

Vaginal delivery of progesterone in donor oocyte therapy

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A prospective cohort study, with 345 women requiring complete progesterone replacement for a donor egg cycle, was used to compare Crinone 8% (90 mg progesterone vaginal gel) twice or once daily versus i.m. progesterone (100 mg), for endometrial development and pregnancy support. Endometrial histology, serum progesterone levels, pregnancy rates, implantation rates, and bleeding patterns were used as outcome measures. Mean serum progesterone concentrations on day 26 were 19.0 ± 2.3 ng/ml for twice and 11.3 ± 6.5 ng/ml for once daily Crinone, versus 65.2 ± 12.5 ng/ml in the i.m. progesterone group. Endometrial histology was 'in phase' for all women in the Crinone groups and most of the i.m. group. Though eight of 42 patients on once daily Crinone had serum progesterone levels under 6 ng/ml, there was no correlation with endometrial development. Only one patient bled on once daily Crinone before the 14th day of progesterone therapy, and she went on to deliver twins. Clinical pregnancy, ongoing pregnancy, implantation, and miscarriage rates were not statistically different among any of the treatment groups. Crinone 8% administered once or twice daily appears to produce the same endometrial development and pregnancy rates as i.m. progesterone in women requiring complete progesterone replacement, and without early bleeding.

Key words: Crinone/donor oocyte/endometrium/luteal support/vaginal progesterone gel

Introduction

Progesterone is an essential hormone in the preparation for and support of pregnancy in the human. Its use in assisted reproduction is widespread. Various methods of delivering progesterone have been developed; each has its advantages and deficiencies. The problems with i.m. injections are the pain, the occasional sterile abscess or allergic response to the oil vehicle, and the need to train in needle use and its proper disposal. The problem with oral administration is the

nearly complete metabolism of the native steroid into metabolites that induce somnolence but scant endometrial effect. Transdermal administration has appeal, but the requirement for large amounts of progesterone (25 mg daily) would make patch size prohibitively large. Also, vaginal suppositories are messy and variable in formulation.

Despite the historic lack of a reliable and acceptable vaginal product, vaginal therapy has been pursued because of the theoretical advantage of delivering the drug (progesterone) to the target organ (uterus) at high efficiency. Evidence of this 'targeting' has been seen in the nearly 10-fold higher endometrial concentrations of progesterone after the vaginal administration of 100 mg micronized progesterone as compared to the same dose given i.m. (Miles *et al.*, 1994). Furthermore, full secretory transformation of the endometrium is produced when serum levels of 1–3 ng/ml of progesterone are produced by vaginal administration, but not when produced by i.m. or nasal delivery (Cicinelli *et al.*, 1993; DeZiegler *et al.*, 1994). Lastly, superior clinical results after vaginal versus i.m. or oral therapy have been reported in several investigations (Devroey *et al.*, 1989; Bourgain *et al.*, 1990; Smits *et al.*, 1992; Friedler *et al.*, 1998). These advantages encouraged Dr Dominique DeZiegler, working in concert with Columbia Laboratories, to develop a more reliable and acceptable vaginal product. Crinone 8% is the result of that effort.

We have been using Crinone 8%, a bio-adhesive gel containing 90 mg of progesterone, for placement in the vagina, in our donor egg and in-vitro fertilization (IVF) programme for the past 3 years. This report briefly summarizes our experience, which has been partly published elsewhere (Gibbons *et al.*, 1998).

Crinone 8% twice daily for replacement

The donor egg programme was selected for our first experience with Crinone 8% because any failure of the product to work would be immediately apparent in low pregnancy rates or increased miscarriage rates (since the patient has no endogenous source of progesterone production). Dose-ranging studies had shown fully appropriate endometrial development at doses of 90 mg every other day, with a failure to induce in-phase endometrium in one of 10 cases on a dose of 45 mg every other day (Fanchin *et al.*, 1997). Therefore, in order to ensure a wide safety margin, we selected a dose of 90 mg twice daily for our initial trial. We reasoned that this dose was four times higher than a dose shown to be fully effective.

We conducted a prospective, randomized, controlled trial comparing pregnancy rates of recipients of donor eggs on two forms of progesterone replacement: Crinone 8% twice daily versus our prior standard of i.m. progesterone 100 mg (Gibbons *et al.*, 1998). We also examined endometrial development during pilot cycles, and serum progesterone concentrations during pilot and treatment cycles.

