Value of Oral Contraceptive Pill Pretreatment before GnRH Antagonist Ovarian Stimulation Protocol on The Outcome of IVF/ICSI

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Abstract

Objective: To evaluate the effect of oral contraceptive pill (OCP) pretreatment in gonadotropin-releasing hormone (GnRH) antagonist ovarian stimulation protocol on the outcome of IVF/ICSI regarding number of retrieved oocyte, oocyte maturation rate, fertilization rate, good quality embryo rate, cycle cancellation rate, pregnancy rate and clinical abortion rate.

Subjects & Methods:
A total of 84 patients, in a prospective controlled clinical trial, had ICSI using GnRH antagonist protocol during the period from February 1st, 2009 to September 30th, 2011 were included in this prospective randomized trial. We compared the IVF outcomes between OCP pretreated (n=43) and no pretreatment group (n=41) in gonadotropin-releasing hormone (GnRH) antagonist ovarian stimulation protocol.

Results: The mean duration of ovarian stimulation and mean amount of gonadotropins in OCP pretreated group was significantly higher than that of no pretreatment group (11.7 ± 2.3 vs. 9.8 ± 1.8 days and 2720.4 ± 1165.0 IU vs. 2295.8 ± 1121.1 IU). The mean number of retrieved oocytes and oocyte maturation rate was significantly higher in OCP pretreated group (10.9 ± 5.3 vs. 7.5 ± 5.2 and 90.8% vs. 73.3%). The number of total gained embryos and the good quality embryo rate was also significantly higher in OCP pretreated group (7.9 ± 0.9 vs. 4.2 ± 1.0 and 69.9 % vs. 48.7%). Fertilization rate was also higher in OCP pretreated group (84.9 ± 0.2% vs. 70.5 ± 0.3%). The implantation and pregnancy rate were higher, although not reaching statistically significant level, in OCP pretreated group (11.6% vs. 10.7% and 45.4% vs. 36.2%).

Conclusion: OCP pretreatment before GnRH antagonist protocol for IVF appears to have reliable benefits in terms of IVF outcomes regarding number of retrieved oocytes, oocyte maturation rate, fertilization rate, and good quality embryo rate. But, it also has a weak point in respect to longer stimulation duration and increased gonadotropin consumption. The OCP pretreated cycle in GnRH antagonist protocol is more advantageous, despite not reaching statistical significant level, in respect to pregnancy rate, and cycle cancellation rate. Well controlled, large scaled studies are needed to support effectiveness of OCP pretreatment before starting GnRH antagonist ovarian stimulation protocol for IVF/ICSI.

Keywords: Gonadotropin-releasing hormone antagonist; Oral contraceptive pill pretreatment; Ovarian stimulation; In vitro Fertilization

Introduction

Gonadotropin-releasing hormone (GnRH) antagonists have been widely used after its first introduction in assisted reproductive technologies to prevent a premature luteinization [1]. GnRH antagonist protocols are preferred for poor responders because of shorter duration and use of lower amount of gonadotropins for ovarian stimulation as compared with traditional GnRH long agonist protocols [2]. However, it induces insufficient synchronization of follicular cohort development and lack of flexibility in the starting day of ovarian stimulation, which is less likely in GnRH agonist long protocols [3]. For getting over these limitations, several pretreatments have been applied [4-7]. Among them, oral contraceptive (OCP) pretreatment has been reported to induce higher numbers of oocytes retrieved compared to no pretreatment group in GnRH antagonist cycles [8].

The effect of this intervention on the probability of pregnancy has so far been examined only in a small randomized controlled trial (RCT) [4]. However, prior to adopting a modification in an already established protocol of treatment such as the daily GnRH antagonist protocol [5], its effect on the probability of pregnancy needs to be evaluated.

In this study, we aimed to evaluate the effect of OCP pretreatment in in vitro fertilization (IVF) cycles using GnRH antagonists by comparison between OCP-pretreated and non-treated groups.

