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Comparison between Outcome of Assisted Reproductive Technique (Art) Cycles with and Without OCP Pretreatment in Infertile Women: A Randomized Clinical Trial

Heidar Z, Mirzamoradi M, Lapavandani RS*, Afshari A and Mirzaee S

Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding author:** Rozita Safaei Lapavandani, Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Email: rozitasafaei@gmail.com

Research Article

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Abstract

The objective of this randomized clinical trial was to assess the effect of pretreatment with oral contraceptive pill (OCP) on assisted reproductive technique outcomes in patient's candidate for assisted reproductive technique (ART). In a randomized clinical trial University-based infertility center, Tehran, Iran. 160 infertile patient who are candidate for IVF, randomly divided into two groups: 80 patients in OCP pretreatment group and 80 patients in non-OCP pretreatment group. The IVF protocol in all patients was standard long GnRH agonist (long protocol). The oocyte number, embryo formation, fertility rate, gonadotropin dose, ovarian cyst formation and cancelled cycles were evaluated. Oocytes number per patient in OCP group was 13.87 and in non-OCP group was 15.22, pregnancy rate in OCP group was 44.7% and in non-OCP was 31.2%, the abortion rate in OCP group was 10.5% and in non-OCP was 3.1%, that there was no significant difference between two groups, embryo formation in two groups was similar. ovarian cyst in OCP group was 2.6% and in non-OCP was 12.5% ($P< 0.05$) so the cancelled cycles due to ovarian cyst in OCP group was less than non-OCP group. Based on our data, OCP pretreatment have no effect on oocyte number, embryo formation, pregnancy rate and abortion, but this pretreatment can decrease the cyst formation so decrease the cancelled cycles in OCP pretreatment.

Keywords: GnRH agonists; Oral contraceptive pill; IVF; Randomized clinical trial

Abbreviations: OCP: Oral Contraceptive Pill; ART: Assisted Reproductive Technique; WHO: World Health Organization; OHSS: Ovarian Hyperstimulation Syndrome; COH: Controlled Ovarian Hyperstimulation; PCOs: Polycystic Ovary Syndrome; RCT: Randomized Clinical Trial.

Introduction

Fertility is reproductive health landmark and infertility is recognized as a global public health problem by the World Health Organization (WHO) [1]. According to WHO, infertility is a disease of reproductive system that patient could not achieve pregnancy after one year or more of regular unprotected sexual intercourses [2]. The prevalence of female infertility is 12.5% and male infertility is 10.1% [3]. Despite efforts in this regard just 35% of couples that treated by assisted reproductive technique (ART) reach to live birth delivery [4].

The first and important step that determine the successful rate of ART is ovarian stimulation that have different treatment strategies [5]. Totally, the base of all ART

techniques are persuade folliculogenesis via prohibition of endogenous LH surge and give a chance to oocyte for maturation [6]. The ovarian stimulation protocols have some side effects such as ovarian cyst formation and ovarian hyperstimulation syndrome (OHSS) (that in this situation the cycles should be cancelled) [7,8] and harmful effects of the hormonal environment on endometrial receptivity [9]. Control of ovarian hyperstimulation is very important. To obtain more mature follicles, the early LH surge should suppress [10].

The estradiol has negative feedback on LH secretion but at the end of follicular phase it has positive feedback on hypothalamus and pituitary so increase the level of plasma estradiol at the end of follicular phase induce LH surge [11]. An important factor that leads to controlled ovarian hyperstimulation (COH) failure and then cancels the ART cycle is premature LH surge in follicular phase, that it increases the number of immature oocyte and decrease the fertilization potential of them. Furthermore, LH surge persuade granulosa cells to luteinization and progesterone production that have different effects on endometrium and its receptivity, so premature LH surge can disrupt all of them [5]. LH surge induce ovulation so to retrieve mature follicles and have successful IVF cycle, it is important to inhibit the abrupt endogenous LH surge.

Contraceptive pills that have progesterone and estrogen suppress the endogenous gonadotropins [12] so block the spontaneous LH surge and therefore ovulation [9]. Also oral contraceptive pill (OCP) pretreatment in clomiphene citrate stimulation to retrieve oocyte and IVF, suppress LH surge [13]. Polycystic ovary syndrome (PCOs) is the most common cause of anovulatory infertility [14], in this way many of infertile women suffer from it. OHSS is more occur in PCOs patient, and use of GnRH agonist increases this risk, so one of the protocols that control this event in ART cycles is the dual pituitary suppression with OCP and GnRH-agonist overlap [15]. In some study OCP administration before ovarian stimulation has some effects such as changes in the amount and duration of prescribed gonadotropins [15,16], number of oocytes, pregnancy rate [17], and thickness of endometrium [18] and its receptivity. Another important role of OCP pretreatment is better synchronization of follicular growth during ovarian stimulation [19].

