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Original Article

Does oral contraceptive benefit the IVF/ICSI outcomes? A retrospective cohort study

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Abstract: Oral contraceptive pretreatment (OCP) is commonly used to suppress cyst formation, to schedule the treatment plan, to induce endometrial bleed in oligomenorrhea patients, and to avoid ovarian hyperstimulation syndrome. The published studies on OCP have not been powered to assess the impact of OCP on likelihood of pregnancy. In this retrospective cohort study we examined if OCP benefit the clinical outcomes in a series of consecutive patients undergoing long GnRH-a down-regulation protocol with IVF/ICSI treatment between January 2011 and July 2012. The study included 3115 cycles with and 1079 cycles without oral contraceptive administrations. Compared with patients without OCP, patients with OCP required lower duration and dosage of gonadotropin stimulation; had a similar average number of oocytes retrieved, cancellation rate, and OHSS rate; but the patients with OCP had lower implantation rate, PR per transfer, and PR per cycle started. Theresults were similar regardless the level of ovarian reserve. This study indicates that Oral contraceptive may have unfavorable impact on pregnancy in long GnRH-a down-regulation with IVF/ICSI cycles.

Keywords: Oral contraceptive pill, in vitro fertilization (IVF), implantation rate, pregnancy rate

Introduction

The common practice of down-regulation with GnRH-a prior to ovarian stimulation with gonadotropins in IVF/ICSI cycles has been reported to yield beneficial outcomes [1, 2]. In the long GnRH-a protocol, down-regulation therapy is initiated posterior to occurrence of spontaneous ovulation, which is normally in the midluteal phase. However, women undergoing midluteal initiation of GnRH-a treatment may have received the agent in the early stage of luteal phase, due to the variation in duration of menstrual cycles among the women. Down-regulation started in a not optimal timing may associate with poor outcomes [3]. In addition, administration with GnRH-a may interfere with early pregnancy [4]. It has been reported [5] that the unexpected spontaneous pregnancy may occur during the flare-up phase of GnRH-a administration and GnRH-a administration initiated in midluteal phase also increase the possibility of ovarian cyst formation [6-8]. Thus, OCP in GnRH-a cycles may be applied. However, the impact of dual suppression with OCP and GnRH-a on IVF/ICSI outcomes has not been consistent.

This study is to compare the COH performance and IVF/ICSI results between patients undergoing GnRH-a suppression with and without OCP pretreatment, and to assess the impact of OCP on IVF/ICSI outcomes.

Materials and methods

Patients

This was a retrospective, noninterventional, single-center cohort study of patients undergoing long GnRH-a protocols with IVF/ICSI treatment at the Center of Reproductive Medicine in Tongji hospital between January 2011 and July 2012. A series of 4194 IVF/ICSI cycles were enrolled, including 1079 cycles undergoing long GnRH-a down-regulation initiated in midluteal phase without OCP and 3115 cycles undergoing long GnRH-a protocols with OCP. Institutional Review Board approval was exempted since all

Table 1. Demographics

	Without OCP	With OCP	*P* value
No. of cycles	1079	3115	
Age (years)	30.5±4.4	30.0±4.2	0.000
BMI (kg/m^2)	20.7 (15.5-39.2)	21 (13.6-37.8)	0.001
Duration of infertility (years)	4 (1-20)	4 (1-19)	NS
Primary infertility (%)	50.23% (542/1079)	54.99% (1713/3115)	0.007

Note: NS = not significant.

patients underwent the routine IVF/ICSI treatment without any clinical experiment.

Protocol for COH

All patients underwent COH with GnRH-a long protocol. Briefly, in patients without OCP, subcutaneous injection of 0.1 mg GnRH-a (Decapeptyl [Ferring, Switzerland] or Diphereline [Ipsen, Australia]) daily from midluteal phase of the previous cycle, which was reduced to 0.05 mg once adequate down-regulation was achieved. As for patients with OCP, administration with OCP (Marvelon [Organon, Netherlands] or Diane-35 [Bayer, Germany]) was started from the day 3 or day 5 of the previous cycle, and last for consecutive 21 days. Down-regulation was started with 0.05 mg GnRH-a on the 18-21th day of the cycle. The complete pituitary suppression was confirmed by serum E2 level < 30 pg/ml and serum LH level < 2 mIU/ml. Ovarian stimulation with recombinant FSH (Gonal-F [Serono, Switzerland] or Puregon [Organon, Netherlands]) was started with administration of 150-300 IU/d intramuscularly. The FSH dosage was adjusted according to ovarian response which was assessed by ultrasound and serum E2 level. Recombinant hCG (Serono, Switzerland) was given to trigger follicle maturation when at least two follicles reached a mean diameter of 18 mm. Oocytes retrieval were performed transvaginally 34-36 hours after hCG injection. ICSI was performed when sperm quality was unexpectedly low on the day of oocytes retrieval or low or no fertilization in previous cycles.

