

The effect of clomiphene citrate as the first-line treatment of infertile women with polycystic ovarian syndrome (PCOS) in fetal sex: a clinical trial

Infertile with polycystic ovarian

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Abstract

Aim: The purpose of this study was to determine the effect of clomiphene citrate on fetal sex in PCOS patients who underwent ovulation treatment with clomiphene citrate in comparison with the general population. Material and Method: This study was based on prospective randomized clinical trial comparing the effect of clomiphene as the first-line management of ovulation induction of the PCOS patients and a control group including pregnant ladies without any underlying gynecological disease during January 2013 to December 2015 and was performed in a private infertility clinic (Dr. Rasekh sub special infertility office). The study included 878 patients divided into two groups including 65 patients treating with clomiphene citrate and a control group of 813 pregnant ladies who referred to our office for obstetrics follow-up during this period. Results: Among all the 65 successful pregnancies by infertile women using clomiphene, two pregnancies were as triplets and 16 were twins, and all 85 babies were born alive. Among the 85 babies, 58.82 % were female, and 41.17% were male. After reviewing the drug dosage used by patients, we understood that the majority of mothers with daughters (63%) had used high doses of clomiphene citrate (150-200mg /day) and had repeated cycles of treatment while the initial dosage in this trial was 50-100 mg/day. Discussion: This research shows that the women with anovulatory problems who used clomiphene citrate in a higher therapeutic dosage are more likely to have female babies while using clomiphene citrate in low dosage will not affect the sex of the fetus.

Keywords

Clomiphene Citrate; Infertility; PCOS; Fetal Sex

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Introduction

Infertility is a disease of the reproductive system defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Ovulatory disorders are common causes of subfertility and infertility due to anovulation or oligo-ovulation caused by Polycystic Ovary Syndrome (PCOS) [2]. PCOS is characterized by ovulatory dysfunction and hyperandrogenism, and it is the most common cause of infertility in women [3]. The diagnosis of PCOS has life-long implications with increased risk of infertility, metabolic syndrome, type 2 diabetes mellitus, and possibly cardiovascular disease [4]. It should be considered in any adolescent girl with hirsutism, persistent acne, menstrual irregularity, or obesity [5]. Approximately two-thirds of patients with PCOS, whether adolescent or adult, have anovulation symptoms [6]. Clomiphene is the most common used pharmacologic agent, and it is considered as the first line treatment for PCOS patients because it's of low cost, relative ease of use and minimal side effects [7]. Clomifene is a mixture of two geometric isomers, enclomifene (E-clomifene) and zuclomifene (Z-clomifene). These two isomers have been found to contribute to the mixed estrogenic and anti-estrogenic properties of clomiphene [8].

Clomifene (INN) or clomiphene (USAN) is a selective androgen receptor modulator (SERM) that increases production of gonadotropins by inhibiting negative feedback on the hypothalamus leading to up-regulation of the hypothalamic–pituitary–gonadal axis [9]. The most common adverse drug reaction associated with the use of clomiphene (>10% of patients) is reversible ovarian enlargement [10].

Less common effects (1-10% of patients) include visual symptoms (blurred vision, double vision, floaters, eye sensitivity to light), headaches, vasomotor flushes (or hot flashes), abnormal uterine bleeding and/or abdominal discomfort [11].

Rare adverse events (<1% of patients) include high blood level of triglycerides, liver inflammation, reversible baldness and/or ovarian hyperstimulation syndrome [12].

Clomifene can lead to multiple ovulation, hence increasing the chance of twins (10% of births instead of ~1% in the general population) and triplets [13].

Some studies have warned that if clomiphene citrate is used for more than a year, it may increase the risk of ovarian cancer [14]. This may only be the case in those who have never been and did not become pregnant. The incidence of fetal and neonatal abnormalities in patients using clomiphene for fertility is similar to that seen in the general population. There is no data to indicate a higher rate of congenital anomalies or spontaneous abortions after using this drug [15].

The purpose of this study was to determine the effect of clomiphene citrate in anovulatory infertile patients with anovulation problems caused by PCOS under ovulation treatment with clomiphene citrate therapy on fetus sex verification in comparison with the general population.

