Original Article

The Effect of Normalization of FSH/LH Ratio on the Response to Induction of Ovulation and Pregnancy Rate in Polycystic Ovary Syndrome Patients

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ABSTRACT

Objectives: To determine the role of normalization of FSH/LH ratio on the response to induction of ovulation and pregnancy rate in patients with polycystic ovarian disease.

Materials and Methods: This is a randomized controlled trial including 126 infertile women with PCOS attending to infertility clinic, Kasr Al-Ainy Maternity Hospital, Faculty of Medicine, Cairo University, from December 2021 until May 2022. Patients were divided into 2 equal groups:

- Group A (63 women): received OCPs for 3 successive cycles and after withdrawal bleeding of last cycle received clomiphene citrate 100 mg tablet orally started on 2nd day to 6th day of the cycle for five consecutive days for another 3 cycles.
- Group B (63 women): didn't receive pre-treatment OCPs.

Results: The rate of normalization of FSH/LH ratio after COC pills was higher in group A 51/63 (81.0%). Ovulation rate, endometrial thickness at the day of HCG injection and clinical pregnancy rate after induction of ovulation were statistically significant higher in group A compared with group B. Also, total doses of gonadotropin used and percent of cases needed gonadotropin using for induction of ovulation were statistically significant lower in group A compared with group B.

Conclusion: In infertile PCOS patients, normalization of FSH/LH ratio in by using of a short pretreatment course of COCs could be used as it was proved to enhance ovulation rate, endometrial thickness at the day of HCG injection and clinical pregnancy rate. Also, it decreases need for using and total doses of gonadotropin and its side effects.

Key Words: Combined oral contraception, ovulation induction, PCOS, pregnancy.

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INTRODUCTION

One of the most prevalent endocrine conditions affecting women who are fertile is polycystic ovarian syndrome, or PCOS. 5–10% of females who are of reproductive age are affected. In addition to disfiguring the lady with hirsutism and trunk obesity, it may also have an impact on her infertility through oligo/amenorrhea.[1]

The cause of almost 75% of anovulatory infertility cases is polycystic ovary syndrome. Although the exact mechanism of anovulation in PCOS is still unknown, research suggests that the aberrant endocrine environment is reflected in the halted antral follicle growth characteristic of anovulatory PCOS women. Premature maturation of a fraction of follicles in the polycystic ovary has been observed.[2]

These follicles' granulosa cells, which normally have a diameter of 3-5 mm as opposed to the regular dominant follicle's 10 mm, appear to develop responsiveness to LH at a much earlier stage than in the normal cycle. A premature resumption of meiosis and the subsequent release of a "premature oocyte" were proposed as the results of elevated LH levels during the follicular phase of the menstrual period. The vicious loop of aberrant steriodogenesis, folliculogenesis, aberrant oocyte maturation, decreased endometrial receptivity, and early pregnancy loss, however, seems to be partially attributed to the interaction of many variables.[3]

The anti-estrogen clomiphene citrate (CC), which has a cumulative singleton live-birth rate of 72%, is still the first-line medication indicated for inducing ovulation. Tragically, Potential issues from (CC) could arise: First off, women with PCOS may be more susceptible to ovarian hyperstimulation syndrome due to their overabundance of follicles. Second, the rate of mature oocytes following oocyte retrieval is lower than anticipated due to the non-uniform proliferation of excessive follicles.

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Third, irregular menstrual cycles are a common feature of PCOS-affected women. Because of these factors, researchers have recommended pretreatment with combination oral contraceptives (COCs) in order to balance the FSH/LH ratio before inducing ovulation, followed by regulated ovarian stimulation.[4]

The FSH/LH ratio is typically 1:1, indicating that blood levels of both FSH and LH are comparable. Women with PCOs frequently have FSH levels between 4 and 8, whereas their LH levels are typically between 10 and 20. When the ratio is inverted, it can increase to two or three.[5]

In addition to being useful for cycle scheduling, pretreatment with COCs can help control follicular growth and minimize follicle development.[6]

Nonetheless, studies on the impact of COCs on PCOS patient outcomes have shown contradictory findings. While some writers found no substantial benefit effects, others reported considerably higher clinical pregnancy rates and reduced OHSS rates.[7]

The aim of this study is to determine the role of normalization of FSH/LH ratio on the response to induction of ovulation and pregnancy rate in patients with polycystic ovarian disease.

