Decreased gonadotropin requirements in once daily compared to twice daily administration: a prospective, randomized study

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Abstract

Objective Despite the lack of any scientific data, many ART programs split the daily gonadotropin dose during ovarian stimulation, while others give the entire dose during a single administration, usually at night.

Design Prospective randomized.

Patient(s) 213 women undergoing IVF/ICSI cycles at a single private ART center.

Intervention(s) Gonadotropin administration once daily compared to twice daily.

Main outcome measure(s) Gonadotropin usage, clinical and ongoing PR

Results There were 110 women in the once daily compared to 103 in the twice daily arm. All cycles were blastocyst

transfers. There was a significantly lower FSH use in the once daily arm compared to the twice daily arm (1507.5 ± 517.5 IU vs. 1702.5 ± 622.5 , $P=0.015$), and a trend towards lower hMG use in the once daily arm (1342.5 ± 562.5 IU vs. 1462.5 ± 645.0 , $P=0.15$), without compromising clinical pregnancy rate (PR) (71.8% vs. 70.9%, $P = \text{NS}$) or delivery/ongoing PR (58.2% vs. 62.1%, $P = \text{NS}$). There were no differences in age, body mass index (BMI), peak estradiol, peak progesterone, retrieved oocytes, fertilized oocytes, number of ET, or PR.

Conclusions Once daily administration is associated with lower gonadotropin usage without compromising success rates.

Keywords Gonadotropins · Ovarian stimulation · QD administration · BID administration · Blastocyst · ART · Pregnancy rate · ET

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Capsule There is a significantly decreased FSH requirement in once daily compared to twice daily gonadotropin administration without compromising success rates in ART.

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Introduction

Despite the lack of any prospective and randomized data, many ART programs split the daily gonadotropin dose during ovarian stimulation when the dose exceeds 4 vials daily, while others give the entire dose during a single administration, usually at night, to the detriment of patient comfort and convenience. The only published study dealing with once or twice daily administration was a retrospective non-randomized study in which using gonadotropins twice a day was associated with a higher pregnancy rate [1]. Currently, there are no published studies in the literature addressing whether this practice alters gonadotropin usage, number of retrieved oocytes, or ART outcome. In the only recent non-randomized study presented in an abstract form that retrospectively evaluated gonadotropin once compared

to twice a day administration in 1,211 women as part of the Endometrin study [2], of which 35.8% of participants used a twice a day administration, there were no differences in duration of treatment, number of retrieved oocytes, or pregnancy rates. We initiated a prospective, randomized study to evaluate whether any differences existed in gonadotropin requirements and outcome data between once or twice daily administration in ART. Our null hypothesis was that there is no difference in outcomes between the two groups.

Materials and methods

In the present study, a prospective, randomized, comparative trial of 213 IVF/ICSI cycles with blastocyst transfers performed at our institution between January 2006 and June 2010 was undertaken. The trial is registered at www.clinicaltrials.gov as NCT 00740025. Women were prospectively randomized in a sequential order. Patients (age <43, range 21–42) were randomized to receive either once daily (QD) or twice daily (BID) injections of gonadotropins SC, and all patients received a mixed combination of FSH and hMG at 1:1 ratio mixed in a single syringe using a Q-cap (minimum 1 vial (75 IU) Bravelle; 1 vial (75 IU) Menopur; maximum 3 Bravelle; 3 Menopur). For those patients receiving twice daily injections, both hMG (Menopur®, Ferring, Parsippany, NJ) and FSH (Bravelle®, Ferring, Parsippany, NJ) were given in the am and pm. For those patients assigned to receive once daily injections, hMG and FSH were given in the pm. Dose adjustments were made, as needed, by physician (FIS) preference 5 days after stimulation start as previously described [3]. Included in the study were long luteal down regulated cycles ($n=175$), antagonist cycles ($n=30$), and microdose flare cycles ($n=8$). Only cycles with blastocyst transfers were included. Exclusion criteria included donor oocyte cycles, PGD, and FET cycles. All women underwent ovarian stimulation using one of 3 stimulation protocols: long luteal GnRHa, GnRH antagonist, or microdose flare GnRHa. When at least 3 follicles reached 16–18 mm in diameter, 5,000–10,000 IU of urinary hCG (Novarel, Ferring, Parsippany, NJ) was administered SC, and oocyte retrieval was performed 35 h later. All patients received IM P (50 mg) along with vaginal estradiol (2 mg bid) starting the day after oocyte retrieval. All women underwent ICSI. Oocytes were rinsed and denuded using a hyaluronidase solution combined with mechanical stripping, and ICSI was performed 4–6 h later. Embryos were cultured in groups under mineral oil in droplets of culture media (P1/Cleavage stage, Irvine Scientific, Santa Ana, CA) with 10% serum substitute supplement. Embryos were grown in sequential medium (Global Medium, Life Global, CT). All embryos were cultured under 37 C in a 5% O₂, 5% CO₂ environment for 5 days. All ET were performed under ultrasound guidance using a Wallace Sure-view catheter (Marlow, Irvine Scientific,

