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ASSISTED REPRODUCTION

Influence of pituitary suppression with triphasic or monophasic oral contraceptives on the outcome of in vitro fertilization and embryo transfer

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Abstract *Purpose*: To compare the clinical outcome of IVF treatment after pituitary suppression with two different oral contraceptives (OCs).

Methods: 65 patients who received IVF treatment was classified into 2 groups based on the difference of OCs they used for pituitary suppression before ovarian hyperstimulation. Group 1 included 36 patients who received monophasic OCs. Group 2 included 29 patients who received triphastic OCs. Both groups received the OCs from the 5th day of the cycle for consecutive 21 days. The hormone profiles after OCs and clinical outcome of IVF treatment were compared between two groups. Two-sample *t*-tests and X2 tests were used for statistical analyses. $P < 0.05$ was considered statistically significant.

Results: The mean age and basal hormone profiles were comparable between two groups. After ovulation suppression with different OCs, the day 2 FSH and LH value revealed statistically significant difference between two groups(4.2 ± 1.8 vs 6.0 ± 2.6; 2.7 ± 2.0 vs 4.2 ± 3.3 respectively). The numbers of oocyte per retrieval and fertilization rate were comparable between two groups, but higher quality embryos as revealed by the cleavage speed were noted in the triphastic OCs group. Although statistically not significant, higher implantation rate and pregnancy rate were also noted in the triphastic OCs group.

Conclusions: Different OCs for pituitary suppression can result in different hormone profiles. Ovulation induction in IVF treatment should be individualized according to these hormone changes to achieve the optimal clinical outcome. Triphastic OCs exceeds monophastic OCs in producing good quality embryo in IVF-ET treatment.

Keywords Early cleavage embryo · In vitro fertilization · Oral contraceptives · Ovulation induction

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Introduction

Pituitary suppression with oral contraceptives (OCs) and gonadotropin releasing hormone agonist (GnRH-a) before ovarian hyperstimulation is frequently been used in vitro fertilization (IVF) treatment. Previous studies have reported that combined use of OCs and GnRH-a improved the IVF outcome [1]. OCs can normalize of the leutinizing hormone (LH) / follicle stimulating hormone (FSH) ratio and reduce ovarian androgen concentrations [2] Pituitary suppression with OCs before ovarian hyperstimulation has been reported to circumvent the initial gonadotropin flare response [3]. Anovulation induced by OCs, showing bilateral ovarian quiescence, has also been reported to reduce miscarriage rate in the following pregnancy [4]. OCs also can reduce the incidence of functional ovarian cyst formation, shorten the time required to achieve pituitary suppression and decrease gonadotropin requirements [5]. The use of OCs prior to controlled ovarian hyperstimulation (COH) allows for convenient cycle scheduling as well as for ovulation suppression so that subsequent GnRH-a treatment cannot stimulate residual corpus luteum function [6]. Since so many positive reports have been published concerning OCs in IVF treatment, combined use of OCs and GnRH-a down regulation has become a standard protocol in IVF therapy today. However, hundreds of OCs are currently available on the market. Until now, there is no univocal conclusion about which type

of OCs products the best result on the outcome of IVF treatment. The objective of our study was to compare the effect of two different compositions OCs on the change of serum hormone level and also their influence on the following clinical outcome of IVF-ET.

