Middle East Fertility Society Journal (2014) 19, 243–247

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.org
www.sciencedirect.com

ORIGINAL ARTICLE

Comparison between two clomiphene citrate protocols for induction of ovulation in clomiphene resistant polycystic ovary syndrome☆

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Received 12 May 2013; accepted 29 May 2013
Available online 7 December 2013

KEYWORDS
Polycystic ovary syndrome;
Clomiphene resistance

Abstract *Objective:* To compare two protocols of CC therapy for induction of ovulation in a group CC resistant PCOS women.

Study design: Double blind randomized controlled trial.

Subjects and methods: 260 nulliparous CC resistant PCOS women randomized between two groups; In the first group each patient received 200 mg/day for 5 days while the second group received 100 mg/day for 10 days, both starting on day 3 of progestin induced withdrawal bleeding.

Main outcome measures: Ovulation defined as at least one follicle reaching ⩾14 mm diameter, and confirmed by timed serum progesterone. Secondary outcome measures included; number of dominant follicles, endometrial thickness, clinical pregnancy rate, and live birth rate.

Results: The extended protocol resulted in significantly higher ovulation, pregnancy, and live-birth rates than the high dose protocol (p 0.001). Serum FSH levels on day 6 of treatment were comparable between the two groups while the level on day 11 was significantly higher in the second

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Peer review under responsibility of Middle East Fertility Society.

Production and hosting by Elsevier

☆ *Synopsis:* extended CC treatment is more effective than high doses in clomiphene resistant PCOS.

http://dx.doi.org/10.1016/j.mefs.2013.05.012

group (p 0.02). Serum LH levels were comparable both on days 6 and 11. Patients on longer protocol (group II) required a longer time to ovulate (18 ± 4.4 versus 14 ± 3.6 days) but had a significantly higher endometrial thickness at the time of ovulation. (p 0.02) FSH and LH levels were comparable between responders and non-responders in both groups.

Conclusions: The current study reports significantly higher ovulation and pregnancy rates with the longer lower dose protocol probably because of prolonged FSH rise. Study web address: ACTRN12611000639921.

1. Introduction

The polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility; accounting for approximately 75% of the cases (1). Clomiphene citrate (CC), the first agent introduced into general practice for ovulation induction, is still considered the first therapeutic option for this condition (2). Debated is the definition of clomiphene resistant anovulation (CRA), and several attempts have been made to achieve an agreement, avoiding long-term exposure to CC and foreseeing alternative strategies (3). However, since over 75% of ovulations occur within a dose range of 100–150 mg/day for 5 days; CRA was defined as the absence of ovulation after using this dose (4). CRA is an unpredictable and for the most part unexplainable event encountered in up to 25% of PCOS patients (3,5). Some studies showed that CRA is more likely in patients who are insulin resistant, obese and hyperandrogenic (6) and genetic predisposition has been suggested (7). Nevertheless, it is virtually impossible to predict who will respond to which dose of CC if at all (3,5,6). Most of the studies that addressed CRA focused on predictors, associations and alternative treatments rather than trying to explain the phenomenon. To know why the drug does not work in CC resistant PCOS patients, we should revise how it works in CC sensitive women i.e. those who ovulate in response to the drug. When administered to ovulatory woman CC increases GnRH pulse frequency, while in anovulatory women with PCOS in whom GnRH pulse frequency is already abnormally high (8), CC increases pulse amplitude rather than frequency (9). In either case, serum levels of both FSH and LH rise during CC treatment, and fall thereafter. It has been estimated that CC in the standard 100 mg dose for 5 days causes 50% increase in endogenous FSH (10). If this FSH rise fulfilled the requirements of the leading follicle/s they will be pushed through the final part of their growth trajectory till ovulation (11). It has been suggested that the duration of FSH rise is more important than magnitude for follicular development (12). In successful CC treatment cycles; follicular growth occurs in parallel with rising serum estrogen, ultimately triggering an LH surge and ovulation. This study was conducted to address two main questions; *first* can CC resistance be overcome by increasing the dose or duration of CC, and which is more effective? *Second*; where is the problem in CRA; is it central in the hypothalamus being less sensitive to the drug requiring a higher dose or longer duration? or peripheral in the ovarian follicles which require higher FSH levels to be recruited for growth? To address these two questions; two CC protocols were tried, endocrine response to them was monitored, and clinical response in terms of ovulation and pregnancy was assessed.

2. Patients and methods

260 Nulliparous CC resistant PCOS women among the attendants of university infertility clinics between January 2009 and January 2012 were assessed for eligibility, among them 230 cases were selected for the study. Diagnosis of PCOS relied on the previous NIH- NICCHD definition (13) (Zawadzki, and Dunaif 1992) which relies on the presence of chronic anovulation, and clinical and/or biochemical evidence of hyperandrogenism excluding other related disorders. To be eligible for inclusion in the study; patients should be diagnosed as having clomiphene resistance anovulation (CRA) documented by lack of response to CC at the standard 100 mg/day for 5 days within 3 months from inclusion in the study. Therefore the same patients served as historical control group for the current study. Institutional Review Board (IRB) approval was obtained on the study protocol from the ethics committee of Alexandria faculty of medicine and informed consent was taken from all included subjects. The study was retrospectively registered in Australia and New Zealand clinical trial registry (ANZCTR) and its web address is: ACTRN12611000639921. After progestin induced withdrawal bleeding, basal endocrine evaluation and vaginal sonographic examination were done. Cases found to have baseline ovarian cysts or uterine pathology were excluded. Patients were then randomized using computer generated tables to undergo one cycle of induction using one of two protocols of CC (clomid®; Hochest Marion Russel, Cairo, Egypt). In the first group each patient received 200 mg/day for 5 days while the second group received 100 mg/day for 10 days, both starting on day 3 of progestin induced withdrawal bleeding. Allocation was placed in sealed envelopes opened on the first day of treatment for each patient by infertility unit administrator. Placebo tablets were used to make the two regimens alike and each patient received four tablets for 10 days to allow blinding. Serum FSH and LH were assayed on day 6 and on day 11 of treatment. Patients were followed by follicle scanning in the hospital infertility unit by limited number of blinded senior sonographers according to the unit schedule starting from day 6 of treatment. The frequency of follicle scanning was tailored till dominance was confirmed or excluded. HCG was not given and progesterone was assayed one week after presumed ovulation or 2 weeks after the last observation in presumed anovulatory cases. The primary outcome measure was the occurrence of ovulation