PATIENTS AND METHODS

This is a randomized controlled trial including infertile women with PCOS attending to infertility clinic, Kasr Al-Ainy Maternity Hospital, Faculty of Medicine, Cairo University, From December 2021 until May 2022.

- Inclusion criteria:

Infertile patient with polycystic ovaries (PCOS), aging between 18-35 years, diagnosed according to Rotterdam criteria which includes at least two of the following: Oligo - or anovulation, hyperandrogenism (Clinical and/or biochemical) & ultrasound picture of Polycystic ovaries, were enrolled in the study. Patients with FSH/LH ratio ≥ 1:2 and body mass index (BMI) ranging from 18 to 30 kg/m^2, were also included .

- Exclusion criteria:

Patients with FSH >10, AMH<1, known endocrine or medical disorders (e.g: diabetes, hypothyroidism.. etc.) and other factors of infertility (Tubal or male-factors or Uterine factor) were excluded.

Sample size:

The study group's ovulation rate/cycle was higher than the control group's (38.4% vs. 15.2%; *P=0.001*), according to data from a previous study[8]. Based on these findings, we calculated the minimum proper sample size of 57 participants in each group. Assuming a drop-out ratio of 10%, the sample size will be 126 women total of both groups. The sample size was calculated using MedCalc® Statistical Software version 19.5.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020), with the type-1 error (α) set at 0.05 and the power (1-β) at 0.80.

Randomization allocation:

The patients were allocated into two groups using a computer-generated randomization sheet created with Stats Direct version 3 to guarantee that every participant had an equal opportunity to participate.

- Group A (63 women): was administered oral clomiphene citrate 100 mg tablets for three consecutive cycles after the last cycle's withdrawal bleeding. The tablets were taken five days a week from day two to day six of the menstrual cycle.

- Group B (63 women): was not given OCPs and instead was given an oral clomiphene citrate 100 mg tablet for five days straight, spanning three cycles, from day two to day six of the menstrual cycle.

Ethical considerations:

Patients who were willing to participate signed informed written consent forms after being fully told about the nature and goals of the current investigation. Individuals were free to leave the research at any time without fear of losing their access to proper medical treatment. The Cairo University Faculty of Medicine's Obstetrics and Gynecology Department's Ethical Research Committee accepted the study procedure. The substitution of codes for participant-identifying information (e.g., using numbers instead of names to identify participants) preserved data confidentiality.

Study interventions and procedures:

According to enrollment criteria; selected candidates were subjected to:

a) Complete history taking including personal history, menstrual history, obstetric history, contraceptive history, medical, Surgical and Family history.

b) General, abdominal and local examination with special emphasis on vital signs, BMI, signs of chronic medical disorders, abdominal masses, scars, cervical or vaginal pathologies.

c) Investigations: Routine work-up of infertility were requested in all couples as: Semen analysis, hysterosalpingiogram (HSG), Hormonal profile (baseline

F.S.H, L.H, E2, prolactin, T.S.H and A.M.H) on the 3rd day of a spontaneous or progesterone induced menstrual bleeding before starting the study.

d) Transvaginal ultrasound examination "folliculometry": for measuring total number and size of dominant follicles following ovulation induction.

- Patients were then classified into two groups:

Group A (study group): received 3 successive cycles of COCs before induction.

Group B (control group): No COCs pre-treatment before intervention.

The control group did not receive COC pretreatment, while the research group (the COCs group) received pretreatment with COCs for three months. 20 mg of ethinyl estradiol (E2) and 75 mg of gestodene (Femogesal tablets), made by TECHNOPHARMA Egypt, were used as the COCs pretreatment. Each tablet was taken once a day for 21 days, beginning on the second day of the menstrual cycle. The FSH/LH ratio was then tested for normalization in the experimental group by repeating the hormonal measurements (FSH and LH).

