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Original article

Effect of Oral Contraceptive Pill Pretreatment on Pregnancy Rates in Patients Stimulated with GnRH Antagonists and rFSH for ICSI

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Abstract

Background: After the recent introduction of GnRH antagonists in ovarian stimulation, OCP has been used for cycle scheduling purposes. Cycle programming has become more difficult with the use of GnRH antagonists, as stimulation initiation is dependent on the occurrence of menstruation. To overcome this limitation in the GnRH antagonist protocol, patients can be offered the use of pretreatment with oral contraceptive pills (OCP). ***Objective:*** To evaluate the effect of oral contraceptive pills (OCP) pretreatment on pregnancy rate in GnRH antagonist cycles. ***Design:*** Observational cohort study. ***Setting:*** Observational study performed at Sri Ramachandra institute of higher education & research Chennai. ***Patients:*** Total 115 patients included in the study from January 2019 to December 2019.
All patients divided into two groups, oral contraceptives pretreated group (n-64) and oral contraceptives non treated group (n-51).
Results: All oral contraceptives pretreated patients required significantly higher dose of gonadotropins (4745±1476 versus 3659±1230;P <0.0005) and significantly longer days of stimulations (12.2±1.2 versus 10.5±0.8;P <0.0005) in comparison to non-oral contraceptives treated group. There were no difference in total oocytes retrieved and fertilization rate. There were no other differences in cycle characteristics between groups. Implantation and pregnancy rates were not affected by OCP pretreatment. ***Conclusions:*** OCP pretreatment use for synchronization of follicles and cycle scheduling in GnRH-antagonist protocol, though it may be associated with longer stimulation and higher gonadotropin consumption but similar pregnancy rates.

Keyword: IVF, OCP, GnRH, Antagonist

Introduction

Gonadotropin-releasing hormone (GnRH) antagonist protocols are characterized by shorter stimulation period and use of lower quantities of gonadotropins as compared with the long GnRH-agonist protocol [1,3]. However, in a long GnRH-agonist protocol there is flexibility in the starting day of gonadotropin stimulation, which is lacking in the GnRH-antagonist protocol. To overcome this limitation in the GnRH antagonist protocol, patients can be offered the use of pretreatment with oral contraceptive pills (OCP) [4,7]. Moreover, a previous study has shown that OCP pretreatment before GnRH antagonist led to higher numbers of oocytes retrieved compared to the standard GnRH antagonist protocol [11]. On the other hand, longer stimulation periods and increased consumption of recombinant FSH (rFSH) were needed for stimulation [10,11]. The effect of this intervention on the probability of pregnancy has so far been examined only in a small randomized controlled trial (RCT).

The objective of the present study was to assess the effect of OCP pretreatment on pregnancy rates in patients stimulated with recombinant FSH (rFSH) and GnRH antagonist for IVF.

Materials and methods

Patients

Between Jan 2019 and Dec 2019, a GnRH-antagonist protocol was used in 115 patients . In 64 of these cycles, OCP pretreatment was administered for cycle scheduling. The use of pretreatment with OCP was for synchronisation of follicles before COH.

Ovarian stimulation protocols

OCP pretreatment was administered for 21 days, starting on cycle days 2–3. At the end of the OCP period prior to gonadotropin stimulation, vaginal ultrasound was performed to establish ovarian and uterine quiescence. Five days after OCP discontinuation, ovarian stimulation was commenced using rFSH at a starting dose

of 225 to 300 IU/day depending on age, AFC, AMH and D2 FSH & E2. The dose was adjusted after 5 days according to the patient's individual E2 response and follicular development. In the non-OCP protocol, gonadotropin stimulation was started on day 2 or 3 of the menstrual cycle, with a similar policy for the starting dose as in the OCP protocol. In both protocols, GnRH-antagonist was started when the leading follicle reached ≥14 mm in diameter, and was continued until the day of human chorionic gonadotropin (hCG) administration. Ovulation was triggered with 250 mcg of rHCG when at least three follicles measuring 17 mm were detected by ultrasound scan. Oocyte collection, ICSI and luteal phase support were performed in the same manner in both protocols, in accordance with our hospital and laboratory standard of care and practice. Embryo transfer was deferred in patients who had an elevated progesterone on the day of hCG trigger (>1.5ng/ml), or who had risk of OHSS or women who had an agonist trigger for final oocyte maturation or who had thin endometrium. Embryo transfer was done in the rest of patients who had no risk for embryo transfer failure. Upto 3 embryos were transferred on the second day or third day after oocyte retrieval. Serum β hCG was measured on the 14th day of embryo transfer. Serum β hCG values more than 25mIU/ml was considered as positive test for pregnancy. Transvaginal sonography was done after 2 weeks of serum beta HCG estimation to confirm site of pregnancy, number of sacs and cardiac activity.