Subjects & Methods

A total of 84 patients indicated for ICSI using GnRH antagonist protocol during the period from February 1st, 2009 to September 30th, 2011 were included in this prospective randomized trial. Patients were prospectively selected from our IVF center

Inclusion criteria were: age <39 years; ≤3 previous assisted reproduction (ART) attempts; body mass index (BMI) of 18–29 kg/m2; regular menstrual cycles; no polycystic ovaries according to Rotterdam definition; no endometriosis > stage II; basal hormonal levels of FSH (<10 IU/l) and LH (<10 IU/l) at initiation of stimulation for the non-OCP group and at initiation of OCP in the OCP group; and no previous poor response to ovarian stimulation. Poor ovarian response was characterized either by cancellation of the cycle due to poor follicular development after at least 10 days of gonadotropin stimulation, or by retrieval of less than five cumulus–oocyte– complexes (COCs) at oocyte retrieval.

The study population were divided into 43 patients used OCP pretreatment in previous menstrual cycle before starting GnRH antagonist protocol for IVF (OCP pretreated group), and 41 patients used no medication before GnRH antagonist protocol for IVF (no pretreatment group). Randomization was done using computer-generated program and all IVF cycles carried out in our center

In OCP pretreated group, daily OCP (Yasmin®, Bayer Schering Pharma AG, Berlin, Germany) was applied from the first day of previous menstrual cycle. after OCP discontinuation, the ovarian stimulation was done with gonadotropin from the second day of menstrual cycle as usual as extensively described. Briefly, the dose of gonadotropins was determined on an individual basis according to the age, Day 3 FSH value and echographic characteristics of the ovaries. Patients underwent serial transvaginal ultrasound starting on Day 6 of ovarian hyperstimulation. The patients underwent pituitary downregulation with daily GnRH antagonist (Cetrotide®, Merck-Serono, Geneva, Switzerland) from mid or late follicular period of this cycle applied when dominant follicle reached to 12 or 13 mm. When two or more follicles reached 16 - 18 mm in diameter 10,000 IU of hCG (Choriomon, IBSA, Lugano3, Suisse) was administered. Trans-vaginal ultrasound guided oocyte pick-up (OPU) was performed 34-36 hours later and then, maturity and quality of retrieved oocytes was evaluated. Embryo transfer was performed 48–72 h after the oocyte collection.

The IVF outcomes such as retrieved oocyte number, oocyte maturation rate, fertilization rate, good quality embryo rate, cycle cancellation rate, pregnancy rate and clinical abortion rate were compared between OCP pretreated and no pretreatment group. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer.

Statistical analysis was performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). Each variable was presented as mean ± standard deviation. Student's t -test and Chi-square test were used wherever appropriate. P -value of < 0.05 was considered statistically significant.

Results

The mean age and body mass index in OCP pretreated and non-pretreated groups were similar (34.6 ± 3.1 vs. 35.1 ± 3.5 years and 22.3 ± 2.6 kg/m2 vs. 21.7 ± 1.9 kg/m2). The basal follicle stimulating hormone (FSH) level (10.2 ± 3.7 IU/mL vs. 9.1 ± 2.9 IU/mL) was also similar between two groups. The primary infertility rate tended to be higher in non-pretreated group (66.1% vs. 55.4%) but not statistically significant. The mean duration of infertility was longer in control group (5.1 ± 2.7 years vs. 4.7 ± 2.3 years) but, also, not statistically significant (Table 1).

	OCP pretreated group (n = 43)	No pretreatment group (n = 41)	P - value
Age of female (yr)	34.6 ± 3.1	35.1 ± 3.5	NS
BMI (kg/m2)	22.3 ± 2.6	21.7 ± 1.9	NS
Duration of infertility (yr)	4.7 ± 2.3	5.1 ± 2.7	NS
Primary infertility (%)	55.4	66.1	NS
Secondary infertility (%)	44.6	33.9	NS
Basal serum FSH (mIU/mL)	10.2 ± 3.7	9.1 ± 2.9	NS

