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ARTICLE

Is it possible to reduce the incidence of weekend oocyte retrievals in GnRH antagonist protocols?

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Abstract A retrospective analysis of a large, randomized clinical trial (Engage) assessed whether adjusting the start day of ovarian stimulation and/or day of human chorionic gonadotrophin (HCG) trigger could minimize oocyte retrieval during weekends without adverse effects on clinical outcome. Patients received recombinant FSH/gonadotrophin-releasing hormone (GnRH) antagonist regimens, with stimulation starting on day 2 or 3 of menses. HCG was administered when at least three follicles of ≥17 mm were present on ultrasound scan or 1 day later. The frequency distribution of the day of reaching the HCG criterion relative to stimulation initiation was analysed to determine the optimal stimulation start day (cycle day 2 or 3) depending on the weekday at which menses started, to minimize weekend retrieval. The number of oocytes retrieved and pregnancy rates were not affected by start day and/or delay in HCG administration in regularly ovulating women aged 18–36 years with bodyweight 60–90 kg, body mass index 18–32 kg/m^2 and menstrual cycle length 24–35 days. In recombinant FSH/GnRH antagonist regimens, it appears possible to minimize weekend oocyte retrieval by selecting the cycle day to initiate stimulation, day 2 when menses starts Friday–Tuesday, otherwise day 3 and if necessary in combination with a 1-day HCG delay.

KEYWORDS: cycle start day, GnRH antagonist protocol, HCG delay, oocyte retrieval, recombinant FSH

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Introduction

Recombinant FSH/gonadotrophin-releasing hormone (GnRH) antagonist regimens have been shown to be safe and effective for women undergoing ovarian stimulation for IVF and intracytoplasmic sperm injection (ICSI). Two pivotal trials, using follitropin beta injection in combination with the GnRH antagonist ganirelix acetate, have demonstrated high ongoing pregnancy rates: 45% in an open-label, non-controlled multicentre trial of 60 IVF patients (Pang et al., 2003) and 38.1% for 750 subjects in the active-control arm of a recent double-blind, randomized, comparator-controlled, multicentre trial (Engage; Devroey et al., 2009).

A recombinant FSH/GnRH antagonist protocol has several advantages for physicians and patients. Compared with GnRH agonist long luteal down-regulation protocols, GnRH antagonist stimulation protocols result in a reduced duration of stimulation, with a lower total dose of recombinant FSH needed to reach the same criterion for human chorionic gonadotrophin (HCG) administration (Tarlatzis et al., 2006). Moreover, the treatment regimen is simpler for the patient, and the reduced number of injections required may reduce the burden of infertility treatment, encourage lower drop-out rates and improve patient compliance (Verberg et al., 2008). With regard to safety, GnRH antagonist regimens are associated with a highly significant reduction in incidence of ovarian hyperstimulation syndrome compared with the GnRH agonist long protocol (Al-Inany et al., 2011).

In some IVF units, there is a desire to avoid oocyte retrieval on weekends. Many assisted reproduction centres now use oral contraceptives as a means to schedule ovarian stimulation cycles in women stimulated with recombinant FSH and a GnRH antagonist; ovarian stimulation can be started during a 2—5-day interval after withdrawal of the oral contraceptive. Comparable ongoing pregnancy rates were achieved in a GnRH antagonist and GnRH agonist protocol using oral contraceptives before treatment (Garcia-Velasco et al., 2011). However, it has been shown that pretreatment with an oral contraceptive in GnRH antagonist protocols, besides complicating the treatment protocol, is associated with a decreased probability of ongoing pregnancy in the fresh transfer cycle (Griesinger et al., 2010). Thus, providing a means for cycle scheduling without pretreatment with an oral contraceptive would improve the patient-centred protocol while maintaining its simplicity.

Previous studies have shown that in recombinant FSH/GnRH agonist protocols, scheduling the starting day of ovarian stimulation was a useful method to avoid oocyte retrieval on weekends, reducing the amount of overtime worked, decreasing cost and inconvenience without compromising IVF outcome (Ben-Chetrit et al., 1997; Nakagawa et al., 1997). In addition, a recent retrospective analysis indicated that simple advancement or delay of HCG administration in a GnRH antagonist protocol may allow clinicians to avoid weekend oocyte retrieval without adversely affecting live birth rates (Tremellen and Lane, 2010). Therefore, the primary objective of the current retrospective analysis was to assess whether adjusting the starting day of ovarian stimulation based on the weekday of start of menses, if necessary combined with delaying the triggering of final oocyte maturation with HCG, could minimize the occurrence of oocyte retrieval during weekends in a recombinant FSH/GnRH antagonist regimen.

Materials and methods

Study design

This study conducted a retrospective analysis of data from the reference arm (recombinant FSH/GnRH antagonist) of the Engage trial (Devroey et al., 2009), a multicentre, randomized, double-blind, double-dummy, active-controlled, non-inferiority clinical trial involving women undergoing ovarian stimulation for IVF. The study was conducted in 34 centres (14 in North America, 20 in Europe) between June 2006 and January 2008. The study was conducted in accordance with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. An independent data safety monitoring board was appointed to monitor the safety of subjects participating in the trial, and written informed consent was provided by all patients (ClinicalTrials.gov identifier NCT00696800).

Subjects

Women aged 18—36 years with bodyweight 60—90 kg, body mass index 18—32 kg/m^2, menstrual cycle length of 24—35 days, access to ejaculatory spermatozoa and indication for ovarian stimulation before IVF or ICSI were eligible for inclusion in the study. Further details of the patient inclusion and exclusion criteria can be found in the original publication (Devroey et al., 2009).

Treatment

This retrospective data analysis focused on the active control arm of the Engage trial. In this arm, patients received once-daily 200 IU recombinant FSH (follitropin beta,

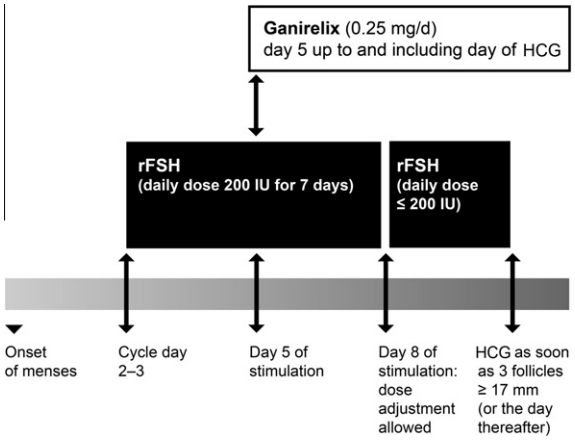

Figure 1 Study design (recombinant FSH treatment arm of the Engage trial). The recombinant FSH dose could be reduced from day 6 onwards when required in the opinion of the investigator. HCG = human chorionic gonadotrophin; rFSH = recombinant FSH.