Statistical analysis

The collected data were analysed with SPP statistics software 23.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used continuous variables. To find significant difference between the bivariate samples in independent groups the unpaired t-test was used. To find the significance in categorical data Chi-Square test and Fishers exact test was used. In all above statistical tools the probability value 0.05 is considered as significant level.

Results

There were no differences within each age group between the pretreated OCP and non-OCP treated patients in demographic and baseline clinical parameters (Table 1&2). The IVF cycle characteristics and laboratory data are presented in Table 3. The stimulation for the patients taking the oral contraceptive was on average of longer duration than for the Non-OCP group and pregnancy rates similar in both groups.

Table 1: Demographic characteristics between the groups

DEMOGRAPHIC CHARACTERISTICS	NON OCP GROUP (N=51)	OCP GROUP B (N=64)	P value
Age (years)	29.49±3.5	29.94±3.1	0.47
Duration of infertility (years)	7.8±4.4	7.1±3.8	0.66
BMI (kg/m2)	26.55±5.3	26.1±4.4	0.40

Table 2: Ovarian reserve between the groups

OVARIAN RESERVE	NON OCP GROUP (N=51)	OCP GROUP (N=64)	P value
D2 FSH (mIU/ml)	6.6±2.2	6.6±2.2	0.95
D2 LH (mIU/ml)	4.9±2.9	4.5±2.0	0.34
D2 E2 (pg/ml)	48.07±17.5	48.7±23.7	0.94
AFC (n)	12.6±2.5	12.6±3.4	0.95
AMH (ng/ml)	2.3±0.9	2.4±1.01	0.49

Table 3: IVF cycle characteristics in OCP and non-OCP cycles

PARAMETERS	NON OCP GROUP (N=51)	OCP GROUP (N=64)	P value
Duration of stimulation (Days	10.51±0.88	12.2±1.26	0.00
Total dose of Gn (IU)	3659.80±1230.8	4745.63±1476.01	0.000
ET (mm)	10.04±1.8	9.6±1.7	0.21
E2 – Trigger day (pg/ml)	3732.55±1745.99	2988.4±1434.13	0.014
P4 on the day of trigger (ng/ml)	1.13±0.5	1.0±0.2	0.14
NO.Oocytes	16.02±7.1	15.38±6.3	0.59
Fertilization rate(%)	68%	71%	0.72
Implantation rate(%)	41%	43%	0.81
Pregnancy rate(%)	29%	33%	0.64

There was no evidence of an 'OCP effect' on the number of oocytes retrieved, nor on the Fertilization, Implantation and Pregnancy rates.

Discussion

In this study we evaluated the effect of OCP pretreatment prior to GnRH-antagonist protocol for cycle scheduling in IVF treatment. We found that OCP pretreatment was associated with a longer length of stimulation and an increase in the total dose of gonadotropins needed for stimulation. The OCP pretreatment did not affect the magnitude of the ovarian response in terms of the number of oocytes retrieved. The implantation and pregnancy rates were not affected by OCP pretreatment. Endometrial thickness was not affected by OCP.

There is limited body of data in the literature on the use OCP pretreatment prior to GnRH antagonist protocol including three prospective randomized studies [10,11]. However, these studie include relatively small numbers of patients and cycles. Overall, our findings on the effect of OCP pretreatment prior to GnRH antagonist protocol on cycle characteristics, magnitude of ovarian response and pregnancy outcome are in accordance with these studies [10,11]. In all studies including this study, longer stimulation period and higher total dose of gonadotropins were needed in the OCP pretreatment cycles [8–10]. Similar to our results, in two studies [9,10], OCP pretreatment had no effect on the final number of mature follicles whereas in one study [11] the OCP pretreatment resulted in

an increase in the number of mature follicles and in the number of oocytes retrieved. Finally, in our study as in previous studies, the implantation and pregnancy rates were not affected by the use of OCP pretreatment [9,10].

Conclusion

OCP pretreatment for cycle scheduling in GnRH-antagonist protocol is a valid modality with comparable IVF outcome to the non-OCP protocol. The longer stimulation and higher total dose of FSH are the only drawbacks that we found in this modification. The weight of these drawbacks has to be measured against the gain in enabling cycle scheduling.

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