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Original article

New protocol for commencing the GnRH antagonist in assisted conception treatment cycles: elimination of the premature LH surge with similar pregnancy rates

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Abstract – GnRH antagonists have been used with increasing frequency in assisted reproduction treatments over the past few years and have been associated with quicker and more profound LH suppression and shorter treatment cycles than conventional GnRH agonists. Usually, these are commenced on day 6 of FSH stimulation without allowing for patient variation in response to treatment. The study was aimed at individualising this protocol to the patients' ovarian response. The control group included 215 treatment cycles where the GnRH antagonist was commenced on day 6 of FSH stimulation. A new individualised protocol was formulated, applied to practice and 172 treatment cycles following that were analysed. The study group had no premature LH surges (LH > 10 iu·mL^{-1}) compared to the control group who had a rate of 4.1%. There was also a higher fertilisation and clinical pregnancy rate in the study group ($P = 0.06$). It is concluded that the new individualised GnRH antagonist protocol eliminates premature LH surges in assisted conception treatment cycles and may improve clinical pregnancy rates compared to the conventional protocol of "day 6 commencement".

GnRH antagonist / premature LH surge / IVF

1. INTRODUCTION

Gonadotrophin releasing hormone (GnRH) antagonists have been used with increasing frequency in assisted reproduction treatments over the past few years and have been associated with quicker and more profound Luteinising hormone (LH) suppression and shorter treatment cycles than conventional GnRH agonists [1, 2].

The usual regime of using GnRH antagonists is to commence administration on day 6 of FSH stimulation in all patients [3, 4]. However, there is a great variation amongst patients in the way they respond to stimulation. There are GnRH receptors at the endometrium and the significance of these is still unclear [5], although it is known that delayed GnRH antagonist commencement will allow better endometrial maturation

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[6]. Also the antagonistic and almost complete suppression of LH reduces the total stimulation on the follicle [7] and the effect of this too early in the cycle is also unclear. For these reasons it would seem sensible to delay commencing the GnRH antagonist as much as possible and utilising it for the intended purpose of suppressing premature luteinisation and ovulation.

The objective of this study was to optimise the way the GnRH antagonist is used in assisted conception treatment cycles based on the patient's individual response.

2. MATERIALS AND METHODS

2.1. Patients

The control group included 215 treatment cycles where the GnRH antagonist was commenced on day 6 of recombinant follicle stimulating hormone (rFSH) stimulation. The cycles where reviewed and the results analysed and then a new protocol was formulated where commencement was based on ultrasonographic findings alone. A new individualised protocol was formulated, applied to practice and 172 treatment cycles following that were analysed.

2.2. Stimulation

Patients eligible for IVF with regular menstrual cycles of 24 to 35 days and two follicular serum FSH levels of less than 10 $iu \cdot L^{-1}$ were commenced on daily recombinant gonadotrophin injections (Gonal-F® or Puregon®) from day 2 of their cycle at 05:00–07:00. The starting dose (150–450 IU) was dependent on age, follicular FSH and previous ovarian response to treatment. The treatment cycle was cancelled by day 8 or 9 of FSH stimulation if less than 3 follicles of greater than 10 mm size developed. Insemination involved IVF or ICSI based on the cause of infertility and previous assisted reproduction treatment history.

2.3. Monitoring

In the control group, pelvic transvaginal ultrasonography (TVUS) was performed on day 6 of FSH stimulation as well as measurement of serum LH and oestradiol (E2). In the study group, pelvic TVUS was performed on day 5 of FSH stimulation (07:00–09:00) and the number and size of follicles in each ovary were recorded. Serum LH and E2 were measured for analysis purposes. The GnRH antagonist (Ganirelix) in the study group was commenced when one follicle reached 17 mm diameter or two or more follicles reached 14 mm. Based on the number and size of follicles, patients had the TVUS repeated one or two days later until the criteria for commencement were met (Fig. 1). In both groups, GnRH antagonist was administered at 22:00 on day 6 of FSH stimulation (control group) or day of decision to commence antagonist (study group) and then every 24 h until and excluding the day of hCG administration.