Table 1: Comparison of baseline characteristics in both study groups

	OCP pretreated group (n = 43)	No pretreatment group (n = 41)	P - value
Duration of COH (day)	11.7 ± 2.3	9.8 ± 1.8	0.0001
Dosage of gonadotropin (IU)	2720.4 ± 1165.0	2295.8 ± 1121.1	0.054
E2 on hCG day (pg/mL)	1170.8 ± 1267.3	1086.0 ± 877.5	NS
EM thickness on hCG day (mm)	10.4 ± 2.6	10.0 ± 2.4	NS
Number of retrieved oocyte	10.9 ± 5.3	7.5 ± 5.2	0.053
Number of matured oocyte	9.9 ± 4.3	5.5 ± 4.1	0.052
Oocyte maturation rate (%)	90.8	73.3	0.052
Number of total gained embryo	7.9 ± 0.9	4.2 ± 1.0	0.053
Good quality embryo rate (%)	69.9	48.7	0.054
Number of transferred embryo	2.6 ± 0.9	2.3 ± 1.0	NS
Fertilization rate (%)	84.9 ± 0.2	70.5 ± 0.3	0.017
Implantation rate (%)	11.6	10.7	NS
Pregnancy rate/embryo transfer (%)	45.4	36.2	0.304
Clinical abortion rate (%)	41.7	42.1	NS
Cycle cancellation rate (%)	13.5	17.5	NS

Table 2: Comparison of IVF/ICSI outcomes in both study groups The mean duration of ovarian stimulation in OCP pretreated group was significantly longer than that of no pretreatment group (11.7 ± 2.3 vs. 9.8 ± 1.8 days). Mean amount of gonadotropins for controlled ovarian stimulation in OCP pretreated group was higher than that of control group (2720.4 ± 1165.0 IU vs. 2295.8 ± 1121.1 IU). The mean number of retrieved oocytes and oocyte maturation rate was significantly higher in OCP pretreated group than that of no pretreatment group (10.9 ± 5.3 vs. 7.5 ± 5.2 and 90.8% vs. 73.3%). The number of total gained embryos and the good quality embryo rate was also significantly higher in OCP pretreated group than that of control group (7.9 ± 0.9 vs. 4.2 ± 1.0 and 69.9 % vs. 48.7%). Fertilization rate was also higher in OCP pretreated group (84.9 ± 0.2% vs. 70.5 ± 0.3%). The implantation and pregnancy rate were higher, although not reaching statistically significant level, in OCP pretreated group (11.6% vs. 10.7% and 45.4% vs. 36.2%). The clinical abortion rate also showed no significant difference between two groups. The cycle cancellation rate tended to be lower in OCP pretreated group than OCP non-treated group but not statistically different.

Discussion

The present study was scheduled to evaluate the effect of oral contraceptive pill (OCP) pretreatment in gonadotropin-releasing hormone (GnRH) antagonist ovarian stimulation protocols on the outcome of IVF/ICSI regarding number of retrieved oocytes, oocyte maturation rate, fertilization rate, good quality embryo rate, cycle cancellation rate, pregnancy rate and clinical abortion rate.

The retrieval of good quality oocyte is a very important factor to achieve pregnancy in infertile women undergoing IVF/ICSI. To gain good quality embryo, growth of finely matured oocyte is firstly needed. To get more matured oocytes, the synchronized growing of follicles is one of important factor. During COH, most of the early antral follicles are required to grow coordinately in response to exogenous gonadotropins thus accomplishing simultaneous functional and morphological maturation [10].

Marked discrepancies of follicular size at the end of COH may be counterproductive since they imply that a substantial fraction of FSH-sensitive follicles fail to undergo satisfactory maturation. This phenomenon potentially reduces the number of viable oocytes and embryos and the probability of conception. Selection of good embryos for transfer depends on embryo cohort size: implications for the `mild ovarian stimulation' debate [10]. The number of embryos available for transfer predicts successful pregnancy outcome, especially in older women with normal ovarian hormonal reserve testing [11]. Low maturation rate of oocytes in GnRH antagonist cycles was thought to be due to older ages of patients receiving the antagonist protocol, or asynchronous follicular development and a limited number of dominant follicles due to ovarian stimulation without pituitary suppression in GnRH antagonist protocols.

Asynchronous multi-follicular growth during COH may be a direct consequence of size heterogeneities of early antral follicles during the early follicular phase [12]. Luteal estradiol administration strengthens the relationship between day 3 FSH and inhibin B levels and ovarian follicular status [13]. Some follicles are able to respond to lower FSH levels than others by their intrinsic sensitivity to FSH, and start their development during the late luteal phase [14]. Since larger follicles are more FSH responsive than are smaller follicles, exogenous gonadotropin administration is likely to intensify further size discrepancies of growing follicles during COH [15]. Follicular development begins during the luteal phase of the human menstrual cycle. Hence, COH protocols such as midluteal long protocol, suppression of luteal FSH secretion could prevent untimely and uncoordinated development of FSH sensitive follicles during the luteal-follicular transition and faster follicular growth synchronization during COH can be obtained [16].