All donor egg recipients were treated with oestradiol patches (Estraderm®; Ciba Pharmaceuticals Co., Summit, NJ, USA) or oestradiol (Vivelle®; Novartis

Pharmaceuticals Corp., Summit, NJ, USA) and progesterone replacement in the mock and treatment cycles. Oestradiol patches were changed every other day according to the following dosing regimen: days 1 and 3, one 0.05 mg patch; day 5, one 0.1 mg patch; days 7 and 9, two 0.1 mg patches; days 11 and 13, four 0.1 mg patches; and day 15 and every other day thereafter, two 0.1 mg patches. If a pregnancy occurred, oestradiol replacement therapy was continued for a total of 8 weeks from embryo transfer. During transfer cycles, this dosing regimen was adjusted as necessary in order to synchronize conditions for embryo transfer for the donor and the recipient. Day 15 was defined as the day for egg retrieval from the donor.

Crinone 8% was administered twice daily each morning (between 0600 and 1000 h) and evening (between 2000 and 2300 h) starting from the morning of idealized cycle day 15 (day of egg retrieval) and continued thereafter. This dose was continued for 2 weeks if no pregnancy occurred or for a total of 8 weeks in the event that a pregnancy occurred. Women in the i.m. group received a 100 mg injection of progesterone each morning (between 0600 and 1000 h) from idealized cycle day 15 and continued thereafter.

Fertilization was performed using standard insemination or intracytoplasmic sperm injection (ICSI), according to semen quality and prior outcomes. Up to 10 zygotes were kept in culture. The best three or four were selected for embryo transfer 3 days after egg retrieval, which corresponded to day 18 of the replacement cycle. Embryos were replaced transcervically using the Wallace or Soft-Pass catheter without ultrasound guidance.

Pregnancy testing was done 14 ± 1 day and 16 ± 1 day after embryo transfer. Those who achieved pregnancy were continued on oestradiol and progesterone for a total of 8 weeks after embryo transfer. Ultrasound was performed 3–4 weeks after embryo transfer to assess pregnancy status. Chemical pregnancies were recorded but were not considered clinical pregnancies. Implantation rate was defined as the total number of gestational sacs in the study group divided by the total number of embryos transferred in the same group.

A biochemical pregnancy was defined as a transitory increase in human chorionic gonadotrophin (HCG) concentrations, followed by a decrease in cases where no gestational sac was seen on ultrasound. Clinical pregnancies were defined by the visualization of a gestational sac. As a comparison group, all recipients using standard i.m. progesterone from April 1997 to June 1998 were evaluated in the same way.

The results of 54 treatment cycles on twice daily Crinone 8% compared with 19 cycles on i.m. progesterone are shown in Table I.

We were encouraged that the implantation and pregnancy rates all had a tendency (non-significant) to be higher on Crinone 8%. Based on these results, we were confident that Crinone 8% used twice daily produced normal endometrial development and pregnancy support that was at least equal to our standard i.m. regimen. Moreover, it was greatly preferred by patients who had used i.m. injections before.

Table I. Results of randomized trial of Crinone 8% twice daily versus progesterone 100 i.m. once daily for support of donor egg recipient cycles

	Crinone 8% twice daily	Progesterone 100 mg i.m. once daily
Number of patients completing pilot cycles	54	19
Number of 'out-of-phase' endometria	0	1 (dosing error)
Number of fresh embryo transfers	54	18
% Pregnant (including chemical)	54 (29)	39 (7)
% Clinically pregnant (gestational sac seen)	48 (26)	28 (5)
% Spontaneous miscarriages	31 (8)	20 (1)
% Elective terminations	8 (2 ^a)	0 (0)
% Of cycles with pregnancy at the end of the first trimester	33 (18)	22 (4)
% Implantation (sacs/embryos transferred)	23 (42/180)	18 (11/62)

^a1 for omphalocele, 1 for unwanted triplets.

Crinone 8% once daily for replacement

Having gained confidence that Crinone 8% twice daily worked well, we again focused on the dose-ranging studies of DeZiegler (Fanchin *et al.*, 1997) which suggest that even once daily Crinone is apt to be twice more than is needed. If patients could thus get by with only one application a day, this would be both more convenient and more affordable. Therefore, with Institutional Review Board approval, we invited women in the donor egg programme to use Crinone 8% once rather than twice daily in their pilot and treatment cycles using donor eggs.

The materials and methods used are identical to those described above, except that Crinone was given only once a day from idealized cycle day 15 onward, between 2000 and 2300 h.

Forty-two women have completed pilot cycles and fresh transfers on daily Crinone 8% (April 1997–June 1998). No patients on daily Crinone 8% have had out of phase endometrial development (Figure 1). Results are given in Table II, where they are compared to all cycles in women opting for i.m. therapy instead (1996–1998). Furthermore, pregnancy rates have been as high, and miscarriage rates as low, as compared to i.m. therapy.

