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Research Article

Cetrolix Protocol versus Conventional Clomiphene Citrate Protocol in Women with Unexplained Infertility Undergoing Intrauterine Insemination: A Randomised Prospective Study

Abstract

Objective: The primary goal of this study was to compare the ovulation and pregnancy rates in women with unexplained infertility undergoing intrauterine insemination utilizing an antagonist (cetrolix) protocol versus the commonly used clomiphene citrate regimen.

Patients and Methods: This was a randomized controlled study performed at Assisted Reproductive Techniques Center of Ain Shams University Maternity Hospital, over a 2-year period, between Jan 2014 and Jan 2016, and included 80 women,with unexplained infertility undergoing intrauterine insemination (IUI), were randomised into two groups. Group I (n=40) received the antagonist protocol: human menopausal gonadotropins were given from Day 2 to reach a dominant follicle of 18-22 mm, intramuscularly. Then, cetrolix (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. Group II (n=40) receivd the clomiphene citrate protocol: clomiphene citrate given 100 mg/d from Day 2 to Day 6 and then human menopausal gonadotropin (hMG) to reach a dominant follicle of 18-22 mm, intramuscularly. Follow up until day of hCG, 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 primary outcome was clinical pregnancy rate defined as the presence of intrauterine gestational sac detected by ultrasound at 5-weeks' gestation . 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: In this study

Conclusions: It seems that clinical pregnancy rates were significantly higher by cetrolix protocol

Introduction

Infertility is the inability to conceive after one year or more of regular coitus with no contraception. Epidemiological researches have reported that about 80% of couples had conceived during that period. It is postulated that nearly 15% of couples are infertile in developed nations [1]. There has not been reported a substantial rise in demand for the treatment of infertility in the last decade [2]. Implantation, of the embryo, depends on the embryo quality and the endometrial receptivity. It is estimated that failure of implantation accounts for approximately 50% to 75% of lost pregnancies [3].

Intrauterine insemination (IUI) is a common therapy and during 2001-2004 in Europe, the conception rate in IUI cycles had ranged between 11.4% and 12.6% [4] and the rate of multiple births between 11.2% and 13.1%. As shown by the ESHRE Capri Workshop Group on IUI [4], inspite of the utilization of induction of ovulation programs and the manipulation of semen samples, the conception rates in IUI cycles are not significantly higher than the results produced after ordinary or timed coitus. Actually, IUI had not been considered as an assisted reproductive technique (ART) inspite of its common use [5]. The ESHRE Capri Workshop Group reported the role of individual topics in the efficacy of IUI therapy. One of the topics was the insemination time which was done 32-36 hours after HCG injection [4]. However, it looks that among healthy women, the best time to become pregnant is if coitus occurred up to six days before ovulation [6].

Superovulation with usual doses of gonadotropins induces pregnancy in 10-15% of couples, as stated by large clinical trials [7-9]. 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 [10]. It is a simple, noninvasive, and non-expensive 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 [11-13].

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).

Patients and Methods

This study was carried out in a private IVF centre in conjunction with Assisted Reproductive Techniques Center of Ain Shams University Maternity Hospital after the approval of the Research Ethics Committee, during the period between Jan 2014 to Jan 2016and included 80 women 80 women, with unexplained infertility undergoing intrauterine insemination (IUI), were randomised into two groups. Group I (n=40) received the antagonist protocol: human menopausal gonadotropins were given from Day 2 to reach a dominant follicle of 18-22 mm, intramuscularly. Then, cetrolix (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. Group II (n=40) received the clomiphene citrate protocol: clomiphene citrate given 100 mg/d from Day 2 to Day 6 and then human menopausal gonadotropin (hMG) to reach a dominant follicle of 18-22 mm, intramuscularly. Follow up until day of hCG.

