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ARTICLE

GnRH antagonist pre-treatment: one centre's experience for IVF–ICSI cycle scheduling

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Abstract Scheduling gonadotrophin-releasing hormone antagonist (GnRH-ant) cycles for IVF intracytoplasmic sperm injection in patients is a challenge because of unpredictable ovum retrieval procedures on weekends, when less manpower is available. Recently, the use of GnRH-ant pre-treatment to delay an IVF and intracytoplasmic sperm injection (ICSI) cycle showed no negative effect on clinical pregnancy rates. An age-matched, case-control study was conducted to evaluate the effectiveness of such pre-treatment for scheduling purposes. Patients (n = 140) undergoing their first ovarian stimulation for IVF–ICSI were included. Patients starting their stimulation on Tuesdays or Wednesdays were most likely to have their ovum retrieval procedure on Saturdays. Seventy patients received a 3-day course of GnRH-ant before starting stimulation, and were compared with 70 age-matched controls not receiving pre-treatment. The main outcomes were the proportion of ovum retrieval procedures occurring on Saturdays, clinical pregnancy rate and live birth rates. A five-fold reduction in the number of ovum retrievals occurred on Saturdays compared with controls (7.1% versus 34.3%; OR 0.15; 95% CI 0.05 to 0.42; $P < 0.001$), with no significant differences in clinical pregnancy rate (40.9% versus 37.5%) and live birth rate (27.3% versus 31.3%). GnRH-ant pre-treatment is an effective tool for scheduling of GnRH-ant cycles.

KEYWORDS: cycle scheduling, gonadotropin-releasing hormone antagonist, in-vitro fertilization, programming

Introduction

Scheduling of IVF and intracytoplasmic sperm injection (IVF–ICSI) cycles has always been a concern for fertility units because of the difficulty faced in distributing the workload evenly during the week and avoiding unplanned procedures over the weekend. Cycle scheduling has obvious, social and economic benefits. It improves the organization of shifts for doctors,

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embryologists, technicians and nurses, ensuring a better work–life balance. It also favours adequate management of the limited manpower available on weekends.

Over the past decade, gonadotrophin-releasing hormone antagonist (GnRH-ant) cycles have been increasingly used worldwide in assisted reproductive techniques. Unlike GnRH agonist (GnRHa), GnRH-ant induces an immediate and reversible suppression of gonadotrophin production without 'flare-up', which results in a significantly shorter treatment period (Devroey et al., 2009). Furthermore, success rates of GnRH-ant cycles are largely similar to GnRH-a cycles, with a significant reduction in the incidence of severe ovarian hyperstimulation syndrome (Al-Inany et al., 2011; Kolibianakis et al., 2006a).

For cycle scheduling, GnRH-a is still superior to GnRH-ant cycles because it offers flexibility in the selection of the stimulation start date (when the down-regulation is achieved) compared with the totally random nature of spontaneous menses in GnRH-ant cycles. Three different strategies have emerged to manage GnRH-ant cycle scheduling: (i) a flexible start day for stimulation (i.e. either day 2 or day 3 of the menstrual cycle (Devroey et al., 2009); (ii) delay or advance in the HCG administration by 1 day (Tremellen and Lane, 2010); and (iii) use of either oestradiol or progestogens pre-treatment in the late luteal phase or oral contraceptive pill in the cycle preceding the IVF cycle (Cedrin-Durnerin et al., 2007). Few studies, however, have evaluated the usefulness of these strategies for the purpose of scheduling (Blockeel et al., 2012; Guivarc'h-Leveque et al., 2011). Indeed, studies have focused mainly on the effect of these strategies on clinical pregnancy rate (CPR) and live birth rate (LBR), with conflicting conclusions to date (Al-Inany et al., 2011; Garcia-Velasco et al., 2011; Hauzman et al., 2013; Smulders et al., 2010).