However, this luteal suppression of FSH cannot be achieved in GnRH antagonist COH protocols. Therefore, marked follicular size discrepancies would be occurred in GnRH antagonist COH cycles.

OCP pretreatment might exert a suppressive effect on the cohort of existing follicles. Fanchin et al. (2003) showed that luteal E2 administration synchronizes the follicular cohort and is associated with more follicles and oocytes retrieved [13]. As demonstrated by Van Heusden et al. (1999), OCP is able to suppress the luteofollicular transition and the endogenous FSH rise occurs 3 days after OCP withdrawal [17]. The same effect is described by De Ziegler et al. (1998) after E2 withdrawal [18]. In another study, OCP pretreatment in GnRH antagonist cycles in low responders, also, resulted in improving ovarian response by intrinsic gonadotropins before COH [19].

In the present study, the baseline characteristics of IVF cycles between both groups were comparable. In OCP pretreated group it presented improvement of fertilization rate and gained more number of fertilized embryo than that of OCP non-treated group even if longer duration and larger used dose of gonadotropin for ovarian stimulation.

According to previous meta-analysis regarding OCP pretreatment in GnRH antagonist cycles [20], OCP pretreatment was associated with an increased gonadotropin consumption and increased duration of stimulation without improvement of ongoing pregnancy rate. There were many other studies which concerned to OCP pretreatment and IVF outcomes in GnRH antagonist cycles. Among them, Kolibianakis et al. [21], reported that OCP pretreated GnRH antagonist COH cycles have no significant benefit in ongoing pregnancy rates and moreover results in a significantly higher early pregnancy loss of compared to non-OCP cycles. In another systemic review and meta-analysis analyzed by Griesinger et al. [22], OCP pretreatment in GnRH antagonist for COH have no significant benefit in increasing ongoing pregnancy rates. A recent study focused on compromised group like as low responders [23]. The study showed higher number of retrieved and matured oocytes, and fertilized oocytes in OCP pretreatment group in low responders which was defined as elevated basal FSH level (>8.5 mIU/mL), and/or antral follicle count <5. In the present study, the number of gained embryo and oocyte fertilization rate were higher in cycles of OCP pretreatment.

In conclusion, OCP pretreatment before GnRH antagonist protocol for IVF appears to have reliable benefits in terms of IVF outcomes regarding number of retrieved oocytes, oocyte maturation rate, fertilization rate, and good quality embryo rate. But, it also has a weak point in respect to longer stimulation duration and increased gonadotropin consumption. The OCP pretreated cycle in GnRH antagonist protocol is more advantageous, despite not reaching statistical significant level, in respect to pregnancy rate, and cycle cancellation rate. Well controlled, large scaled studies are needed to support effectiveness of OCP pretreatment before starting GnRH antagonist ovarian stimulation protocol for IVF/ICSI.