Discussion

Administering progesterone for replacement therapy has been challenging. When administered orally, > 90% of progesterone is metabolized during first hepatic pass, and the metabolites cause dizziness and drowsiness. Although synthetic progestins have been developed to resist degradation by the gut and liver, these compounds are commonly avoided over concerns of teratogenesis. Progesterone i.m. is an effective alternative; however, this route is generally not preferred by patients due to pain associated with injections that must be given for weeks. Vaginal routes have been used successfully in donor egg replacement cycles as

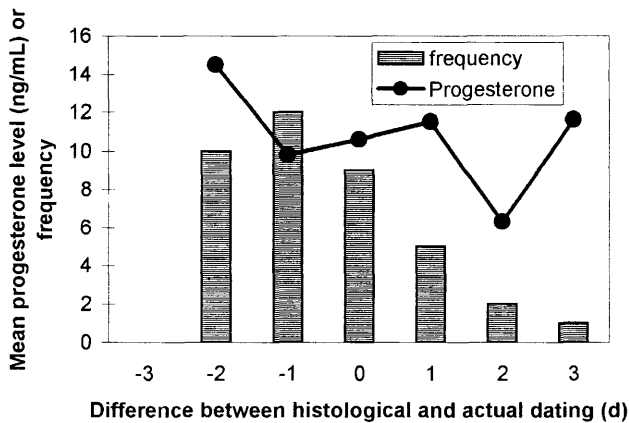


Figure 1. Endometrial development on once daily Crinone 8%. Bars to the left of zero indicate cases in which development lagged behind expectation; bars to the right indicate advanced development. No cases show lagging development sufficient to be diagnosed as luteal insufficiency. No correlation between serum progesterone and endometrial development was noted.

Table II. Results of Crinone 8% once daily for support of donor egg recipient cycles

	Crinone 8% once daily	Progesterone 100 mg i.m. daily
In-phase endometria	100% (42 of 42)	95% (235 of 249)
Mean serum progesterone on cd26	11.3 ± 6.5 ng/ ml	65.2 ± 12.5
Mean endometrial thickness on cd26	10.3 ± 2.8 mm	10.0 ± 3.2
% Embryos implanting	21.4 (34 of 159)	19.0 (151 of 797)
% Clinically pregnant [(+)gestational sac]	45.6 (21 of 46)	41 (102 of 249)
% Spontaneously miscarrying	14.3 (3 of 21)	25 (25 of 102)
% Ongoing pregnant	39.1 (18 of 46)	31 (77 of 249)

well as IVF, but conventional suppositories have variable formulations, require frequent dosing, and are associated with a messy discharge.

Crinone is a vaginal gel containing micronized progesterone in a diluted emulsion system, which leads to the controlled and sustained-release of progesterone. These characteristics allow for less frequent administration and limit the variability in absorption. Previous findings have shown that a local direct vagina-to-uterus transport takes place with the use of Crinone, despite the presence of sub-physiological plasma progesterone concentrations.

The prolonged attachment of vaginal epithelial cells and retention within the vagina should allow for administration intervals of up to 48 h. In a preliminary European study, de Ziegler *et al.* (1994) evaluated 42 women in a double-blind, randomized trial comparing three doses of Crinone (45, 90 and 180 mg) when administered every other day. Secretory transformation was observed in the endometrium of all women who participated in this study.

In this study, we evaluated the use of Crinone vaginal gel for twice and once daily administration. Though this was not a randomized trial, all patients were treated concomitantly over a brief interval and were thus treated under the same

protocols, with the only systematic difference being the manner of progesterone replacement. Crinone 8% given once or twice daily for situations requiring complete progesterone replacement induced normal endometrial histology in all of the cases we reviewed. We deliberately chose the late luteal phase for endometrial assessment because our earlier work had clearly shown a much stronger relationship between pregnancy rates and the late (day 26 ± 1) versus the early (day 21 ± 1) biopsies. Moreover, excellent pregnancy support has been observed. The only case of early bleeding we observed was in a patient who went on to deliver twins. These results confirm the ability of the once-daily regimen of Crinone 8% to prepare and support pregnancy. It appears to work at least as well as i.m. therapy, and we had sufficient power to detect 25% differences in clinical pregnancy rates. Daily Crinone 8% (90 mg) has now become our standard approach for women requiring full progesterone replacement in donor egg and cryo-thaw cycles.

These results confirm the ability of once and twice daily Crinone 8% to prepare and support pregnancy, perhaps as well as i.m. therapy. This regimen has now become our standard approach in women needing donor oocyte therapy.

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