In 2011, a randomized controlled trial involving 69 patients showed that the administration of a 3-day course of GnRH-ant before the initiation of ovarian stimulation had no significant affect on the ongoing pregnancy rate (Blockeel et al., 2011). This pre-treatment regimen was therefore selected for evaluation for the purpose of scheduling of GnRH-ant cycles. In this study, an age-matched case-control study was conducted. Patients whose ovum retrieval day was anticipated to occur on Saturdays were given a GnRH-ant pre-treatment regimen, and the affect of this pre-treatment on the ovum retrieval day, CPR and LBR was evaluated.

Materials and methods

Study design and population

This study was approved by the Centralized Institutional Review Board at SingHealth Services, Singapore on 9 July 2010 (reference: 2010/447/D). Our centre operates on a 6-day working week from Monday to Saturday.

This is a case-control study of patients undergoing their first ovarian stimulation for IVF–ICSI at the KKIVF Centre in KK Women's and Children's Hospital. Despite applying the flexible start of ovarian stimulation on day 2 or day 3, and varying the administration of human chorionic gonadotrophin (HCG) injection 1 day earlier or later, 34–45% of patients beginning their ovarian stimulation on Tuesday or Wednesday still had their ovum retrieval procedures landing on a Saturday. Therefore, from July to December 2012, all the women whose day 2 of the menstrual cycle occurred on a Tuesday or a Wednesday were prospectively recruited as our study group (pre-treatment group). Those women received a daily GnRH-ant injection (Ganirelix, Orgalutan, 0.25 mg subcutaneous injection; MSD, USA) from menstrual cycle day 2 to day 5. This was followed by initiation of ovarian stimulation from day 5 of the cycle. GnRH-ant (Ganirelix, Orgalutan, 0.25 mg subcutaneous injection; MSD, USA) was re-started with a flexible-start regimen after 4–6 days of stimulation. Our control group was selected retrospectively from a historical group deriving from hospital records, and included patients who had started their first ovarian stimulation on a Tuesday or Wednesday from January 2011 to June 2012. Each patient from the pre-treatment group was age-matched with a patient from the control group. The controls received the standard ovarian stimulation starting from day 2 of the cycle (**Figure 1**). Daily sub-cutaneous injections of gonadotrophins were used for ovarian stimulation, such as recombinant FSH (rFSH: Puregon, MSD, USA or Gonal-F, Merck Serono, S.p.A, Italy) or human menopausal gonadotrophins (Menopur; Ferring Pharmaceuticals, Germany). The gonadotrophin dose was decided on the basis of each patient's ovarian reserve parameters (day 2 or 3 FSH level, antral follicle count and anti-Müllerian hormone (AMH) level). Patients with normal ovarian reserve tests received between 150 and 225 IU of gonadotrophins, whereas patients with diminished ovarian reserve received higher doses of gonadotrophins or a combination of recombinant FSH and human menopausal gonadotrophin.

IVF–ICSI treatment protocol

A total of 10,000 IU intramuscular HGC injections (Pregnyl, MSD, USA) was administered when three or more follicles measured 17 mm or more in diameter (averaged orthogonal measurements). Ultrasound-guided transvaginal oocyte retrieval was carried out 36 h after HCG administration, and the oocytes were fertilized on the same day by IVF or ICSI. Embryo transfer was carried out on day 2 or day 3 of embryo culture, and luteal phase support was achieved with either vaginal progesterone (200 mg three times a day, micronized progesterone, Utrogestan, Besins-International, France) or progesterone (50 mg intramuscularly daily; Biologici Italia Laboratories SRL, Italy) or HCG (1000 IU intramuscularly every 3 days; Pregnyl, MSD, USA).

Outcome measures and statistical analysis

The primary end-point was the number of ovum retrieval procedures on Saturdays, and the secondary end-points were the total dose of FSH used during ovarian stimulation, total number of oocytes retrieved, cancellation rates, CPR and LBR. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with a fetal cardiac activity 4 weeks after embryo transfer. A live birth was defined as the delivery of a viable fetus after 24 weeks of gestation.