Embryos were scored according to cleavage stage, blastomere size and shape, and fragmentation. Embryos were classified as Class 1 to Class 4 and only Class 1 and Class 2 embryos were transferred. Fewer than three embryos were transferred on the day 2 or 3 after oocyte retrieval. Excessive high-quality embryos were cryopreserved for subsequent FET cycles. The luteal phase was supported with 60 mg P injections IM from the day of oocyte retrieval.

Pregnancy outcomes

Biochemical pregnancy was defined as a serum hCG > 20 IU/L 2 weeks after transfer but declined to negative afterward. Clinical Pregnancy was defined as a serum hCG level > 20 IU/L and confirmed by observation of gestational sac on transvaginal ultrasound scan 5-7 weeks after transfer. Implantation rate was defined as the number of gestational sacs present on ultrasound scan 5-7 weeks after transfer divided by the number of embryos transferred.

Statistical analysis

Shapiro-Wilks test was used to evaluate the normality of the data distribution. Mean and standard deviation were calculated for continuous variables with normal distribution. Median (and range) were presented for variables with non-normal distribution and percentage (and number) was presented for categorical variables. We compared patients with OCP and those without overall and by three subgroups classified by level of ovarian reserve based on antral follicles count. These three subgroups are low ovarian reserve (≤7 follicles), intermediate ovarian reserve (8-20 follicles), and high ovarian reserve (≥21 follicles). Groups were compared with one-way analysis of variance (ANOVA) with Bonferroni adjustment, student's t- test or Mann-Whitney U-test as appropriate. Differences between proportions were evaluated with chi-square test and the Fisher exact test. Missing data were excluded per test. A *P* value < 0.05 was considered statistical significance. SPSS version 13.0 (SPSS Inc.) was used for statistical analysis.

Results

Demographic data were shown in **Table 1**. Patients undergoing OCP prior to GnRH-a down-regulation were younger and had higher body mass index, as compared to patients without OCP pretreatment, whereas these difference were small with limited clinical importance.

Table 2. COH performance and IVF/ICSI outcomes

	Without OCP	With OCP	*P* value
No. of cycles started	1079	3115	
No. of cycles with ET	841	2403	
Duration of gonadotropins (days)	11 (7-20)	10 (6-24)	0.000
Dosage of gonadotropins (IU)	2581.7±977.8	2293±882.5	0.000
Peak endometrial-thickness (mm)	11.4±2.6	11.0±2.3	0.000
No. of follicles > 14 mm	11.8±4.4	12.3±4.6	0.002
E2 on the day of hCG (pg/mL)	4745 (428-45717)	5000 (427-90285)	0.006
P on the day of hCG (ng/mL)	1.05 (0.1-10.1)	1.03 (0.0-9.7)	0.010
No. of oocytes retrieved	14.4±7.1	14.5±7.2	NS
Cancellation rate (%)	22.1 (238/1079)	22.8 (712/3115)	NS
OHSS rate (%)	16.9 (182/1079)	17.4 (542/3115)	NS
Embryos transferred per cycle (%)	1651/841	4780/2403	
Implantation rate (%)	36.0 (595/1651)	30.2 (1443/4780)	0.000
PR per transfer (%)	50.3 (423/841)	44.7 (1074/2403)	0.005
PR per cycle started (%)	39.2 (423/1079)	28.5 (423/3115)	0.000

Note: NS = not significant.

COH performance and IVF/ICSI outcomes were presented in **Table 2**. Patients with OCP required lower duration and dosage of gonadotropin stimulation compared with patients without OCP pretreatment. The number of follicles with diameter > 14 mm and serum E2 level on the day of hCG injection were higher in patients with OCP compared with those without, while the peak endometrial-thickness and serum P level were lower in patients with OCP. The average number of oocytes retrieved and embryos transferred, cancellation rate, and OHSS rate were similar between the two comparison groups. Patients who did not undergo OCP had a better pregnancy results, in terms of implantation rate, PR per ET, and PR per started cycle.

