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SHORT COMMUNICATION

Oral contraceptive pretreatment and half dose of ganirelix does not excessively suppress LH and may be an excellent choice for scheduling IUI cycles

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Abstract

Purpose To assess the effects of using a reduced dose of ganirelix with oral contraceptive pretreatment in a pilot study of COH using pure FSH for intrauterine insemination (IUI)

Methods Patients received oral contraceptive (OC; 30 μg ethinyl estradiol/150 μg desogestrel) for 14–21 days and rFSH (50–225 IU/day SC) was started on day 4 after OC discontinuation. Ganirelix acetate (125 μg/day) was started with a lead follicle diameter of 14 mm.

Results Of the 25 subjects who started oral contraceptives, one was cancelled due to an excessive response, and one subject was not included in the analysis because she did not receive ganirelix until the lead follicle was 18 mm. Median (range) starting FSH dose was 100 (50–225), cumulative rFSH dose was 1000 (675–2175) IU over 10 (9–17) days. Duration of ganirelix acetate treatment was 4.0 (2–5) days. Seven subjects (30.4%) delivered ten babies (three pregnancies were twins). There were no biochemical pregnancies or miscarriages. Of the 16 subjects with measurement of LH on the day of HCG administration, only one was under 0.5 mIU/ml (0.4), and only one was over 10 mIU/ml (17.7), and that subject delivered twins.

Conclusion OC pretreatment afforded flexibility in scheduling while a reduced dose of ganirelix avoided excessive suppression of LH. The excellent results in this pilot study for IUI suggest this regimen could be further evaluated for scheduling IUI and IVF cycles.

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Introduction

GnRH antagonists make it possible to develop controlled ovarian stimulation (COS) regimens that are more "patient-friendly" because they are able to prevent premature elevation of LH and ovulation with only a few daily subcutaneous injections. However, without some method of cycle programming such as oral contraceptive (OC) pretreatment, the timing of oocyte retrieval or intrauterine insemination (IUI) is dependent on the onset of the menstrual cycle, making antagonist regimens less attractive for programs and patients that need the flexibility of scheduling of these procedures. Unfortunately, OC pretreatment when combined with a full dose of antagonist causes a more marked suppression of LH levels, and in some women, increased early pregnancy loss [1, 2]. Although supplementing LH apparently may counteract these adverse effects [3, 4], the addition of another medication complicates the COH procedure.

In a dose-ranging study of ganirelix for IVF [5], although the ideal dose was 0.25 mg, the implantation rate was only mildly decreased and the mean LH level was only mildly increased on half that dose. Because OC pretreatment also suppresses LH levels, we speculated that adding OC scheduling to the 0.125 mg dose might yield LH levels and an implantation rate similar to the 0.25 mg "ideal" dose. The present study was designed as a pilot to assess the utility of OC with the half-dose of ganirelix in women receiving COS for IUI. This approach could benefit COS/IUI patients, because it has been shown that women

undergoing COS/IUI who have premature luteinization have a reduced outcome [6].

Materials and methods

This open-label single arm trial assessed the efficacy and convenience of a "half dose" of ganirelix acetate (Ganirelix Acetate Injection; Organon USA Inc, Roseland, NJ, USA) with pretreatment using a 30 μg ethinyl estradiol/150 μg desogestrel OC (Desogen®, Organon USA Inc, Roseland, NJ, USA) in normogonadotropic women undergoing COS for IUI. Institutional Review Board approval was obtained prior to study initiation and patient enrollment.

