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ORIGINAL ARTICLE

Pregnancy rate after ovulation triggering with gonadotrophin releasing hormone agonist versus human chorionic gonadotrophin in women undergoing controlled ovarian stimulation/ intrauterine insemination

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KEYWORDS

GnRH agonist;
Ovulation triggering;
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Abstract *Background:* GnRHa is as effective as hCG for ovulation triggering, apart from LH surge, FSH surge is also induced.

Objective: To compare triggering of ovulation by inducing endogenous LH surge (GnRHa) or using hCG in hMG stimulated cycles for intrauterine insemination (IUI).

Setting: Prospective randomized study.

Materials and methods: Out of the three hundred and eighty patients scheduled for IUI, after exclusion of 28 women, 352 were assigned to two groups: hMG/GnRHa (study group, $n = 176$) were assigned for receiving HP hMG followed by triggering by GnRHa and hMG/hCG (control group, $n = 176$) were assigned for HP hMG followed by hCG for ovulation triggering. Intrauterine insemination was done using freshly prepared semen 36 h after triggering of ovulation. Luteal phase support was done by 1500 IU hCG, 12 h after the triggering of ovulation.

Results: LH levels significantly ($p < 0.001$) increased in the hMG/GnRHa group than in the hMG/hCG group. No significant differences were seen between the basal LH, progesterone levels before and 8 days after triggering in both groups. The duration of the luteal phase was similar in both groups. Pregnancy rates per cycle were 17.61% for GnRHa and 13.06% for hCG respectively ($p = 0.23$).

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Conclusions: There is no difference between GnRHa and hCG as regards pregnancy rate in women undergoing hMG stimulation for IUI cycles.

1. Introduction

In normal menstrual cycle, a cascade of events drives ovulation which is initiated by a surge of Luteinizing Hormone (LH) from the pituitary. This LH induces resumption of oocyte meiosis and follicular rupture. In protocols for ovarian stimulation, exogenous hCG is used to achieve final oocyte maturation and ovulation (1,2). Unfortunately, given its significantly longer half-life [> 24 h vs. 60 min for LH], hCG is associated with a high risk of OHSS (3,4). Several years ago the concept that a bolus of gonadotrophin-releasing hormone agonist (GnRHa) can replace hCG as a trigger of final oocyte maturation was introduced. GnRHa trigger offers important advantages, including almost complete prevention of ovarian hyperstimulation syndrome (OHSS), induces an endogenous surge of FSH in addition to the LH surge and finally the option to individualize luteal-phase support based on ovarian response to stimulation (5). However, lower probability of pregnancy is to be expected with the use of GnRHa instead of hCG for ovulation triggering (6).

GnRHa receptors have been described in the human endometrium and corpus luteum (CL). Damage of CL leading to an insufficient luteal phase and negative effect on oocytes, embryo and endometrium quality, have been suggested as reasons for lower pregnancy rate (7,8). However, Fauser et al. (1) showed that endogenous FSH and LH surge induced by GnRHa is physiological with luteal phase steroid concentration close to those of normal cycles. Endometrium receptivity proved to be greater than observed after exogenous hCG administration.

Cochrane review (9) evaluated and compared different ovarian stimulation protocols for IUI for all indications. They concluded that based on the available results gonadotrophins might be the most effective drugs when IUI is combined with COS. When gonadotrophins are used for ovarian stimulation low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chances to encounter negative effects from ovarian stimulation such as multiple pregnancy and OHSS are limited with low dose gonadotrophins.

The aim of this study was to evaluate the effect of triggering ovulation by inducing endogenous LH surge (GnRHa) or using (hCG) in hMG-stimulated cycles on pregnancy rate in patients undergoing intrauterine insemination (IUI).

2. Materials and methods

As regards sample size calculation, we proposed pregnancy rate differences as zero assuming 15% pregnancy rates after treatment, supposing; significance level of 0.05 and a statistical power of 80%. Expecting a 5%–10% loss, and after exclusion of 28 women; 352 women were included and finally 176 women planned to be included in each group.

All patients gave informed consent and the study was approved by local ethics committee for scientific research.

This randomized study was conducted during the period of January 2010 and May 2012. Three hundred and eighty stimulated cycles in 380 infertile women undergoing intrauterine insemination were studied. Twenty-eight patients were excluded; don't reach the point of triggering therapy (6) non-responsive, (4) spontaneous ovulation, (7) excessive number of follicles, (5) did not follow treatment as advised, and (6) lost to follow-up. Inclusion criteria for infertile couples are the following [hormonal profile, investigations for ovulation, tubal patency, semen analysis: within normal], age of the female 18–37 years. Exclusion criteria were a history of OHSS, poor response, PCOS patients, and patients with one ovary, unilateral tubal patency and previous ovarian surgery. Women with unexplained infertility were diagnosed based on a normal semen analysis according to WHO criteria, confirmed tubal patency and ovulatory menstrual cycles based on midluteal phase progesterone levels or ultrasonic follicle tracking.

All patients included in the study were subjected to complete history taking and clinical examination.

2.1. Protocol for ovarian stimulation

All women had no history of induction of ovulation or hormonal therapy for the 3 months that preceded the stimulated cycle, with accepted basal hormonal profile (FSH, LH, TSH, Prolactin and serum E2 level) within 3 months of the current treatment cycle.

Ovulation stimulation was done by using low dose step-up protocol. After basal ultrasound pelvic examination, ovarian stimulation begins on the 3rd to the 5th day of the cycle [according to cycle length] for 7 days. Starting with 75 IU highly purified hMG (Merional; IBSA, Lugano, Switzerland) was administered once daily IM. After 7 days, TVS folliculometry was done, the dose of hMG was tailored according to the response. Endometrial thickness evaluated by TVS of $\geqslant$8 mm was considered adequate. Ovulation was triggered when at least one follicle reached $\geqslant$18 mm in diameter. At this stage, women were divided randomly into the following two groups by using random table (computer software Open Epi version 3.21): study group (hMG/GnRHa) and control group (hMG/hCG).

Patients were allocated to either group using the randomization mentioned while allocation concealment concentrated on preventing selection and confusing biases. In the hMG/GnRHa group [176 women] two ampoules of triptorelin, 0.2 mg SC (Decapeptyl FERRING Pharmaceutical Pvt. Ltd, Mumbai, India), while in the hMG/hCG group (176 women) hCG, 10,000 IU, IM (Choriomon, IBSA, Switzerland) were used for triggering ovulation Figure 1. Sonographic evidence of ovulation (by changes in the ultrasound measurement of follicle size or the follicle usually disappears from the ultrasound view completely) was considered necessary after 24 and 48 h of drug administration.

Intrauterine insemination was done using fresh semen obtained from the husband. All the samples were prepared by swim-up. Insemination was done 36 h after triggering of