Inclusion criteria

1. Primary or secondary infertility ≥ one year
2. Participant age: 18 - 37
3. Diagnosis of unexplained infertility ≤ 36 months
    a. Anti-Müllerian hormone ≥ 0.4 ng/mL and/or folliclestimulating hormone ≤13 IU/L in early follicular phase
    b. Regular cycle of 25–35 days, positive ovulation tests, and/or midluteal progesterone ≥25 mmol/L in an unstimulated cycle
    c. Normal semen analysis according to WHO 2010 criteria
    d. No uterine cavity abnormalities
    e. Normal Fallopian tubes
4. Negative genitourinary test for chlamydia and gonorrhea ≤ one year

Exclusioncriteria

1. Body mass index (BMI) ≥35 kg/m2
2. Ongoing conception

All included women were subjected to revising history and examination sheets with particular emphasis on personal history: age, residence, education level and socioeconomic status, Complaint regarding infertility, obstetric history including parity and gravidity and ultrasound for any uterine or tubal abnormality, the number of ovarian follicles and the diameter of the dominant follicle. The endometrium was measured at the greatest anterioposterior dimension under a longitudinal section.

A simple computer-generated randomisation was done by an independent statistician in a ratio of 1:1 and transferred into sealed opaque envelopes.

Group I assigned to the antagonist protocol group, women were given human menopausal gonadotropins ((Pergonal, Serono, Rome, Italy)) from Day 2 to reach a DF of 18e22 mm. The LH was then measured and cetrolix 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.

Group II received clomiphene citrate (CC) and human menopausal gonadotropin (hMG) (Pergonal, Serono, Rome, Italy). An oral dose of CC (200 mg/ day) was given on cycle day 2 through cycle day 6 and three doses of hMG (150 IU/day) were administered on cycle day 7, 9, and 11. Follicular survey was done on cycle day 8, 11, and 13.

The semen was prepared with Enhance (Percoll) method using three different density (95%, 70%, 50% Percoll) gradient centrifugation. All patients received IUI 34–36 hr after hCG injection. Progesterone was given since day 3 post-IUI. All Clinical pregnancy was detected as a positive urine pregnancy test 2 weeks post-IUI and confirmed by transvaginal ultrasonography of intrauterine gestational sac. If a pregnancy occurred, women were advised to continue the aspirin 81 mg through 6 weeks after IUI.

The outcome of interest is the difference in the rate of biochemical and clinical pregnancies, resulting from one cycle of treatment, between the two intervention groups. Adverse effects were reported. 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 methods

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and XLSTAT™ version 2014.5.03 (Addinsoft™, NY, USA).Normally distributed numerical variables were presented as mean (SD) and intergroup differences were compared using the unpaired *t* test. Skewed numerical variables and discrete variables were presented as median (interquartile range) and between-group comparisons were done using the Mann-Whitney test. Categorical variables were presented as number (%) and inter-group differences were compared using the chi-squared test with Yates' continuity correction or Fisher's exact test, when appropriate. Ordinal data were compared using the chi-squared test for trend. A two-sided p-value <0.05 was considered statistically significant.

Results

This current study was conducted in Ain Shams University Maternity Hospital during the period between Jan 2014 to Jan 2016 a total of 80 women with history of unexplained infertility were included in the study.

Baseline characteristics, 80 couples suffering from infertility were enrolled in this study, after being randomly assigned to two groups, 40 in each. There was no statistically significant difference ($p > 0.05$) between both groups regarding the age, duration, and type of infertility, and the male partner quality of semen (concentration