Healthy female partners of infertile couples who were scheduled for COH/IUI and fulfilled the clinical criteria were eligible to participate. Subjects had to meet the following inclusion criteria: ≥18 and ≤38 years of age at the time of screening, normal menstrual cycle with a range of 24 to 35 days and an intra-individual variation of ±3 days and body mass index<29 kg/m^2 with a lower weight limit of 50 kg (110 lbs) and an upper limit of 90 kg (198 lbs) and be willing to sign the informed consent form. Subjects were excluded from participation in the study if they had: a history of/or current endocrine abnormality such as polycystic ovary syndrome; (treated) hyperprolactinemia or evidence of ovarian dysfunction; any previous COS cycles for IUI; history of no or low ovarian response to FSH/hMG treatment; abnormal cervical smear according to the Papanicolaou (≥class III) or Bethesda (≥CIN 1) scale; a serum FSH level on days 2 to 4 of menses of greater than 10 mIU/ml; ovarian abnormality that would interfere with adequate ultrasound monitoring; known GnRH or GnRH analog hypersensitivity; contraindication for the use of gonadotropins; contraindication for the use of oral contraceptives; use of hormonal preparations within 1 month prior to date of consent (except thyroid medications); hypertension, epilepsy, diabetes, cardiovascular, gastrointestinal, hepatic, renal, pulmonary, or abdominal disease; alcohol or drug abuse; administration of investigational drugs within 12 months. All subjects had bilaterally patent fallopian tubes by hysterosalpingogram, had no history of endometriosis or other abnormality, and either a semen analysis acceptable for IUI or were using donor sperm. Of the 23 couples completing the study, three were using donor sperm, three had a male factor, and the remainder had idiopathic infertility.

Subjects took an OC once daily for 14 to 21 days beginning on days 1 to 3 of menses, after which OC administration was discontinued. Recombinant FSH (Follistim®, Organon USA Inc, Roseland, NJ, USA) at a starting dose of 50–225 IU was administered subcutaneously once daily beginning on the evening of day 4 after discontinuation of the OC. The FSH dose was chosen by each clinician based on the patient's age and antral follicle count.

Ganirelix acetate (125 μg/day; Ganirelix Acetate Injection, Organon USA Inc., Roseland, NJ, USA) was started when the lead follicle reached a mean diameter of 14 mm and was given each morning including the morning of hCG. During ganirelix acetate treatment, the dose of rFSH could be adjusted, depending on the individual ovarian response as assessed by USS. A blood sample for serum LH measurement was taken on the morning that ganirelix was begun and on the day of hCG administration. Human chorionic gonadotropin (10,000 IU; Pregnyl®, Organon USA Inc., Roseland, NJ, USA) was administered when at least two follicles with a diameter of ≥17 mm were observed. The decision as to whether to cancel the cycle for excessive response was based on individual discussion of the risks with the patient. IUI was performed on the following two mornings (approximately 12 and 36 h after hCG administration). Luteal support was provided with vaginal micronized progesterone, 200 mg twice daily.

Patients were assessed for the following parameters: number of follicles over 10 and 14 mm mean diameter, rFSH starting and total dosage, number of days on FSH and on ganirelix, and pregnancy outcome. Pelvic USS was done on the day following hCG.

Results

Of the 25 subjects enrolled, mean (range) age was 34 (29–38) years, mean day 3 FSH was 7.5 (4–10) mIU/ml, and mean weight was 136.5 (110–175) lbs. One subject was cancelled due to an excessive response, and one subject was removed from analysis because she did not receive ganirelix until the lead follicle was 18 mm.

The mean (range) of serum LH (mIU/ml) before starting ganirelix (*n*, 18) was 2.7 (0.75–11.5). The mean LH level on the day of HCG (*n*, 16) was 4.5 (0.4–17.7).

The median (range) duration of FSH administration was 10 (9–17) days; ganirelix was given for 4 (2–5) days. On the day of HCG there was a mean of 5.3 follicles over 10 mm, and 3.8 follicles of at least 14 mm. No patient had ovulation of any follicles on the morning after hCG injection. Median starting FSH dose was 100 and cumulative rFSH dose was 1000. Seven subjects (30.4%) delivered ten babies (three pregnancies were twins). There were no biochemical pregnancies or miscarriages, but there was one vanishing twin.