Santa Ana, CA). A pregnancy test was performed 10–12 days after ET. Biochemical pregnancies were recorded as negative. Pregnant patients underwent a vaginal ultrasound at 6–7 week and the number of gestational sacs was recorded. Statistical analysis was performed using a two-way ANOVA and *t*-test to test for significance. $P<0.05$ was considered significant. Our center's Institutional Review Board approved the study.

Results

A total of 213 cycles in 180 women were evaluated, 110 in the QD and 103 in the BID arm. There were a total of 4 canceled cycles for poor response or premature luteinization (2%), 3 in the QD and 1 in the BID groups ($P = \text{NS}$). There were no differences per initiated cycle in age, BMI, days of stimulation, peak E₂, number of retrieved oocytes, number of MII oocytes, fertilization rate, number of ET, clinical and ongoing/delivered PR. However, there was a significantly lower FSH use in the QD compared to the BID group (1507.5 ± 517.5 IU compared to 1702.5 ± 622.5 , $P=0.015$), and a trend towards a lower hMG use in the QD arm (1342.5 ± 562.5 IU compared to 1462.5 ± 645.0 , $P=0.15$), (Table 1). The clinical PR was 78/110 (71.8%) in the QD and 73/103 (70.9%) in the BID groups ($P = \text{NS}$), and the delivery/ongoing PR was 64/110 (58.2%) in the QD and 64/103 (62.1%) in the BID groups ($P = \text{NS}$). The miscarriage rates were 14/78 (17.9%) in the QD and 8/79 (10.2%) in the BID groups ($P = \text{NS}$). The incidence of second trimester loss was 2/14 (14.2%) in the QD, and 2/8 (25%) in the BID groups. There was one ectopic pregnancy in each group (0.4%).

We also analyzed the outcome in women who used a long luteal protocol ($N=175$); 94 were in the QD group and 81 in the BID group. Again, there were no differences per initiated cycle in age, basal FSH, BMI, days of stimulation, peak E₂, number of retrieved oocytes, number of MII oocytes, fertilization rate, number of ET, clinical and ongoing/delivered PR. As noted for the total study group, there was a significantly lower FSH use in the QD compared to the BID group (1446.9 ± 504.4 IU compared to 1614.8 ± 534.4 IU, $P=0.034$), and a trend towards a lower hMG use in the QD arm (1273.8 ± 548.4 IU compared to 1381.5 ± 573.5 IU, $P=0.20$), (Table 2). The IR was 56.2% in the QD compared to 54.0% in the BID group ($P = \text{NS}$), clinical PR was 80/94 (85.1%) in the QD and 66/81 (81.5%) in the BID groups ($P = \text{NS}$), and the delivery/ongoing PR was 70/94 (74.5%) in the QD and 60/81 (74.1%) in the BID groups ($P = \text{NS}$). The miscarriage rates were 10/94 (10.6%) in the QD and 6/81 (7.4%) in the BID groups ($P = \text{NS}$). There were no cases of OHSS in either group.

There were 18 elective single embryo transfer (eSET) cases (18/213, 8.5%), 6 in the QD group and 12 in the

Table 1 ART outcome in QD compared to BID dosing in 213 cycles in 180 women

	QD	BID	<i>P</i>
Number of cycles	110	103	
Age (yrs) (mean ± SD)	32.4±4.3	32.9±4.2	NS
BMI (mean ± SD)	23.8±4.2	23.5±3.6	NS
Days of stimulation (mean ± SD)	9.89±0.81	9.71±0.65	NS
Total FSH (IU) (mean ± SD)	1507.5±517.5	1702.5±622.5	0.015
Total hMG (IU) (mean ± SD)	1342.5±562.5	1462.5±645.0	NS
Peak E ₂ (pg/mL) (mean ± SEM)	2,404±234.5	2,073±132.0	NS
Peak P (ng/dl) (mean ± SEM)	1.04±0.89	0.97±0.57	NS
Oocytes retrieved (mean ± SD)	12.8±5.8	13.6±6.0	NS
MII oocytes (mean ± SD)	9.56±4.51	9.87±4.44	NS
Fertilization rate%	84.7%	84.5%	NS
ET (mean ± SD)	2.1±0.6	2.0±0.7	NS
Clinical PR/initiated cycle (%)	79/110 (71.8%)	73/103 (70.9%)	NS
Ongoing/delivered PR (%)	64/110 (58.2%)	64/103 (62.1%)	NS
Multiple gestation rate	33/79 (41.7%)	34/73 (46.5%)	NS

BID group. The clinical PR in those undergoing eSET was 13/18 (72.2%) and the delivery rate was 12/18 (66.7%). The clinical PR was 6/6 (100%), and the delivery rate was 5/6 (83.3%) in the QD group, as compared to 7/12 (58.3%) and 7/12 (58.3%), respectively, in the BID group.

