared to those who are receiving IVF without ES. This study took place at on fertility center in Madrid and recruited subjects from January 2017 – October 2018.[2] 558 patients were eligible but due to the inclusion and exclusion criteria outlined in Table 1.0, the study had a total of 352 patients, ages 18-50 years old, enrolled.[2] One unique aspect of this study compared to the other two is that it was focused specifically on egg donor IVF versus a

patient using their own eggs.[2] A web based randomization system was used for the concealed allocation of 176 participants to two separate groups and then instructions were provided to the intervention group for ES as this is impossible to keep blinded from the patient.[2] The ES group was instructed to arrive at an outpatient setting with a full bladder 5-10 days prior to the start of menstruation for the procedure which involved a pipelle inserted into the cervix to scratch all four walls of the uterine cavity.[2] The control group followed IVF protocols concurring with the standards of the fertility clinic.[2] Live birth rate was compared amongst the two groups in the study. The authors defined live birth rate as "the birth of a live baby beyond the 24 weeks of pregnancy.[2] 19 total subjects withdrew from this particular study (15 from the ES group and 4 from the control group) but they were still included in the ITT analysis.[2]

The outcomes of this study are offered in Table 4 and were measured using RR, 95% CI, and p-value. The data reported 54.5% in the ES group had a live birth compared to 48.3% of the control group with a live birth.[2] The p-value of 0.286 indicates that these results are not statistically significant.[2] The RR was barely larger than 1 (95% CI; 0.92-1.39) supporting that the probability of a live birth with ES was just slightly higher than the probability of a live birth in the control group.[2] The dichotomous data provided in this study allowed the NNT to be calculated which supported a small treatment effect. For every 17 patients who underwent ES while receiving IVF, 1 more patient will have a live birth when compared to the control group.

**Table 4** Rodrigues et al.[2] Treatment Outcomes

| **Study** | **EER** | **CER** | **RR (95% CI)** | **P – value** | **NNT** |
|---|---|---|---|---|---|
| Rodriguez et al.[2] | 0.545 | 0.483 | 1.13 (0.92-1.39) | 0.286 | 17 |

**DISCUSSION:**

All three studies reviewed revealed a degree of validity when answering the clinical question because they utilized randomized allocation, ensured similar baseline characteristics and demographics between subjects, monitored subjects for an adequate amount of time to record results, and lost less than 20% of their subjects to follow up. Although blinding subjects to the procedure once allocated to one of two groups was not possible, there was objective data measured. The studies included an ITT analysis making the results more realistic when thinking about real-life problems patients encounter while receiving medical treatment that may alter the course or outcome. The treatment effect resulted from the studies was determined to be small, meaning in order to obtain the desired outcome of a live birth, a large number of patients would have to be treated first. All studies included a p-value greater than 0.05, indicating that the live birth rate measured in those with ES in addition to IVF versus those without ES were not significant or precise.

The primary outcomes of Olesen et al. consisted of patients that met the inclusion criteria of having one or more prior implantation failures.[5] A further subgroup analysis specifying the number of recurrent implantation failures provided more information on the effect of ES.[5] Patients in the ES group with one previous failed implantation had a live birth rate of 31.9% compared to the control group's 23.0%.[5] Patients in the ES group with three or more previous failed implantations had a live birth rate of 39.4% versus 23.5% in the control group without ES.[5] Although these results suggest that there may be more benefit for ES with IVF in women with a history of recurrent implantation failures, generalizability is lacking because the study does not look at the outcomes for women with no history of prior implantation failure.[5] Compare

this finding to the two other studies, which did not find any difference in live birth rate with subgroup analyses.

Rodriguez et al. only performed the study at one clinic in Madrid, exhibiting limitations in generalizability.[2] Lensen et al. shows increased generalizability with data from 13 different clinics spread amongst 5 different countries.[1] Olesen et al. took place in four separate fertility clinics and the steps of each IVF treatment was determined by that specific clinic, leaving room for differences in protocols that should be more standardized to truly compare accurate results particularly when discussing embryo transfer while also decreasing generalizability.[5] Another limitation to note when discussing results of the three studies is the specific ES procedural techniques performed in each study. The procedure was performed on different days in each of the three studies and it was not explicitly stated the number of scratches or timing from scratching to embryo transfer. Lensen et al. had high rates of embryo transfers between both groups which aided in limiting performance bias however, did not consider the quality of embryo being transferred.[1] Olesen et al. ensured that the quality of transferred embryos did not significantly differ from each subject and each group.[5]

## CONCLUSION:

In conclusion, ES does not increase live birth rates in women receiving IVF treatment. The treatment effect was found to be small based on the difference of live birth rate between the control and experimental groups. Evidence from the three RCTs reviewed exhibited data that was not statistically significant. Future studies to further investigate the effect of ES with IVF on live birth rate may be better understood with standardized timing and technique of the procedure in addition to embryo quality. The future studies should also consider reviewing cost and adverse effects at a greater length.

**REFERENCES:**


1. Lensen S, Osavlyuk D, Armstrong S, et al. A randomized trial of endometrial scratching before in vitro fertilization. *N Engl J Med.* 2019;380(4):325-334. Doi:10.1056/NEJMoa1808737.
2. Izquierdo Rodriguez A, De La Fuente Bitaine, Laura, Spies K, et al. Endometrial scratching effect on clinical pregnancy rates in patients undergoing egg donor in vitro fertilization cycles: the endoscratch randomized clinical trial (NCT03108157). *Reprod Sci.* 2020;27. doi: 10.1007/s43032-020-00204-8.
3. Infertility. Centers for Disease Control and Prevention web site. https://www.cdc.gov/nchs/fastats/infertility.htm. Updated December 2019. Accessed October 5, 2021.
4. Paulson R, Barbieri R, Eckler K. In vitro fertilization. In: Post TW, ed. *UpToDate.* UpToDate; 2021. Accessed October 5, 2021. https://www/uptodate.com/contents/in-vitro-fertilization
5. Olesen MS, Hauge B, Ohrt L, et al. Therapeutic endometrial scratching and implantation after invitro fertilization: a multicenter randomized controlled trial. *Fertil Steril.* 2019; 112(6):1015-1021. doi:10.1016/j.fertnstert.2019.08.010.