and motility), as shown in Table 1. Also, there was a no statistically significant difference ($p > 0.05$) between both groups regarding the mean progressive motility percent before processing, as shown in Table 1. Semen quality before and after preparation. There was no statistically significant difference in semen quality in terms of concentration ($p > 0.05$), progressive motility ($p > 0.05$), and morphology between the two study groups either before or after preparation, as shown in Table 1. Before preparation, the mean semen concentration in the antagonist protocol group was 42.5 ± 12.9 million and in the clomiphene group was 41.4 ± 11.6 million ($P > 0.05$). After preparation, the mean semen concentration was 21.7 ± 6.8 million in the antagonist protocol group and 22.3 ± 5.9 million in the clomiphene group ($P > 0.05$). Additionally, the progressive motility before preparation in the antagonist protocol group 42.9± 9.2% and the clomiphene group was 43.8 ± 6.4% ($P > 0.05$). After preparation, the progressive motility in the antagonist protocol group 32.6 ± 8.9 % and the clomiphene group was 33.4 ± 7.3 % ($P > 0.05$), as shown in Table 1. As regards the morphology (% of normal forms), in group I, it was 32.6 ± 8.9 and group II, it was 33.4 ± 7.3 with no significant difference between the two groups ($P > 0.005$). Primary outcome of the study The number and rate of clinical pregnancy as determined by the presence of fetal heart pulsations at 6-weeks' gestation was 12 patients (30%) in the antagonist protocol group and 8 patients (20%) in the clomiphene group, ($p < 0.05$); as shown in Table 2. Secondary outcomes of the study, the mean number of DFs was greater in the antagonist protocol group (5.7±1.6DF) compared with that of the clomiphene group (2.8±1.3DF). Statistically, this difference is significant with $p < 0.005$. In addition, there was a highly significant difference detected between both groups regarding estrogen level at hCG day, as shown in Table 1. LH also was significantly lower in antagonist group (5.4 ± 2.1) compared with that in the clomiphene group (11.6 ± 1.8; $p < 0.05$).

Moreover, there was no significant difference detected between both groups in the rate of twin pregnancies, where the number of twin pregnancies in the antagonist protocol group were 4 compared with 3 cases only in the clomiphene group ($p < 0.05$), as shown in Table 2. Moreover, both groups showed no triplet pregnancies. Mild ovarian hyper stimulation syndrome (OHSS) occurred in 2 (5%) of the antagonist protocol group versus 3 (7.5 %) of the clomiphene group ($p > 0.05$). No severe OHSS occurred in both groups.

*Analysis using independent student's t-test. NS = non-significant, S = significant.

Table 1

	Group I (40)	Group II (40)	P- value
Age	30.4 ± 2.3	32.1 ± 3.5	> 0.05
Menarche age	11.1 ± 3.2	11.5 ± 3.8	> 0.05
Body mass index (kg/m2)	28.3 ± 3.8	27.6 ± 3.6	> 0.05
Previous gravidity	1 ± 0.8	1 ± 0.6	> 0.05
Type of infertility 1ry 2ry	 18 22	 19 21	> 0.05
Duration of infertility	7.8 ± 3.1	7.6 ±2.8	> 0.05
Education ≤High school >High school	 13 27	 12 28	> 0.05
Occupation House wife Employed/business Woman	 29 11	 27 13	> 0.05
Number of developing follicles at insemination	5.7±1.6	2.8±1.3	< 0.05
Mean diameter of dominant follicles at insemination	24.2 ± 1.5	19.2± 2.6	< 0.05
Mean endometrial thickness	10.2 ± 1.9	7.3 ± 1.7	< 0.05
Semen concentration before preparation (in millions)	42.5 ± 12.9	41.4 ± 11.6	> 0.05
Progressive motility before preparation	42.9± 9.2	43.8 ± 6.4	> 0.05
Morphology (% of normal forms)	56.7 ± 12.3	55.8 ± 10.8	> 0.05
Semen concentration after preparation (in millions)	21.7 ± 6.8	22.3 ± 5.9	> 0.05
Progressive motility after preparation (%)	32.6 ± 8.9	33.4 ± 7.3	> 0.05
Estradiol level at hCG d	923.4 ± 65.1	744.1 ± 34.6	< 0.05
LH at d of hCG	5.4 ± 2.1	11.6 ± 1.8	< 0.05

Table 2

Pregnancy rates	Group I No. (%)	Group II No. (%)	P
Biochemical pregnancy	12 (30)	8 (20)	< 0.05(sig)
Clinical pregnancy	10 (25)	6 (15)	< 0.05(sig)
Twins	4 (10)	3 (7.5)	> 0.05
Mild ovarian hyperstimulation	2 (5)	3 (7.5)	> 0.05
Severe ovarian hyperstimulation	0	0	--

