Experience with progesterone gel for luteal support in a highly successful IVF programme

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Efficacy of luteal support from single daily administration of Crinone® 8% (progesterone gel) was tested in 43 women in an IVF programme with historical pregnancy rates >50%. Results were compared with those achieved in 46 women concurrently undergoing IVF and receiving 50 mg i.m. progesterone, and with historical data. Pregnancy rates (PR) were evaluated approximately 2 weeks after undergoing IVF by human chorionic gonadotrophin (HCG) measurement (total PR), by ultrasound 2–4 weeks later (clinical PR), and by counting births. Prior experience with other progesterone formulations was compared with that of Crinone 8%. Demographic and IVF characteristics were comparable for both concurrently treated groups. Total PR, clinical PR and live birth rates were similar for the Crinone and the concurrent i.m. progesterone groups: 31 (72.1%) versus 34 (73.9%); 26 (60.5%) versus 28 (60.9%), and 23 (53.5%) versus 23 (50%) respectively. Clinical PR and live birth rates were also similar to the last data reported to the Society for Assisted Reproduction Therapy. Overall acceptability of Crinone 8% was excellent. Among subjects with prior i.m. injection experience, most patients (69.2%) agreed that the gel was easier to use, less painful (76.9%) and less time-consuming (61.5%) than i.m. injections. In conclusion, Crinone 8% offers an appreciable improvement, as it provides an effective luteal support option that avoids painful i.m. injections.

Key words: assisted reproduction/Crinone/luteal support/progesterone/vaginal progesterone

Introduction

The need for luteal support in IVF programmes has been universally recognized (Soliman et al., 1994). The optimal form by which this support must be administered, however, remains a source of debate. Many European programmes have replaced i.m. with vaginal progesterone after the vaginal route was shown to be at least as effective as i.m. injections for priming endometrial receptivity (Bourgain et al., 1990) and preparing and sustaining pregnancy in donor egg (Devroey et al., 1989) and regular IVF cycles (Smits et al., 1993). Yet all the vaginal progesterone preparations that have been used to date require cumbersome multiple daily administrations in order to provide sustained endometrial effects and effective support during the luteal phase.

In contrast with vaginal route findings, oral progesterone was inappropriate for inducing the endometrial transformations normally seen in the luteal phase (Bourgain et al., 1990) and providing adequate support during the luteal phase in IVF cycles (Licciardi et al., 1999). The lack of proper endometrial effects seen with even large doses of oral progesterone has been linked to the high rate of progesterone metabolism during hepatic first-pass, which is responsible for a bioavailability of <10% (Nahoul et al., 1987, 1993). Hence, oral progesterone is not an acceptable option for luteal support in IVF.

Despite promising results, American clinicians have been notoriously reluctant to use vaginal progesterone in their IVF practice. This is due in part to concerns that vaginal progesterone might not provide sufficient plasma progesterone concentrations to ensure the high pregnancy rates (PR) reported by several groups in the USA (Centers for Disease Control, 1998; Gardner and Lane, 1998). The low concentrations of plasma progesterone reported by teams who used vaginal suppositories have fuelled these concerns (Schmidt et al., 1989). The lack of a pharmaceutical product appropriately designed for vaginal use has also been a factor that has limited the use of vaginal administration. In fact, vaginal progesterone use has remained marginal in IVF programmes in the USA, despite promising results obtained with early vaginal formulations (Simon et al., 1986; Sauer et al., 1987; Schmidt et al., 1989; Steingold et al., 1989). The medical community also questioned the reliability of progesterone release and absorption from products that have not been thoroughly tested and/or not specifically formulated for vaginal use.

Now, with the availability of the controlled and sustained-release vaginal progesterone gel, Crinone® 8% (Serono Laboratories, Randolph, MA, USA) a pharmaceutical grade product exists for delivering progesterone vaginally. This product has been formally indicated for progesterone supplementation in assisted reproductive therapy (ART) by the Food and Drug Administration (FDA) and other European agencies including the British Medicine Control Agency (MC-A). Approval by the FDA was based on the demonstration of product efficacy, even in complete absence of endogenous production of progesterone by the ovaries (Gibbons et al., 1998; Jobanputra et al., 1999). In the present trial, the efficacy of single daily administration of the sustained-release progesterone vaginal gel, Crinone 8%, for luteal support was
tested in a highly successful IVF programme having ongoing (>20 weeks) pregnancy rates that routinely exceed 50%.

