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ORIGINAL STUDY

The effect of using letrozole alone protocol versus using letrozole and human chorionic gonadotropin protocol on induction of ovulation in polycystic ovarian syndrome patients: A prospective cohort study

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Abstract

Background: This study seeks to question the customary utilization of human chorionic gonadotropin (HCG) in straightforward letrozole induction methods, proposing its restricted requirement in particular instances, perhaps diminishing expenses, and anxiety for infertile couples.

Patient and methods: This prospective cohort study was done at the assisted reproductive unit in Ahmed Maher teaching hospital in Cairo. The study includes 132 infertile women aged 18–35 with polycystic ovary syndrome, free from other medical disorders and not taking conflicting medications.

Prerequisites involve normal hysterosalpingography and semen analysis. Participants were evenly divided into two groups: the first receiving letrozole exclusively for ovulation induction, and the second receiving letrozole with HCG when suspected ovulation maturity occurred.

Following a 2-week period, both groups underwent a pregnancy test, and individuals with positive results received a transvaginal ultrasound one week later for clinical pregnancy confirmation.

Results: The results of the pregnancy tests were the same in both groups, with 15 (22.7 %) women testing positive. The *P* value was 1. Regarding clinical pregnancy, the group that received only Letrozole had 14 (21.2 %) pregnancies, which was somewhat higher than the group that received Letrozole and HCG, which had 13 (19.7 %) pregnancies. However, this difference was not statistically significant (*P* value = 0.829).

Conclusion: The study indicates that the letrozole-only regimen is slightly more effective than the letrozole + HCG strategy for fertility treatment in women with PCOS, particularly in terms of achieving clinical pregnancy. The results additionally suggest that HCG should only be used in situations where intrauterine insemination is necessary or for persons who have been diagnosed with luteinized unruptured follicle syndrome.

Keywords: Induction of ovulation, Infertility, Letrozole, Polycystic ovary

1. Introduction

Letrozole, a third-generation nonsteroidal aromatase inhibitor, blocks estrogen synthesis, increasing gonadotropins and pregnancy rates [1].

Its benefits include increased endometrial stimulation, reduced multiple pregnancy, fewer side effects, and prompt clearance from blood. The first pilot study used letrozole for polycystic ovary syndrome (PCOS) induction in 2000 [2,3].

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A randomized study found letrozole superior to clomiphene for treating anovulatory infertility in PCOS women. It also increased live birth and ovulation rates, with a pregnancy rate of 20–27 %/cycle [4,5]. In another study which compares the effect of Letrozole alone with Letrozole Plus N-Acetylcysteine on pregnancy rate in patients with PCOS, the pregnancy rate was 7.5 % in the letrozole alone group [6].

Human chorionic gonadotropin (HCG) hormone replaces luteinizing hormone at mid-cycle, leading to oocyte maturation and ovulation [7]. It stimulates the corpus luteum to produce progesterone, maintaining pregnancy, and is essential for infertility treatment protocols, enhancing endometrial quality [8,9].

PCOS requires two Rotterdam criteria: chronic anovulation, hyperandrogenism, and ultrasound polycystic ovaries [10]. PCOS incidence ranges from 6 % to 21 % when ESHRE/ASRM 2003 criteria are applied [11]. Infertility (clinical definition) is currently defined as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles [12].

The study aims to demonstrate the unnecessary use of HCG as a trigger in simple letrozole induction protocol in PCOS infertile couples, assuming that letrozole-alone protocol will not increase clinical pregnancy rate. This study is the first to compare letrozole alone and letrozole/HCG protocols in PCOS patients seeking fertility.

2. Patients and methods

Study design: This study employed a prospective cohort design and was conducted in the assisted reproductive unit at Ahmed Maher Teaching Hospital in Cairo. The study commenced in November 2022 and concluded in November 2023.

