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Original Article

Antagonist protocol versus clomiphene in unexplained infertility: A randomized controlled study

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ABSTRACT

Objective: The primary purpose of this randomized controlled trial study was to compare clinical pregnancy rates and ovulation parameters in female patients of unexplained infertility undergoing intrauterine insemination (IUI) using an antagonist protocol versus a conventional clomiphene citrate protocol.
Materials and methods: This was a multicenter parallel randomized controlled, open-label trial. A central randomization center used computer generated tables to allocate treatments. We conducted the study in two centers: Saudi Center and Samir Abbas and Assisted Reproductive Techniques Center of Cairo University, Cairo, Egypt between January 2011 and January 2014. Six hundred and twenty-two couples with unexplained infertility were randomized into two equal groups with 27 excluded after randomization: the antagonist protocol group and the clomiphene group. Antagonist protocol: human menopausal gonadotropins were given to 298 patients from Day 2 to reach a dominant follicle of 18–22 mm, intramuscularly. Then, orgalutrone (0.25 mg) was subcutaneously started from Day 6 or Day 7 until the day of human chorionic gonadotropins (hCG; that was given in the dose of 10,000 IU, intramuscularly) when follicles reached 18–22 mm. Afterward, the IUI of 0.5 mL was done from 34 hours to 36 hours using IUI catheter without guidance of ultrasonography and with an empty urinary bladder. The clomiphene citrate protocol was clomiphene citrate given 100 mg/d to 297 patients from Day 2 to Day 6 and follow up until day of hCG. The clinical pregnancy rate detected with ultrasound confirmed fetal heart pulsations at 6-weeks' gestation (4 weeks after IUI). The number of dominant follicles, level of serum estradiol, and luteinizing hormone at the day of hCG injection and the incidence of twin or triplet pregnancies in both groups were secondary outcome measures.
Results: The clinical pregnancy rate in the antagonist protocol group was significantly ($p < 0.001$) higher than in the clomiphene group. It was 80 patients (27%) in the antagonist protocol group versus 41 patients (14%) in the clomiphene group. The mean number of dominant follicles was significantly ($p < 0.001$) greater in the antagonist protocol group (4.36 ± 1.36 dominant follicles) compared with the clomiphene group (2.71 ± 0.96 dominant follicles). In addition, the rate of twin pregnancies was 15 cases in the antagonist protocol group versus six cases only in the clomiphene group ($p = 0.047$). The luteinizing hormone also was significantly lower in the antagonist group (2.1 ± 1.3) compared with that in the clomiphene group (9.5 ± 3.6).
Conclusion: IUI clinical pregnancy rates were significantly higher by antagonist protocol.

Introduction

Results of intrauterine insemination (IUI) done in natural menstrual cycles are subtle [1,2]. That is why most clinics use IUI in controlled ovarian hyperstimulation cycles. In addition, there is inadequate evidence to recommend or advise against IUI, either

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with or without ovarian hyperstimulation, above the conventional timed intercourse or the reverse [3].

However, the need for IUI is still high because the prevalence of unexplained infertility is up to 20% for couples after the initial diagnostic workup. This number may increase if cases of mild male infertility added to it [4].

Superovulation with usual doses of gonadotropins induces pregnancy in 10–15% of couples, as stated by large clinical trials [1,5,6]. The drawbacks of this method were an increase in the incidences of twin pregnancy (15–20%) and triplets (5–10%), thus rendering IUI as an unsafe technique in stimulated cycles [5–11]. It is a simple, noninvasive, and nonexpensive method in assisted reproductive techniques but with a low pregnancy rate.

Many studies have proved the value of gonadotropin-releasing hormone antagonist as an effective method to prevent premature luteinization. However, most of these studies failed to find a significant improvement in clinical pregnancy rates in ovarian induction IUI cycles [12].

Hence, the rationale intended for this randomized controlled study was to test the hypothesis that the antagonist protocol can lead to a higher rate of pregnancy in patients with unexplained infertility undergoing IUI, than the standard or the most common protocol using clomiphene citrate without premature rise of luteinizing hormone (LH).

Materials and methods

The study was conducted in the Saudi centers Samir Abbass and Assisted Reproductive Techniques Center of Cairo University, Cairo, Egypt during the period from January 2011 to January 2014.