Discussion

To our knowledge, our present study is the only randomized, prospective, comparative study in the literature. It shows that once daily administration of gonadotropins (up to 450 IU/day) does not alter ART outcome compared to twice daily administration. Our study also shows an unexpected

significantly lower amount of FSH use and a trend towards hMG use in the QD group, resulting in financial savings in addition to better comfort and possibly compliance. While this was an unexpected finding of our study, it is important to note that a single administration of FSH has been previously shown to result in adequate serum levels for at least 36 h, and therefore it is safe to assume that another FSH administration 12 h later would be unlikely to alter serum levels beyond those achieved by a single administration. This also begs the question whether daily administration of gonadotropins is even needed (as compared to every 36–48 h).

The first study addressing the QD compared to BID dosing and ART success was in 1988. In that retrospective uncontrolled study, Murphy et al. evaluated 77 women stimulated

Table 2 ART outcome in QD compared to BID dosing in women using a long luteal protocol (*N*=175)

	QD	BID	<i>P</i>
Number of cycles	94	81	
Age (yrs) (mean ± SD)	32.2±4.3	32.8±4.2	NS
Basal FSH (IU/L)	8.06±3.15	8.45±3.42	NS
BMI (mean ± SD)	23.5±3.9	23.6±3.9	NS
Days of stimulation (mean ± SD)	9.87±0.83	9.69±0.65	NS
Total FSH (IU) (mean ± SD)	1446.9±504.4	1614.8±534.4	0.034
Total HMG (IU) (mean ± SD)	1273.8±548.4	1381.5±573.5	NS
Peak E ₂ (pg/ml) (mean ± SEM)	2363±1710.0	2174±1323.9	NS
Peak P (ng/dl) (mean ± SEM)	1.10±0.94	1.00±0.57	NS
Oocytes retrieved (mean ± SD)	13.2±5.8	14.1±6.1	NS
MII oocytes (mean ± SD)	8.31±4.06	8.50±3.92	NS
Fertilization rate%	84.7%	84.5%	NS
ET (mean ± SD)	2.1±0.6	2.0±0.7	NS
Clinical PR/initiated cycle (%)	80/94 (85.1%)	66/81 (81.5%)	NS
Ongoing/delivered PR (%)	70/94 (74.5%)	60/81 (74.1%)	NS
Multiple gestation rate	33/70 (47.1%)	26/60 (43.3%)	NS

with 2 ampoules of hMG daily between August and December 1984 and compared their outcome with 67 women who had twice-daily hMG (total 4 ampoules) between February and June 1985, and showed that BID dosing was associated with a higher pregnancy rate compared to QD dosing [1]. This study suffers from many deficiencies including that the QD group used only 2 hMG ampoules daily compared to 4 in the BID group during 2 different time points, rendering the conclusions invalid [1]. More recently, Schnell et al. retrospectively evaluated the Endometrin study data in 1211 cycles with a mixture of day 3 and day 5 transfers [2]. In the original study, centers were allowed to administer gonadotropins to the participating women according to their own protocols, i.e. QD or BID [4]. In the retrospective analysis, 777 women were in the QD group compared to 434 (35.8%) who were in the BID group. The results showed that there were no differences in age, BMI, duration of treatment, number of oocytes, or ongoing pregnancy rates [2]. Our study confirms the above findings in a more homogeneous group using only blastocyst transfer cycles in a single center with a single physician performing the monitoring, oocyte retrieval, and embryo transfers.

Our study also confirms prior results that a single administration of FSH and HMG in a single injection results in adequate ovarian stimulation and ART outcome, and obviates the need for two separate injections by mixing both in a single syringe [5, 6]. A 1:1 ratio of FSH and HMG seems to offer the best ART outcome [5].

Despite the fact that only 8.4% of our cycles were eSET, the delivery rate was respectable. We have been performing eSET since 2004, but patient resistance remains our biggest barrier to increasing the number of eSET cycles, as many prior groups have experienced [5]. We believe that patient education, insurance mandates, improving ART success, and financial incentives will result in increasing use of eSET [7].

In a recent Resolve survey, 92% of women undergoing IVF prefer once daily dosing [8]. Women can be assured now that this also does not compromise their success. In the age of patient friendly ART, physicians should strive to use the least amount of injections without compromising success.

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