Title: Comparing Two Types of Endometrial Activation Prior to Embryo Transfer

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Protocol – Comparing Two Types of Endometrial Activation Before Embryo Transfer: A Pilot Study

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Purpose

To determine if two types of endometrial activation (Pipelle curette or Shepard catheter) prior to embryo transfer result in similar live birth rates. Also to determine if patients experience similar pain from both types of endometrial activation.

Hypothesis

1. We predict that the Pipelle curette and Shepard catheter will have similar live birth rates when performed in the cycle before embryo transfer.
2. We predict that endometrial activation with the Shepard catheter will be less painful than the Pipelle curette.

Background and Significance

Assisted reproductive technologies (ART), including in vitro fertilization (IVF), are methods used to treat infertility, which affects approximately 10% reproductive aged women (1). Physicians at the Women's Institute perform over 300 embryo transfer procedures every year. Despite advances and improvements in ART over the past three decades, clinical pregnancy rate and live birth rate remain 30-40% and 20-30% (2). Implantation is essential for successful ART and IVF procedures, and many interventions have been studied to possibly improve implantation rates and thus pregnancy and live birth rates (3).

Endometrial activation is one such intervention, sometimes referred to as endometrial "activation" or "scratch," and it is defined by the Cochran Collaboration as "intentional endometrial injury, such as endometrial biopsy or curettage, in women undergoing ART" (4).

In 2003, Barash et al. found that implantation rates, clinical pregnancy rates, and live birth rates were more than twofold higher in women who underwent endometrial biopsy in the cycle before subsequent IVF treatment (3). A Cochrane Review which examines endometrial activation prior to IVF similarly has concluded that endometrial activation prior to the embryo transfer cycle significantly improves clinical pregnancy rates and live birth rates in women undergoing ART. Although the type of endometrial procedure is not specified, the timing activation was found be most effective when performed in the cycle prior to the embryo transfer (4).

The mechanism of increase endometrial receptivity is still unknown; however three proposed hypothesis exist. The first hypothesis proposes that local activation of the endometrium induces endometrial decidualization which increases the probability of embryo implantation. The second hypothesis is that endometrial healing following endometrial activation increases secreted cytokines, interleukins, growth factors, macrophages, and dendritic cells which are beneficial to embryo implantation. The final hypothesis suggests that endometrial maturation is abnormally advanced during ovarian stimulation, so endometrial activation may lead to better synchronicity between the endometrium and the embryo (4).

Endometrial activation has been found to have clear benefit in pregnancy and live birth rates in a Cochrane Review (4), however no uniform technique has been determined. Our objective is to compare two types of endometrial disruption – a vigorous endometrial biopsy with a Pipelle curette and a four quadrant endometrial "scratch" using a Shepard insemination catheter – to determine if the live birth rates are equivalent for the two methods. We also will compare pain with the two types of endometrial activation. By comparing two distinct types of endometrial activation, we hope to determine which method is both effective and tolerable to patients.

The Shepherd catheter is a 1.8 mm malleable insemination catheter that can be curved to traverse the cervix. It is also used by some physicians in the Women's Institute to perform saline infusion sonography. When the catheter is inserted under ultrasound guidance, it is often placed in the subendometrial tissue, and causes deflection and disruption of the endometrium but is tolerated well. The Pipelle is a 3.1 mm semi-rigid catheter with an internal stylet plunger. A biopsy is performed by placing the catheter into the uterus, withdrawing the stylet to create suction, and aspirating endometrial tissue into the catheter.

A study done by Leclair et al. found that the mean pain that women had when the Pipelle was used for an endometrial biopsy was 6.2±2.4 on a visual analog scale from 1-10 (5). Pain with the Shepard catheter has not been studied when it is used for endometrial biopsy.

Type of Study
This will be a non-blinded randomized control trial with parallel treatment arms.

Study Population
Female patients at the CMC Women's Institute undergoing IVF with either a fresh or frozen embryo transfer.

