Endometrial infusion of human chorionic gonadotropin at the time of blastocyst embryo transfer does not impact clinical outcomes: a randomized, double-blind, placebo-controlled trial

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Objective: To determine whether endometrial hCG infusion at the time of human blastocyst transfer impacts implantation rates.
Design: Randomized double-blinded placebo-controlled trial.
Setting: Academic.
Patient(s): Infertile couples with the female partner less than 43 years old (n = 300) undergoing fresh or frozen ET of one or two blastocysts.
Intervention(s): Patients undergoing ET were randomized into either a treatment or a control group. The treatment group received an infusion of 500 IU of hCG diluted in ET media. The control group received a sham infusion of ET media. Infusions were done using a separate catheter less than 3 minutes before actual ET.
Main Outcome Measure(s): Sustained implantation rate: ongoing viable gestation (primary outcome) and ongoing pregnancy rate (secondary outcome).
Result(s): A total of 473 blastocysts were transferred into 300 patients. There were no differences between the two groups in sustained implantation rate (48.1% in the hCG group, 44.2% in the control group) or ongoing pregnancy rate (58.8% in the hCG group, 52.0% in the control group).
Conclusion(s): Endometrial infusion of hCG at the time of blastocyst ET does not improve sustained implantation rates.
Clinical Trial Registration Number: NCT01643993. (Fertil Steril® 2014;102:1591–5. ©2014 by American Society for Reproductive Medicine.)
Key Words: hCG, intrauterine hCG, implantation rate, pregnancy rate, embryo transfer

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While clinical implantation and delivery rates continue to rise in couples attempting to conceive using assisted reproductive technology (ART), the process remains relatively inefficient. It remains common for euploid embryos with optimal morphokinetic parameters to be transferred into

sonographically normal endometrial cavities and still fail to achieve implantation.

While some of these failures may reflect the suboptimal endocrine milieu accompanying controlled ovarian hyperstimulation to attain multifollicular development; implantation rates are also far from perfect in recipients of oocyte donation or when transferring cryopreserved embryos where endometrial preparation and timing should be closer to physiologic.

While appropriate endocrine dynamics may assure adequate endometrial preparation and timing, the process of implantation is a paracrine/juxtacrine-mediated phenomenon that is controlled locally. Among the factors important in implantation is hCG (1). Intrauterine infusion of hCG and exposure of cultured human endometrial epithelial cells has been shown to upregulate proteins known to be involved with implantation (2, 3). This has led some investigators to suggest that endometrial augmentation with infusion of hCG might lead to enhanced implantation rates.

Mansour et al. found that intraendometrial infusion of 500 IU of hCG during cleavage-stage ET significantly enhanced implantation rates (29.5% in controls vs. 41.6% after hCG infusion) (4). While these results were most provocative, several questions remain. The hCG infusion into the endometrial cavity was dyssynchronous with the physiological timing of embryonic hCG secretion, which typically begins at the morula stage (5). At that time, the embryo would be localized to the fallopian tube in natural conception, making it an unusual time to provide a paracrine signal.

Blastocyst ET (day 5 or 6 of embryo development) is becoming more prevalent, in particular to enhance selection for elective single ET (eSET). Furthermore, with the broad clinical application of vitrification, the practice of frozen ET (FET) has become increasingly common.

To date there are no published studies on the impact of endometrial hCG infusion in the perinidatory interval to determine whether the benefit identified at the cleavage stage extends to transfers done at the blastocyst stage. Prior studies also have not evaluated the impact of hCG infusion in FET cycles, which may be different from its impact in fresh ETs. This randomized controlled trial seeks to determine whether hCG infusion in the minutes before blastocyst transfer meaningfully impacts implantation and delivery rates in fresh and FET cycles.

MATERIALS AND METHODS

Patient Population

All patients undergoing fresh or frozen ET within the ART program where the female partner was less than 43 years of age were offered participation. Patients were recruited by the clinical research team and recovery room staff. Patients could not be simultaneously participating in another prospective clinical trial at the center, but there were no other inclusion/exclusion criteria. Specifically, there were no restrictions based on any aspect of clinical care before or after the infusion and transfer. All embryos are cultured until day 6 regardless of patient age or the size or quality of the embryo cohort. All fresh transfers within the program occur at the blastocyst stage on day 6 of embryonic development. In FET cycles, once an adequate endometrial thickness and pattern have been obtained, typically at least 7 mm and trilaminar, IM P in oil is started and FET is performed on the sixth day of P administration. Patients, in consultation with their physicians, elect between transfer of one or two blastocysts. Per practice routine, real-time quantitative polymerase chain reaction–based comprehensive chromosome screening (CCS) was offered to all patients (6, 7). Patients of advanced reproductive age or with a history of failed implantation were encouraged to incorporate CCS before ET. Patient enrollment extended from August 2012 to December 2013. All participants were followed clinically until their final disposition: pregnancy test for those who failed to conceive, 8 gestational weeks if pregnant with normal growth, or through the time of any pregnancy loss. Patients with ongoing gestations were discharged to their obstetricians for ongoing care, and final outcomes were then assessed after delivery. All data collection was performed at Reproductive Medicine Associates of New Jersey.

Experimental Design

A random number function was used to create variable blocks of four to eight with patients assigned to the two groups in a 1:1 allocation. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes. Two sets of randomization schemes were used: one for fresh ET and one for FET. The study group received endometrial infusion of ET media (synthetic serum substitute and Medicult BlastAssist from Origio) laden with 500 IU of purified-urinary placental hCG (Novarel, Ferring Pharmaceuticals), and the sham control group received endometrial infusion of ET media only.

An embryologist opened the randomization envelope on the afternoon before the day of planned ET to allow time for preparation and equilibration for the next day's use. The embryologist prepared the infusion mixture by dissolving 20,000 IU of urinary hCG powder with 0.8 mL of ET media. The mixture was then stored in a preequilibrated tri-gas incubator. While there are no definitive studies demonstrating that there is equivalent potency of hCG at 37°C (temperature of culture incubator), times in vivo do not produce meaningful degradation of the molecule, nor are there any data to suggest that such a diminution would have occurred.

The usual steps were taken to prepare for ET. The patient was positioned, and a speculum was placed to visualize the cervix. The embryologist loaded 20 μL of the ET media with or without hCG into a Wallace catheter and handed it to the physician, who then advanced it into the cavity under direct ultrasound visualization to the approximate depth of the actual ET that would follow. The media were infused into the endometrial cavity, and the catheter was discarded. The embryologist then used a new Wallace catheter to load the embryo(s) in 20 μL of ET media and handed it to the physician who then performed the transfer per standard protocol. The speculum was removed immediately afterwards. The time between the infusion and ET was less than 3 minutes. Both the physician performing the transfer and the patient were