Continuous variables were summarized in mean and SD or median and range for pre-treatment and control groups; categorical variables were presented as number of cases and

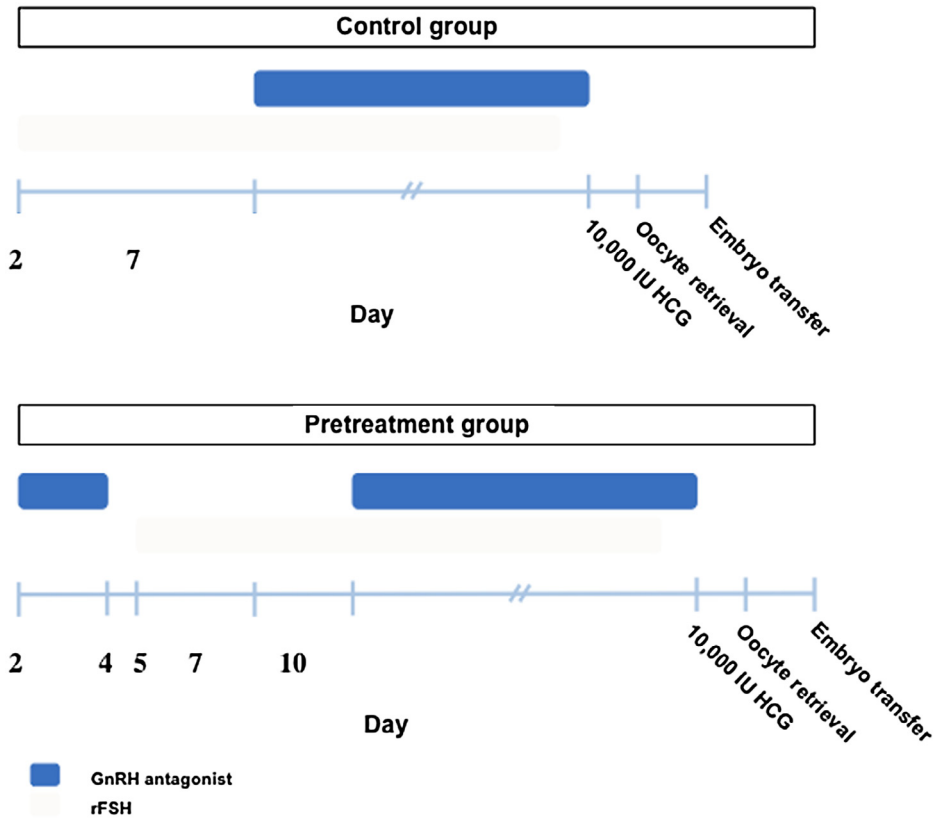

Figure 1 Gonadotrophin-releasing hormone antagonist pre-treatment and control groups.

percentages. The two-sample t-test or Wilcoxon–Mann–Whitney test was used to compare the two groups for continuous variables, and the chi-squared test was used to compare the two groups for categorical variables. For the primary outcome to seek the association between ovum retrieval day and GnRH pre-treatment, the control group was used as reference in logistic regression model. All potential confounders were analysed in a univariate model and the *P*-values lower than 0.20 were inserted into the multivariable model for adjustment of confounding variable. They same analysis was conducted for CPR and LBR. All tests were two-sided, and a *P*-value of less than 0.05 was considered as statistically significant. All statistical analyses were carried out using SAS version 9.2.

Results

A total of 140 patients were included in the analysis (70 patients per group). Patients' demographics and clinical characteristics are presented in Table 1. Both groups were comparable for age, race, body mass index, parity, basal early follicular phase FSH, AMH, and duration of infertility. They only differed in primary infertility diagnosis ($P = 0.023$). Diminished ovarian reserve and polycystic ovary syndrome were over-represented, whereas male and idiopathic subfertility were under-represented in the pre-treatment group.

The pre-treatment group had a five-fold reduction in the number of ovum retrieval procedures occurring on Saturday compared with the control group (7.1% versus 34.3%; $P < 0.001$), and this difference remained the same after adjustment for age and infertility diagnosis (OR 0.14 95% CI 0.05 to 0.41; $P < 0.001$). The number of days of ovarian stimulation, starting dose of FSH and number of oocytes retrieved were similar in both groups. Univariate analysis revealed that the total dose of FSH was significantly lower (over 600 IU) in the pre-treated group ($P = 0.008$) (Table 2).