The inclusion criteria for this study are as follows: women with PCOS who are unable to conceive, aged between 18 and 35 years, without any other medical conditions, and not taking any medications that could affect the results (such as other infertility meds or insulin sensitizers). Additionally, it is required that the participants have normal hysterosalpingography results and semen analysis within the parameters set by the WHO.

Exclusion criteria: Women who are unable to conceive due to reasons other than PCOS, aged younger than 18 years and more than 35 years, with additional medical conditions, taking medications that may interfere with fertility such as other infertility drugs, insulin sensitizers, or hormones, and having abnormal hysterosalpingography or sub-normal semen analysis.

Estimation of sample size: Previous studies have shown that the rate of clinical pregnancy after letrozole induction for one cycle is approximately 18 %. We expect that using HCG as a trigger may reduce the rate of clinical pregnancy to 13 %. Therefore, we will consider an effect size of 0.009. To validate this impact, we determined that a total of 120 women with PCOS should be separated into two equal groups. This estimation was based on a significance level (alpha) of 5 % and a statistical power of 80 %. We choose to enroll a total of 132 women, factoring in a 10 % attrition rate.

The participants were separated into two groups of equal size. The first group consisted of participants who were receiving letrozole only to induce ovulation, whereas the second group included subjects who were also getting letrozole for ovulation induction together with HCG when ovulation maturity was suspected.

A team of investigators in the assisted reproductive unit was present at the hospital to explain the study to women with PCOS who were seeking infertility treatment. Subsequently, the investigator requested the participants who met the specified criteria to provide their consent and complete the data record form. The form encompassed personal details such as name, age, employment, residence, and telephone number, as well as information regarding BMI, medical history, and surgical history.

During the field of work, we visited the assisted reproductive clinic 2 days/week during the whole length of this study. 1 day for the letrozole monotherapy protocol and the other day for the letrozole plus HCG protocol. For each day we chose the patients using a simple random sampling technique using random tables for the patients who attended our clinic and they were candidates for ovulation induction by unit doctors then randomly picked a subset of patients. We followed the local guidelines of our unit for induction of ovulation in infertile couples which was established by our unit professors.

The Letrozole monotherapy protocol for ovulation induction commences on either the 3rd or 4th day of the menstrual cycle and lasts for 5 days, with a daily dosage of 5 mg. The process of ovulation was monitored by transvaginal ultrasonography from day 11 until the dominant follicle reached maturity, which is typically between 16 and 22 mm in size.

Subsequently, the pair was directed to engage in regular sexual intercourse three times/week for a duration of 1 week.

The participants in the second group adhered to the same regimen as the first group, with the addition of HCG (5000 IU) when follicular maturity was

determined by transvaginal ultrasonography. Subsequently, the pair received guidance to engage in sexual intercourse after a period of 24 h.

After a duration of 2 weeks, a pregnancy test was conducted for both groups. Individuals who tested positive for pregnancy were further checked 1 week later using transvaginal ultrasonography to verify the presence of a clinical pregnancy. Ultimately, we computed the ratio of clinical pregnancy for each group.

The null hypothesis posits that there is no discernible disparity in the proportion of clinical pregnancy between the two groups. This idea has been examined through the utilization of the chi square test.

The statistical analysis involved coding and inputting the data into the Social Sciences statistical software (SPSS) version 28, developed by IBM Corp. in Armonk, NY, USA. The data was summarized by calculating the mean and standard deviation for quantitative variables, and by determining the frequencies (number of cases) and relative frequencies (percentages) for categorical

variables. Group comparisons were conducted using an unpaired *t*-test ($n = 12$). A χ^2 test was conducted to compare categorical data. The exact test was employed instead when the anticipated frequency was below 5 [13,14]. *P* values below 0.05 were deemed statistically significant.

3. Results

3.1. Demographics of the patients

A cohort of 132 individuals diagnosed with PCOS were divided into two comparable groups. The first group included of people who were only experiencing letrozole for ovulation induction, whereas the second group included subjects who were getting both letrozole for ovulation induction and HCG when suspected ovulation maturity occurred. [Tables 1 and 2](#), along with [Figs. 1 and 2](#), illustrate the distribution of patient characteristics, including age, BMI, employment, and the type of infertility, among the different groups.