Materials and methods

Patient selection
Study participation was offered to women who were undergoing IVF at the Colorado Center for Reproductive Medicine during a period of 15 months (July 1997 to October 1998). For practical reasons, study participation was limited to women living in the geographical vicinity of the programme. Patients were not eligible for inclusion in the study if they had a history of dysfunctional uterine bleeding, current urogenital disease, or previous allergic response to a product containing progesterone. In addition, patients were not permitted to use any product containing progesterone or another progestin during the IVF treatment cycle. Patients were only allowed to receive one study treatment cycle. Thus, patients who had been previously enrolled would be excluded from participating in the study during a subsequent IVF cycle. All patients provided written consent after having been duly informed of possible risks. The study protocol and informed consent form were reviewed and approved by an independent Institutional Review Board (IRB).

Results from this group were compared with: (i) a group of control patients obtained by identifying 46 consecutive IVF patients who were enrolled beginning October 1997, had satisfied similar inclusion criteria, but had received luteal support from i.m. progesterone (50 mg/day); and (ii) historical IVF data reported for 1996 to the Society for Assisted Reproduction Therapy (SART) (CDC, 1998), i.e. the last set of data reported prior to Crinone use.

Study design
This was an open-label trial designed to assess efficacy and tolerability of the vaginal progesterone gel, Crinone 8%. A group of subjects (n = 43) was recruited to receive Crinone 8%, and the results were compared with those of two control groups. One comparison group consisted of a similar size sample of women (n = 46) undergoing IVF concurrently but receiving luteal support from progesterone supplied by i.m. injections (50 mg/day), while the second was based upon historical data from 1996 reported to SART (CDC, 1998).

Stimulation protocols
Study participants received ovarian stimulation according to a standardized protocol involving luteal phase gonadotrophin-releasing hormone (GnRH) agonist down-regulation. In accordance with this protocol, 0.5 mg of leuprolide acetate (Lupron®, TAP Pharmaceutical Inc., Deerfield, IL, USA), administered daily by s.c. injection, was initiated during the luteal phase. This dose was continued until ovarian suppression was achieved, as confirmed by oestradiol concentrations and sonography. This dose was reduced by one-half with the onset of ovarian stimulation and continued until human chorionic gonadotrophin (HCG) administration. Ovarian stimulation was initiated using human menopausal gonadotrophin (HMG) or recombinant FSH. The typical starting dose was set at 225 to 450 IU/day for 5 days, based on prior responses to HMG and/or basal FSH values. Further dosing adjustments were based on ultrasound findings and plasma hormone concentrations, as previously described (Schoolcraft et al., 1991; Meldrum, 1992, 1996). Briefly, when at least two follicles were ≥18 mm in diameter, 10 000 IU of HCG (Profasi®, Serono Laboratories, Inc., Randolph, MA, USA) were administered. Oocyte retrieval was performed 35 to 36 h after HCG administration.

Less than 10% of the patients designated as poor responders were administered a different ovulation stimulation treatment known as ‘microflare’ (Schoolcraft et al., 1997). This treatment consisted of 0.02 mg leuprolide acetate, administered twice daily by s.c. injection beginning on cycle day 3, following 2–4 weeks of oral contraceptive use. On cycle day 5, HMG or recombinant FSH treatment was initiated at the dose of 600 IU/day, while continuing leuprolide acetate. The remainder of the microflare protocol was similar to that of the standardized protocol, which is routinely used in our practice. The frequency in which the microflare protocol was employed was similar (<10%) in both control groups.

Luteal support
Luteal support was initiated 2 days after oocyte retrieval irrespective of whether this was provided from the vaginal gel or i.m. injections. In the vaginal progesterone gel study group, 43 women undergoing IVF cycles applied single daily doses of Crinone 8%. In either case, luteal support was continued until the pregnancy test was performed and for up to 12 weeks in case of pregnancy. The 46 other infertile women undergoing concurrent IVF cycles who served as a control group received luteal support from daily i.m. injections of progesterone (50 mg).