Due to the importance of ovarian stimulation protocol for infertile women and some of infertility treatment side effects such as ovarian cyst formation and premature LH surge and following that, cancellation the IVF cycle and on the other hand suppression effect of OCP on these side effects, this randomized clinical trial (RCT) was conducted to compare outcome of standard GnRH agonist long protocol with and without OCP pretreatment on cancelled cycles and ART outcomes. *This study received IRCT id: 2014112316705N3*

Material and Method

Patient Population

In this research, which is a randomized clinical trial, one hundred- and sixty-women undergoing IVF treatment at the university-based infertility center in Mahdiyeh hospital, Tehran from 2014 to 2015 were divided random simple and based on random number table into two groups: OCP group that one period pretreated by OCP and non-OCP group that they take no OCP pretreatment. This study was done on infertile women that treated by standard GnRH agonist long protocol.

Inclusion Criteria Were

1) No endocrine disorder, 2) levels of FSH <10 IU/l, 3) normal uterus based on transvaginal sonography.
Exclusion criteria were: 1) Azoospermia, 2) OCP contraindication.

Ovarian Stimulation

In OCP group, OCP administrate from day 3-4 of menstruation and after 15-18days transvaginal sonography was done, if ovaries were normal short acting GnRH agonist (Cinafact, Cinagen factory) 40 IU/ SQ/ daily was administrated. From day 2-3 of menstruation gonadotropin administration was started. ward protocol (Gonal F 150-300IU/daily based on ward protocol ,based on patient age and patient ovarian reserve, Merck serono company) after 5 days stimulated, transvaginal sonography was done and stimulation continue and every 2-3 days transvaginal was repeated, whenever at least 3 follicle with 17-19 size were detected, 10000 HCG (Choriomon, Fering company) administrated and 35-36 hours after ovarian puncture was done and after ovum injection by embryologist, at day 3 and 4 embryo transfer was done and luteal phase, 14 days late BHCG level was checked and if positive, support by progesterone continued, supported by Cyclogest sup 400mg, twice a day.(Actoverco company). One week later, an transvaginal sonography was performed, and data were recorded in other group. all steps are the same except OCP administration. In both group if there was any pathology in ovary including ovarian follicle >12mm cycle was cancelled.

Statistical Analysis

The result of quantitative variables presented with mean ± SD and quantitative result presented by percent. Chi-

square or Fisher tests were used to compare the qualitative variables and independent t-test or Mann-Whitney test were used to compare the quantitative variables. All tests were two-tailed evaluated with a confidence level of 95% ($P < 0.05$). Data were analyzed using SPSS software version 19 and SAS version 9.1.

Ethical Consideration

This study has been approved by the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU. REC.1393.14).

Result

One hundred and sixty women undergoing IVF, prior to initiation of stimulation, randomized were divided into receive OCP pretreatment or non-OCP pretreatment. Twenty patients (non-OCP group: n = 16, OCP group: n = 4) did not start IVF cycle after the initial consultation for personal reasons. Based on Table 1, the average age of OCP group was 30.42 ± 4.11 and non- OCP was 30.75 ± 4.30, BMI in OCP group was 25.45 ±2.26 and in non-OCP group was 24.81 ±2.44, oocytes number per patient in OCP group was 13.87±8.79 an in non-OCP group was 15.22±7.60, and the use of gonadotropin vials in OCP group was 31.60±7.49 and in non-OCP group was 30.91±8.3, that in all mentioned variables there was no significant difference between two groups. The embryo formation in two groups was similar, too. Pregnancy rate in OCP group was 44.7% and in non-OCP group was 31.2%, the abortion rate in OCP group was 10.5% and in non-OCP was 3.1%, that there was no significant difference between two groups.

Variable	OCP group	Non-OCP group	P value
Age	30.42 ± 4.11	30.75 ± 4.30	0.645
BMI	25.4 ± 2.26	24.81 ± 2.44	0.115
FSH level	5.52 ± 31.3	6.08 ± 2.52	0.251
AMH level	3.28 ± 1.68	5.28 ± 4.21	0.447
Infertility duration	11.76 ± 1.61	11.29 ± 1.05	0.065
Gonadotropin vials number	31.60 ± 7.49	30.91 ± 8.31	0.0824
Oocyte number	13.87 ± 8.79	15.22 ± 7.60	0.331
Embryo number	42 55.3%	36 56.2%	
Pregnancy rate	34 44.7%	20 31.2%	0.102
Cancelled cycle due to ovarian cysts	2 2.6%	8 12.5%	0.03

Table1: Baseline characteristics and outcomes of ART in the OCP and non-OCP groups.

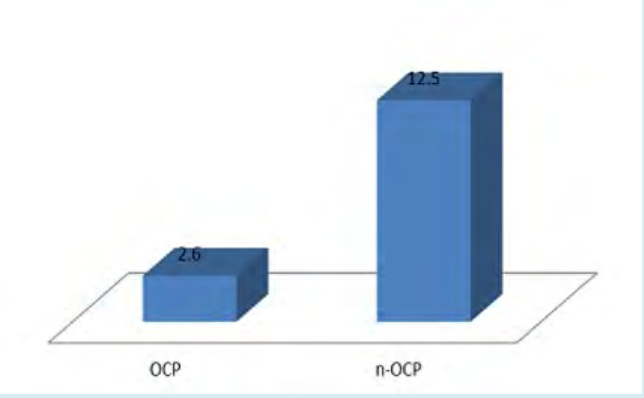

Figure 1: Cancelled cycle due to ovarian cyst in OCP and non-OCP groups.