Discussion

OCs may be used to schedule the start of controlled ovarian stimulation in GnRH antagonist cycles to synchronize the

follicular cohort and to allow scheduling of egg retrieval. In a previous study using OC pretreatment and 0.25 mg of ganirelix, we found that the level of LH on the day of hCG administration 12 h after ganirelix was below 0.5 mIU/ml in almost half of the subjects, and there was a significant association of such low levels with very early (biochemical) pregnancy loss [1]. In another prior study, OC pretreatement was also associated with increased early pregnancy loss [2]. While this adverse effect can probably be obviated by adding some form of LH activity [3, 4], this adds further complexity to the COS regimen compared with the use of only pure FSH. In the present study, using half the usual dose of ganirelix, there was only one subject who had a LH level below 0.5 mIU/ml, all pregnancies were clinical, all delivered, and the high incidence of twins in this small series was consistent with very good egg quality. On the day of hCG only one LH level was over 10 mIU/ml (17.7, immediately before ganirelix injection), and that patient had intact follicles 24 h after that level and delivered twins. The clinical pregnancy rate and delivery rate were 30% (7/23). A much larger series will be necessary to assess the rate of successful pregnancy, the incidence of biochemical and clinical pregnancy loss and the incidence of premature LH surge and ovulation, but this pilot study suggests that a similar regimen could be used for "friendly" reduced stimulation IVF.

Premature luteinization has been shown to occur in about a third of COS/IUI cycles with a markedly reduced pregnancy rate [6]. In that study, use of a GnRH agonist normalized the success rate in those patients, raising the possibility that routine use of a GnRH antagonist for COS/IUI could also improve the rate of successful pregnancy. However, the use of GnRH antagonists for COS/IUI has met with variable success. Allegra et al, using a starting FSH dose of 75–150 IU reported a pregnancy rate per cycle of 19% compared to 11.1% without antagonist and found a marked decrease of premature LH surge and premature luteinization [7]. Using a uniform starting dose of 100 IU of FSH, Gomez-Palomares et al. reported a pregnancy rate of 38% versus 14% without antagonist, although there was a triplet pregnancy in the group receiving antagonist [8]. In contrast, in a multicenter randomized trial the ongoing pregnancy rates were the same with (12.6%) and without (12.0%) ganirelix [9]. In that study, about 85% of the subjects received less than 100 IU for the starting dose of FSH. In a further multicenter randomized trial Crosignani et al. reported success rates of 12.2% and 12.6% using a uniform dose of 50 IU of FSH [10]. The striking contrast among these studies strongly suggests that a benefit to the antagonist depends on a higher level of ovarian stimulation than 50–75 IU. However, even including these latter studies, a recent meta-analysis [11] has shown a significant increase of the pregnancy rate using antagonist (odds ratio 1.56, CI 1.05–2.33).

In the present study using OC pretreatment, there was a trend toward a high rate of twins. Since follicles of 10 mm or more can sometimes ovulate, the synchronization of the follicular cohort by OC pretreatment and the ability to allow follicles to reach 17 mm or more without a premature LH rise could increase multiple pregnancy in parallel with increased pregnancy success. Further refinement of FSH dosing, or perhaps a later onset of stimulation [12], or administration of hCG with only one follicle of 17 mm may make such a regimen satisfactory for COS/IUI. The use of antagonist in IUI cycles having excessive response will facilitate conversion of those cycles to IVF by preventing premature ovulation.

In summary, the present pilot study suggests that OC pretreatment with half the usual dose of ganirelix could be an excellent choice for patient-friendly reduced stimulation IVF or for IUI cycles where flexibility is required for scheduling. In order to be satisfactory for IUI, it will be necessary to further study the optimal starting dose of FSH and/or a later onset of stimulation following cessation of OC. Randomized studies for IUI and for IVF would be appropriate given these satisfactory preliminary results.

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