2.4. Outcome measures and statistical analyses

Patients' and treatment characteristics were compared and the main outcomes were the following: total FSH used, treatment length, day of GnRH antagonist commencement, premature LH surge rate, peak E2 levels, number of oocytes and embryos produced and clinical pregnancy rates. Unpaired student *t*-tests were performed for comparison of means after the Levene test confirmed equality of variances and the Mann-Whitney U test was used in groups with unequal variances. A χ^2 test was performed for binomial values. Values of P less than 0.05 were considered statistically significant at the 95% confidence level. The software used was SPSS™ (Version 9.0.0).

3. RESULTS

The two groups were comparable as demonstrated in Table I. The study group had no

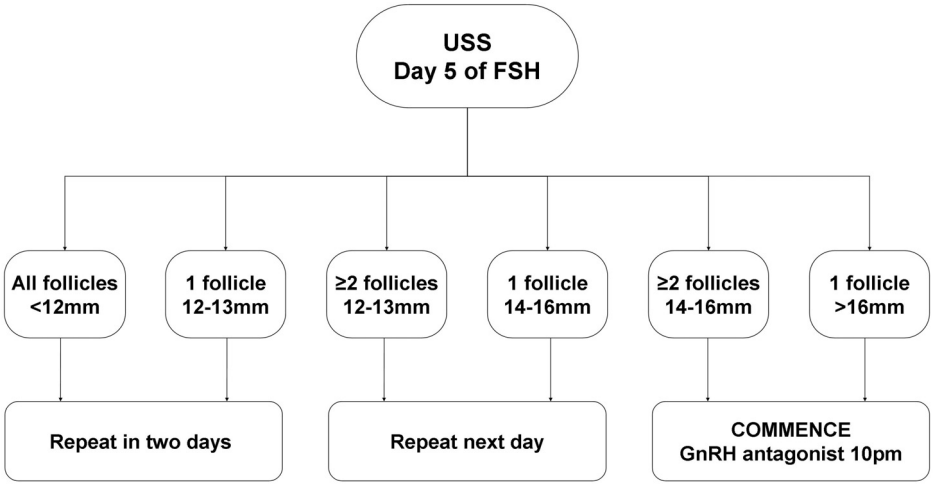

Figure 1. The new protocol used for GnRH antagonist commencement.

premature LH surges (LH > 10 iu·mL^{-1}) compared to the control group which had a rate of 4.1%. Also the E2 per oocyte retrieved was significantly higher in the study group compared to the controls. There was a higher fertilisation and clinical pregnancy rate in the study group although this did not reach statistical significance ($P = 0.06$). Commencement of the GnRH antagonist in the study group was later in the stimulation cycle (6.57 vs. 6.00). Details of the day of commencement of the antagonist in the study group are depicted in Figure 2 along with the pregnancy rates for each subgroup. The pregnancy rate differences did not reach statistical significance.

4. DISCUSSION

Despite an average delay in commencing the antagonist there is elimination of the premature LH surges in treatment cycles for assisted conception when an individualised protocol for scheduling GnRH antagonist commencement is used compared to a fixed day of commencement. The fast responding patients would induce an LH surge on day 5 and would render the oocyte inappropriate for fertilisation due to premature luteinisation. On the contrary, in the slow responding patients, follicles mature before inducing an LH surge which would occur after day 6 and a delay in GnRH antagonist administration will allow the follicles to grow without depriving them of the LH pulsatile stimulation during folliculogenesis. This is why it is not appropriate to use protocols for commencing the GnRH antagonist on a fixed day in the cycle, and the individualised protocol covers both groups by either preventing a day 5 surge or allowing a later maturation. When looking at the commencement day of the antagonist using our protocol, it can be demonstrated (Fig. 2) that only about one third of the cycles needed commencement on day 6 of the cycle and that another one third of the cycles commencement was required on day 5. The rest were mainly day 7 and more, up to day 12. Pregnancy rates for day 6 commencement were as good as the rest of the cycles although the numbers were too small to allow statistical confirmation or exclusion. This is an area

Table I. Comparison of the two protocol groups.