The ovarian cyst formation in OCP group was 2.6% and in non-OCP was 12.5% ($P< 0.05$) so the cancelled cycles due to ovarian cyst formation in OCP group was less than non-OCP group (Figure 1).

AMH level in OCP group was 3.28 ± 1.68 and in non-OCP was 4.21±5.28, an FSH level in OCP group was 5.52 ± 31.3 and in non-OCP was 6.08± 2.52, that there was no significant difference between two groups.

Evaluation based on multivariate logistic regression model showed that administration of OCP was not an effective factor in successful pregnancy, as there was no relationship between pregnancy rate and OCP adminastration with three factors including age, body mass index and infertility duration (Table 2).

Item	B	S.E.	Wald	p-value	Old ratio	95.0% CI for OR	
						lower	Upper
OCP	-0.446	0.368	1.468	0.226	0.64	0.311	1.317
Age	-0.005	0.046	0.012	0.914	0.995	0.91	1.088
BMI	0.127	0.081	2.473	0.116	1.136	0.969	1.331
Duration	0.105	0.134	0.607	0.436	1.11	0.853	1.445
constant	-4.09	2.921	1.96	0.161	0.017		

Table 2: Multivariate Logistic Regression Model to Determine the Relationship between OCP Use and Positive Pregnancy Rate.

Also, evaluation based on multivariate linear regression model 22, considering the effect of OCP adminastration on oocyte number, and in presence of age, body mass index and duration of infertility, showed that OCP adminastration had no effect on oocyte number (Table 3).

Item	Unstandardized coefficients		Standardized coefficients	T	Sig.
	B	Std.Error	Beta		
OCP	3.447	11.163		0.309	0.758
Age	1.637	1.45	0.099	1.129	0.261
BMI	-0.045	0.177	-0.023	-0.256	0.798
Duration	0.37	0.311	0.105	1.19	0.236
constant	0.063	0.534	0.011	0.118	0.906

Table 3: Multivariate Linear Regression Model to Determine the Relationship between OCP Consumption and Ovarian Response (Oocyte Count).

Discussion

Ovarian stimulation protocol is the first and important factor to determine the successful ART outcome that has different treatment strategies [5]. IVF protocols include GnRH antagonist and GnRH agonist [10], in GnRH agonist protocol the number of oocytes, fertilization rate and pregnancy rate increase and the quality of embryo is better [20], but increase the risk of ovarian cyst formation in compared to GnRH antagonist [21]. Contraceptive treatment before administration of GnRH analogue improve the outcome of ART in some patients such as polycystic ovarian syndrome [15,22].

The present study has shown that, one period OCP pretreatment in GnRH agonist cycles is not associate with pregnancy rates per started cycle, a systematic review and meta-analysis that evaluates the effect of OCP pretreatment in antagonist cycle on ongoing pregnancy indicated that this pretreatment had no effect on pregnancy rate, too [17]. In another study on 80 patients, compared the effect of OCP pretreatment in agonist GnRH and antagonist GnRH protocols, they indicated that there was no significant difference in pregnancy rate between two protocols [23]. Based on a pilot trial study, the OCP therapy before ART can improve the pregnancy rate, especially in endometriosis patient, that it may be caused by endometrial effect of OCP [24].

The results of the current research has demonstrated that OCP pretreatment in GnRH agonist cycle have no significant effect on oocyte number, embryo formation and pregnancy loss that this data confirmed by another RCT which indicate that OCP pretreatment had no effect on number of cumulus–oocyte complexes (COCs) [17], number of oocyte [25,26], blast formation and number of 2PN embryos [23]. According the result of another RCT, OCP pretreatment decrease the risk of pregnancy loss in GnRH antagonist cycle [27,28], That decrease may be due to GnRH antagonist administration. The results of the current study are in agreement with Chen S-U et al and Biljan MM et al that indicated OCP pretreatment decrease the ovarian cyst formation in GnRH agonist ovarian stimulation protocol and then cancelled cycle decreased [8,29,30], this may be due to facts that suppression of pituitary in the early follicular phase, shortens the time required to achieve pituitary suppression [29], so the formation of ovarian cyst decrease. Pretreatment with only progesterone decrease the risk of cyst formation in GnRH agonist cycle and only estrogen pretreatment have no important effect on ART outcomes [27]. The important issue in OCP pretreatment is, this protocol had no negative effect

on recruitment of follicles and pregnancy rate.

Conclusions

Pretreatment with OCP in GnRH agonist ovarian stimulation protocol, suppress the cyst formation in ovaries, thus decrease the risk of IVF cycle cancellation. The oocyte number, embryo formation, pregnancy rate and pregnancy loss in both group (OCP pretreatment and non-OCP) were similar, so the prescription of OCP before the initiation the ovarian stimulation specially in GnRH agonist long protocol can decrease some ART related risks.

Conflict of Interest

The authors have no conflict of interest.

Foundation

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