Luteal Support for IVF/ICSI Cycles with Crinone 8% (90 mg) Twice Daily Results in Higher Pregnancy Rates Than with Intramuscular Progesterone

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Background: The use of progesterone for luteal support has been demonstrated to be beneficial in assisted reproductive cycles, yet the optimal route of progesterone administration has still not been established. This article is a retrospective study in a tertiary reproductive medical unit to compare luteal progesterone supplementation with vaginal gel or intramuscular progesterone.

Methods: A total of 144 *in vitro* fertilization or intracytoplasmic sperm injection cycles were analyzed, 67 cycles using vaginal gel 90 mg twice daily and 77 cycles using intramuscular progesterone 50 mg daily as luteal support.

Results: Both groups had similar mean age, cause of infertility, baseline hormone levels, dosage of recombinant follicle-stimulating hormone, number of retrieved and fertilized oocytes, and number of transferred embryos. The vaginal gel group had significantly lower mid-luteal serum progesterone levels but higher implantation rate (32.5% *vs.* 18.5%, $p = 0.001$) and ongoing pregnancy rate (55.2% *vs.* 32.5%, $p = 0.006$). Within each group, mid-luteal serum progesterone levels between pregnant or non-pregnant patients were comparable. For patients with serum estradiol levels on day of human chorionic gonadotropin greater than 5,000 pg/mL, vaginal gel still resulted in better ongoing pregnancy and implantation rates.

Conclusion: The use of vaginal progesterone gel twice daily for luteal support results in better pregnancy outcomes than intramuscular progesterone. A high local progesterone effect from vaginal gel might improve endometrial receptivity under extraordinarily high serum estradiol levels. [*J Chin Med Assoc* 2008;71(8):386–391]

Key Words: assisted reproductive technology, Crinone, luteal phase, pregnancy rate

Introduction

During assisted reproductive technology (ART) treatment, the use of gonadotropin-releasing hormone (GnRH) agonists and the aspiration of follicular fluid can lead to a relative progesterone deficit and inappropriate preparation of the endometrium for embryo implantation. Supplementation of progesterone or human chorionic gonadotropin (hCG) in the luteal phases after *in vitro* fertilization (IVF) cycles significantly improves fertility outcomes compared with no treatment.[1] No significant difference has been found between hCG and progesterone in terms of pregnancy or miscarriage rates, but the odds of ovarian hyperstimulation syndrome (OHSS) are more than 2-fold higher with treatment involving hCG.[2]

Progesterone can be administered by oral, intramuscular or vaginal routes, but the optimal route has not yet been established. Although there is increasing evidence that vaginal and intramuscular progesterone are at least equally effective in IVF treatment outcomes,[3,4] lower clinical pregnancy and delivery rates when using vaginal progesterone rather than intramuscular progesterone-in-oil has been reported in a meta-analysis of randomized trials.[5] However, through the use of vaginal progesterone, painful application of intramuscular

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injections and their complications, such as local soreness, abscesses, and inflammatory reactions, were avoided.[6]

High serum estradiol levels achieved through ovarian hyperstimulation have been claimed to reduce endometrial receptivity,[7] and progesterone has been found to improve implantation by regulating the immune response.[8] Vaginal gel can produce significantly higher endometrial progesterone levels than intramuscular injection, and vaginal progesterone gel is used twice daily rather than once daily. The purpose of this study was to compare the efficacy of these 2 forms of luteal phase support during IVF and intracytoplasmic sperm injection (ICSI) cycles, with ongoing pregnancy rate as the primary outcome.

Methods

This retrospective study was approved by the Institutional Ethics Review Board of National Taiwan University Hospital. All patients recruited in this study underwent complete infertility evaluation, including early follicular phase serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol levels. Controlled ovarian hyperstimulation was performed using the long GnRH agonist protocol. Buserelin nasal spray (Supremon, Hoechst, Frankfurt am Main, Germany), 200 μg four times daily, was administered 7 days before the estimated start of the next menses. After downregulation was achieved (menstrual bleeding occurred and serum estradiol < 50 pg/mL), the dose of buserelin was halved (100 μg four times daily) and ovarian stimulation was commenced the next day with a daily subcutaneous dose of 200 IU recombinant FSH (Puregon; Organon, Oss, The Netherlands). After giving 4 days of recombinant FSH, transvaginal ultrasonography and serum hormone analysis (estradiol, progesterone, LH) were performed every other day, and the dose of recombinant FSH was adjusted according to the ovarian response.

When at least 2 follicles had reached a diameter of 18 mm or more, buserelin nasal spray and recombinant FSH were stopped and a single bolus of 10,000 IU hCG (Profasi; Serono, Geneva, Switzerland) was administered intramuscularly. Ultrasound-guided transvaginal oocyte retrieval was then performed 34–36 hours after hCG administration. Subsequently, IVF or ICSI was performed. Embryo transfer was done on day 3 after oocyte retrieval. According to the guidelines of the Taiwan Society for Reproductive Medicine, no more than 3 embryos could be transferred to women < 35 years of age, and no more than 4 embryos to women aged ≥ 35 years. Luteal support commenced 2 days after oocyte retrieval.

We analyzed all the fresh IVF or ICSI cycles conducted by 2 attending physicians of National Taiwan University Hospital from September 2005 to April 2007. These 2 doctors had different luteal support protocols: one used oral estradiol valerate (Estrade; Synmosa, Taipei, Taiwan) 6 mg twice daily combined with vaginal progesterone gel (Crinone 8%; Fleet Laboratories, Watford, UK) 90 mg twice daily, and the other used estradiol valerate 6 mg twice daily with intramuscular progesterone-in-oil (Progesterone; Tai Yu, Hsinchu, Taiwan) 50 mg daily. In total, there were 67 IVF or ICSI cycles using Crinone and 77 cycles using intramuscular progesterone in this study.

Mid-luteal serum progesterone levels were obtained 9 days after oocyte retrieval. Serum hCG levels were checked 16 days after oocyte retrieval, and a level above 50 IU/L was considered positive. Ultrasound examination was performed 1 week later to confirm clinical pregnancy and determine the number of intrauterine gestational sacs. The implantation rate was defined as the ratio of the number of gestational sacs to the number of embryos transferred. The presence of at least 1 viable fetus at 12 weeks of gestation was classified as ongoing pregnancy. Serum FSH, LH, estradiol and progesterone levels were measured by means of chemiluminescence immunoassay (Immulite 2000; DPC, Flanders, NJ, USA). Patients' serum samples were assayed immediately upon sample acquisition.

The 2 progesterone supplementation protocols were retrospectively compared for implantation rate, clinical pregnancy rate and ongoing pregnancy rate. Mid-luteal serum progesterone levels were compared between clinically pregnant and non-pregnant patients. Ongoing pregnancy and implantation rates between high (≥ 5,000 pg/mL) and low (< 5,000 pg/mL) serum estradiol levels on the day of hCG administration were also analyzed. All data were analyzed using the commercially available software package SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and presented as mean ± standard deviation or number (%). Statistical analysis was carried out using Mann-Whitney U test for continuous data and χ^2 test for categorical data. Differences were considered to be significant when $p < 0.05$.

Results

The demographic data and treatment outcomes of the 2 luteal support protocols are shown in Table 1. There were no significant differences between the protocols in terms of age distribution, infertility causes, baseline