Original Article

Effect of Pretreatment with Oral Contraceptive Pills on Intracytoplasmic Sperm Injection Outcome in Females with Polycystic Ovary Syndrome

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Abstract

Background: Oral contraceptive pills (OCPs) are considered cornerstone in treatment of polycystic ovarian syndrome (PCOS). Prior to controlled ovarian stimulation (COS); OCPs are given to suppress natural luteinizing hormone and follicle stimulating hormone secretion. Though, little is known about the possible effectiveness of OCPs in assisted reproductive techniques outcome including oocytes', embryos' qualities, and pregnancy rate. **Objective:** To study the effects of OCPs pretreatment in PCOS women on intracytoplasmic sperm injection (ICSI) outcome. **Materials and Methods:** About 72 sub-fertile females with PCOS were included (depending on Rotterdam criteria). They were divided into two groups: those who were pretreated with OCPs for 1 month and those who did not. were subjected to ICSI cycles Then outcomes of the two groups were evaluated. **Results:** the OCPs pretreated women were significantly needed higher doses of gonadotropins during COS $P < 0.01$. No significant differences was found $P > 0.5$ in the number and quality of oocytes and embryos. The pregnancy rate was higher in the OCPs pretreated women compared to those who did not (33.33% versus 23.33%) Whereas, the incidence of ovarian hyperstimulation syndrome (OHSS) was lower in the OCPs pretreated women compared to those who did not (16.6% versus 26.6%). **Conclusions:** Pretreatment with OCPs can improve ICSI outcome (higher pregnancy rate and lower OHSS incidence). However, higher doses of gonadotropin are needed.

Keywords: OCPs, OHSS and pregnancy rate, oocyte and embryo quality, PCOS

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common reproductive and endocrine disorder worldwidely that impacts the reproductive health of 4%–18% young females. It exhibits various symptoms; as irregular menses, obesity, hirsutism and sub-fertility.[1,2] The diagnosis was established according to Rotterdam consensus workshop which includes the presence of two out of three criteria: irregular menstrual cycle (oligo- or amenorrhea), clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries through transvaginal ultrasound examination.[3]

Decreased fertility is a common complication of PCOS. It has been reported that up to 20% of female sub-fertility cases are due to PCOS.[4] It was found that serum and follicular fluid kisspeptin are positively correlated with the cumulative recombinant FSH medication used by sub-fertile PCOS women undergoing ICSI, addressing the possible role of kisspeptin in improving the pregnancy rate in PCOS patients with a lower incidence of OHSS.[5] Oral contraceptives (OCs) are the first-line treatment

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protocol for menstrual abnormalities and hirsutism/acne in females with PCOS. OCs decreases ovarian androgen production by encouraging negative feedback on LH secretion thus, reducing hyperandrogenism. Also; they increase liver-produced sex hormone binding globulin, lowering blood levels of free androgens, inhibiting the peripheral conversion of testosterone into dihydrotestosterone (DHT), binding of the last to DHT receptor, additionally they act by decreasing the release of adrenal androgen.[6] The oral contraceptive pills (OCPs) are the most widely used treatment modality for PCOS. Undisputedly, they suppress production of androgens, thus improving menstrual dysfunction and skin problems. They also might decrease insulin sensitivity and ameliorate obesity.[1]

Anovulation in PCOS is associated with decreased FSH levels and the arrest of antral follicle growth during its final stages of maturation. It has been postulated that OCPs usage prior to downregulation/COS prevent endogenous FSH rise which will lead to improved follicular homogeneity, allow more large follicles to be formed and more retrieved oocytes.[7] OCPs pretreatment in PCOS women reduces the LH/FSH ratio as well as the serum dehydroepiandrosterone level which can improve ICSI outcome.[8]

Some studies showed that a one cycle of OCPs pretreatment prior to pituitary down regulation for high responder women such as those with PCOS might distinctly reduce the incidence of OHSS, the rate of cycle cancelation and improve pregnancy rate of this population.[9] However, some voices against OCPs pretreatment are still, claiming that it might have no effects on follicular dynamics, hormonal levels, number of retrieved oocytes, number of good quality embryos, pregnancy rate, and OHSS development in sub-fertile patients with PCOS undergoing ICSI.[10] However, recently there have been an increasing number of studies reporting the use of OCPs pretreatment may be potentially related to impaired pregnancy outcomes after fresh embryo transfers.[11,12] So, this work was done because evaluation to the role of OCPs pretreatment in improving ICSI pregnancy outcome in women with PCOS still needs further studies.