References

1. Martinez-Salazar J, Cerrillo M, Quea G, Pacheco A, Garcia-Velasco JA. GnRH antagonist ganirelix prevents premature luteinization in IUI cycles: rationale for its use. Reprod Biomed Online 2009;19:156-61.
2. Berin I, Stein DE, Keltz MD. A comparison of gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist fl are protocols for poor responders undergoing in vitro fertilization. Fertil Steril 2010;93:360-3.
3. Depalo R, Lorusso F, Palmisano M, Bassi E, Totaro I, Vacca M, et al. Follicular growth and oocyte maturation in GnRH agonist and antagonist protocols for in vitro fertilisation and embryo transfer. Gynecol Endocrinol 2009;25:328-34.
4. Orvieto R, Rabinson J, Meltzer S, Zohav E, Anteby E, Homburg R. Substituting HCG with GnRH agonist to trigger final follicular maturation: a retrospective comparison of three different ovarian stimulation protocols. Reprod Biomed Online 2006;13:198-201.
5. Nogueira D, Friedler S, Schachter M, Raziel A, Ron-El R, Smitz J. Oocyte maturity and preimplantation development in relation to follicle diameter in gonadotropin releasing hormone agonist or antagonist treatments. Fertil Steril 2006;85:578-83.
6. Fanchin R, Schonçuer LM, Cunha-Filho JS, Méndez Lozano DH, Frydman R. Coordination of antral follicle growth: basis for innovative concepts of controlled ovarian hyperstimulation. Semin Reprod Med 2005;23:354-62.
7. Fanchin R, Méndez Lozano DH, Schonçuer LM, Cunha-Filho JS, Frydman R. Hormonal manipulations in the luteal phase to coordinate subsequent antral follicle growth during ovarian stimulation. Reprod Biomed Online 2005;10:721-8.
8. Oehninger S. Ovulation induction in IVF. Minerva Ginecol 2011;63:137-56.
9. Arslan M, Bocca S, Mirkin S, Barroso G, Stadtmauer L, Oehninger S. Controlled ovarian hyperstimulation protocols for in vitro fertilization: two decades of experience after the birth of Elizabeth Carr. Fertil Steril 2005;84:555-69.
10. Devreker F, Pogonici E, De Maertelaer V, Revelard P, Van den Bergh M, Englert Y. Selection of good embryos for transfer depends on embryo cohort size: implications for the 'mild ovarian stimulation' debate. Hum Reprod 1999;14:3002-8.
11. Opsahl MS, Blauer KL, Black SH, Lincoln SR, Thorsell L, Sherins RJ. The number of embryos available for transfer predicts successful pregnancy outcome in women over 39 years with normal ovarian hormonal reserve testing. J Assist Reprod Genet 2001;18:551-6.
12. Fanchin R, Cunha-Filho JS, Schonçuer LM, Kadoch IJ, Cohen- Bacri P, Frydman R. Coordination of early antral follicles by luteal estradiol administration provides a basis for alternative controlled ovarian hyperstimulation regimens. Fertil Steril 2003;79:316-21.
13. Fanchin R, Cunha-Filho JS, Schonçuer LM, Righini C, de Ziegler D, Frydman R. Luteal estradiol administration strengthens the relationship between day 3 follicle-stimulating hormone and inhibin B levels and ovarian follicular status. Fertil Steril 2003;79:585-9.
14. Klein NA, Battaglia DE, Fujimoto VY, Davis GS, Bremner WJ, Soules MR. Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. J Clin Endocrinol Metab 1996;81:1038-45.
15. McNatty KP, Hillier SG, van den Boogaard AM, Trimbos-Kemper TC, Reichert LE Jr, van Hall EV. Follicular development during the luteal phase of the human menstrual cycle. J Clin Endocrinol Metab 1983;56:1022-31.
16. Fanchin R, Salomon L, Castelo-Branco A, Olivennes F, Frydman N, Frydman R. Luteal estradiol pre-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists. Hum Reprod 2003;18:2698-703.
17. van Heusden AM and Fauser BC (1999) Activity of the pituitary-ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. Contraception 59,237–243.
18. de Ziegler D, Jaaskelainen AS, Brioschi PA, Fanchin R and Bulletti C (1998) Synchronization of endogenous and exogenous FSH stimuli in controlled ovarian hyperstimulation (COH). Hum Reprod 13,561–564.
19. Kim CH, Jeon GH, Cheon YP, Jeon I, Kim SH, Chae HD, et al. Comparison of GnRH antagonist protocol with or without oral contraceptive pill pretreatment and GnRH agonist low-dose long protocol in low responders undergoing IVF/intracytoplasmic sperm injection. Fertil Steril 2009;92:1758-60.
20. Bodri D, Sunkara SK, Coomarasamy A. Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis. Fertil Steril 2011;95:164-9.
21. Kolibianakis EM, Papanikolaou EG, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Effect of oral contraceptive pill pretreatment on ongoing pregnancy rates in patients stimulated with GnRH antagonists and recombinant FSH for IVF. A randomized controlled trial. Hum Reprod 2006;21:352-7.
22. Griesinger G, Venetis CA, Marx T, Diedrich K, Tarlatzis BC, Kolibianakis EM. Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists for IVF: a systematic review and meta-analysis. Fertil Steril 2008;90:1055-63.
23. Franco JG Jr, Baruffi RL, Mauri AL, Petersen CG, Felipe V, Cornicelli J, et al. GnRH agonist versus GnRH antagonist in poor ovarian responders: a meta-analysis. Reprod Biomed Online 2006;13:618-27.