The effectiveness of clomiphene citrate in LH surge suppression in women undergoing IUI: a randomized controlled trial

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Objective: To study the effectiveness of clomiphene citrate (CC) in preventing a premature LH surge during controlled ovarian stimulation in women undergoing assisted reproduction.
Design: Prospective, randomized, controlled trial.
Setting: University hospital.
Patient(s): Two-hundred thirty couples with mild male factor, or unexplained infertility.
Intervention(s): Couples were randomized to receive human menopausal gonadotrophins (hMG) followed by CC or hMG alone until the day of hCG.
Main Outcome Measure(s): The primary outcomes were the incidence of a clinical pregnancy and premature LH rise. Secondary outcomes were the E_2 levels, number of mature follicles, and endometrial thickness as determined on the day of hCG.
Result(s): The number of patients who had a premature LH surge was significantly lower in the hMG + CC group (5.45% vs. 15.89%). Additionally, the mean E_2 levels (pg/mL) and the number of mature follicles were also significantly higher in the hMG + CC group (360.3 ± 162.9 vs. 280 ± 110.0 and 2.4 ± 0.97 vs. 1.3 ± 1.1, respectively), although there was no significant difference regarding number of canceled cycles, endometrial thickness, or clinical pregnancy rate.
Conclusion(s): The addition of CC to hMG has been proven to be effective in reducing premature LH surges without compromising the pregnancy rate. (Fertil Steril® 2010;94:2167–71. ©2010 by American Society for Reproductive Medicine.)

Key words: COS, IUI, CC, premature LH surge

Intrauterine insemination (IUI) with partner or donor sperm is a commonly practiced method of assisted reproduction. The procedure involves directly introducing washed spermatozoa into the uterine cavity, thereby bypassing several of the natural barriers in the female genital tract (e.g., vagina, cervix) which may be the source of the infertility. In combination with controlled ovarian stimulation (COS), it has proved to be a cost-effective line of treatment for many forms of infertility (1). Its main indications are mild male factor, cervical factor, and cases of unexplained infertility (2, 3).

The technical simplicity, associated lower costs, and low incidence of complications make it a natural choice for many couples attempting to conceive (1). Additionally, because most cases of infertility are relatively mild in nature and can be overcome with the proper diagnosis and treatment, many andrologists, gynecologists, and reproductive endocrinologists alike recommend up to six cycles of IUI before embarking on more invasive procedures (e.g., IVF) (2, 4, 5). This has been confirmed by a recent Cochrane review on couples with unexplained infertility, which demonstrated that the success rates with IUI are similar to those achieved with IVF/intracytoplasmic sperm injection in this patient population (6).

Clomiphene citrate (CC) has been the most widely used treatment for fertility enhancement for the past 40 years. Clomiphene was a revolutionary advance in reproductive medicine and quickly became popular for induction of ovulation, owing to its ease of administration and minimal side effects. It acts as a selective estrogen receptor modulator, similarly to tamoxifen and raloxifene. All three drugs are competitive inhibitors of estrogen binding to estrogen receptors and have mixed agonist and antagonist activity depending on the target tissue. Most evidence suggests that the primary site of clomiphene action is the hypothalamus, where it appears to bind to hypothalamic estrogen receptors, thereby blocking the negative feedback effect of circulating endogenous estrogen and resulting in an increase in plasma levels of FSH and LH (7).

One of the major challenges facing using gonadotropin stimulation with IUI is the occurrence of a premature LH surge and consequent luteinization before ovarian follicle maturation. It has been suggested that 24%–36% of IUI cycles suffer from premature LH

Received September 19, 2009; revised January 24, 2010; accepted January 26, 2010; published online March 16, 2010.
H.A.-I. has nothing to disclose. H.A. has nothing to disclose. W.E.-K. has nothing to disclose. A.N. has nothing to disclose. E.E.-K. has nothing to disclose. A.A.-S. has nothing to disclose.
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surge. This might negatively influence treatment outcome and can result in procedure cancellation. Obviously, this represents both an economic and a psychologic burden for patients (8, 9) and an additional hurdle for clinicians to overcome.

Several strategies have been proven to be effective for preventing the occurrence of premature LH surges during ovarian stimulation. The gold standard is the use of pituitary down-regulation with a GnRH agonist, but it is associated with an explicit need for additional doses of gonadotropins and increased cost of care. Recently, GnRH antagonists have emerged as a strong competitor, with documented improvements in pregnancy rates (9, 10). Other interventions have been tried with varying degrees of success, including ethinyl E_2 plus norethindrone (11) and mifepristone (12).

Earlier work has proved that CC and oral contraceptive pill pretreatment were able to suppress LH in minimal-stimulation IVF cycles (13). Therefore, the use of CC with IUI would be a natural progression if it can be proved to prevent premature LH surges in COS/IUI cycles. The rationale is that its antiestrogenic effect may suppress premature LH rise while maintaining a positive influence on ovarian follicle development. The use of CC for this indication would open the door for very friendly stimulation protocols in COS/IUI and IVF cycles.