The embryo transfer cancellation rate was similar in both groups (5.7% for the pre-treatment group versus 8.6% in the control group). Hence, 64 patients in the control group and 66 patients in the pre-treatment group proceeded to embryo transfer (Table 2).

The CPR and LBR did not differ significantly between the two groups: CPR 40.9% and 37.5%; LBR 27.3% and 31.3% for the pre-treatment and control groups, respectively. Both CPR and LBR were still comparable after adjustment for age, infertility diagnoses, starting and total dose of FSH, and number of oocytes retrieved in the multivariable model with respective odds ratio of 1.32 (0.55 to 3.15), and 0.91 (0.39 to 2.13) (Tables 2 and 3).

Discussion

GnRH-ant cycles have several benefits over the long GnRH-a IVF cycles. They are associated with higher patient acceptability and lower risk of ovarian hyperstimulation syndrome. GnRH-ant scheduling, however, is a challenging aspect because of the highly variable cycle start date. Even distribution of cases during the weekdays, and avoidance of

Table 1 Patients' baseline demographics and characteristics.

	Overall (n = *140*)	*Control* (n = *70*)	*Pre-treatment* (n = *70*)
Age (years) mean (SD)	34.8 (3.50)	34.7 (3.53)	34.8 (3.50)
Age group (years)			
< 31 *n* (%)	23 (16.4)	13 (18.6)	10 (14.3)
31 to ≤37 *n* (%)	80 (57.1)	38 (54.3)	42 (60.0)
≥ 37 *n* (%)	37 (26.4)	19 (27.1)	18 (25.7)
Race *n* (%)			
Chinese	105 (75.0)	52 (74.3)	53 (75.7)
Malay	11 (7.9)	4 (5.7)	7 (10.0)
Indians	15 (10.7)	9 (12.9)	6 (8.6)
Others	9 (6.4)	5 (7.1)	4 (5.7)
Body Mass Index (kg/m^2) mean (SD)	23.4 (4.82)	23.2 (5.16)	23.6 (4.52)
Parity			
0 *n* (%)	125 (89.3)	63 (90.0)	62 (88.6)
≥ 1 *n* (%)	15 (10.7)	7 (10.0)	8 (11.4)
Basal FSH (IU/L) mean (SD)	6.9 (4.13)	7.3 (5.10)	6.4 (2.51)
Anti-Müllerian hormone (ng/mL) mean (SD)	4.8 (4.91)	4.1 (4.94)	5.3 (4.88)
Duration of Infertility (year)[a] median (range)	4.0 (0.0–15.0)	4.0 (1.0–13.0)	3.0 (0.0–15.0)
Primary infertility diagnosis[b] *n* (%)			
Male factor	57 (40.7)	34 (48.6)	23 (32.9)
Polycystic ovary syndrome	18 (12.9)	7 (10.0)	11 (15.7)
Tubal obstruction/disease	16 (11.4)	7 (10.0)	9 (12.9)
Diminished ovarian reserve	7 (5.0)	1 (1.4)	6 (8.6)
Idiopathic sub-infertility	17 (12.1)	12 (17.1)	5 (7.1)
Endometriosis	6 (4.3)	4 (5.7)	2 (2.9)
Others	19 (13.6)	5 (7.1)	14 (20.0)

P-values were calculated by chi-square test for categorical variables and two sample t-test for continuous variables.
[a]*P*-value was calculated by Wilcoxon–Mann–Whitney test.
[b]$P = 0.023$.

Table 2 Saturday oocyte retrievals, cycle parameters, clinical pregnancy rates and live birth rates.