	Study (172)	Control (215)	*P* value
Cancelled cycles	15	19	0.8
Age at oocyte retrieval, years	37.4	37.5	0.66
Tubal factor alone infertility (%)	29 (16.9%)	30 (14.0%)	0.57
Male factor alone infertility (%)	36 (20.9%)	54 (25.1%)	0.18
Unexplained infertility (%)	50 (29.1%)	69 (32.1%)	0.54
Other causes of infertility (%)	57 (33.1%)	62 (28.8%)	0.35
Days of gonadotrophin stimulation	11.03	10.98	0.78
Total gonadotrophin used (iu)	3457.5	3320.9	0.21
Day of GnRH antagonist commencement	6.57	6	0.001
Mean number of TVUS performed	5.33	5.1	0.49
Premature LH surge (LH > 10 iu·L^{-1})	0	8 (4.1%)	–
Peak serum oestradiol (pmol·L^{-1})	4944	4598	0.02
Oocytes retrieved	8.4	9.0	0.06
Serum oestradiol per oocyte (pmol·L^{-1})	866.7	587.7	0.001
ICSI cycles (% of total)	61 (38.9%)	75 (36.9%)	0.74
Fertilisation rate	0.594	0.538	0.06
Embryos produced per cycle	4.0	4.5	0.07
Embryos transferred per cycle	2.11	2.26	0.65
Implantation rate (gestation sacs/embryos)	30/300	43/444	0.87
Clinical pregnancy* per completed cycle (%)	40 (25.5%)	35 (17.9%)	0.06

* Fetal heart activity on ultrasound.

needing further investigation. This demonstrates the importance of individualising the way the GnRH antagonist is used since monitoring from day 5 will pick up the cases where premature LH surging can occur. In slow-responding follicles GnRH antagonist was commenced up to day 12 of FSH stimulation allowing for adequate follicle maturation.

Other studies have demonstrated the benefit of this type of protocol based on a follicle size of 14 mm as the cut-off size for GnRH antagonist commencement [8]. In this study the cut-off size was 16 mm for one follicle or 14 mm for more than one follicle demonstrating that it is not only the size but also the number of leading follicles that needs to be considered.

Higher oestradiol levels per oocyte are most probably reflecting higher levels of endogenous pulsatile LH levels since the antagonist is introduced later in the cycle and this has been demonstrated in other studies [9]. Higher fertilisation and clinical pregnancy rates further support the benefit of individualising the protocol for GnRH antagonist use. However, a smaller study including 60 cycles [9] has shown no difference in commencing the antagonist on day 1 or day 6 as far as follicular development and embryo outcome is concerned.

We used strict and detailed criteria for commencing the antagonist but this can be easily simplified in a flow diagram and can be based solely on ultrasonography without increasing the average number of scans

