Dual Trigger for final Follicular Maturation in Normal Responders Undergoing ICSI Cycles: Randomized Controlled Trial

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Abstract: Human chorionic gonadotrophin (HCG) has been successfully used for decades as a surrogate for the natural LH surge for oocyte maturation during IVF cycles. However, due to its prolonged circulatory half-life, a sustained luteotropic activity induced by HCG facilitates the development of ovarian hyperstimulation syndrome (OHSS), the most frequent and life-threatening complication of ovarian stimulation.
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1. Introduction

Human chorionic gonadotrophin (HCG) has been successfully used for decades as a surrogate for the natural LH surge for oocyte maturation during IVF cycles. However, due to its prolonged circulatory half-life, a sustained luteotropic activity induced by HCG facilitates the development of ovarian hyperstimulation syndrome (OHSS), the most frequent and life-threatening complication of ovarian stimulation **(Delvigne and Rozenberg, 2002).**

As an alternative to HCG, triggering final oocyte maturation with a single bolus of gonadotrophin-releasing hormone agonist (GnRHa) has become feasible since GnRH antagonist protocols were introduced into IVF programmes. In contrast to long-acting HCG, the shorter half-life of the endogenous LH surge elicited by GnRHa almost eliminates the risk of OHSS **(Shapiro and Andersen, 2015).**

GnRHa trigger has been demonstrated to result in the retrieval of a higher number of mature oocytes as compared with hCG; However, the use of GnRHa alone as a trigger results in a lower pregnancy rate and an extremely high early pregnancy loss rate due to a luteal phase insufficiency **(Nalini Mahajan, et al., 2016).**

Despite the potential advantages of GnRHa for trigger ovulation, earlier studies have reported compromised pregnancy outcomes after its use. This poor outcome is ascribed to a defective corpus luteum function caused by GnRHa-induced luteolysis and subsequently lower luteal P concentrations **(Humaidan, et al., 2013).**

Several strategies have been proposed to rescue the luteal phase function and improve pregnancy rates after GnRHa trigger. **Shapiro et al. (2011)** initially introduced the concept of dual trigger with a combination of GnRHa and a low-dose HCG, resulting in a high ongoing pregnancy rate of 58% without increasing the risk of OHSS.

Notably, **Griffin et al. (2014)** found that administration of adual trigger consisting of GnRHa plus a standard dose of HCG significantly improved the egg number and maturity for patients with a previous history of >25% immature oocytes retrieved after HCG trigger alone. Unlike the endogenous FSH surge induced by GnRHa trigger, directly adding FSH at the time of HCG trigger significantly increased oocyte recovery and promoted fertilization **(Lamb et al., 2011).**

Furthermore, co-administration of GnRHa and HCG for final oocyte maturation 40 and 34 h prior to oocyte retrieval, respectively, was suggested as a valuable new tool in treating patients with poor oocyte yield despite an apparently normal follicular development and oestradiol levels and in the presence of optimal HCG levels on the day of oocyte retrieval **(Haas et al., 2014).**

On the other hand, in cases of patients with suboptimal response to GnRHa triggering, receiving the dual trigger ovulation regimen could also produce an appropriate number of mature oocytes because oocyte maturation can be salvaged by the added HCG **(Meyer et al., 2015).**

Previous studies show that a dual trigger ovulation regimen significantly improves number and maturity of retrieved oocytes for normal ovarian responders or patients with history of low oocyte yield **(JieZhang, et al., 2017).**

Aim of the Work

To investigate whether dual triggering of final oocyte maturation with a combination of gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (hCG) can improve the live-birth rate for normalresponders in GnRH-antagonist in intracytoplasmic sperm injection (ICSI) cycles out comes.

2. Materials and methods

The inclusion criteria are:

Body mass index 20-35 kg/m^2, and age ≤40 year with the history of infertility for at least 1 year that are candidate for ICSI.

The exclusion criteria are

The presence of endocrine disorders such as diabetes mellitus, hyperprolactinemia, thyroid disorders, polycystic ovary syndrome, congenital adrenal hyperplasia, Cushing syndrome, congenital uterine anomalies disorders, repeated implantation failure, day-3 FSH concentration ≥10 IU/L or serum anti-Mullerian hormone ≤1.0 ng/mL or more than 3.5ng/ml, and azoospermia.

In the next step, high or poor response to COS will be excluded. The poor ovarian response is defined as serum estradiol (E2) level less than 500 pg/mL on the day of triggering or the number of retrieved oocytes less than three. The high ovarian response is defined as an E2 level higher than 3,500 pg/mL on the day of triggering or the number of follicles >20.

Those who met the inclusion criteria, will start ovarian stimulation with a flexible dosage of FSH (150-225 IU) on the second day of the menstrual cycle for 5 consecutive days. On day 6 of stimulation, co-treatment with the GnRH antagonist 0.25 mg/day, will start. Gonadotropins doses will be further adjusted according to vaginal ultrasound measurements of follicular diameter. When at least two leading follicles reach 17 mm in diameter, women will be randomly divided into two groups for final triggering according to a computer-generated randomization table: group I will be triggered by 5000 I.U. hCG alone and group II by 5000 IU hCG plus 0.2 mg of triptorelin. Women with high or poor response to COS will be excluded in this step. Oocyte retrievals will be performed under transvaginal ultrasound guidance 34-36 hr after triggering. Embryo transfers will be performed 48-72 hr after oocyte retrieval.

The luteal phase will be supported by 400 mg vaginal progesterone suppositories twice a day starting on the day of oocyte retrieval. Serum β-hCG will be measured 14 days after embryo transfer, and a value above 50 IU/mL will be considered to be a positive pregnancy. The luteal phase support will be continued until the 10th w of gestation.

The primaryoutcome

clinical pregnancy rate

The secondary outcome

Implantation rate, chemical pregnancy, ongoing pregnancy, and abortion rate.

Power of the study

It is assumed that dual triggering will improve clinical pregnancy rate from 29-44%. Accordingly, the power was set at 80% and it was found that 100 cycles are needed in each group to detect this difference.

Ethical consideration

This study protocol is approved by Obstetrics and gynecology department Benha University. A midwife not involved in the study will randomize women according to the randomization table on the day of triggering final oocyte maturation and the physicians were blinded. Oral informed consent will be obtained from each participant.

Statistical analysis

Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Illinois, USA (SPSS) will be used for all statistical calculations. Chi-squared test and the sample t-test test will be used for comparing categorical data.

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