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Original Article

Final oocyte maturation with a dual trigger compared to human chorionic gonadotropin trigger in antagonist co-treated cycles: A randomized clinical trial

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ABSTRACT

Objective: This clinical trial compared the effect of a dual trigger treatment (combination of gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (hCG) and hCG alone on oocyte quality and metaphase II oocytes' number.
Methods: It was done on infertile couples who were undergoing intracytoplasmic sperm injection with GnRH-antagonist cycles in two infertility centers of Tehran. The main outcome measures were metaphase II oocytes' number, clinical pregnancy, abortion, and implantation rates per cycle.
Results: A total of 126 normal responder women who were considered for in vitro fertilization were equally divided into two groups: control (hCG trigger) and investigation (dual trigger) groups. The control group received the hCG trigger (10,000 IU) and the investigation group received the dual trigger (0.2 mg of Triptoreline plus 5000 IU of hCG). The metaphase II oocytes' numbers, rates of clinical pregnancy, abortion and implantation were not significantly different between the two groups (P = 0.42, 0.70, 0.77, 0.80, respectively). Good quality embryos was significantly higher in the dual trigger group (P = 0.04).
Conclusion: Final oocyte maturation with dual trigger improves the number of good quality embryos in normal responder women. Further research with larger sample size is needed to characterize the effect on oocyte quality and pregnancy rate.

1. Introduction

There is an endogenous luteinizing hormone (LH) surge for final oocyte maturation in a natural cycle [1–4]. Human chorionic gonadotropin is used for triggering fertilization cycles after controlled ovarian stimulation [1,2]. Also, gonadotropin-releasing hormone agonist (GnRH-agonist) has been used in the past 25 years for triggering the final oocyte maturation [5–7].

Some studies have shown that using GnRH-agonist bolus in the GnRH-antagonist cycle can make endogenous surge of LH and follicle stimulating hormone (FSH) available and it is more physiological than gonadotropin surge [2–4,8–10]. The GnRH-agonist bolus can replace GnRH receptors instead of GnRH-antagonist and flare up both endogenous gonadotropins, similar to natural mid-cycle surge of LH and FSH [8]. In FSH mid-cycle surge, a flare-up can promote LH receptors' formation in luteinized granulose cells, cumulus expansion and nuclear maturation. FSH surge helps to begin the oocyte meitotic process [7,8].

Another advantage of GnRH-agonist trigger in in vitro fertilization (IVF) cycles with a GnRH-antagonist protocol can be decreased risk of ovarian hyper stimulation syndrome [9,11]. Comparing only GnRH-agonist trigger with standard luteal phase support and hCG trigger, researchers have found out a higher abortion rate and reduced implantation, ongoing pregnancy and live birth rates in GnRH-agonist triggering [1,9,12].

Administering GnRH-agonist alone for final oocyte maturation decreases early corpora lutea. So the most important point in GnRH-agonist triggering is luteal phase support. Some studies have presented good results after modified luteal phase support with

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GnRH-agonist triggering [7,12–15]. Several methods have been proposed but two are commonly used. One method is a combination of estrogen and progesterone (American method). The other is using a reduced dosage of human chorionic gonadotropin at oocytes' retrieval day and alternately during luteal phase (European method).

Recently, a new proposed method called "dual trigger" combines a single dosage of GnRH-agonist with a reduced dosage of hCG for triggering high responder women in IVF or intracytoplasmic sperm injection cycles [9,12,15]. In addition to preventing ovarian hyper stimulation syndrome, this new method saves luteal phase support without the need to add anything else [16].

In 2008 Schachter and colleagues compared hCG trigger (5000 IU) and dual trigger (5000 IU human chorionic gonadotro pin + 0.2 mg triptorelin). They found a higher implantation rate in their investigation group. Ongoing pregnancy rates were higher in the investigation group only in completed cycles but not in all started cycles [16].

Lin and colleagues designed another study for normal responders who were not in high risk of ovarian hyper-stimulation syndrome. It compared a standard dosage of human chorionic gonadotropin (6500 IU of recombinant hCG) versus dual trigger (0.2 mg of triptorelin and 6500 IU of recombinant hCG) in in vitro fertilization cycles in an antagonist protocol. They found significant improvement in mature oocytes, implantation rate, clinical pregnancy rate and live birth rate in their dual trigger group [9].

In light of the promising results from previous studies on dual trigger, we sought to investigate the effect of this method on final oocyte maturation by combining a low dosage of hCG and a single dosage of GnRH-agonist for normal responders. Hence, we compared dual trigger (a combination of GnRH-agonist and hCG) and hCG trigger for improving embryo quality in GnRH-antagonist cycles.