- Next, from the second to the sixth day of the menstrual cycle, each patient received 100 mg of clomiphene citrate.

- On the eleventh day of the cycle, patients were notified for vaginal ultrasonography-based follicular monitoring. Once an ovarian response was not observed (at least one follicle with a mean diameter of 10 mm), gonadotropin injections were initiated at a daily dose of 75 IU, given intraperitoneally, and then followed up every two days until ultrasound inspection revealed active follicular development.

- Once a dominant follicle appeared, the FSH dosage was kept constant until the follicle reached a 17 mm diameter. 24 hours following the last gonadotropin injection, human chorionic gonadotropin (hCG) (5,000 IU, IM) was administered when no more than three leading follicles measuring 17 mm were seen.

- After 35 days of treatment, the absence of follicular development or the absence of prominent follicles of 14 mm in diameter were seen as signs that the cycle should be stopped (canceled cycles).

- Following an HCG injection, patients were instructed to schedule a timed sexual encounter within 34–36 hours.

Study outcomes:

Primary outcomes: most important measurable outcomes to evaluate are the rate of normalization of FSH/LH ratio after 3 successive cycles of COCs and the subsequent effect on successful induction of ovulation (1-3 dominant follicles measure >17mm & Rates of clinical pregnancy). Pregnancy was defined as an evidence of intrauterine gestation on ultrasound.

Secondary outcomes: To evaluate impact of normalization of FSH/LH ratio on incidence of cycle cancellation, duration and dose of gonadotropin, endometrial thickness at the day of human chorionic gonadotropin injection & the incidence of OHSS.

Statistical analysis:

The IBM SPSS 22 (Statistical Package for the Social Science; IBM Corp., Armonk, NY, USA) computer program for Microsoft Windows was used to do all statistical computations. Number and percentage formats were used for categorical data, and the chi-square and Fischer exact tests were used to compare intergroup differences. For trend analysis, ordinal data were compared using the chi-squared test. Data was examined using the Kolmogorov-Smirnov test to see if they were regularly distributed. Continuous numerical variables were reported as mean and standard deviation; when the data were parametrically normally distributed, the differences between two groups were compared using the unpaired t-test; otherwise, when the data were skewed or non-parametric, the differences between two groups were compared using the Mann-Whitney test. When less than, P values were statistically significant when less than 0.05.

RESULTS

This randomized controlled trial was conducted on 126 women to study the effect of normalized FSH/LH ratio in PCOS patients via the use of a short pre-treatment course of COCs on the success of ovulation induction and pregnancy rate.

Candidate Women were divided into two groups; group A "induction by CC and/ or HMG with COCs pretreatment" and group B" induction by CC and/or HMG without COCs pretreatment". Results of the study were summarized in the following tables.

Table (1) shows that women in (group A) were statistically significant older compared with (group B) 27.40 ± 5.60 vs. 25.21 ± 5.58 years ($p= 0.030$). On the other hand, there were no significant differences between both groups regarding BMI and type of infertility 24.51 ± 4.06 vs. 22.86 ± 4.19 kg/m^2 ($p= 0.26$) & 31 (49.2%) vs. 32 (50.8%) ($p= 0.859$), respectively.

Table (2) shows that ovulation rate after induction was statistically significant higher in (group A) compared with (group B) 3.63 ± 2.20 vs. 1.65 ± 1.06 ($p <0.001$).

Table 1: general patient characteristics

	Group A	Group B	*P value*
Age	27.40 ± 5.60	25.21 ± 5.58	*0.030**
BMI	24.51± 4.06	22.86 ±4.19	*0.26*
Type of infertility			
Primary	31(49.2%)	32(50.8%)	*0.859*
Secondary	32(50.8%)	31(49.2%)	
FSH/LH ratio before starting the study	0.52 ± 0.14	0.47± 0.12	*0.043**