Variable	*Overall* (n = *140*)	*Control* (n = *70*)	*Pre-treatment* (n = *70*)
Saturday retrieval[a] *n* (%)	29 (20.7)	24 (34.3)	5 (7.1)
Embry transfer cancelled *n* (%)	10 (7.1)	6 (8.6)	4 (5.7)
Starting FSH dose mean (SD)	278 (135)	299 (151)	258 (115)
Total FSH dose[b] mean (SD)	2557 (1513)	2895 (1773)	2218 (1113)
Days of stimulation mean (SD)	9.1 (2.13)	9.5 (2.21)	8.8 (2.01)
Oocytes retrieved mean (SD)	11.2 (8.25)	11.7 (8.86)	10.6 (7.61)
Overall clinical pregnancy rate/embryo transfer *n* (%)	51 (39.2)	24 (37.5)	27 (40.9)
Clinical pregnancy rate/embryo transfer by age group (years)			
<31 *n* (%)	12 (54.5)	8 (66.7)	4 (40.0)
31 to ≤37 *n* (%)	34 (44.7)	15 (42.9)	19 (46.3)
≥37 *n* (%)	5 (15.6)	1 (5.9)	4 (26.7)
Overall live birth/embryo transfer *n* (%)	38 (29.2)	20 (31.3)	18 (27.3)
Live birth/embryo transfer by age group (years)			
< 31 *n* (%)	10 (45.5)	6 (50.0)	4 (40.0)
31 to ≤ 37 *n* (%)	24 (31.6)	13 (37.1)	11 (26.8)
≥ 37 *n* (%)	4 (12.5)	1 (5.9)	3 (20.0)
Number of births *n* (%)			
Singleton	29 (76.3)	18 (90.0)	11 (61.1)
Twin	9 (23.7)	2 (10.0)	7 (38.9)

[a]$P < 0.001$.
[b]$P = 0.008$.

Table 3 Associations between gonadotrophin-relasing hormone pre-treatment and cycle outcomes.

Clinical outcomes	*Odds ratio (95% CI)*	*P-value*[a]
Oocyte retrieval day		
Univariable model		
Pre-treatment versus control	0.15 (0.05 to 0.42)	<0.001
Multivariable model		
Pre-treatment versus control	0.14 (0.05 to 0.41)	<0.001
Age		NS
31 to ≤37 versus <31	0.92 (0.27 to 3.10)	NS
≥37 versus <31	1.12 (0.28 to 4.43)	NS
Primary infertility diagnosis		NS
Clinical pregnancy rate		
Univariable model		
Pre-treatment versus control	1.15 (0.57 to 2.34)	NS
By age group		
<31 ($n = 37$)	0.33 (0.06 to 1.91)	NS
31 to <37 ($n = 84$)	1.15 (0.46 to 2.86)	NS
≥37 ($n = 50$)	5.82 (0.57 – 59.3)	NS
Starting FSH dose (units = 50)	0.81 (0.69 – 0.94)	0.010
Total FSH dose (units = 50)	0.99 (0.97 – 1.00)	0.045
Oocytes retrieved	1.05 (1.00 – 1.10)	0.040
Multivariable model		
Pre-treatment versus control	1.32 (0.55 to 3.15)	NS
Age (years)		NS
31 to ≤37 versus <31	0.65 (0.23 to 1.83)	NS
≥37 versus <31	0.17 (0.04 to 0.81)	0.027
Starting FSH dose (units = 50)	1.11 (0.77 to 1.60)	NS
Total FSH dose (units = 50)	0.99 (0.97 to 1.02)	NS
Oocytes retrieved	1.04 (0.98 to 1.11)	NS
Primary infertility diagnosis		NS
Live birth		
Univariable model		
Pre-treatment versus control	0.83 (0.39 to 1.76)	NS
By age group (years)		
<31 ($n = 45$)	0.67 (0.12 to 3.64)	NS
31 to <37 ($n = 124$)	0.62 (0.23 to 1.64)	NS
≥37 ($n = 110$)	4.00 (0.37 to 43.4)	NS
Multivariable model		
Pre-treatment versus control	0.91 (0.39 to 2.13)	NS
Age (years)		NS
31 to ≤37 versus < 31	0.61 (0.22 to 1.66)	NS
≥37 versus <31	0.20 (0.05 to 0.81)	0.024
Primary infertility diagnosis		NS

NS = not statistically significant.
[a]*P*-value was calculated by logistics regression model.

unplanned procedures over the weekends, becomes difficult. Therefore, despite its obvious advantages, scheduling difficulties have hindered the wide implementation of GnRH-ant cycles.