Inclusion Criteria:

- All patients undergoing embryo transfer who are in the cycle prior to their embryo transfer

Exclusion Criteria:

- Patients not undergoing embryo transfer
- Known pregnancy
- Active pelvic infection
- Known endometrial hyperplasia or cancer
- Inability to tolerate endometrial catheter placement
- Severe cervical stenosis
- Patients who will receive operative hysteroscopy in the cycle prior to embryo transfer

Materials and Methods

1) After Institutional Review Board approval is obtained, patients will be consented in the cycle prior to their fresh or frozen embryo transfer.
2) Demographic data including age, gravity and parity, reason for infertility, BMI, fresh or frozen embryo transfer, prior IVF cycles and results, ovarian reserve (AMH), prior ART attempts, prior ART outcomes, embryo stage and quality at time of cryopreservation, technique of cryopreservation (slow-cooled for vitrified), own eggs or donor eggs, ovarian stimulation regimen, number of oocytes retrieved, number fertilized, number of embryos cryopreserved, whether or not preimplantation genetic testing (PGT) was performed, type of hormonal regimen for frozen embryo transfer, and endometrial thickness before transfer as measured by ultrasound, will be recorded on a data collection sheet.
3) Patients will be randomized by sealed envelopes containing randomized numbers (either 1 or 2) which corresponds with the research group. 1 will be vigorous endometrial biopsy with a Pipelle curette. 2 will be 4 quadrant endometrial activation with a Shepard insemination catheter.

4) During the cycle prior to their embryo transfer, patients will come to the Women's Institute between cycle days 21-27 for the endometrial activation procedure.
5) For patients in group 1, physicians will insert the Pipelle curette into the uterus and remove an adequate endometrial sample using vigorous motion.
6) For patients in group 2, physician will insert the Shepard insemination catheter into the uterus at 12:00 and then withdrawn. The catheter will be turned one-quarter turn and withdrawn. This will be repeated two more times so that 4 endometrial quadrants will have been touched by the catheter.
7) Immediately following the endometrial procedure, patients will be given a Numerical Rating Scale for pain, on which they will circle the number which best correlates with the patient they experienced during the procedure. This data will also be collected on the data collection sheet.
8) The rest of the IVF cycle and embryo transfer will proceed by standard protocol.
9) After the embryo transfer, additional data will be collected for the data collection sheet including number of embryos, grade and stage of the embryos, number of embryos transferred, pre-implantation genetic testing, type of freezing (slow freeze vs. vitrification), difficulty of the transfer procedure, implantation rate, positive pregnancy test, live birth rate.

Independent Variables

The independent variable is type of endometrial activation – vigorous Pipelle curette vs. four quadrant placement of the Shepard insemination catheter.

Outcome Variables

Our primary outcome variable is live birth rate. Our secondary outcome variables are pain (using a numerical pain scale), implantation rate, and positive pregnancy tests, ultrasound evidence of pregnancy, implantation rate, birth rate, and incidence of multiple pregnancies (twins or more).

Confounding Variables

Variables which may confound the results are patient age, frozen or fresh embryo transfer, ovarian reserve, number of embryos, grade and stage of the embryos, number of embryos transferred, pre-implantation genetic testing, previous IVF, previous IVF failure, own eggs or donor eggs, type of freezing (slow freeze vs. vitrification), difficult transfer, ovarian stimulation regimen, type of hormonal regimen for frozen embryo transfer, uterine abnormalities.

We plan to sub-stratify our randomization based on the most important confounding variables: fresh embryo transfer and frozen embryo transfer.

Statistical Analysis
Based on the distribution of the data results, we will plan to use means, standard deviations, and p-values by Chi-squared testing for normally distributed data or medians, interquartile ranges, and p-values by Mann-Whitney testing for non-normally distributed data.

We plan to work with the statisticians from CMC's Dickson Advanced Analytics who used DA2 software.

Sample Size
Based on an 80% power calculation in which a 10% change in live birth rate was deemed to be clinically significant, the sample size needed to attain adequate power is 200 total patients.

Duration
We believe it will take approximately one year to enroll and complete all 200 patients.

Budget
This study does not have a budget. There will be no charge to the patient for the endometrial activation because the physicians have agreed to donate their time, and the procedures will be done in-office.

References

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