Discussion

The current study showed that there is a significant increase in the rate of clinical pregnancies in the antagonist protocol arm versus the clomiphene citrate arm. Secondary outcomes showed a very significant increase both in the level of serum estradiol at the day of hCG and the number of DFs, favoring the arm of antagonist protocol. There is also a marked significant reduction in LH level before hCG in the antagonist group. Moreover, the twin pregnancy rate was similar in the two groups. This was evident as there were 10 patients (25%) of the antagonist protocol and only 6 patients (15%) of the clomiphene group who proved to be pregnant. In addition, the mean serum LH was significantly lower in the antagonist group (5.4 ± 2.1) compared with the clomiphene group (11.6 ± 1.8). Moreover, the mean serum estradiol on the day of hCG was 923.4 ± 65.1pg/dL in the antagonist protocol group compared with 744.1 ± 34.6pg/dL in the clomiphene group. Moreover, the mean number of DFs was 5.7±1.6in the antagonist protocol group versus 2.8±1.3in the clomiphene citrate group.

The results of this study are in favor of the antagonist protocol. Moreover, the rationale behind the hypothesis that the antagonist protocol would increase the rate of clinical pregnancy by increasing the number of follicles and serum estradiol at the day of hCG was well met in our study. In addition, reduced LH in the antagonist group supports that gonadotropin-releasing hormone antagonist has a strong effect

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on pituitary suppression and prevention of premature luteinization. We believe this study was very judgmental as the randomization was well controlled, and baseline characteristics of both groups regarding age, duration and type of infertility, and semen analysis characteristics were all insignificantly variable between both groups. We followed the usual time of IUI after hCG, as there is no consensus about the best time suggested, although it has been mentioned to be anywhere between 12 hours and 60 hours [14]. Although luteal phase support benefit in cycles using antagonist protocol is a matter of unproven research [15-18], we chose to implement luteal support, as it might increase the pregnancy rate [19,20]. Other studies showed that routine luteal-phase support by vaginal suppositories did not improve pregnancy results in clomiphene citrate induced cycles in IUI trials [21], but an evidence-based review recommended to apply luteal-phase support in stimulated IUI cycles only when proven cost-effective [22]. Finally, because the pregnancy outcome of gonadotropin stimulation is significantly higher, it seems more reasonable to compare the protocols with and without antagonists in future studies.

Conclusions

In conclusion, this study was in favor of the routine use of the antagonist protocol in patients with unexplained infertility undergoing IUI procedure. This area of research still needs more investigations to examine other factors that may play a role in the results of IUI.