The comparisons between patients with OCP and those without by three subgroups of ovarian reserve are shown in **Table 3**. In low ovarian reserve group, no differences were found in COH performance, in terms of peak endometrial-thickness, serum E2 level on the day of hCG, serum P level on the day of hCG, the number of follicles with diameter > 14 mm on the day of hCG, the number of oocytes retrieved and the number of high-quality embryos. However, patients with OCP pretreatment required lower dosage and shorter duration of gonadotropins compared with patients without OCP treatment. The cancellation rate, OHSS rate were similar between the two groups. The implantation rate in patients with OCP was lower, as compared to patients without OCP, but there was no difference in PRs.

In intermediate ovarian reserve group, patients undergoing OCP treatment used fewer days and ampules of gonadotropins, obtained fewer oocytes and thinner endometrium than patients without OCP, no differences were found with respect to other COH parameters. The cancellation and OHSS rates were similar between the patients with and without OCP, whereas the pregnancy results were superior in patients without OCP treatment, indicated by higher implantation rate, PR per transfer and PR per started cycles.

In the context of patients with high ovarian reserve, patients with OCP pretreatment required lower dosage of gonadotropins, but endometrial-thickness and the number of oocytes retrieved were also lower, in comparison to patients without OCP. Other COH related variables were similar. No statistically significant differences were found in related to pregnancy outcomes.

Discussion

In this study, we compared the COH performance and IVF/ICSI outcomes between patients with and without OCP and found detrimental effect of OCP on outcomes, as indicated by higher serum E2 level, lower peak endo-

Table 3. COH performance and IVF/ICSI outcomes in patients with low, intermediate, high ovarian reserve

	Low ovarian reserve		Intermediate ovarian reserve		High ovarian reserve	
	Without OCP	With OCP	Without OCP	With OCP	Without OCP	With OCP
Dosage of Gonadotropins (IU)	3714.2±1110.2	3217.8±950.3*	2564.8±850.6	2411.7±848.7*	1845.7±563.3	1710.6±543.7*
Duration of Gonadotropins (days)	11 (8-20)	10 (7-17)*	11 (7-16)	10 (6-21)*	10 (8-15)	10 (7-24)
Peak endometrial-thickness (mm)	11.3±2.6	10.9±2.2	11.4±2.6	10.9±2.3*	11.5±2.8	10.8±2.3*
E2 on the day of HCG (pg/mL)	3118.0 (791-10913)	3208.0 (482-10000)	4623 (428-45717)	4762 (427-75000)	6782 (1000-15000)	6302 (923-90285)
P on the day of HCG (ng/mL)	1.0 (0.2-10.1)	1.0 (0.1-2.4)	1.06 (0.2-6.8)	1.05 (0.0-7.9)	1.1 (3.8)	1.0 (10.0)
No. of follicles > 14 mm	7.6±3.4	7.6±3.8	11.6±4.1	11.5±4.0	15.6±3.5	15.5±4.3
No. of oocytes retrieved	7.8±4.3	8.2±4.3	14.0±6.0	13.3±6.1*	21.1±8.1	19.3±7.9*
No. of high-quality embryos	2 (0-12)	2 (0-11)	4 (0-18)	4 (0-29)	7 (0-18)	6.0 (0-24)
No. of cycles started	121	193	798	2166	160	756
No. of cycles with ET	111	175	649	1790	81	438
Cancellation rate (%)	8.3 (10/121)	9.3 (18/193)	18.7 (149/798)	17.4 (376/2166)	49.4 (79/160)	42.1 (318/756)
OHSS rate (%)	1.7 (2/121)	1.0 (2/193)	13.3 (106/798)	11.4 (248/2166)	46.3 (74/160)	38.5 (292/756)
Implantation rate (%)	36.1 (75/208)	25.1 (86/343)*	35.1 (450/1281)	29.0 (1027/3546)*	43.2 (70/162)	37.8 (330/873)
PR per transfer (%)	47.7 (53/111)	39.4 (69/175)	49.8 (323/649)	42.8 (766/1790)*	58.0 (47/81)	54.6 (239/438)
PR per cycle started (%)	43.8 (53/121)	35.8 (69/193)	40.5 (323/798)	35.4 (766/2166)*	29.4 (47/160)	31.6 (239/756)

Note: *statistically significance.

metrial-thickness, lower implantation rate, and PRs.