Patients and methods

65 patients who received IVF-ET treatment due to tubal dysfunction in our hospital were retrospectively classified into 2 groups according to the difference of OCs they used. Group 1 included 36 patients who received monophasic OCs that contained 150 μg levonorgestrel and 30 μg ethinyl estradiol for 21 tablets (Winstop 30 SC, Winston Pharmacia, Tainan, Taiwan). Group2 included 29 patients who received triphasic OCs that contained levonorgestrel and ethinyl estradiol at 50 μg/30 μg for 5 tablets, 75 μg/40 μg for 6 tablets and 125 μg/30 μg for 10 tablets respectively (Trinordil, Wyeth Medica Ireland, Newbridge Co, Kildare, Ireland). Only women younger than 40 years old and whose partner's semen analysis was normal were included in the study. All patients received blood examination for FSH, LH and E2 serum level before starting the OCs. In both groups, OCs was given from the 5th day of the cycle for consecutive 21 days. Daily buserelin (Suprecur, Hoechst, Frankfurt Am Main, Germany) 0.9 mg was also applied from the 21st day of the cycle until the next menstruation began. The dosage of buserelin then was decreased to 0.45 mg per day. Complete down-regulation of the pituitary was defined as estradiol level < 75 pg/ml and no follicle > 1 cm was measured when the menstruation began. After complete down-regulation, ovulation stimulation was initiated with recombinant follicular stimulating hormone (r-FSH, Gonad-F, Serono, Geneva, Switzerland) with or without human menopausal gonadotropin (HMG, Humegon, Organon, Oss, Holland) according to the hormone data on cycle Day 2. Adjustments in gonadotrophin dosage were individualized according to patient's follicle size and hormone change. Human chorionic gonadotrophin (hCG, Pregnyl, Organon, Oss, Holland) 10000 IU was injected intramuscularly when at least two leading follicles ≥ 16 mm were measured. Transvaginal oocyte retrieval was performed 34–36 h after the injection of HCG. Insemination was routinely performed 6 h after oocyte retrieval. In the following morning, approximately 16–18 h after insemination, the oocytes were checked for the presence of two pronuclei. On the same day, approximately 24 to 26 h after insemination, the embryos were examined if cleavage to the 2-cell stage had occurred. Embryos that had cleaved to 2-cell stage or above were defined as early cleavage embryos. Embryos that had not yet cleaved to the 2-cell stage were defined as non-early cleavage embryos. The embryos then were cultured for another day and routinely transferred on Day 3 after oocyte retrieval. Hormone profiles and clinical outcome of IVF treatment were compared between two groups. Two-sample t-tests and χ^2 tests were used for statistical analysis. $P < 0.05$ was considered statistically significant.

Table 1 The hormone profiles before and after different OCPs

Group	Monophasic OCs	Triphasic OCs	P value
No. of cycles	36	29	
Age (years)	32.0 ± 3.8	33.3 ± 3.4	NS
Basal E_2	54.2 ± 33.3	50.8 ± 28.0	NS
Basal FSH	6.4 ± 2.2	6.7 ± 2.9	NS
Basal LH	6.1 ± 5.1	5.2 ± 2.4	NS
Cycle spotting	5.6% (2/36)	0.0% (0/29)	NS
Day 2 E_2	38.2 ± 20.3	42.1 ± 24.7	NS
Day 2 FSH	4.2 ± 1.8	6.0 ± 2.6	0.002
Day 2 LH	2.7 ± 2.0	4.2 ± 3.3	0.028

Note. Values are mean $\pm$ SD. Two-sample t-tests and χ^2 tests were used for statistical analyses. $P < 0.05$ was considered statistically significant. NS: not significant.

Results

The mean age and basal hormone profiles of the patients were comparable between two groups (Table 1). However, after different OCs administration with the same dosage of GnRH-a for pituitary suppression, there was a significant difference in hormone changes. The FSH value was 4.2 ± 1.8 mIU/ml in Group 1 compared to 6.0 ± 2.6 mIU/ml in Group 2, $P < 0.05$. The LH value was 2.7 ± 2.0 mIU/ml in Group 1 compared to 4.2 ± 3.3 mIU/ml in Group II, $P < 0.05$. The total gonadotropin units for ovulation induction and the level of E2 on the day of hCG injection reveal no statistically difference between two groups. The number of oocytes per retrieval was 9.6 ± 4.4 in the group 1 compared to 9.2 ± 5.0 in the group 2, $P > 0.05$. The number of early cleavage rate was 17.9% (45/251) in group I compared to 31.3% (62/198) in group II, $P < 0.05$. The average number of embryo per transfer was 2.8 ± 0.9 in group I compared to 3.0 ± 1.0 in group II, $P > 0.05$. The clinical pregnancy rate was 50% (18/36) in group I compared to 55.2%(16/29) in Group II, $P > 0.05$. The multiple pregnancy rate was 38.9% (7/18) in group I compared to 56.3% (9/16) in Group II, $P > 0.05$ (Table 2).