Materials and Methods

This prospective cohort, observational study was conducted on 72 sub-fertile women who were collected from the fertility clinic in the High Institute for infertility diagnosis and assisted reproductive technologies/Baghdad/Iraq. The study was approved by an ethical committee of High Institute for Infertility Diagnosis and Assisted Reproductive Technologies (code number 0702-PM-2021M6). Male partners of the involved couples were either have normal semen parameters or with mild to moderate male factor infertility according to WHO criteria 2010.

They were subjected to ICSI cycles with a written consent were taken from them to be involved in the study. PCOS diagnosis was done depending on Rotterdam criteria.[13] Females 25–35 years old. Females with normal ovulation, endometriosis, uterine fibroid, unexplained infertility or with severe male factor were excluded. Females with PCOS were divided into two groups the first (n = 12) include those who was pretreated with OCPs for 1 month and the second group include females with PCOS without OCPs pretreatment (n = 60).

The females of both groups were evaluated in the second day of the menstrual cycle depending on history, physical examination, anthropometric measures (weight, height and body mass index (BMI)) and fertility investigations (E_2), LH, FSH prolactin, trans-vaginal ultrasound for early follicular phase endometrial thickness and seminal fluid analysis for male partner. All females were subjected to controlled ovarian hyper stimulated by r-FSH. Ovulation trigger was done by hCG Ovitrelle 250 µg/0.5 mL injection when 3 leading follicles size reach 17 mm. Oocytes retrieval was done under general anesthesia.

Assessment of oocytes' maturity was done after denudation by using an inverted microscope at 400× magnification. It was accepted that only mature oocytes MII stage were appropriate for ICSI.[14] After 16–17 h following ICSI an assessment of the embryo development represented by fertilization rate (FR), cleavage rate (CR), and embryo quality was done. Embryos with stage specific cell numbers, equal size blastomeres, and 10%–20% fragmentation were considered as good quality (grade I and II), while those with abnormal cell numbers, un equal size blastomeres and with >20% fragmentations were considered as bad quality.[15] FR was calculated by dividing the number of 2 pronuclei (2PN)/the number of injected mature MII oocytes × 100%. CR was calculated by dividing the number of day 2 embryos/the number of zygotes × 100%. At day 3 good quality embryos were transferred. Luteal phase support in form of vaginal progesterone suppositories was commenced from the day of oocyte retrieval. Fourteen days later, pregnancy test was done by measuring beta-hCG in the serum. Chemical pregnancy rate (CPR) was calculated by dividing the total number of females with a positive pregnancy test to the total number of females in whom embryos were transferred to their uterus.

Statistical analysis

Data were subjected to statistical analysis using SPSS, version 4.0, data were expressed as the mean values ± standard deviation (SD) of samples. The Statistical significance of the differences between various groups was determined by student unpaired t test Chi-square.

Differences were considered statically significant for *P* value < 0.05. Test to the total number of females in whom embryos were transferred to their uterus.

Results

The study tried to find if the pretreatment with OCPs prior to pituitary downregulation and controlled ovarian stimulation (COS) can improve ICSI outcome in PCOS women using good quality oocytes and embryos with higher pregnancy rate and lower incidence of OHSS as indicators.

