Evaluation of QD vs. BID dosing of gonadotropins in patients undergoing IVF

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INTRODUCTION

Since the first IVF birth in 1978 (1), clinicians have continued to strive to increase success rates. The introduction of lab techniques such as ICSI (2) and the move to Day 5 embryo transfer have increased the chances of a couple's pregnancy. These innovations are reflected by a 21% increase in pregnancy rates from 1996-2004 in IVF cycles, as reported by SART (3).

Conversely, limited attention has been devoted to increasing patients' satisfaction with their treatment during this time period. Patient stress has been reported to adversely affect outcomes (4). Many factors in an IVF cycle can contribute to patient stress, e.g., fear of needles, cycle cost, and the potential for multiple births. The incidence of multiple births for ART cycles exceeds that of the general population by approximately 11-fold (3), yet physicians are reluctant to reduce the number of embryos transferred for fear of jeopardizing success rates. Reports from previous studies have shown that easing the patient's experience during a cycle can not only help success rates, but can also produce a more satisfied patient, who is more likely to return for treatment in the event of a non-pregnancy and refer others (5).

One way to simplify the patient experience is to reduce the number of injections they must administer during treatment. The authors of an earlier retrospective study reviewed data from two different time periods in their own center and concluded that BID administration of gonadotropins yielded better outcomes than QD (6). However, the BID patients initiated their cycles with four vials of hMG daily, while the QD group initiated their cycles with only two vials of hMG daily. Since this study was not controlled for these confounding variables, the conclusion was not valid.

In a recent clinical trial to evaluate a novel form of vaginal progesterone, physicians were given the choice of combining gonadotropins and administering them as a single injection either once or twice daily. This is the first trial to evaluate the efficacy of administering these medications once (QD) or twice (BID) daily.

MATERIALS AND METHODS

This analysis was part of a multicenter, randomized, open-label (assessor-blinded), parallel-group, Phase III study in 1,211 women undergoing IVF, conducted to compare pregnancy rates following luteal phase support with micronized, naturally-derived progesterone vaginal tablet inserts (Endometrin® BID or TID) or vaginal progesterone gel (Crinone® QD). The study was conducted at 25 sites in the United States between July 2005 and April 2006.

Each study center followed the IVF protocol guidelines in practice at that site. Patients who conceived continued on study drug for approximately 10 weeks.

PATIENT SELECTION

Healthy, premenopausal women between 18 and 42 years of age, with a BMI ≤34 kg/m^2, a baseline FSH ≤15 IU/L, with a history of infertility and requiring IVF, were eligible to enroll in the study.

STUDY PROCEDURES

Pituitary down-regulation was performed with an injectable gonadotropin-releasing hormone (GnRH) agonist, using a long protocol with luteal phase initiation. Documentation of down-regulation, indicated by a serum estradiol level of <50 pg/mL, endometrial lining of <7 mm, and no evidence of ovary activity on transvaginal ultrasound (TVU), was required prior to the start of gonadotropin treatment. Gonadotropin therapy was done in accordance with the usual IVF protocol at each center, with the only requirement being that a minimum of one vial of hMG (Menopur®) had to be used daily. All centers chose to use Menopur® and Bravelle® from Day 1.

Physicians were given the option of combining the FSH and hMG, and administering them as one single daily injection. This was done for approximately two-thirds of the patients (n=777). Gonadotropin stimulation was stopped when the lead follicle mean diameter was at least 18 mm, then a single intramuscular injection of human chorionic gonadotropin (hCG) (Novarel®) was administered to trigger ovulation. Oocytes were retrieved within approximately 36 hours after Novarel® administration, according to site-specific procedures. The only requirement for embryo transfer was that no more than three embryos could be transferred if done on Day 3 post-retrieval and no more than two blastocysts could be transferred if done on Day 5 post-retrieval.

OUTCOME MEASURES

The efficacy variables of pregnancy and live birth rates were determined.

RESULTS

Approximately two-thirds of the patients were treated with gonadotropins QD rather than BID. The demographics of these two patient populations are shown in Table 1. The groups were well-matched except for age, with a greater number of older patients dosing BID.