MATERIALS AND METHODS

This was a prospective, randomized, controlled study carried out during the period from January 2008 to July 2009 at the Department of Obstetrics and Gynecology, Kasr El-Aini Teaching Hospital, Cairo University. Institutional Review Board approval was obtained, and informed consents from participants were attained before randomization. The study protocol was registered at the Australian New Zealand Clinical Trial Registry (ACTRN12607000568415) in accordance with the Declaration of Helsinki and the recommendations of the Committee of Medical Journal Editors.

Patient Population

All patients were subjected to careful history taking, general examination, and local gynecologic examination. Inclusion criteria were mild male factor or unexplained infertility, women partner aged <39 years with regular menstrual cycles, body mass index <32 kg/m^2, normal uterine cavity and fallopian tubes as documented by ultrasound (US), hysterosalpingography, and/or laparoscopy, and normal hormonal profile including FSH, LH, TSH, T, and PRL levels. Mild male factor infertility was defined as the presence of abnormal semen parameters but with >5% normal morphology and >5 × 10^6/mL motile spermatozoa recovered after sperm preparation. Couples were excluded if they were diagnosed with infertility due to other causes, significant cardiovascular, pulmonary, renal, neurologic, or hepatic problems, or presence of ovarian cyst >2 cm before stimulation.

Two-hundred thirty infertile couples were randomized using a computer-generated random number table. Allocation concealment was performed using sequentially numbered, opaque, sealed envelopes. At the time of inclusion, the attending consultant opened an envelope describing the allocation to either the intervention or the control group. Couples assigned to the intervention group received CC + hMG, and couples assigned to the control group received hMG only.

Ovulation Induction and IUI Protocols

On day 3 of the cycle a basal US scan was done and a blood sample was taken for hormonal profile assessment. All subjects received a fixed dose of 75 IU highly purified human menopausal gonadotropin (Merional; IBSA, Lugano, Switzerland), regardless of the response starting from the third day of cycle for 5 days. Subsequently, women randomized to the CC + hMG group received 50 mg CC (Clomid; Aventis pharma S.AE, Global Napi Pharmaceuticals, Cairo, Egypt) three times daily starting from the fourth day of hMG and continued until the day of hCG injection. Women randomized to the hMG-only group maintained hMG injections until the day of hCG injection.

Ovarian stimulation was monitored every other day by vaginal US starting from day 5 of stimulation. When the leading follicle reached a mean diameter of 18 mm, 10,000 IU hCG (Choriomon; IBSA) was administered and IUI scheduled 34–36 hours later. On the day of hCG injection, patients had a serum assay of LH and E_2 as well as US measurement of endometrial thickness. IUI was canceled if fewer than two or more than five follicles with a mean diameter of 16 mm were present, to optimize the chance for pregnancy and reduce the risk of multiple pregnancy, respectively. Canceled cases were not given hCG but were instructed to have timed intercourse.

All patients received luteal phase support in the form of 100 mg micronized progesterone (Uterogestan; October Pharma, Cairo, Egypt), three tablets daily in two divided doses starting the day after insemination and continued for 18 days. Serum hCG levels were determined 14 days after insemination. Progesterone supplementation was continued for a further 2 weeks in the pregnant patients.

Outcome Measures

Clinical pregnancy was defined as a rise in the serum hCG level on serial determinations ≥2 days apart coupled with an intrauterine gestation with fetal heart pulsations demonstrated by transvaginal US at 6–7 weeks' gestation. The primary outcome measures for this trial were the incidence of a clinical pregnancy and premature LH rise. Premature LH rise was defined as LH ≥ 10 mIU/mL on the day of hCG injection. Secondary outcomes were the E_2 levels, number of mature follicles, and endometrial thickness as determined on the day of hCG.

Statistical Analysis

To prevent a type II error, we performed an a priori sample size calculation. Prior data indicated that the premature LH surge rate among the hMG-only group was 20%. If the true rate for the hMG + CC group is 5%, we would need to study 75 couples in each arm to be able to reject the null hypothesis that the rates for the experimental and control groups are equal with a probability of 80%. The type I error probability associated with this test of this null hypothesis is .05. We used an uncorrected chi-squared statistic to evaluate this null hypothesis. Additionally, to compensate for discontinuations, we recruited 115 women in each arm.

Data are expressed as mean ± SD or percentage where applicable. Independent samples were compared using the Student *t* test. The chi-squared test and Fisher exact test were used for categoric data. A *P* value of <.05 was considered to indicate statistical significance. Statistical analysis was done using Arcus Quickstat version I (Research Solutions Ltd, UK).

RESULTS

Two-hundred forty-five infertile couples were screened for inclusion, with 230 couples randomized in a 1:1 ratio to receive hMG + CC or hMG alone for ovarian stimulation. Each couple was included only once in this trial to prevent a possible unit-of-analysis error in interpreting the results.

TABLE 1

Basic characteristics of the study population.

Variable	Group I (n = 115)	Group II (n = 115)	*P* value
Age (y)	27.3 ± 4.7	28.4 ± 2.7	NS
Duration of infertility (y)	3.1 ± 1.9	2.4 ± 1.6	NS
Cause of infertility			
Unexplained infertility	61 (53%)	58 (50.4%)	NS
Mild male factor	54 (47%)	57 (49.6%)	NS
Body mass index (kg/m^2)	28.5 ± 1.6	28.1 ± 3.1	NS

Note: NS = nonsignificant.

Al-Inany. CC prevents LH surge. Fertil Steril 2010.

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