Age, BMI, duration and type of infertility and basal hormonal assessment of the studied groups

Results showed insignificant differences ($P > 0.05$) in the means of age, BMI, and duration of infertility of the OCPs pretreated and OCPs un pretreated groups (as shown in Table 1), cycle day 2 hormonal profile and ET of both groups (as shown in Table 2).

Table 1: Age, body mass index, duration, and type of infertility of the studied groups

Parameters	OCPs pretreated group ($n = 12$) Mean ± SD	OCPs un pretreated ($n = 60$) Mean ± SD	*P* value
Age (years)	30.00 ± 3.8	27.03 ± 4.1	0.11
BMI (Kg/m^2)	29.6 ± 3.3	29.6 ± 4.3	0.99
Duration (years)	7.8 ± 2.7	6.4 ± 3.1	0.30

BMI: body mass index, OCPs: oral contraceptive pills

The total dose of gonadotropins, estradiol level, and endometrial thickness day of trigger and ovarian hyperstimulation of the studied groups

As shown in Table 3 the total used dose of gonadotropins (Gn) was significantly ($P < 0.05$) higher in the OCPs pretreated females compared to those OCPs un-pretreated (1987.5 ± 436.6 versus 1520 ± 428.3). Although the E_2 level and ET at day of hCG trigger were higher in the OCPs pretreated group significant differences was not found ($P > 0.05$). Regarding OHSS development, despite that the OCPs pretreated women tend to be at lower risk than those in the other group (16.6% versus 26.6%) significant difference not found ($P > 0.05$).

The total number of retrieved oocytes, oocytes' maturity, total number of embryos, and embryos' quality of the studied groups

Regarding the total number of retrieved oocytes, their maturity, number and grades of embryos significant differences were not found ($P > 0.05$) between the two groups as shown in Table 4.

Fertilization, cleavage, and chemical pregnancy rates of the studied groups

As shown in Table 5. no statistically significant differences ($P > 0.05$) were found between the studied groups regarding FR and CR despite that they being higher in the OCPs pretreated group. Regarding the CPR, it was higher in the *pretreated* women (33.33% versus 23.33%), although significant difference ($P > 0.05$) not found.

Table 2: Hormones and endometrial thickness of the studied groups

Parameters	OCPs pretreated group ($n = 12$) Mean ± SD	OCPs un pretreated ($n = 60$) Mean ± SD	*P* value
E_2 (pg/mL)	32.3 ± 10.99	42.77 ± 24.8	0.32
LH (IU/L)	3.00 ± 1.9	4.7 ± 2.66	0.14
FSH (IU/L)	5.4 ± 2.4	4.8 ± 1.3	0.39
Prolactin (ng/dL)	31.5 ± 13.01	25.65 ± 11.4	0.26
Endometrial thickness (mm)	3.66 ± 1.03	3.7 ± 1.04	0.88

Table 3: The total dose of gonadotropins, estradiol level, endometrial thickness at day of trigger and ovarian hyperstimulation

Parameters	OCPs pretreated group ($n = 12$) Mean ± SD	OCPs un pretreated ($n = 60$) Mean ± SD	*P* value
Total dose of gonadotropin (IU)	1987.5 ± 436.6	1520 ± 428.3	0.02*
E_2 at day of trigger (pg/mL)	1694.1 ± 938.4	4527.6 ± 13986.1	0.62
Endometrial thickness (mm)	9.66 ± 2.9	10.1 ± 2.4	0.70
OHSS			
Yes	2 (16.6%)	16 (26.6%)	0.60
No	10	44	
Total	12	60	

E_2: estradiol, OHSS: ovarian hyperstimulation syndrome

*Significant difference ($P < 0.05$)

Table 4: The total number of retrieved oocytes, oocytes' maturity, total number of embryos and embryos' quality of the studied groups

