Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer

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Objective: To compare outcomes after intramuscular progesterone (IMP) or 8% Crinone vaginal gel for luteal support for day 3 cryopreserved embryo transfer (CET).
Design: Retrospective cohort study with multivariable analysis.
Setting: Academic medical center.
Patient(s): All autologous and donor egg in vitro fertilization and intracytoplasmic sperm injection patients who had a day 3 CET from January 1, 2008, to April 30, 2011, with luteal support using 25–50 mg/d IMP or 8% Crinone twice daily, initiated 3 days before the CET.
Intervention(s): None.
Main Outcome Measure(s): Implantation rate, clinical pregnancy, and live birth rates per CET.
Result(s): IMP (n = 440) and Crinone (n = 298) recipients were similar for all demographic characteristics and cycle parameters assessed. Although implantation rates did not differ significantly between the two groups (Crinone vs. IMP: 19.6% vs. 30.4%), women supplemented with Crinone had significantly lower rates of clinical pregnancy (36.9% vs. 51.1%) and live birth (24.4% vs. 39.1%) compared with those on IMP.
Conclusion(s): We observed that day 3 CET cycles with 8% Crinone luteal support had a 44% and 49% lower odds of clinical pregnancy and live birth, respectively, compared with those with IMP support. Further studies are required to identify the optimal timing and dose of 8% Crinone vaginal gel for use in CET cycles. (Fertil Steril® 2012;98:1464–9. ©2012 by American Society for Reproductive Medicine.)
Key Words: Crinone vaginal gel, intramuscular progesterone, luteal phase support, frozen, pregnancy

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Progesterone is required for implantation and maintenance of early pregnancy until the luteoplacental shift, which occurs at ~8–10 weeks' gestation. It is the standard of care to provide exogenous P to women undergoing fresh and cryopreserved (CETs) embryo transfers. In fresh IVF cycles, luteal support is necessary because endogenous P is decreased due to GnRH down-regulation and disruption of mural granulosa cells at oocyte retrieval (1–4). In comparison, there is minimal endogenous P production in CET and donor cycles, so pharmacologic support is necessary (5).

The preferred route of administration for P in CET cycles is an area of active research. The current criterion standard is intramuscular progesterone (IMP). Oral P is available but undergoes extensive hepatic metabolism, may cause significant sedation, and has limited bioavailability to achieve secretory endometrium (6). Intravaginal formulations such as 8% Crinone gel or other vaginal inserts are reported to have better patient satisfaction due to limited systemic absorption and ease of use (7). Although good-quality data

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support the equivalence of Crinone and IMP for fresh in vitro fertilization (IVF) cycles (7–13), the most effective P for CET cycles remains to be determined (14–20). The objective of the present study was to assess the efficacy of IMP versus Crinone for P support in CET cycles by comparing implantation and pregnancy rates between the two treatment groups.

MATERIALS AND METHODS

This study was approved by the Partners' Healthcare Institutional Review Board.

Experimental Design

All autologous and egg donor CET cycles with day 1 or day 3 freeze and day 3 embryo transfer performed at Brigham and Women's Hospital from January 1, 2008, to April 30, 2011, were reviewed for the type of P used for luteal phase support. Day 3 ET accompanied by day 3 cryopreservation of supernumary embryos is standard in our program. Patient characteristics, CET cycle parameters, post-thaw embryo survival and morphology, and clinical outcomes were compared between those supplemented with 25 mg IMP for 1 day, then increasing to 50 mg/d (locally compounded at one of two pharmacies: Village Fertility, Waltham, Massachusetts, or Freedom Fertility, Byfield, Massachusetts) and those supplemented with micronized P in 90 mg bioadhesive vaginal gel once per day for 1 day and then twice daily (8% Crinone; Watson Pharmaceuticals) until 10 weeks gestational age. Cycles were excluded for the following reasons: day 2 or day 5 cryopreservation, day 5 transfer, biopsied embryos, no luteal phase support (i.e., natural cycle), IMP dose other than 25–50 mg/d, and P formulations other than IMP or Crinone.