Material and Method

This study is a prospective randomized clinical trial comparing the sexual effect of clomiphene citrate as the first-line management of ovulation induction of the infertile patients and a control group including pregnant ladies without any underlying gynecological disease. This study was performed in a private infertility clinic during 2012 to 2015 and included 878 patients divided into two groups.

The major criteria for the diagnosis of PCOS were oligo- and/or an-ovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries which are in accord with the revised 2003 Rotterdam criteria of PCOS [16], (figure 1). Thyroid function, prolactin level, and husband's sperm analysis were checked for normal values.

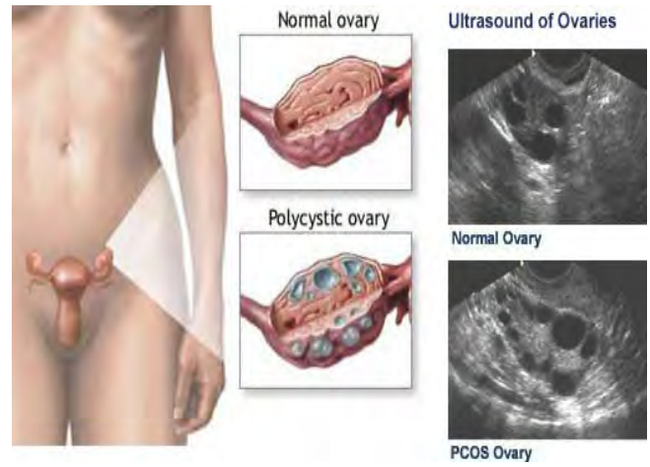


Figure 1. Normal ovary and polycystic ovary

Infertile woman as the definition with diagnoses of PCOS who referred to our sub special infertility clinic and got medication including clomiphene which led to successful pregnancy were included in this study.

Patients with other causes of infertility, infertility which lasts less than one year, and those who got previous treatment(s) for infertility were not included in the study.

The protocol was approved by the ethical investigation committee of our institution, and informed consent was obtained from all the patients after a full informative session. All patients were visited and followed by a single physician.

Based on our statistical data, the fair needed number for performing this study was not equal in each group; All candidates were randomized based on envelope method into either clomiphene citrate group (Group A, n =65) and control group (Group B, n=813).

However, at a dosage of 200 mg, further increments are unlikely to increase pregnancy chances. The patients in the clomiphene group (Group A) received 50-100 mg clomiphene citrate for five days starting from the third day of their menstrual cycle. The standard dosage for first-time takers is 50 or 100 mg of clomiphene per day for five consecutive days, starting early start in the menstrual cycle, usually on the third to fifth day counting from the beginning of the menstrual period. In the absence of success, the dosage can be increased in 4 subsequent cycles with increments of 50 mg (200mg).

To confirm pregnancy β-HCG was measured, and pregnancy was confirmed and followed till nine months to find possible abortion or ectopic pregnancy and finally fetal sex. All data were collected by one physician and by using questionnaire. The data were analyzed by SPSS ver. 22, using Chi-square, Mann-Whitney, and t tests. P values less than 0.05 were considered to be significant.

Results

Among all the 65 successful pregnancies due to using clomiphene citrate by infertile women, 2 pregnancies were as triplets and 16 were twins, and all 85 babies were born alive. Among the 85 babies, 58.82 % were female, and 41.17% were male. After reviewing the drug dosage used by patients, we understood that the majority of mothers with daughters (63%) had used high doses of clomiphene citrate(150-200mg /day) and had repeated cycles of treatment, while the initial dosage in this trial was 50-100 mg/day.

Sex of 813 babies in Group B was as bellow order: [Table 1]

Table 1. Fetal sex in case and control group

Group	MALE	FEMALE	Total
A	50 (58/82%)	35 (41/17%)	85 (100%)
B	417 (51/29%)	396 (48/71%)	813 (100%)

Conclusion

According to the results and in comparison with general population, clomiphene citrate doesn't affect fetal sex in standard dosages (50-100mg/day), but in high doses, it may lead to female sex.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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