Parameters	OCPs pretreated group (n = 12) Mean ± SD	OCPs un pretreated (n = 60) Mean ± SD	*P* value
Total no. of oocytes	13.1 ± 9.3	14.05 ± 8.3	0.81
Mature (MII)	11.6 ± 11.3	11.9 ± 7.4	0.93
Immature (GV + MI)	3.5 ± 5.2	2.0 ± 2.2	0.26
Total No. of embryos	7.1 ± 4.9	7.1 ± 4.7	0.98
Total No. of good quality embryos	7.0 ± 4.7	6.9 ± 4.6	0.98
Total No. of bad quality embryos	0.17 ± 0.4	0.17 ± 0.3	0.97

Table 5: Fertilization, cleavage, and chemical pregnancy rates of the studied groups

Parameter	OCPs pretreated group (*n* = 12) Mean ± SD	OCPs un pretreated (*n* = 60) Mean ± SD	*P* value
Fertilization rate	81.8 ± 20.4	68.7 ± 22.2	0.19
Cleavage rate	100.0 ± 0.0	93.4 ± 20.0	0.43
Pregnancy rate			
Pregnant	4 (33.33%)	14 (23.33%)	0.06
Not pregnant	8	46	
Total	12	60	

OCPs: oral contraceptive pills

Discussion

Infertility is the inability to get pregnant after engaging in unprotected sexual activity for at least a year.[16] A comparison regarding age, BMI, duration and type of infertility, and basal hormonal assessment showed no significant statistical differences in these parameters between the two studied groups. This finding is important to document that the females were comparable in both groups.

The present study showed no significant difference in BMI to exclude the effect of BMI on the results because obesity may affect endometrial decidualization.[17]

Another comparison was done between both groups regarding the total dose of Gn, E_2, and ET at day of trigger and risk of OHSS that required cycle cancelation [Table 3]. In the current study the lowering incidence of OHSS and cycle cancelation rate in the OCPs pretreated group indicating the benefit of OCPs due to their effect on hormonal profile and follicular dynamics by reducing the peak E_2 of the dominant follicle, this result is consistent with that reported by Lan *et al*.[8] although insignificant difference in the cycle cancelation rate and OHSS development between the OCPs pretreated and OCPs un-pretreated women this finding is in agreement with Xiuhua *et al*.[18] and Brechtje *et al*.[19]

Regarding the total dose of gonadotropins during COS in the present study the higher doses of gonadotropin needed for OCPs pretreated in contrast to OCPs unpretreated women may be associated with the fact that pretreatment with OCPs results in more uniformly developed follicular cohort with almost no large follicles before stimulation on day 8. As a result, the criteria of hCG trigger were met later resulting in a prolonged duration of the treatment with an extended period of FSH stimulation leading to production of more follicles and oocytes.[6] The current study agree with Brechtje *et al*.[19] whereas it disagrees with other studies which showed either no difference between OCPs pretreated and OCPs un pretreated groups regarding the dose of gonadotropin stimulation[1,15] or the OCPs pretreated and OCPs un pretreated women need a lower dose of gonadotropin to be stimulated with.[13]

In the current study the insignificant difference between the OCPs pretreated and OCPs un pretreated groups regarding the quality of oocytes and embryos [Table 4] it goes with other previous studies which stated that OCPs has no enhancing effects in improving the quality of oocytes and embryos.[1,15] However; it disagrees with Xiuhua study which showed that OCPs pretreatment can produce more oocytes and good quality embryos.[18] It also disagrees with Lan *et al*.[8] study which suggested that pretreatment lowers the number of retrieved oocytes.

Regarding the CPR which was higher in the OCPs pretreated women it indicates that the pretreatment with OCPs can improve pregnancy rate in PCOS women. This result is consistent with other researches[1,20] which stated that OCPs increase progesterone level which leads to a thick, more vascular and highly receptive endometrium, while it disagrees with others researches showed that pretreatment with OCPs negatively affect PR with a higher incidence of pregnancy loss.[18,19] A comparable PR with no significant difference between both OCPs pre and un-pretreated also had been documented.[19-22]

Conclusion

The OCPs pretreatment of PCOS sub-fertile women improves ICSI outcomes.

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Conflicts of interest

There are no conflicts of interest.

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