Determination of pregnancy status
Pregnancy status was determined by serum β-HCG concentration approximately 2 weeks after embryo transfer (total PR), by ultrasounds 2–4 weeks later (clinical PR), and by counting live births. Biochemical pregnancy wastage was defined as any β-HCG value >5 mIU/ml that did not evolve into a clinical pregnancy [i.e. biochemical (total PR) – clinical PR]. Total pregnancy wastage was defined as the number of positive pregnancies (total PR), which did not evolve into a live birth [i.e. biochemical (total) PR – live births]. All PR data were assessed by reference to the number of embryo transfers, as by design the study compared two forms of luteal support which possibly affected embryo implantation.

Patient acceptability
The acceptability of vaginal progesterone gel was assessed using a patient questionnaire that was completed by each subject after their last administration of Crinone 8%. Subjects were asked to rank their overall experience with the use of Crinone 8% on degree of difficulty of administration, messiness, presence of pain and interference with intercourse. A scale of 1 (very much) to 7 (not at all) was used to assess the subject’s overall experience with the use of Crinone 8% in regard to these factors. In addition, subjects who had previously used other formulations were asked to rank their experience with the use of Crinone 8% versus the use of progesterone given by injection or suppository: easier to use, less painful, takes less time to administer and preferred method. A scale of 1 (strongly agree) to 7 (strongly disagree) was used to assess how each subject’s overall experience with Crinone 8% compared with other previously used progesterone formulations on these aspects of treatment.

Statistical analysis
Although the study was not designed to determine equivalence between i.m. progesterone and Crinone 8%, statistical testing was done as a descriptive analysis. Comparable results in the Crinone 8% and both control groups would be considered supportive for demonstrating efficacy of Crinone 8%.

The three groups of IVF patients were compared using Student’s t-test or Fisher’s exact test, with two-tailed comparisons, or Wilcoxon rank sum test, with one-tailed comparisons. ¥2 statistics were used to analyse discontinuous data.
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Table I. Individual and IVF characteristics for the two concurrent IVF patient groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Crinone 8% once-daily (n = 43)</th>
<th>Lm. progesterone 50 mg daily (n = 46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)a</td>
<td>36.2 ± 4.5</td>
<td>34.5 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>IVF indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced maternal age</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Male factor</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pelvic adhesions</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tubal factor</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Baseline FSH (mIU/ml)b</td>
<td>7.9 ± 2.4</td>
<td>8.3 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Number of IVF attempts prior to studya</td>
<td>1.6 ± 0.9</td>
<td>0.7 ± 0.8</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Days of gonadotrophin stimulationa</td>
<td>9.7 ± 1.2</td>
<td>9.1 ± 1.2</td>
<td>0.02b</td>
</tr>
<tr>
<td>Total dose of gonadotrophin in 75 IU ampoulesa</td>
<td>413 ± 141</td>
<td>39 ± 145</td>
<td>NS</td>
</tr>
<tr>
<td>Peak oestradiol before oocyte retrieval (pg/ml)b</td>
<td>2255 ± 1212</td>
<td>2244 ± 1480</td>
<td>NS</td>
</tr>
<tr>
<td>Number of oocytes retrieveda</td>
<td>16.2 ± 9.0</td>
<td>15.8 ± 7.9</td>
<td>NSb</td>
</tr>
<tr>
<td>Incidence of ICSI (%)</td>
<td>11 (26)</td>
<td>20 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of assisted hatching (%)</td>
<td>28 (65)</td>
<td>33 (72)</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of blastocyst transfers (%)</td>
<td>12 (28)</td>
<td>9 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean number of embryos transferreda</td>
<td>3.2 ± 1.4</td>
<td>3.3 ± 1.2</td>
<td>NSb</td>
</tr>
</tbody>
</table>

*aValues are mean ± SD.

*bWilcoxon rank sum test.

ICSI = intracytoplasmic sperm injection; I.m. = intramuscular; NS = not significant.

Results

Patient and treatment characteristics of the study and concurrent control groups are summarized in Table I. All patient demographic parameters were similar for both groups of IVF patients. Regarding IVF characteristics, there were no clinically significant differences between the two groups, although the number of prior IVF attempts was statistically significantly greater for the Crinone group (P < 0.001), and days of gonadotrophin stimulation were also slightly higher (P = 0.027). Baseline early follicular phase FSH concentrations were similar at 7.9 ± 2.4 and 8.3 ± 2.8 mIU/ml for the Crinone group and i.m. progesterone group respectively. There was no difference in the number of embryos transferred for these two groups of IVF patients.