Table 2: outcome of treatment

	Group A	Group B	*P value*
Ovulation rate after induction "Dominant follicle measure >17mm"	3.63 ± 2.20	1.65 ± 1.06	*< 0.001**
Total doses of Gonadotropin used (IU)	225.00 ± 58.09	567.07± 412.86	*< 0.001**
Endometrial thickness at the day of HCG injection	10.83 ± 3.36	9.92 ± 0.95	*0.045**
Cases needs gonadotropin use for induction	11 (17.5%)	41(68.3%)	*< 0.001**
Incidence of OHSS	0(0%)	2(3.2%)	*0.496*

DISCUSSION

This randomized controlled clinical trial was conducted at outpatient clinic - department of obstetrics and gynecology - Faculty of Medicine - Cairo University from December 2021 until May 2022, to study the effect of normalized FSH/LH ratio in PCOS patients via the use of a short pretreatment course of COCs on the success of ovulation induction and pregnancy rate.

A total of 126 infertile women with polycystic ovaries were enrolled and divided into 2 groups; group A received continuous oral contraceptive pills (OCPs) for 90 days (3 cycles) and after withdrawal bleeding, they received clomiphene citrate 100 mg tablet orally started from day 2 to day 6 of menstrual cycle for five consecutive days for another 3 cycles. Group B didn't receive OCPs and received clomiphene citrate 100 mg tablet orally started from day 2 to day 6 of menstrual cycle for five consecutive days for 3 cycles.

Our study reported that pre-treatment FSH/LH ratio was statistically significant higher in (group A) compared with (group B). The rate of normalization of FSH/LH ratio after COC pills in (group A) was 51/63 (81.0%). Ovulation rate, endometrial thickness at the day of HCG injection and clinical pregnancy rate after induction of ovulation were statistically significant higher in group A compared with group B. Also, total doses of gonadotropin used and percent of cases needed gonadotropin using for induction of ovulation were statistically significant lower in group A compared with group B. Finally, there were no significant differences between study groups regarding incidence of OHSS and percent of cycle cancellation.

Abuazza and associates concurred with our research, stating that great rates of ovulation and pregnancy are achieved when OPCs pills are taken prior to therapy. Thirty-two subfertile women participated in a randomized clinical trial and were found to be unresponsive to clomiphene citrate.[8]

Sangam and Mitra agreed with us, stating that OCP suppression was necessary to obtain the outstanding ovulation and pregnancy rate. This treatment approach offers impoverished and ovulatory women a less expensive option to GnRH therapy. Thirty of the 100 participants in this trial fulfilled the requirements for clomiphen citrate refractory anovulation. The treatment with OCP resulted in notable alterations in the hormonal profile 17. There was a 63% fall in LH levels, a 56% drop in androgen, and a 58% drop in beta estradiol levels. The FSH level dropped as well, though not as much. Out of 30 patients, 23 (76.6%) experienced ovulation, leading to a high ovulatory cycle of 55/75 (73.2%) and a cumulative pregnancy rate of 60% (18/30).[9]

Contrary to our findings, Wei *et al*. claimed that women with OC-induced menstrual periods had a reduced likelihood of clinical pregnancy and live birth with fresh embryo transfer than those with spontaneous menses. Those with OC-induced cycles had a similar pregnancy rate with freeze-all and postponed FET, but a higher abortion rate following FET than those with spontaneous menses. Following FET, the live birthrate was 49.4%, 50.7%, and 60.2%, respectively, in women experiencing OC-induced menses, progestin-induced menses, and spontaneous menses (*P = 0.06*). Progestin-induced menses were linked to comparable rates of live birth, pregnancy loss, and clinical pregnancy. The purpose of this multicenter randomized trial, was to compare the live birth rate following fresh embryo transfer (FET) against frozen embryo transfer (FET) in PCOS patients (Frefro-PCOS). A total of 1508 women were recruited; patients were either provided progestins (P group, n = 283) or OCs (OCs group, n = 902) to bring about menstruation prior

to the initiation of ovarian stimulation, or they were told to wait for spontaneous menses (Control group, n = 323). These three groups were compared in terms of the rates of pregnancy, miscarriage , and live birth following either fresh or frozen embryo transfer.[10]