The results of the study indicate that the percentage of positive BHCG in both groups is 22.7 %, with 15 women in each group. This finding is supported by the data presented in [Table 3](#) and [Fig. 3](#). The statistical analysis did not reveal any significant difference between the two groups, as indicated by the *P* value.

The Letrozole-only group had a total of 14 (21.2 %) clinical pregnancies, as indicated in [Table 3](#) and [Fig. 3](#). In comparison, the Letrozole + HCG group had 13 pregnancies (19.7 %), with a *P* value of 0.829, which was not statistically significant.

4. Discussion

Our research indicates that the letrozole-only regimen is somewhat more effective than the letrozole plus HCG protocol for women with PCOS when it comes to achieving clinical pregnancy. While the letrozole-only group shows a slight advantage in success rates, it's important to emphasize that the

Table 1. The distribution of patient characteristics, including age, BMI.

	Letrozole		Letrozole + HCG		P value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age	26.45	5.25	26.74	4.94	0.746
BMI	28.23	3.36	28.51	3.67	0.652

Table 2. The distribution of patient characteristics, including employment, and the type of infertility, among the different groups.

	Letrozole		Letrozole + HCG		P value
	Count	%	Count	%	
Employment					
Yes	34	51.50	38	57.60	0.484
No	32	48.50	28	42.40	
Infertility					
1ry infertility	47	71.20	48	72.70	0.846
2ry infertility	19	28.80	18	27.30	

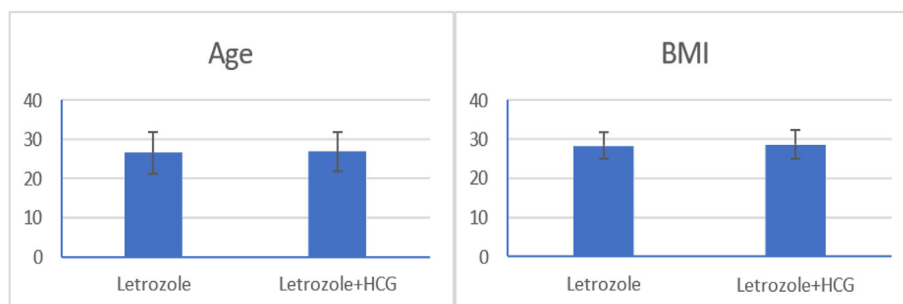


Fig. 1. The distribution of patient characteristics, including age, BMI.

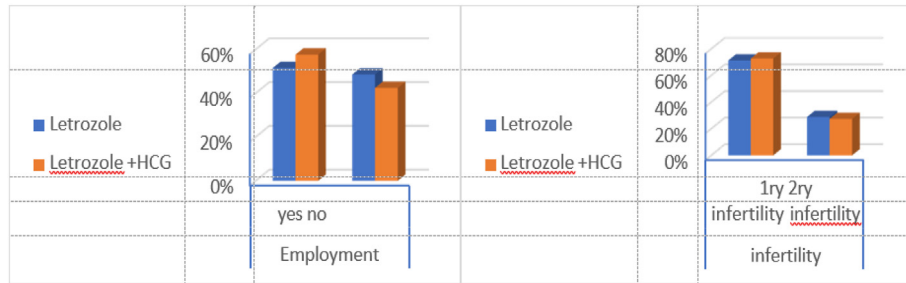


Fig. 2. The distribution of patient characteristics, including employment, and the type of infertility, among the different groups.

Table 3. The percentage of positive BHCG and clinical pregnancies in both groups.

	Letrozole		Letrozole + HCG		P value
	Count	%	Count	%	
BHCG					
Positive	15	22.70	15	22.70	1
Negative	51	77.30	51	77.30	
Clinical pregnancy					
Yes	14	21.20	13	19.70	0.829
No	52	78.80	53	80.30	

difference is not statistically significant. This suggests that both treatments yield comparable results in terms of positive pregnancy tests.