To the best of our knowledge, this is the largest study evaluating the use of GnRH-ant pre-treatment for antagonist cycle scheduling. A 3-day course of GnRH-ant pre-treatment has reduced the probability of Saturday ovum retrieval procedures by 80%. Although this is a small study, underpowered to compare CPR and LBR, our results are reassuringly similar in both groups. We found a higher proportion of spontaneous abortions in the pre-treatment group, although it did not reach statistical significance (OR 2.3; 95% CI 0.6 to 9.8). This trend towards higher spontaneous abortion rates needs to be tested prospectively.

Several other pre-treatment methods have been evaluated for use in GnRH-ant cycles. Only one trial ($n = 93$), however, has compared several different modalities in the same setting, which found no differences in live birth rates overall (Cedrin-Durnerin et al., 2007).

The use of oral contraceptive pill pre-treatment has been fraught with conflicting outcomes. Initial reports suggested that similar outcomes could be obtained with the use of the oral contraceptive pill (Kolibianakis et al., 2006b; Rombauts

et al, 2006). A meta-analysis published in 2010 (Smulders et al., 2010) concluded that the use of oral contraceptive pill pre-treatment was associated with a significant decrease in CPR (Peto OR 0.69, 95% CI 0.50 to 0.9; $P = 0.03$), a longer ovarian stimulation duration, and a higher amount of gonadotrophin used (mean difference 1.44; 95% CI 1.15 to 1.72 days; $P < 0.00001$; and mean difference 231.1 IU; 95% CI 161.5 to 300.8 IU; $P < 0.00001$, respectively). Another meta-analysis has confirmed these findings (Griesinger et al., 2010), although there has been criticism that those meta-analyses were prone to multiple confounders (Garcia-Velasco et al., 2011). More recently, well-designed RCTs have reported that oral contraceptive pill pre-treatment is not deleterious on cycle outcomes (Garcia-Velasco et al., 2011; Hauzman et al., 2013).

Fanchin et al. (2003a; 2003b) first explored the use of oestradiol in the late luteal phase in GnRH-ant cycles to suppress the rise in FSH secretion during the luteal-follicular transition. They showed that the enhanced follicle synchronization led to the recovery of more mature oocytes. A subsequent trial, which randomized 472 patients into oestradiol pre-treatment or control groups, did not replicate Fanchin's findings of an increased number of mature oocytes retrieved. Instead, pre-treatment with oestradiol led to a longer duration of ovarian stimulation (0.8 days), resulting in a higher FSH dose (168 IU) used (Cedrin-Durnerin et al., 2012; Fanchin et al., 2003b). The only randomized-controlled trial evaluating the use of oestradiol pre-treatment to avoid weekend procedures to date involved 76 patients. Blockeel et al. (2012) showed that this strategy reduced the proportion of patients undergoing a weekend procedure from 21% to 3% ($P = 0.029$) while maintaining a similar CPR.

Compared with all pre-treatment options available, the use of GnRH-ant pre-treatment is advantageous over the orally administered options as its duration of use is shorter (3 days versus up to 15 days); however, it is more costly (an average of 150 USD more). Nonetheless, regardless of pregnancy outcome, this extra-cost is partially compensated by the lower total dose of FSH used. This finding, however, should be analysed with caution, because potential bias related to the semi-retrospective design of our study cannot be excluded.

The limitation of the present study is its semi-retrospective, non-randomized design. After comparing the study population with age-matched controls, the two groups were comparable except for the primary infertility diagnosis and total dose of FSH used. Moreover, our results remained consistent after adjustment for these parameters in a multivariate analysis model. Hence, we can conclude that the effect of these differences is negligible.

In conclusion, several alternatives have been evaluated to improve the flexibility of the ovarian stimulation start date in GnRH-ant cycles. We have shown that a 3-day course of GnRH-ant before starting the ovarian stimulation is an efficient scheduling tool for busy fertility units, while maintaining good pregnancy and live birth rates. Further randomized controlled trials would be needed to confirm these findings.

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