Clinical Protocols

Standard controlled ovarian hyperstimulation, insemination, and intracytoplasmic sperm injection (ICSI) protocols were used for fresh autologous and donor egg cycles as previously described (21). Pronuclear zygotes and day 3 embryos were then cryopreserved as outlined below. In preparation for CET, a GnRH agonist was started on cycle day 21 of the prior cycle for pituitary down-regulation, with a combined oral contraceptive lead-in for patients with oligoovulation or polycystic ovary syndrome. Baseline serum testing was performed on cycle day 2. In patients with serum P <3 ng/mL, 3 mg estradiol acetate (Estrace; Warner Chilcott) by mouth twice daily was used to achieve a target endometrial echocomplex (EEC) of ≥ 7 mm. In patients who did not achieve the 7 mm target thickness, estradiol acetate was continued for an additional week. If the EEC still remained <7 mm after an additional week of oral estrogen, the cycle was usually canceled and a different estrogen priming protocol prescribed (e.g., 1–2 mg E_2 per vagina twice daily or 0.3 mg transdermal patch every other day). Progesterone was started in 7.5% of cycles (55/738) with EEC <7 mm (6.7% of Crinone, 7.9% of IMP). Luteal P with IMP or Crinone was initiated 3 days before transfer (i.e., the day of transfer was the fourth day of P for patients receiving day 3 thawed embryos as well as for those receiving day 1 thawed embryos cultured to day 3). The type of P used for luteal support was left to the discretion of the clinician and did not represent a change in institutional protocol during the study period. Supplemental P was continued until 10 weeks' gestation or until a negative serum quantitative hCG. Day 3 ETs were routinely performed with the use of a Wallace catheter (Marlow/Cooper Surgical); difficult transfers were done with a Sureview catheter (Smiths-Medical).

Laboratory Protocols

Two-pronuclear zygotes and day 3 embryos were cryopreserved with the use of Liebo's one-step slow-freeze protocol (22). Embryos were washed in HTF+HEPES buffer, supplemented with 10% human serum albumin, and allowed to equilibrate at room temperature for 10–15 minutes before being transferred to 1.5 mol/L 1,2-propanediol cryoprotectant (PG solution) for a further 12–20 minutes. Straws (0.25 mL; IMV-ZA475 or MT19040/0010; Origio) were loaded with PG solution, followed by air, the embryos in PG solution, air, and then a column of the 1.08 mol/L sucrose. Sealed straws were placed in a controlled rate Biocool freezing machine (FTS), in an ethanol bath at $-6.0°C$ and seeded with supercooled forceps. Cooling at a rate of $-0.4°C$ per minute was carried out to a final temperature of $-40.0°C$. Straws were then plunged into liquid nitrogen for storage.

For thawing, straws were allowed to sit at room temperature for 2 minutes before mixing the contents. The straws were then warmed at 37°C for 3 minutes, followed by a 1-minute incubation at room temperature. Expelled embryos were then serially washed at room temperature in HTF+HEPES supplemented with 10% human serum albumin and incubated at room temperature for 10 minutes before being transferred into growth media (G1.5 [Vitrolife] or Global [Lifeglobal]). Post-thaw viability, morphology, and cell stage were recorded. Our standardized protocol for number of embryos to thaw was applied which, for autologous embryos, takes into consideration the patient's age, the number of embryos to transfer for a fresh cycle, and availability of thawed embryos with blastomere survival of $\geq 50\%$; for donor cycles, two embryos were transferred, with the lead embryo having at least four cells and the other with at least two cells. Day 1 embryos were cultured in G1.5 or Global medium until day 3 for transfer, and cleavage-stage embryos were incubated for a minimum of 2 hours before ET. Number of embryos transferred was determined by the number and morphology of available embryos, patient age at embryo cryopreservation, and clinical history.

Outcome Variables

Female patient demographics, including patient age at cryopreservation and transfer, body mass index (BMI) of patient or embryo recipient, day 3 FSH, parity, number of prior failed cycles and spontaneous abortions, endometrial thickness on day of mapping, percentage of cycles with assisted hatching, uterine-factor infertility, use of a gestational carrier, and outcome in corresponding fresh cycle were compared. A prior failed cycle was defined as any fresh or frozen cycle that did not result in a live birth. Uterine factors included