2. Materials and methods

This randomized clinical trail with a parallel design was done on all intracytoplasmic sperm injection cycles with a GnRH-antagonist protocol at two infertility centers in Tehran. The study was approved by the ethics committee of Tehran University of Medical Sciences (ethics committee registration code: IR.TUMS.REC.1394.1578) and was registered in the clinical trials database.

All participants signed an informed consent before entering the study. Thus, 126 infertile couples with normal responder women were randomly divided into two groups: (1) investigation (dual trigger) and (2) control (hCG trigger) groups (63 participants in each group). The inclusion criteria were: being 18 to 40 years old, having a body mass index between 18 and 35, 3rd day FSH < 10 and regular menstrual cycle between 25 and 35 days, being candidate for IVF for any reasons such as unexplained infertility, tubal factor and ovulation dysfunctions or mild male factor infertility. The exclusion criteria were: 3rd day FSH > 10, anti-mullerian hormone < 1.1, being high risk of ovarian hyper-stimulation syndrome (havingmore than 16 follicles in the last ultrasound before the final oocyte induction), endocrine disorders such as diabetes mellitus, hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, caushing syndrome, poly cystic ovarian syndrome, an anomaly confirmed by HSG or hysteroscopy in the uteri, sever male factor (Azospermia needed TESE or PESA), pervious history and existing signs of ovarian hyper stimulation syndrome (Fig. 1).

2.1. Ovarian stimulation protocols

Transvaginal ultrasound was done in the 3rd day of menstruation for all participants. Then ovarian stimulation began with a fixed dosage of 150–225 IU daily recombinant FSH (Gonal–F; Merk sereno SPA) for five days. On the 6th day of ovarian stimulation, FSH dosage was adjusted according to the ovarian response by monitoring transvaginal ultrasound for follicular development. When follicles became 14 mm in diameter, subcutaneous injection of Cetrorelix (Cetrotide; Merk sereno, Brazil) began 0.25 mg per day along with recombinant FSH. When at least two follicles had reached 17 mm, 0.2 mg Triptoreline (Decapeptyle; Ferring Gmbh) plus 5000 IU hCG (Choragon, Ferring) was administered to the investigation group and 10,000 IU hCG to the control group.

Oocyte was retrieved after 36 h of triggering under transvaginal ultrasound guidance. The retrieved oocytes were incubated in cultured medium. Denudation of oocytes was done by gentle pipetting after a short incubation in 80 IU/mL hyaluronidase. Then oocytes were classified according to their maturation level. Oocytes with the first polar body at the metaphase II stage were considered to have matured and were used for the intracytoplasmic sperm injection procedure [17]. Three parameters considered for embryos on the second (41–44 h after insemination) and the third days (66–71 h after insemination) were (1) fragmentation (2) blastomeres number (3) multi nucleated blastomer number [18].

The morphology score of the embryos was: 4 for regular blastomeres, no fragments, and no multinucleated blastomeres; 3 for regular blastomeres, ≤20% fragments and no multinucleated blastomeres; 2 for unequal sized blastomeres or >50% fragments; 1 for >80% fragmentation or no visible blastomeres. Top quality embryos were determined by 3 or 4 scores and contained at least four cells on the second day [19].

Best quality embryos were selected for transfer on the 3rd days of oocyte retrieval. The additional embryos were cryopreserved by vitrification. Luteal phase support by 50 mg intramuscular progesterone daily with 400 mg Cyclogest twice a day started on the day of oocyte retrieval.

2.2. Outcome

Beta human chorionic gonadotropin (β-hCG) was measured 14 days after embryo transfer for evaluating chemical pregnancy. Clinical pregnancy was confirmed by transvaginal ultrasound at two weeks later. If pregnancy was confirmed, luteal support was continued until the 12th week of gestation. Pregnancy more than 12 weeks of gestation was considered an ongoing pregnancy.

The implantation rate was calculated via dividing the total sac number in ultrasound by the total number of transferred embryos. Risk of ovarian hyper stimulation syndrome was evaluated with ultrasound and clinical examinations. At the end we recorded the number of matured, fertilized, and retrieved oocytes and top quality and cryopreserved embryos for each participant.

2.3. Randomization and blinding

The participants were randomly allocated into two groups using a balanced block randomization technique with an application entitled "sealed envelope" [20]. Eligibility assessment of the participants and their allocation was conducted by two infertility fellowships under the supervision of the main researcher responsible for the project. The researcher in charge of measuring the outcomes and the statistical analyzer were both blind to the allocation of participants to the groups.

2.4. Statistical analysis

The total estimated sample size in each group was 63 women. Continued variables were presented as mean with standard

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