Discussions

Ovarian stimulation following suppression with OCs has been clinically applied since 1988 [7]. Ovulation suppression with OCs before ovarian hyperstimulation has been reported to reduce functional cyst formation, induce bilateral ovarian quiescence, and allows for more convenient cycle

Table 2 Comparison of the clinical outcome between two groups

Group	Monophasic OCs	Triphasic OCs	*P* value
Total unit of gonadotrophin	2015 ± 860	2075 ± 929	NS
Peak E2 level	2247 ± 1080	2183 ± 1013	NS
No. of oocytes	9.6 ± 4.4	9.2 ± 5.0	NS
P4	h1.2 ± 0.8	0.9 ± 0.5	NS
No. of embryos transferred	2.8 ± 0.9	3.0 ± 1.0	NS
Fertilization rate	74.0% (251/339)	77.0% (198/257)	NS
Cleavage rate	96.0% (241/251)	96.0% (190/198)	NS
Early cleavage rate	17.9% (45/251)	31.3% (62/198)	0.001
Clinical pregnancy rate	50.0% (18/36)	55.2% (16/29)	NS
Implantation rate	27.7% (28/101)	30.2% (26/86)	NS
Multiple pregnancy rate	38.9% (7/18)	56.3% (9/16)	NS

Note. Values are mean ± SD. Two-sample *t*-tests and χ^2 tests were used for statistical analyses. $P < 0.05$ was considered statistically significant. NS: not significant.

scheduling. Today, pretreatment with OCs before starting IVF cycle has become a standard regime in many IVF centers. However, to our knowledge, there is still no universal conclusion about which type of OCs suits best in current IVF therapy. Since varying degree of residual ovarian activity may exist during different OCs therapy, it is quite important to discuss their influence on the hormone change and embryo quality in the following IVF cycle.

In general, monophastic OCs are usually preferred due to its price, tolerance, and long established effect [8]. Although the incidence of cycle spotting revealed no statistical difference between two groups in our study, more residual ovarian activity was found in patients on triphasic OCs as revealed by the higher Day 2 FSH and LH value. Since the basal data between these two groups were no statistically significant. The different OCs used is the main cause of day 2 data difference. Rabe et al. reported the same finding and attributed this to a relatively low progestogenic activity in the triphastic OCs than that in the monophastic OCs [9]. As elevated LH level in the stage of follicle recruitment is supposed to have negative influence on the quality of oocyte [10]. For patients who have a high basal LH value, monophastic OCs may be a more suitable choice. In our study, although patients on triphastic OCs had a higher LH level than those on monophastic OCs, their clinical results seems to be better. For the past few years, the role of LH in control ovarian hyperstimulation remains highly controversial. Some studies have reported better clinical result with FSH-only stimulation [11]. Daya et al. reported the results of a meta-analysis and found that the use of purified FSH was associated with higher pregnancy rates [12]. On the contrary, some studies suggested that preparations that contain LH may be superior to those that contain only FSH. Van Wely M et al. in their study concluded with that "use of hMG resulted in higher clinical pregnancy rates than did use of recombinant FSH in IVF/ICSI cycles after GnRH agonist down-regulation [13]". Westergaard LG et al. also reported a significantly higher clinical pregnancy rate per started cycle in the HMG group than the FSH-only group [14]. In our study, we did not choose the ovulation agents blindly but decided it by the Day 3 FSH/LH level after down regulation. We added exogenous LH in stimulation regimen according to the value of LH and find no significant difference on the E2, P4 level at the day of hCG administration between two groups. The number of oocyte per retrieval, the fertilization rate, the cleavage rate of embryo were also all comparable between two groups. In our result, we found more good quality embryos in the patients who used triphastic OCs according to the speed of cleavage [15]. Although statistically not significant, higher implantation rate and pregnancy rate were also noted in the triphastic OCs group.

Conclusions

We found patients may present varying degree of hormone change after different OCs prescription. Instead of a fixed type of ovulation stimulation regime, a more flexible induction protocol which based on the Day2 LH level is necessary to achieve the optimal outcome of IVF treatment. Since patients with triphastic OCs for pituitary suppression produced better quality embryos in our study. Accordingly, we recommend routine triphastic OCs pretreatment before starting the following IVF-ET treatment.

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