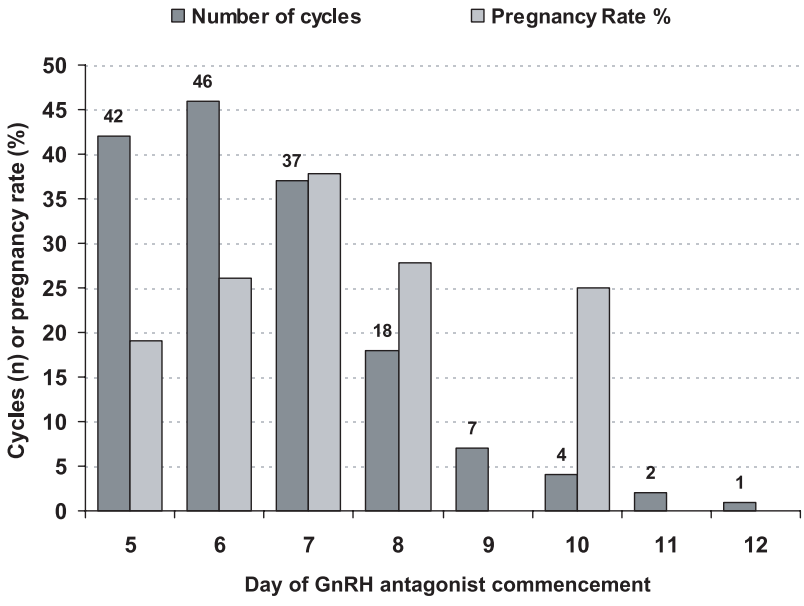

Figure 2. Day of commencement of GnRH antagonist using the new protocol and clinical pregnancy rate achieved.

needed. Laboratory services may be unavailable in some units during weekends and by using this protocol the problem can be bypassed also improving cost effectiveness since serum hormonal assays are unnecessary.

Overall pregnancy rates were not very high but the average female age was 37 years since this particular treatment was a selected group of patients. There was a trend for improved clinical pregnancy rates and this can be explained by an improved maternal environment since implantation rates were very similar. Both groups were comparable and statistical significance could be reached with larger numbers and a future randomised prospective study would provide a stronger case eliminating any bias.

REFERENCES

[1] Garcia-Velasco JA, Isaza V, Vidal C, Landazabal A, Remohi J, Simon C, Pellicer A. Human ovarian steroid secretion in vivo effects of GnRH agonist versus antagonist (cetrorelix). Hum Reprod 2001, 16: 2533–2539.

[2] Olivennes F, Belaisch-Allart J, Emperaire JC, Dechaud H, Alvarez S, Moreau L, Nicolellet B, Zorn JR, Bouchard P, Frydman R. Prospective randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin). Fertil Steril 2000, 73: 314–320.

[3] Felberbaum RE, Albano C, Ludwig M, Riethmuller-Winzen H, Grigat M, Devroey P, Diedrich K. Ovarian stimulation for assisted reproduction with HMG and concomitant midcycle administration of the GnRH antagonist cetrorelix according to the multiple dose protocol a prospective uncontrolled phase III study. Hum Reprod 2000, 15: 1015–1020.

[4] Albano C, Felberbaum RE, Smitz J, Rietmuller-Winzen H, Engel J, Diedrich K, Devroey P. Ovarian stimulation with HMG results of a propespective randomized phase III European study comparing the luteinizing hormone, e-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buselin. Hum Reprod 2000, 15: 523–531.

[5] Shemesh M. Actions of gonadotrophins on the uterus. Reproduction 2001, 121: 835–842.

[6] Kolibianakis E, Bourgain C, Albano C, Osmanagaoglu K, Smitz J, Van Steirteghem A, Devroey P. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. Fertil Steril 2002, 78: 1025–1029.

[7] Huirne JAF, Lambalk CB. Gonadotrophn-releasing-hormone-receptor antagonists. Lancet 2001, 358: 1793–1803.

[8] Ludwig M, Katalinic A, Banz K, Schroder AK, Loning M, Weiss JM, Diedrich K. Tailoring the GnRH antagonist cetrorelix acetate to individual patients' needs in ovarian stimulation for IVF: results of a prospective, randomized study. Hum Reprod 2002, 17: 2842–2845.

[9] Kolibianakis EM, Albano C, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Initiation of gonadotropin-releasing hormone antagonist on day 1 as compared to day 6 of stimulation: effect on hormonal levels and follicular development in in vitro fertilization cycles. J Clin Endocrinol Metabol 2003, 88: 5632–5637.