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ORIGINAL ARTICLE

Triggering ovulation with gonadotropin-releasing hormone agonist versus human chorionic gonadotropin in polycystic ovarian syndrome. A randomized trial

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KEYWORDS

Gonadotropin-releasing hormone (GnRH) agonist;
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Polycystic ovarian syndrome (PCOS)

Abstract *Objectives:* To compare GnRH agonist to hCG for triggering ovulation in polycystic ovarian syndrome treated with clomiphene citrate. *Study design:* Prospective randomized study. *Materials & methods:* Eighty five infertile women with PCOS participated in a randomized allocation concealed prospective trial and had induction of ovulation with clomiphene citrate. GnRH agonist 0.2 mg subcutaneously (group 1) or hCG 10,000 IU intramuscularly (group 2) was given to trigger ovulation. Primary outcome was mid-luteal serum progesterone, while secondary outcomes were ovulation rates and clinical pregnancy rates along 3 cycles. *Results:* No difference was found between group 1 and group 2 regarding mean serum progesterone and clinical pregnancy rates in each cycle. Cumulative pregnancy rates were similar (17.14% versus 20% respectively; $P = 0.332$). Ovulation rates were 80% versus 68.6% ($P = 0.413$); 94.3% versus 90.9% ($P = 0.669$); 97.1% versus 93.7% ($P = 0.603$) in the two groups respectively. However, a significant rise in number of patients with mid-luteal serum progesterone >10 ng/mL was noted in the 3rd cycle between both groups, ($P < 0.0001$ for group 1 while $P = 0.007$ for group 2). *Conclusion:* Triggering ovulation with GnRH-a after treatment with clomiphene citrate in PCOS, in view of its known protective effect against OHSS, may be an effective physiological alternative

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to conventional hCG without compromising luteal function and pregnancy rates after repeated cycles of treatment.

1. Introduction

Gonadotropin-releasing hormone agonist (GnRH-a) has been used to suppress gonadotropins in several conditions including endometriosis, uterine fibroids, central gonadotropin-dependent precocious puberty (1), where gonadotropin suppression does not occur immediately, but there is a transient increase ''flare'' in sex hormone levels, followed by a lasting suppression of hormone synthesis and secretion (2).

When using GnRH analogues to trigger ovulation, the mean concentration of LH as measured by radioimmunoassay may be actually raised although there is reduced pulsatile secretion and so the bioactive LH is markedly reduced (3,4), where the GnRH-a induced surge consists of two phases; a short ascending one (4 h) and a long descending one (20 h), with subsequent induction of an FSH surge comparable with the surge of the natural cycle (5).

Kol and Itskovitz-Eldor stated that when using GnRH-a to trigger ovulation in IVF cycles, the LH surge is associated with a rapid rise of progesterone and the attainment of peak E2 levels through the first 12 h after GnRH-a administration which is followed by a temporary suppression of progesterone biosynthesis and a gradual drop in E2 levels during the 24 h before follicle aspiration. After oocyte retrieval, a second rise in progesterone and continuous fall in E2 are noted, reflecting transitions from follicular to luteal phase in ovarian steroidogenesis (6).

A single dose of GnRH-a is able to trigger a pre-ovulatory LH/FSH surge, leading to oocyte maturation in women undergoing ovarian stimulation for IVF or induction of ovulation in vivo while luteolytic effect induced by GnRH analogue trigger, has a protective effect against development of ovarian hyper-stimulation (7). Results of a recent metanalysis suggested that the results of using GnRH agonist and hCG were comparable regarding the numbers of oocytes capable of being fertilized and undergoing embryonic cleavage (8). Also, incidence of empty follicle syndrome was found to be similar in a retrospective study (9). A recent international retrospective analysis of 275 IVF cycles showed a pregnancy rate of 41.8% per cycle and 0.72% risk of severe OHSS after triggering ovulation with GnRH followed by luteal support (10). On the other hand, Youssef et al. in their systematic review of 11 RCT's concluded that GnRH triggering had a negative effect on pregnancy and live birth rates in fresh autologous IVF/ICSI cycles but certainly reduced the risk of OHSS (11).

This study was designed to find out whether triggering ovulation with GnRH agonist compared to hCG in patients with PCOS in non-IVF cycles and in the absence of luteal support, would provide a difference as regards ovulation rates, mid-luteal serum progesterone levels and clinical pregnancy rates.

2. Materials and methods

This randomized, allocation-concealed, prospective study was conducted in Maternity and Children Hospital in Assiut and Assiut University Maternity hospital, Egypt, during the period from November 2010 to August 2012 after being approved by the local institutional ethics and research committee, where 137 infertile women with PCOS were initially enrolled to participate in the study (Fig. 1) where women were considered eligible if having two or all of the following: Oligo- or anovulation manifested by menstrual irregularities especially, oligomenorrhea which was defined as cycle duration between 35 days and six months (12), polycystic ovary morphology on trans-vaginal ultrasound scan done by expert radiologist, with the presence of 12 or more follicles in either or both ovaries measuring 2–9 mm in diameter, and/or increased ovarian volume >10 mL (13) and clinical or biochemical evidence of hyper-androgenism in the form of acne or hirsutism using modified Ferriman–Gallwey scoring system (14). Presence of one of the followings was considered sufficient to exclude women from enrollment to the study: male or other female factors of infertility, past history of abdomino-pelvic surgery, medical or endocrinal disorders that can affect fertility as hyper-prolactinemia, thyroid diseases or endometriosis. Forty three patients were excluded due to the presence of male factor, tubal factor, hyper-prolactinemia or hypothyroidism. Nine eligible patients declined participation in the study while eighty-five patients accepted and an informed consent was obtained then they had induction of ovulation starting from day 3 of the cycle with Clomid® 50 mg, Aventis Pharma Limited, UK, two tablets daily for 5 successive days followed by folliculometry using vaginal 4.5 MHz endocavity transducer and Sonoace® 8800 digital gaia system, starting at day 10 of the cycle till leading follicle reached 18–22 mm in diameter. Endometrial thickness was measured at the time of follicular maturation and ensured being $\geqslant 7$ mm (15). Participants were randomized into two groups using a computer-generated sequence and the randomization list was held in a secure box and the participants were assigned to their groups using sequentially-numbered opaque sealed envelopes that were opened at the start of study. Women assigned to Group 1, received single dose triptorelin (Decapeptyl® 0.1 mg/mL prefilled syringe, Ferring, Switzerland) 2 syringes (0.2 mg) subcutaneously, while women assigned to Group 2, received single dose hCG (Choriomon® 5000 IU vials, IBSA, Switzerland) 2 vials (10,000 IU) intramuscularly. The injections were given at follicular maturation and instructions were given for planned intercourse within the following 36 h which was confirmed by patients on next visit to obtain blood samples. 2 mL of blood samples was taken for serum progesterone assay 7 days after ovulation trigger and the samples were collected in dry tubes then centrifuged and serum stored at 2–8 °C until hormonal assay by enzyme immunoassay and fluorescent