Total (biochemical) pregnancy rates achieved in women receiving Crinone (72.1%) were similar to those seen in the i.m. group (73.9%) (NS). Clinical pregnancy rate and live births rate in the two concurrent IVF groups and the historical data reported to SART are shown in Table II. The Crinone and i.m. IVF groups respectively were similar for clinical pregnancy rate at 60.5% (26/43) versus 60.9% (28/46); and for live birth rate 53.5% (23/43) versus 50% (23/46). Live birth rate in the Crinone group (53.5%) was similar to the historical results reported to SART for the younger two age groups (57.7% for women aged <35 and 51.7% for women aged 35–39 years). Comparing the Crinone 8% group, whose mean age was 36.2 ± 4.5 years, to the comparable age group reported to SART actually suggested a trend towards improved results (53.5 versus 51.7% for Crinone and historical data respectively).

The rates of biochemical pregnancies (n) and total pregnancy wastage (n) were also similar for the Crinone and concurrent i.m. controls: 16.1% (5) versus 17.6% (6) and 22.6% (7) versus 32.3% (11) respectively.

Overall, acceptability of Crinone 8% when used daily for luteal support in IVF was excellent (see Table III). Of the 43 women who responded to the questionnaire, 55.8% had no difficulty administering the gel. For 46.5% of the women, the gel did not at all interfere with intercourse.

Most of the women who responded to the questionnaire and had previously used i.m. injections agreed that the gel was easier to use (9/13 or 69.2%), less painful (10/13; 76.9%) and less time-consuming (8/13; 61.5%). Furthermore, a majority (10/13; 76.9%) of these women strongly agreed that they preferred treatment with the vaginal gel to i.m. injections.

Women who responded to this questionnaire and had previously used progesterone suppositories agreed that the gel was easier to use (10/18; 76.9%) and less painful (8/18; 44.4%) and less time-consuming (11/18; 61.1%). Furthermore, a majority (15/18; 83.3%) of these women agreed that they preferred treatment with the vaginal gel compared with suppositories.

Discussion

When using luteal support provided by Crinone 8%, the pregnancy rates obtained in this study were comparable with results routinely achieved at our institution over the past years (CDC, 1998). In 43 women receiving Crinone 8%, total PR, clinical PR and live birth rates were 72.1 and 60.5 and 53.5% per embryo transfer respectively. To provide a current comparison, we examined the results of 46 consecutive women undergoing IVF at our centre who received luteal support from i.m. progesterone during the same period. There were no clinically significant differences between the IVF character-
Table II. IVF outcome in women receiving luteal support from Crinone 8% or intramuscular progesterone

<table>
<thead>
<tr>
<th>IVF outcome</th>
<th>Vaginal</th>
<th>Intramuscular progesterone</th>
<th>Data from last report by SART (CDC, 1998)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crinone 8%</td>
<td>Concurrent controls</td>
<td>&lt;35 years of age</td>
</tr>
<tr>
<td>No. of transfers</td>
<td>43</td>
<td>46</td>
<td>164(a)</td>
</tr>
<tr>
<td>No. of biochemical pregnancies (%)</td>
<td>31 (72.1)</td>
<td>34 (73.9)</td>
<td>104 (63.4)</td>
</tr>
<tr>
<td>No. of clinical pregnancies (%)</td>
<td>26 (60.5)(b)</td>
<td>28 (60.9)</td>
<td>–</td>
</tr>
<tr>
<td>No. of live births (%)</td>
<td>23 (53.5)(b)</td>
<td>23 (50)</td>
<td>–</td>
</tr>
<tr>
<td>Single</td>
<td>14</td>
<td>11(c)</td>
<td>–</td>
</tr>
<tr>
<td>Multiple</td>
<td>9</td>
<td>7(c)</td>
<td>–</td>
</tr>
</tbody>
</table>

\(a\) Data calculated from last report to Society for Assisted Reproduction Therapy (SART) (CDC, 1998), the last set of data not including women receiving Crinone 8%.
\(b\) Difference between Crinone and concurrent intramuscular (NS).
\(c\) Data unavailable for five patients.