Ethics

This study followed the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act, and was approved by the Medical Ethical Review Committee of Cairo University and Samir Abbas Ethical Committees.

The purpose of this study was clearly explained in Arabic language to all participants before their enrolment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited to this study couples with unexplained infertility that were eligible to undergo IUI. Criteria of unexplained infertility was as follows: (1) women with a body mass index 18–30 kg/m^2 with unexplained infertility; with (2) confirmed bilateral patent fallopian tubes (hysterosalpingography or laparoscopy); in addition to (3) normal ovulation evidenced by midluteal serum progesterone > 10 ng/mL and regular menstrual cycles; and finally (4) husband semen analysis with mean sperms count > 15 million sperm/m:, motility > 32%, and morphology > 4% normal form [13].

Female patients with bilateral tubal block, uterine distorted anatomy (submucous fibroids or Asherman syndrome), and hydrosalpinx were not included. In addition, female patients with hyperprolactinemia or thyroid dysfunction were excluded.

All eligible patients were randomized into the two study groups using the matched pairs randomized block design based on age and period of infertility. The two study groups were the antagonist protocol group and the clomiphene citrate protocol group.

Procedures

All enrolled patients were subjected to a full history taking, general and local examination. Hormonal profile and pelvic ultrasound were done for female patients and semen analysis after 4–7 days of abstinence was done for male patients.

Women assigned to the clomiphene group were given clomiphene citrate (Clomid, Sanofi-Aventis, Bourgoin-Jallieu, France) 100 mg from Day 2 to Day 6. Then, the monitoring of ovulation was continued until the dominant follicle (DF) was 18–22 mm. Hence, LH and estradiol were measured, and human chorionic gonadotropin (hCG; Choriomon; IBSA, Lugano, Switzerland) was given at a dose of 10,000 IU, intramuscularly. Afterwards, IUI of 0.5 mL was done from 34 hours to 36 hours, using an IUI catheter without guidance of ultrasonography and with an empty urinary bladder.

However, women assigned to the antagonist protocol group were given human menopausal gonadotropins (Merional; IBSA) from Day 2 to reach a DF of 18–22 mm. The LH was then measured and ganirelix acetate (Orgalutrone; Merck Sharp & Dohme, Quebec, Canada) 0.25 mg subcutaneously was started from Day 6 or Day 7 until the day of hCG that was given in the dose of 10,000 IU intramuscularly when follicles reached 18–22 mm. Afterwards, the IUI of 0.5 mL was done from 34 hours to 36 hours using an IUI catheter without guidance of ultrasonography and with an empty urinary bladder. The aims of these modifications were to avoid premature LH surge and to ensure a high oocyte count available at the time of insemination. Both groups had the same luteal phase support by cyclogest 400 mg vaginal suppository for 2 weeks.

The primary end point was clinical pregnancy rate, as detected by the presence of an intrauterine sac with positive heart pulsations at 6-weeks' gestation done at 4 weeks after IUI in each group. The secondary end points were the number of DFs, levels of LH, and serum estradiol at the day of hCG injection and the incidence of twin or triplet pregnancy in both groups.

Statistical analysis

All statistical tests were done using a significance level of 95%. A value for $p < 0.05$ was considered statistically significant. SPSS software (version 20.0, SSPS Inc., Chicago, IL, USA) was used for the statistical analyses. Data were presented as mean ± standard deviation for continuous variables and as frequency and percent for categorical variables. Comparisons between the two groups were done using Pearson Chi-square test for categorical variable and the unpaired Student t test for continuous variables.

A sample size calculation was done to calculate the number of patients needed in each group, with an alpha level < 0.05 and power > 90%. The sample size used was sufficient to achieve a power more than 90%.

Results

All patients (655) who came to the centers were asked to participate in the study. Twenty-three patients refused to participate, and 10 patients were excluded before randomization for different causes; thus, leaving a population of 622 eligible patients who were randomized in this trial. Twenty-seven patients were excluded after randomization. The dispositions of these patients are shown in Figure 1.

Baseline characteristics

Six hundred and twenty-two couples suffering from infertility were enrolled in this study, after being randomly assigned to two groups, 311 in each. Only 595 patients were included in the analysis. There was no statistically significant difference ($p > 0.05$) between both groups regarding the age, duration, and type of