In long GnRH-a protocols, OCP was reported to be efficient in preventing cyst formation and to be used for scheduling the day of initiation of GnRH-a administration. OCP was also used to induce endometrial bleed in oligomenorrhea patients, to improve the ovarian response in poor responders and, somewhat paradoxically therefore, to reduce the incidence of ovarian hyperstimulation syndrome in women with polycystic ovarian disease [9, 10]. However, the impact of OCP on pregnancy results in IVF/ICSI cycles remained a controversy. Among patients with low ovarian response, OCP supplementation reduced duration and doses of gonadotropins, but pregnancy outcomes were not improved [11]. Similarly, the study by Biljan suggested that OCP shortened the time of pituitary desensitization and decreased the gonadotropin requirements. However, they reported increased PRs PRs in patients who underwent OCP pretreatment [12]. Another study showed that long GnRH-a cycles with OCP yielded a comparable implantation rate and PR with those in cycles without OCP [13]. Patients with high ovarian response, dual suppression of OCP and GnRH-a can decreased the cancellation rate, and increased PR and ongoing PR [14].

In our study, by overall comparison of COH performance and pregnancy outcomes between patients with and without OCP pretreatment, we observed decreased duration and doses of gonadotropins in patients taking OCP, which is in line with the previous studies [11, 12]. Patients with OCP obtained higher number of follicles with diameter > 14 mm and higher serum E2 level on the day of hCG. However, the number of oocytes retrieved was not increase. IVF/ICSI outcomes, in terms of implantation rate and PRs, were also better in patients without OCP. Increased levels of E2 may alter the implantation window span of endometrium, thus affect embryo implantation [15, 16]. Some studies showed that OCP might benefit patients by increasing the number of oocytes retrieved [13, 17], which was not in agreement with our findings. OCP may enhance the stimulating effect of gonadotropins, as indicated by increased follicles > 14 mm, whereas the eventual retrievable oocytes were not increased in our series. Furthermore, our results suggested that OCP have a detrimental effect on endometrium development, with respect to lower peak endometrial-thickness in OCP group. It has been reported that suitable endometrial-thickness is an important factor in IVF/ICSI success [18]. Therefore, we may consider that the impaired pregnancy results observed in OCP group might attribute to the elevated E2 profile and decrease endometrial-thickness.

Studies have been performed in the context of GnRH-antagonist cycles of patients [19]. Data are lacking for the impact of OCP on outcomes in IVF/ICSI cylcles with long GnRH-a protocol. In the present study, we found that OCP decreased the duration and dosage of stimulation, which may cost-effectively benefit the patients, but the implantation rate was decreased. In intermediate ovarian reserve group, OCP shortened duration and doses of gonadotropins. However, peak endometrial-thickness, the number of oocytes retrieved, implantation rate, and PRs decreased. Such inferior outcomes may be related with the fact that OCP hampered the endometrial-development and impaired receptivity of endometrium. Of note, although the reduced oocytes obtained in OCP group may not have a significant effect on pregnancy success in fresh cycles because of acceptable number of high-quality embryos, the cumulus-pregnancy rate might be limited due to reduced available embryos in subsequent FET cycles. Among patients with high ovarian reserve, administration with OCP offered some benefits. First, the time required for pituitary desensitization was shortened. Secondary, the cancellation rate and risk of OHSS appeared to be lower in OCP group. However, the differences did not reach statistically significant. Lastly, patients with OCP supplementation obtained similar PRs to that in patients without OCP. Thus, OCP may be recommended to patients with high ovarian response, especially those who have high potential to suffer OHSS. However, when deciding whether OCP should be used, it should be cautious that OCP might be associated with decreased endometrial-thickness in these patients.

The study included data from a large series of consecutive patients enrolled within two years period in a single center. The patients with OCP and without were enrolled concurrently. This ensured the comparability of the two comparison groups in the methodologies of biochemi-

cal and clinical measurements, treatment protocols, and definitions of outcome. Only the first two cycles were included in the analyses. This has reduced the confounding effect of data of various IVF/ICSI cycles from the same patient. The limitation of our study is its retrospective, non-randomized nature, thus selection bias may exist. Furthermore, some confounding factors, such as various causes of infertility, were not considered in our analses.

In conclusion, OCP has a detrimental effect on pregnancy outcomes in IVF/ICSI cycles. This effect may be associated with elevated serum E2 level and impaired endometrial-thickness. OCP should not be recommended to patients with low or normal ovarian response. However, it might be reasonable to apply OCP in patients with high ovarian response, such as patients with high risk of OHSS.

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Disclosure of conflict of interest

None.

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