Table III. Subjective evaluation of Crinone by questionnaire responded to by 43 women

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Very much</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>Difficulty of administration</td>
<td>0 0 2.3 2.3 4.7 34.9 55.8</td>
<td></td>
</tr>
<tr>
<td>Messiness: leakage</td>
<td>9.3 7.0 2.3 9.3 18.6 44.2 9.3</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0 2.3 0 2.3 2.3 11.6 8.1</td>
<td></td>
</tr>
<tr>
<td>Interferes with intercourse</td>
<td>4.7 4.7 2.3 7.0 9.3 25.6 46.5</td>
<td></td>
</tr>
</tbody>
</table>

Values are percentages. Patients were asked to answer questions on a scale of 1 to 7.

Vaginal progesterone for luteal support

rates were found when luteal support was provided either with repeated HCG administrations or exogenous progesterone. Hence, because of the inherent difficulty in assessing the specific role of exogenous progesterone in the presence of very large endogenous production, the efficacy of the new controlled and sustained-release vaginal gel (Crinone 8%) was tested in women totally deprived of endogenous progesterone. Achieving endometrial receptivity in women with premature ovarian failure was considered the best evidence of efficacy of luteal support provided by this controlled and sustained-release formulation. In donor egg IVF recipients, twice-daily (Gibbons et al., 1998) and once-daily administration of 8% progesterone gel (Jobanputra et al., 1999) reliably resulted in in-phase endometrial biopsies and pregnancy rates similar to those seen in the historical IVF data reported to SART (CDC, 1998). In the 13 subjects who had prior experience with i.m. progesterone (69%) preferred Crinone 8% to i.m. injections for several reasons.

The strength of the present trial evaluating luteal support from the vaginal progesterone gel resides in the high pregnancy rates regularly achieved by the IVF programme that conducted this testing. In conditions featuring historically high pregnancy rates, a possibly inadequate efficacy of luteal support from the new vaginal gel presumably would have become more promptly apparent.

Results obtained with the vaginal progesterone gel were compared to those seen in a comparably sized group of 46 women who underwent IVF during the same period. While women were not randomly assigned to either i.m. or vaginal progesterone, the control group was nonetheless arbitrarily composed. It consisted of 46 IVF patients not included in the...
vaginal progesterone study mainly due to geographical reasons, which precluded the multiple evaluations required by the study protocol, but who satisfied all the other inclusion criteria.

The dosing regimen chosen for administering the vaginal progesterone gel was one application of the Crinone 8% per day until a pregnancy test was performed. This treatment regimen was continued for a total of up to 12 weeks in case of pregnancy. Selection of the once-daily regimen was based on evidence in the donor egg IVF model showing that histological findings and pregnancy rates for the twice-daily and once-daily regimens of Crinone 8% were equivalent (Jobanputra et al., 1999).

The convenience of single daily administration of Crinone should be obvious. In addition, the fact that relatively small amounts of progesterone (90 mg/day) can provide efficient luteal support is a consequence of direct vagina-to-uterus transport that characterizes vaginal administration of progesterone (Miles et al., 1994; de Ziegler, 1995; Bullett et al., 1997; Fanchin et al., 1997). The controlled and sustained-release gel optimizes this property inherent to the vaginal route of administration since delivery is provided over time (Bullett et al., 1997). One important practical consequence of the direct vagina-to-uterus transport of vaginally administered progesterone or "first uterine pass effect" is the uselessness of plasma progesterone measurements. Because of the direct transport to the uterus, proper uterine impregnation of progesterone is achieved, despite low peripheral concentrations (Cicinelli et al., 2000).

Our results show that luteal support in IVF, including during early pregnancy, can be effectively provided by once-daily administration of the controlled and sustained-release progesterone gel, Crinone 8%. Minimal side effects make this approach more acceptable to a greater number of patients than daily i.m. injections that are both painful and associated with other complications such as sterile abscesses. The fact that, historically, pregnancy rates in excess of 50% were commonly achieved in this programme and remained unchanged when luteal support was provided from vaginal progesterone supports evidence of efficacy for this product. The origins of our high pregnancy rate are multi-factorial and revolve around a meticulous attention to detail. Notably, we believe that most important of these factors are the quality of the culture media used (Gardner and Schoolcraft, 1999), the technique of non-traumatic embryo transfer under ultrasound guidance (Schoolcraft et al., 1999), and the use of selected stimulation protocols for poor responders (Schoolcraft et al., 1997).

In conclusion, our data showed that progesterone delivered from the new controlled and sustained-release vaginal gel appears to be as effective as daily i.m. progesterone at providing luteal support, thus rendering painful injections or multiple daily dosing with other vaginal progesterone formulations unnecessary.

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