TABLE 1: DEMOGRAPHICS

CHARACTERISTIC	GONADO-TROPINS QD (n=777)	GONADO-TROPINS BID (n=434)	P-VALUE
Race			
Caucasian	585 (75%)	324 (75%)	
African-American	50 (6%)	24 (6%)	
Asian	34 (4%)	27 (6%)	
Hispanic	76 (10%)	41 (9%)	
Other	32 (4%)	18 (4%)	0.682

TABLE 1: DEMOGRAPHICS (CONT'D)

CHARACTERISTIC	GONADO-TROPINS QD (n=777)	GONADO-TROPINS BID (n=434)	P-VALUE
Age	32.5	34.0	<0.001
<35	509 (66%)	228 (53%)	
35-37	163 (21%)	117 (27%)	
38-40	87 (11%)	67 (15%)	
41-42	18 (2%)	22 (5%)	<0.001
BMI	25.0	24.9	0.181
<18.5	16 (2%)	10 (2%)	
18.5 - 24.9	403 (52%)	219 (51%)	
25.0 - 29.9	229 (30%)	124 (29%)	
>30.0	128 (16%)	79 (18%)	0.854

Stimulation outcomes and ongoing pregnancy rates show that patients responded well when gonadotropins were administered either QD or BID, indicating no advantage to BID administration **(Table 2)**.

TABLE 2: GONADOTROPIN STIMULATION OUTCOMES

CHARACTERISTIC	GONADO-TROPINS QD (n=777)	GONADO-TROPINS BID (n=434)	P-VALUE
Duration of TX (days)	10.0	10.6	
No. oocytes	14.0	13.4	0.225
No. embryos transferred	2.4	2.3	0.033
No. embryos Day 3 transfer	2.6	2.6	0.559
No. embryos Day 5 transfer	2.0	2.0	0.552
Cont Preg Rate (%)	41.3	40.6	0.808

When results were analyzed by BMI, they were similar between groups **(Figure 1)**. Results for the <18.5 population were highly variable, but the number of patients in each group (16 in the QD group and 10 in the BID group) is too small to make any valid conclusions.

When results were compared by age, there was no statistically significant difference in outcomes between any of the age groups **(Figure 2)**. While numerically, the results for the 35-37 year old group were higher with BID dosing, this is probably just a statistical anomaly, as there is no clinical reason to believe that patients within this narrow age range would respond better to BID dosing than those who are either younger or older. Furthermore, as stated previously, these differences were not statistically significant.

FIGURE 1: CONTINUING PREGNANCY RATES AS A FUNCTION OF BMI

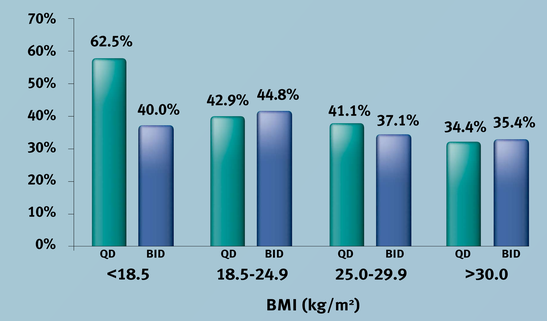
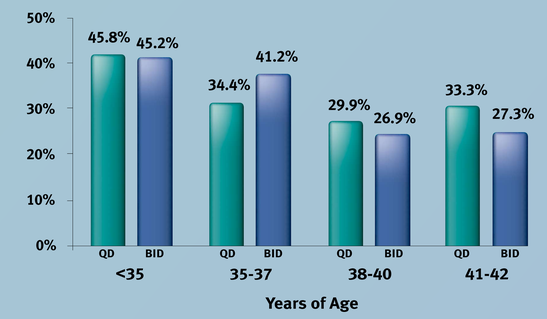


FIGURE 2: CONTINUING PREGNANCY RATES AS A FUNCTION OF AGE



CONCLUSIONS

There is a common belief in the reproductive endocrinology community that BID dosing of gonadotropins provides a more stable serum level over the course of treatment. It has previously been demonstrated that serum levels remain elevated for 36 hours after a single injection of Bravelle® (data on file). We have shown in this study that mixing Bravelle® and Menopur® in a single syringe and dosing once daily yielded the same outcomes as dosing twice daily. In a recent survey of patients who administered their gonadotropins BID, 92% said they would prefer QD dosing (7). A QD dosing schedule can be part of a more patient-friendly treatment regimen, offering greater patient convenience and comfort by reducing the number of injections a patient has to administer and receive.

REFERENCES

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