Middle East Fertility Society Journal (2014) **19**, 287–292

Middle East Fertility Society

Middle East Fertility Society Journal

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ORIGINAL ARTICLE

Mini-dose long gonadotropin-releasing hormone (GnRH) agonist versus agonist flare stimulation protocol for *in vitro* fertilization poor responders

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Received 16 May 2013; accepted 8 October 2013
Available online 19 November 2013

KEYWORDS

Mini-dose GnRH long agonist;
GnRH agonist flare;
Poor responders;
IVF/ICSI

Abstract *Objectives:* To compare 2 stimulation protocols, mini-dose long gonadotropin releasing hormone (GnRH) agonist versus agonist flare for *in vitro* fertilization poor responders.

Design: Prospective comparative nonrandomized clinical trial.

Setting: Dr. Samir Abasss IVF center, Jeddah, Kingdom of Saudi Arabia from april 2012 to December 2012 on 50 women undergoing IVF/ICSI fulfilling the criteria of poor responders.

Material and methods: Patients were allocated into 2 groups, group 1 (n = 25) received mini-dose long agonist and group 2 (n = 25) received agonist flare protocol.

Main outcome: Number of oocytes retrieved (primary outcome), duration of stimulation (days), peak E2 level on the day of hCG injection, number of fertilized oocytes, number of transferred embryos and pregnancy rate/cycle.

Abbreviations: GnRH, gonadotropin releasing hormone; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; HCG, human chorionic gonadotropin; FSH, follicular stimulating hormone; E2, estradiol; COH, controlled ovarian hyper stimulation; AFC, antral follicle count; hMG, human menopausal gonadotropin

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Peer review under responsibility of Middle East Fertility Society.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.mefs.2013.10.001

Results: Both groups were comparable regarding age, body mass index and duration of infertility (years). The difference in basal FSH and duration of stimulation (days) does not reach statistical significance (p value 0.833 and 0.373 respectively). There was a high statistical difference between both groups regarding peak E2 on day of hCG injection, number of oocytes retrieved, number of fertilized oocytes, number of transferred embryos; which is higher in the mini-dose agonist group (p value 0.00).

Pregnancy rate/cycle was higher in the mini-dose agonist group (9/25 vs. 6/25) however this difference does not reach statistical significance (p value 0.355) which may be attributed to small sample size or advanced maternal age.

Conclusion: Mini-dose long GnRHa stimulation protocol appears to be more beneficial for poor responders than GnRHa agonist flare.

1. Introduction

Poor response is one of the frustrating problems which is faced in COH (controlled ovarian hyper stimulation); it occurs in 10–25% of all IVF cycles (1); and unfortunately associated with high cancelation rate, low pregnancy rate and in young women it is the first sign of ovarian aging and early menopause.

There is still no universal definition of poor responders and several criteria were used which is badly reflected on its management (2).

Poor response is due to poor ovarian reserve which may be due to woman's age $\geqslant$40 years, previous ovarian surgery or irradiation, chromosomal anomalies such as turner syndrome, endometriosis, benign or malignant ovarian tumors, chemotherapy, decreased number of FSH receptors available in granulosa cells, (3) the presence of a special FSH receptor-binding inhibitor in the follicular fluid, and the presence of autoantibodies against granulosa cells (4); and can be predicted from number of developing follicles and/or the number of oocytes retrieved after conventional stimulation protocol, total dose of gonadotropins used for ovarian stimulation; Eric et al. define poor response as number of mature follicles $<$2–5; number of mature oocytes retrieved $\leqslant$3; single dominant follicle; mean daily gonadotropin dose $\geqslant$300 IU; total gonadotropin dose $>$40 ampules (5). And also poor response can be predicted if patient age $\geqslant$40 years (6), previous canceled IVF cycle due to poor response (7), peak E2 level at time of trigger $<$300–500 pg/ml, day 3 FSH $>$15 μ/ml (8), poor or no response to clomiphine challenge test, anti-mullerian hormone (AMH) which correlates with antral follicles (9).

Sonographic assessment of ovarian reserve includes decreased antral follicle count, decreased ovarian volume and decreased stromal blood flow (10,11).

Treatment of poor responders to COH who are undergoing IVF remains a challenge and many protocols were proposed to improve the outcome including increasing the dose of gonadotropins; but it was found ineffective, use of recombinant purified FSH instead of HMG, luteal initiation of gonadotropins depending on the recruitment of the growing follicles starts in the luteal phase but the results were disappointing (8,12,13).

GnRH agonist flare including short, ultrashort and luteal phase agonist including long protocol, agonist stop, mini-dose agonist, antagonist were also tried (14–16).

Addition of adjuvant therapy to the stimulation protocol as growth hormone, corticosteroids, testosterone, aromatase inhibitors and DHEA (dehydro epiandro sterone) were also tried but unfortunately the improvement of the pregnancy rate is quite low and up till now no single protocol is universally perfect for poor responders (17–19).

In our study we compare 2 stimulation protocols (mini-dose long GnRH agonist vs. agonist flare) in poor responders regarding peak E2 (Estradiol) level at time of HCG injection, duration of stimulation (days), number of oocytes retrieved, fertilization rate, number of embryos transferred and pregnancy rate.

2. Material and methods

Our study was a prospective non randomized comparative study which was conducted in Dr. Samir Abasss IVF center, Jeddah, Kingdom of Saudi Arabia from April 2012 to December 2012 on 50 women fulfilling the criteria of poor response to COH and candidates for IVF. Group 1 (n = 25 women) received mini-dose long GnRH agonist and group 2 (n = 25 women) received GnRH agonist flare.

2.1. Inclusion criteria

Ovarian volume $<$3 (20), antral follicle count (AFC) $<$ 6 (21,22), day 3 FSH $>$8 IU/l (23) and history of previous canceled IVF trial due to poor response.

2.2. Exclusion criteria

Single ovary, severe endometriosis, endocrine or metabolic disorders.

Our study was approved by the ethics committee of the center and fulfilling the ethical considerations in accordance with the declaration of Helsinki for medical research involving human subjects. An informed consent was taken from all women who agreed to participate in our study.

2.3. Stimulation protocol

In both groups pretreatment was done with oral contraceptive pills (Gynera, Schering-plow: plough) in the cycle preceding stimulation. In group (1) triptorelin (decapeptyl depot 3.75 mg, Ferring, Malmo, sweden) was taken once IM on day 21 of the OCP cycle, in group (2) treptorelin (decapeptyl 0.1 mg) was administrated SC daily from 1st of withdrawal bleeding till the day of hCG administration.

In both groups gonadotropin (hMG) (Menogon, ferring pharmaceuticals, Germany) was initiated on day 3 of the cycle in a dose of 450 IU daily intramuscular injection. Once 2 or