Lastly, Farquhar *et al*. conducted searches through MEDLINE, EMBASE, PsycINFO. The Cochrane Central Register of Controlled Trials, and the Cochrane Menstrual Disorders and infertility Group Specialized Register. The aim of this study was to determine whether pre-treatment with combination OCPs, progestogens, or estrogens in ovarian stimulation protocols influences results in infertile couples having ART. Additional electronic materials on the Internet, reference lists of pertinent studies, and ESHRE abstracts were searched. Using a pre-treatment did not appear to have any impact on the total number of live births. On the other hand, compared to no pre-treatment, coupled OCP in GnRH antagonist cycles is linked to a larger dose of gonadotrophin therapy, longer durations, and fewer clinical pregnancies. Finally, more oocytes are retrieved in estrogen-pretreated GnRH antagonist cycles than in cycles without pre-treatment; however, a greater dosage of gonadotrophin therapy is required. Either no influence was detected for the other outcomes, or there weren't enough studies in the subgroup to allow for pooling.[11]

Strength points of the study is the relatively large sample size and the novelty of the idea. The results of this study may be used to halt the liberal use of ovarian drilling in PCOS patients with high LH level with its detrimental sequalae on ovarian reserve and formation of pelvic adhesions. However, this study has limitations. The significant statistical difference in terms of age & pre-treatment FSH/LH ratio reflecting the slight lack of similarity in patients base-line characteristics.

CONCLUSION

In infertile PCOS patients, normalization of FSH/LH ratio in by using of a short pretreatment course of COCs could be used as it was proved to enhance ovulation rate, endometrial thickness at the day of HCG injection and clinical pregnancy rate. Also, it decreases need for using and total doses of gonadotropin and its side effects. More studies with larger sample size are required for conformation of our results and conclusions.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. EISSA, M. E. Polycystic ovarian syndrome (PCOS) this mysterious disease. MOJ Women Health, 2021, 4.2: 40-43.
2. Umer, S. Q. & Sadeq, T. W. Management Infertility by Hormones Replacement Therapy in Women with Polycystic Ovarian Syndrome. Polytechnic Journal, 2020, 10.1: 170-174.
3. Deliwala KJ, Patel ZJ., Shah PT., *et al*. Study of hundred cases of infertility in polycystic ovarian syndrome and its management outcome. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 2020, 9.8: 3377-3381
4. Pan JX, Liu Y, Ke ZH, Zhou CL, *et al*. Successive and cyclic oral contraceptive pill pretreatment improves IVF/ICSI outcomes of PCOS patients and ameliorates hyperandrogenism and antral follicle excess. Gynecol Endocrinol. 2019, (4):332-6. .
5. Kyrou, I., Karteris, E., Robbins, T., Chatha, K., *et al*. Polycystic ovary syndrome (PCOS) and COVID-19: an overlooked female patient population at potentially higher risk during the COVID-19 pandemic. BMC medicine, 2020, 18(1), 1-10.
6. Song SY, Yang JB, Song MS, Oh HY, *et al*. Effect of pretreatment with combined oral contraceptives on outcomes of assisted reproductive technology for women with polycystic ovary syndrome: a meta-analysis. Arch Gynecol Obstet. 2019 Sep; 300(3):737-750.
7. Salvador, J., Gutierrez, G., Llavero, M., Gargallo, J., *et al*. Endocrine Disorders and Psychiatric Manifestations. Endocrinology and Systemic Diseases, 2021, 311-345.
8. Abuazza M, Soliman BS, Seim SG, *et al*. Effect Of Oral Contraceptive Pills Pretreatment On Ovarian Response In Patient with Clomiphene Resistant. Zagazig University Medical Journal. 2020 Mar 1;26(2):279-86.
9. Sangam K, Mitra N. Oral contraceptive pills in the management of clomiphene resistant anovulation. Int J Med Res Rev. 2015; 3(10):1182-7
10. Wei D, Shi Y, Li J, Wang Z, Zhang L, *et al*. Effect of pretreatment with oral contraceptives and progestins on IVF outcomes in women with polycystic ovary syndrome. Human Reproduction. 2017, 1; 32(2):354-61.
11. Farquhar C, Rombauts L, Kremer JA, Lethaby A, *et al*. Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2017 May 25;5(5):CD006109.