References

1. teVelde ER, Eijkemans R, Habbema HD (2000) Variation in couple fecundity and time to pregnancy, an essential concept in human reproduction. Lancet 355: 1928–1929.
2. KablyAmbe A, López Ortiz CS, Serviere Zaragoza C, Velázquez Cornejo G, Pérez Peña E, et al. (2012) Consenso nacional Mexicano de reproducción Asistida. GinecolObstetMex 80: 581–624.
3. Norwitz ER, Schust DJ, Fisher SJ (2001) Implantation and the survival of early pregnancy. N Engl J Med 345: 1400–1408.
4. ESHRE Capri Workshop Group (2009) Intrauterine insemination. Hum Reprod Update 15: 265-277.
5. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, et al. (2009) International Committee for Monitoring Assisted Reproductive Technology, World Health Organization: International committee for monitoring assisted reproductive technology (ICMART) and the world health organization(WHO) revised glossary of ART terminology, 2009. Fertil Steril 92: 1520-1524.
6. Wilcox AJ, Weinberg CR, Baird DD (1995) Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 333: 1517-1521.
7. Bonduelle ML, Dodd R, Liebaers I, Van Steirteghem A, Williamson R, et al. (1988) Chorionic gonadotrophin-beta mRNA, a trophoblast marker, is expressed in human 8-cell embryos derived from tripronucleate zygotes. Hum Reprod 3: 909–914.
8. Lopata A, Hay DL (1989) The potential of early human embryos to form blastocysts, hatch from their zona and secrete HCG in culture. Hum Reprod 4: 87–94.
9. Reinisch N, Sitte BA, Kähler CM, Wiedermann CJ (1994) Human chorionic gonadotrophin: a chemoattractant for human blood monocytes, neutrophils and lymphocytes. J Endocrinol 142:167–170.
10. Bourdiec A, Bédard D, Rao CV, Akoum A (2013) Human chorionic gonadotropin regulates endothelial cell responsiveness to interleukin 1 and amplifies the cytokine-mediated effect on cell proliferation, migration and the release of angiogenic factors. Am J Reprod Immunol 70: 127-138.
11. Bourdiec A, Shao R, Rao CV, Akoum A (2012) Human chorionic gonadotropin triggers angiogenesis via the modulation of endometrial stromal cell responsiveness to interleukin 1: a new possible mechanism underlying embryo implantation. Biol Reprod 87: 66.
12. Berndt S, Blacher S, Munaut C, Detilleux J, Perrier D'Hauterive S, et al. (2013) Hyperglycosylated human chorionic gonadotropin stimulates angiogenesis through TGF-β receptor activation. FASEB J 27: 1309–1321.
13. Palomino WA, Argandoña F, Azúa R, Kohen P, Devoto L (2013) Complement C3and decay-accelerating factor expression levels are modulated byhuman chorionic gonadotropin in endometrial compartments during the implantation window. Reprod Sci 20: 1103-1110.
14. Ragni G, Maggioni P, Guermandi E, Testa A, Baroni E, et al. (1999) Efficacy of double intrauterine insemination in controlled ovarian hyper stimulationcycles. Fertil Steril 72: 619-622.
15. Albano C, Smitz J, Tournaye H, Riethmuller-Winzen H, Van Steirteghem A, et al. (1999) Luteal phase and clinical outcome after human menopausal gonadotrophin/gonadotrophin releasing hormone antagonist treatment for ovarian stimulation in in-vitro fertilization/intracytoplasmic sperm injection cycles. Hum Reprod 14: 1426-1430.
16. De Jong D, Macklon NS, Fauser BC (2000) A pilot study involving mini-mal ovarian stimulation for in vitro fertilization: extending the "follicle- stimulating hormone window" combined with the gonadotropin-releasing hormone antagonist cetrorelix. Fertil Steril 73: 1051-1054.
17. Ragni G, Vegetti W, Baroni E, Colombo M, Arnoldi M, et al. (2001) Comparison of luteal phase profile in gonadotrophin stimulated cycles with or without a gonadotrophin-releasing hormone antagonist. Hum Reprod 16: 2258-2262.
18. Kolibianakis EM, Bourgain C, Platteau P, Albano C, Van Steirteghem AC, et al. (2003) Abnormal endometrial development occurs during the luteal phase of nonsupplemented donor cycles treated with recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. Fertil Steril 80: 464-466.
19. Pritts EA, Atwood AK (2002) Luteal phase support in infertility treatment: a metaanalysis of the randomized trials. Hum Reprod 17: 2287-2299.
20. Tarlatzis BC, Fauser BC, Kolibianakis EM, Diedrich K, Devroey P (2006) GnRH antagonistsin ovarian stimulation for IVF. Hum Reprod Update 12: 333-340.
21. Kyrou D, Fatemi HM, Tournaye H, Devroey P (2010) Luteal phase support in normo-ovulatory women stimulated with clomiphene citrate for intrauterine insemination: need or habit? Hum Reprod 25: 2501-2506.
22. Cohlen BJ (2009) Should luteal phase support be introduced in ovarian stimulation/IUI programs? An evidence-based review. Reprod Biomed Online 19: 4239.

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