Additionally, our data strongly support the null hypothesis, which asserts that there's no significant difference in the rates of clinical pregnancy between the two approaches. This is a crucial insight for healthcare providers and patients as it affirms the effectiveness of the letrozole-only strategy without the added complexity of HCG treatment.

We propose that HCG should be reserved for specific situations, such as when intrauterine insemination is required or for patients who have been diagnosed with luteinized unruptured follicle syndrome. In these cases, HCG can help facilitate

ovulation, thereby increasing the chances of conception. By limiting the use of HCG, we can help reduce the financial burden often faced by couples undergoing fertility treatments. This is particularly important given the emotional and financial stress that infertility can impose.

By streamlining treatment options, we not only alleviate some of this stress but also promote a more relaxed atmosphere for couples trying to conceive. Reducing the pressure associated with timed intercourse can contribute to a more supportive and less anxious experience. Overall, our findings encourage a more thoughtful application of HCG, focusing on maximizing treatment effectiveness while also prioritizing the emotional well-being of patients.

4.1. Conclusion

The study indicates that the letrozole-only regimen is slightly more effective than the letrozole + HCG strategy for fertility treatment in women with PCOS, particularly in terms of achieving clinical pregnancy. The results additionally suggest that HCG should only be used in situations where intrauterine insemination is necessary or for persons who have been diagnosed with luteinized unruptured follicle syndrome.

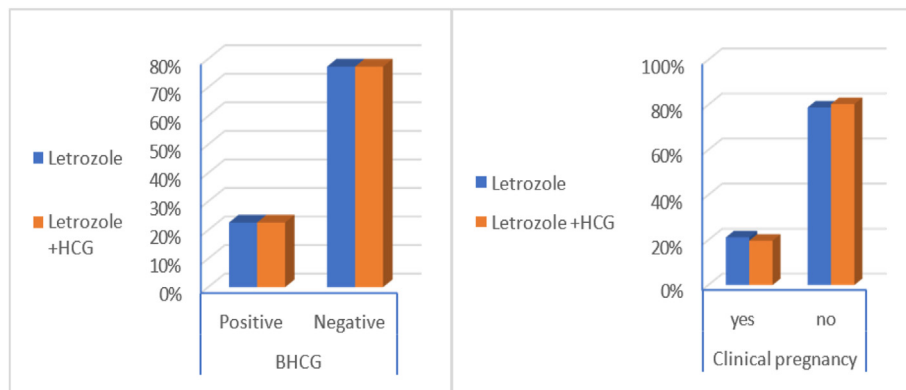


Fig. 3. The percentage of positive BHCG and clinical pregnancies in both groups.

4.2. Limitations

It was expected as being a cohort study to be expensive and time consuming to conduct.

Ethics approval and consent to participate

The study proposal has been reviewed and approved by the General organization for teaching hospitals and institutes research ethics committee no. HAM00170 on 9/11/2022 to be conducted. The informed consent was obtained from infertile couples after a full declaration of study to them.

Consent for publication

Consent for publication was obtained from all participants before to their recruitment in the study, and subsequently, following a comprehensive explanation of the study's objectives and methodologies.

Authors' contributions

A.A.K., A.M.S.; conceptualization, methodology, software. A.A.K, M.I.E; data curation, writing-original draft preparation, and supervision. S.A., A.A.K; visualization, investigation. H.M.; software, validation. A.K., A.A.K.; writing-reviewing and editing. All authors read and approved the final manuscript.

Availability of data and materials

The data that support the findings of this study are available from [Data.mendeley.com](https://data.mendeley.com) site, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are, however, available from the authors upon reasonable request and with permission of Mendeley data site from: <https://data.mendeley.com/drafts/f9z2vk3brp>.

Conflict of interest

There are no conflicts of interest.

Institutional Review Board (IRB) Approval Number

HAM00170.

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