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ORIGINAL ARTICLE

Short, semi-short or long GnRH agonist treatment regimens in women ICSI candidate; which is proper in preventing premature LH surge?

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KEYWORDS

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Abstract Objectives: Investigation of two discontinuous GnRH agonist (GnRH-a) protocols (Short and semi-short) versus traditional long protocol in preventing premature LH surge in women undergoing Intra-cytoplasmic sperm injection (ICSI). Study design: Single blind randomized trial study. Setting: Fatemezahra Infertility and Reproductive Health Research Center, Babol, Iran. Materials and methods: 139 patients who were undergone ICSI, randomly divided into three groups. In short protocol group (n = 40), GnRH-a (buserelin acetate) was initiated midluteally and ceased at the onset of the next cycle. Group of semi-short protocol (n = 41) initiated GnRH-a the same as short protocol group and discontinued at the fourth day of the next cycle. Group of long protocol (n = 38) was initiated midluteally and continued until the day of HCG injection. Ovarian stimulation was performed with gonadotropin. As primary outcome occurrence of premature LH surge was evaluated and as secondary outcome the duration and total dose of consumed gonadotropin, number of oocytes retrieval, number of formed blastocyst and pregnancy rate were investigated. Main outcome measures: No undesired LH surge occurred in the three groups, although the mean of LH at administration day of HCG was significantly higher in short protocol group ($P \leqslant 0.05$). No significant difference was observed in the number of mature oocyte, and number and quality of blastocyst, duration and total dose of consumed gonadotropin and pregnancy rate among three groups. Major conclusion: In the ICSI protocol, discontinuation of GnRH-a on the first or fourth day of ovarian stimulation does not enhance a premature LH surge.

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1. Introduction

Assisted Reproductive Technology (ART) is a latest reasonable treatment option for women with different causes of infertility following failure of other treatments. GnRH agonist (GnRH-a) evolved approaches to ovarian stimulation in poor gonadotropin responders who involve premature ovulation in

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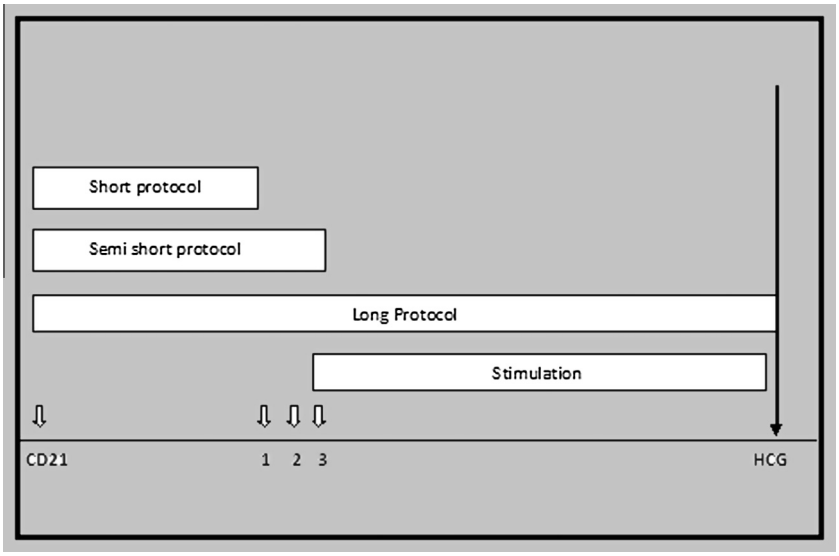

Figure 1 GnRH agonist protocols.

ART (1). Better follicular growth and oocyte maturation were seen with GnRH-a treatment (2). Although, GnRH-a secretion and LH pulses play a limited role in early stages of follicle development (3), however, it suppresses endogenous gonadotropin and prevents early LH surge during ovarian stimulation and helps exogenous gonadotropins act more effectively for late-stage growth of a dominant follicle (3,4). Early discontinuation of GnRH-a has advocates for its advantages: fewer injections for patient, lower exposure of GnRH-a, cost effectiveness and etc. In order to improve higher rate of oocyte retrieved or pregnancy outcome, several studies have raised concerns regarding finding the appropriate dose or protocol of GnRH-a which are controversial (5–13). Beckers et al. assessed luteal phase characteristics following early cessation of GnRH-a during ovarian stimulation in IVF cycle and revealed after earlier cessation of GnRH-a in the follicular phase, and an undesired rise in LH is prevented and even recovered to some extent (14); however, Cantineau reported that there is a similarity in pregnancy outcome between women with and without unwanted LH surges (15).

In none of mentioned studies on discontinuous GnRH-a regimens, vitrified-warm blastocyst has been transferred in ICSI candidates for better outcome. As the main outcome measure in this study, we evaluated short and semi-short protocol versus traditional long GnRH-a (Buserelin) regarding premature LH surge in the patients that received vitrified-warm Blastocyst. We also assessed the duration and total dose of consumed gonadotropin, number of oocytes retrieval, number of formed blastocyst and pregnancy rate.

2. Method and material

This randomized, single-blind clinical trial registration was recorded in Iran Registry of Clinical Trial (IRCT). The registration number was 201310311760N26. The study was conducted from May to December 2014 at Infertility and Reproductive Health Research Center affiliated to Babol University of Medical Sciences and was approved by the ethics committee of Babol University of Medical Science.

The women aged 18–35 years, having Body mass index (BMI) $\leqslant 32\ kg/m^{2,}$ who were candidate for intracytoplasmic sperm injection (ICSI) were included in the study. All of the processes were described for the participants and they signed informed consent. Exclusion criteria were the history of irregular menstruation, polycystic ovary syndrome, sever endometriosis, poor response to stimulation or hyperstimulation in previous cycles, and consuming any medicines for stimulation two months prior to treatment.

2.1. Randomization and processing

135 women underwent downregulation with GnRH-a (Buserelin Acetate, Cinnafact, 1 mg/ml) with daily dose 50 IU SC initiated in the middle of luteal phase (prestimulation cycle on days 21–24) by the patients. Prior to Gonadotropin administration, down-regulation was ascertained by Transvaginal sonography (TVS) with inactive ovaries, endometrial thickness up to 3 mm, and E2 $\leqslant$ 200 pmol/L.

After confirming downregulation, the patients were randomly divided into three groups by using packets which included computerized randomization.

In the short group, buserelin stopped on the day of stimulation. In semi-short group, buserelin continued up to day 4 of gonadotropin administration and long group received the routine long protocol; buserelin continued up to the administration day of HCG.

For ovarian induction, Gonal F (Gonal F, Merck Serono, Switzerland) was started on the cycle day 3 or 4 and continued until the day of HCG administration (Fig. 1). Ovarian response was monitored using serial TVS by a sonographer. The process was blinded from the sonographer and also laboratory technician in laboratory. The reproductive expert was choosing the dose of Gonal F according to patient's ovary response. When at least two follicles larger than 16 mm were observed, 10,000 IU of HCG (pregnyl,®organon, oss, the Netherlands) was intramuscularly administered. Under TVS guidance, oocytes were retrieved.