ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Vitrified blastocyst transfer cycles with the use of only vaginal progesterone replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial

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Objective: To assess the noninferiority of vaginal P (Endometrin) compared with daily intramuscular P for replacement in programmed vitrified-warmed blastocyst transfer cycles and to assess the noninferiority of vaginal P in combination with intramuscular progesterone every third day compared with daily intramuscular P.
Design: Three-arm randomized controlled noninferiority study. To enable early recognition of inferiority if present, an a priori interim analysis was planned and completed once ongoing pregnancy data were available for 50% of the total enrollment goal. The results of this interim analysis are presented here.
Setting: Assisted reproduction technology practice.
Patient(s): Women undergoing transfer of nonbiopsied high quality vitrified-warmed blastocyst(s) in a programmed cycle.
Intervention(s): Vitrified-warmed blastocyst transfer with mode of P replacement determined by randomization to either: (1) 50 mg daily intramuscular P only; (2) 200 mg twice daily vaginal Endometrin; or (3) 200 mg twice daily Endometrin plus 50 mg intramuscular P every 3rd day.
Main Outcome Measure(s): Live birth. The primary outcome of this interim analysis was ongoing pregnancy.
Result(s): A total of 645 cycles were randomly assigned to one of the three treatment arms, received at least one dose of P replacement therapy according to this assignment and underwent vitrified-warmed blastocyst transfer. These cycles were included in the intention-to-treat analysis. The study team, including the statistician, were blinded to the identity of the treatment arms, which were randomly labeled "A," "B," and "C" in the dataset. Ongoing pregnancy occurred in 50%, 47%, and 31% of cycles in arms A, B, and C respectively. Although arm C had an rate of positive hCG equivalent to the other two arms, the rate of pregnancy loss for arm C was significantly higher than for either of the two arms, resulting in a more than one-third lower rate of ongoing pregnancy. There were no statistically significant differences for any outcome tested between arms A and B. Results of a per-protocol analysis were nearly identical to those of the intention-to-treat analysis. On completion of these analyses, arm C was revealed to be the vaginal P only arm.
Conclusion(s): Relative to regimens inclusive of intramuscular P, vaginal-only P replacement for vitrified-warmed blastocyst transfer results in decreased ongoing pregnancy, due to increased miscarriage, and should be avoided. Randomization to the vaginal-only arm was terminated with these findings. This trial is ongoing to assess the noninferiority of the vaginal plus every 3rd day intramuscular P arm compared with daily intramuscular P in terms of live birth.

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Human embryo implantation and ongoing pregnancy require progesterone (P) influence on the endometrium. A classic series of studies conducted by Csapo et al. more than 40 years ago demonstrated that early removal of the corpus luteum, the primary source of endogenous P production during preimplantation and early pregnancy, resulted in pregnancy loss (1, 2). In programmed assisted reproduction cycles with cryopreserved embryo transfer, ovulation and corpus luteum formation typically do not occur; endometrial preparation therefore requires exogenous P replacement (3). Multiple routes of P administration are available. Vaginal and intramuscular are preferred routes, whereas oral P is generally avoided owing to poor bioavailability and inferior assisted reproductive technology (ART) outcomes (4–8). Patients undergoing assisted reproduction have significant concerns regarding daily injections of intramuscular P, the most common being injection-associated pain, fear of hitting a blood vessel, and injection of the medication at the wrong site (9). Surveys have indicated that when given the choice, most patients prefer vaginal over intramuscular P administration for a variety of reasons, including greater convenience, ease of use, and less pain (10–12).

Data on micronized vaginal P preparations for luteal support in fresh autologous in vitro fertilization (IVF) cycles, where corpora lutea form and secrete endogenous P, provide strong evidence of equivalence (or even superiority) compared with intramuscular P in terms of pregnancy and birth outcomes (10, 11, 13–21). On the basis of these largely prospective data, many centers have moved to vaginal regimens for the majority of patients undergoing autologous IVF with fresh embryo transfer. However, it is not known whether the vaginal route provides outcomes equivalent to intramuscular P replacement for medicated cryopreserved embryo transfer cycles. Sufficient prospective data are lacking, particularly for vitrified-thawed blastocyst transfer. A Cochrane review performed in 2010 reviewed the four available randomized controlled trials comparing vaginal and intramuscular routes of P replacement, i.e., for transfer of cryopreserved or donor embryos in a programmed endometrial preparation cycle. That review found no statistically significant differences regarding live birth, clinical pregnancy, or miscarriage (22). However, the largest study, which evaluated autologous transfers of embryos cryopreserved at the cleavage stage, enrolled only 354 subjects (23). The other trials evaluated fresh transfers of embryos derived from donor oocytes. Only one study assessed live birth as an outcome (24). The authors of the Cochrane review therefore concluded that "there was insufficient statistical power to reach definitive conclusions" and that "more studies are needed to evaluate if there is an optimal route of progesterone administration." Recent retrospective studies comparing vaginal progesterone and intramuscular P for replacement in cryopreserved embryo transfer cycles have yielded conflicting results (25–28). One retrospective analysis of 194 cryopreserved embryo transfer cycles reported a higher live birth rate when P was injected intramuscularly once every 3 days in addition to daily vaginal P administration ($P=.0015$ vs. vaginal P alone) (29).

Therefore, we set out to determine whether P replacement via vaginal administration, either alone or in combination with intramuscular P every 3rd day, is inferior to daily intramuscular P in terms of pregnancy and live birth following transfers of vitrified-warmed blastocysts. Here we report results from the planned interim analysis of this ongoing randomized controlled noninferiority trial, which demonstrate a significantly lower ongoing pregnancy rate among patients receiving vaginal P replacement with the use of Endometrin alone compared with those receiving intramuscular P, either alone or in addition to vaginal P.

MATERIALS AND METHODS

Patients

This ongoing clinical trial, begun in October 2014, is open to patients undergoing transfer of vitrified-warmed blastocyst-stage embryos at Shady Grove Fertility (SGF), a large private reproductive medicine practice in the mid-Atlantic region of the United States. Subject enrollment and cycle monitoring were performed at 14 SGF offices located in the District of Columbia, Maryland, Virginia, and Pennsylvania. Oocyte retrieval and in vitro culture, vitrification, and transfer of embryos were performed at one of three SGF laboratories located in Rockville and Towson, Maryland, and Chesterbrook, Pennsylvania. This registered trial (ClinicalTrials.gov NLM identifier NCT02254577) was approved by the Schulman Associates Institutional Review Board (SAIRB-13-0028) and is being conducted in compliance with good clinical practice guidelines. After giving written informed consents, subjects were screened based on the following inclusion and exclusion criteria. Inclusion criteria: (1) female age 18–48 years; (2) Having available blastocyst(s) cryopreserved by vitrification method at SGF. Exclusion criteria: (1) requirement for fresh embryo(s); (2) requirement for a gestational carrier; (3) embryo(s) for transfer from cryopreserved oocytes; (4) embryo(s) for transfer cryopreserved more than once; (5) embryo(s) for transfer cryopreserved by slow-freeze method; (6) embryo(s) for transfer cryopreserved before blastocyst stage; (7) presence of any clinically relevant systemic disease contraindicated for assisted reproduction or pregnancy; (8) history of more than three failed cycles of