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Comparative Effectiveness of Three Ovarian Hyperstimulation Protocol in *In Vitro* Fertilization (IVF) Cycles for Women with Polycystic Ovary Syndrome

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to evaluate the efficacy of specific *in vitro* fertilization (IVF) protocols for patients with polycystic ovary syndrome (PCOS), and therefore, analyze the first-rank intention IVF protocol.

Material/Methods: In this study, 408 PCOS patients (464 treatment cycles) were enrolled and assigned to one of 3 groups: group 1 [oral contraceptive long-term regimen group (OC-L protocol group, n=91)], group 2 (GnRH antagonist protocol, n=80), and group 3 [follicular phase long-term regimen group, C_1-L protocol group n=293]. The endpoints are the number of eggs, oocyte maturation rate, high-quality embryo rate and clinical pregnancy rate after fresh embryos transfer, the incidence of ovarian hyperstimulation syndrome and abortion rate.

Results: The number of eggs, oocyte maturation rate, and high-quality embryo rate in the C_1-L protocol group were significantly higher than those in the other 2 groups. The fertilization rate and cleavage rate of the 3 groups were not significantly different. After fresh embryo transplantation, the pregnancy rate of C_1-L protocol group was significantly higher than that of the other groups.

Conclusions: This study showed that the super-long downregulation in follicular phase regimen has advantages of simple treatment process, high oocyte maturation rate, high quality embryo rate, and pregnancy rate. It is a good choice for PCOS patients to promote ovulation during IVF.

MeSH Keywords: Ovarian Hyperstimulation Syndrome • Ovulation Induction • Polycystic Ovary Syndrome

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Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive age women. It causes scanty menstruation and even amenorrhea, which often leads to infertility [1]. Because of a higher sensitivity and excessive response to gonadotropins, women with PCOS are often confronted with higher risks of ovarian hyperstimulation. Moreover, the growth of these follicles depends on individual heterogeneity during controlled ovarian hyperstimulation and the ratio of mature oocytes to mature follicles is sometimes less satisfactory [2–4]. Although the number of retrieved oocytes from PCOS patients undergoing *in vitro* fertilization (IVF) is quite favorable, poor oocyte quality, low fertilization rate, and high miscarriage rate are still severe problems [5–8]. In practice, there is not a standard guideline to date when determining the dose of gonadotropin. Clinicians are required to make individualized treatment plans for patients according to their clinical experience. A primary measure in these clinical studies aims to obtain optimal oocytes while minimizes the risk of ovarian hyperstimulation syndrome (OHSS), besides optimizing follicular growth and oocyte quality. This remains challenging and is still the subject of debate.

To our knowledge, PCOS women would benefit from a longer time of pituitary downregulation to better inhibit the luteinizing hormone (LH) and androgen levels. It has been suggested that the main potential cause of follicle excess could be attributed to excessive androgen levels [9,10]. The antagonist protocol is often clinically practiced helping avoid OHSS in patients with certain risk factors. The incidence of OHSS could be reduced to a large extent by using gonadotropin-releasing hormone agonist (GnRH-agonists) for ovulation induction and subsequent cryopreservation of all fertilized oocytes or embryos [11].

Therefore, in this current research, we sought to compare the effectiveness of 3 protocols in women with PCOS undergoing IVF, and to identify the optimal intention protocol for use in clinical practice.

Material and Methods

Study design

This study was a single-center retrospective study performed in the IVF Center of The Second Hospital affiliated to Wenzhou Medical University (China), from January 2014 to December 2017.

The inclusion criterion for the study included the diagnostics of PCOS, which was made based on the following symptoms: oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries. In addition, the diagnosis was also based on the exclusion of other PCOS-like syndromes, such as adrenal dysfunction, congenital adrenal hyperplasia, androgen-producing tumors, etc. Also, patients were treated for their ovulatory disorder first before undergoing IVF to avoid factors potentially impacting the co-primary endpoints such as basal LH level, the P level on the human chorionic gonadotrophin injection day.

Institutional review board and consenting of patients

Informed consents stating the risks of different protocols were signed by patients undergoing controlled ovarian hyperstimulation in China. All participants were required to sign the Permission and Information Sheet, indicating that they were well-informed about participation in the research process. They had an opportunity to withdraw from the research at any time prior to the publication of the research findings. No conflict of interest exited in the study. There was no funding provided from the companies of producing the medicines, or any other drug company. The Institutional Review Board approved the study.

Treatment protocol

Group 1 (IVF_1, OC-L protocol)

From the second day of menstrual cycle, a monophasic combined contraceptive pill was orally administrated daily for 28 consecutive days. Subcutaneous injection of triptorelin 0.1 mg was given on day 21 of oral contraceptive pill (OCP) administration and continued until the triggering day. Gn was started on the next menstrual on day 3.

Group 2 (IVF_2, GnRH antagonist protocol)

Gn injection with a dose of 75–200 IU daily was started on day 2 of the menstrual cycle, when the dominant follicle reached a diameter of 14 mm or the level of estradiol were >400 pg/mL; GnRH antagonist 0.25 mg was given daily afterwards. Treatment with antagonist and Gn was continued until the triggering day.

Group 3 (IVF_3, C_1-L protocol)

GnRH-a (3.75 mg) was intramuscularly injected on day 3–5 of the menstrual cycle. Downregulation was confirmed 30–35 days later and Gn was started at the same time. Considered the follicular phase long-term regimen group.

Oocyte collection and zygote scoring

For all treatments, when there were 3 or more follicles that reached ≥17 mm, oocyte retrieval was carried out 36 hours

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Table 1. The comparison of sociodemographic and clinical characteristics (χ±s).

	C1	Gn-ant	OC	P	P1: 2	P2: 3	P1: 3
Duration of infertility (y)	3.34±2.30	3.71±4.01	3.65±2.63	0.54	0.39	0.89	0.37
Maternal age (y)	30.25±3.54	30.54±4.96	29.75±3.34	0.40	0.60	0.22	0.25
BMI	21.45±3.65	21.05±2.76	24.03±4.08	<0.001	0.48	<0.001	<0.001
Basal hormone levels							
LH (U/L)	6.65±4.74	4.37±2.02	7.04±3.74	0.003	0.001	0.001	0.49
E_2 (pg/mL)	53.0±30.93	47.42±14.34	46.83±17.51	0.15	0.22	0.90	0.09
FSH (U/L)	6.27±2.13	7.48±1.86	5.63±1.21	<0.001	<0.001	<0.001	0.01
Endometrial thickness (mm)	5.59±1.79	5.30±1.52	4.10±1.22	<0.001	0.28	<0.001	<0.001
Trigger day							
LH (U/L)	0.75±1.11	1.76±2.22	1.18±1.34	0.001	<0.001	0.01	0.01
E_2 (pg/mL)	3570.36±1707.30	2337.84±1566.41	2279.58±1201.66	<0.001	<0.001	0.83	<0.001
P (ng/mL)	1.02±0.54	1.33±2.49	0.92±1.64	0.219	0.15	0.09	0.57
Endometrial thickness (mm)	11.11±2.32	10.40±2.01	10.01±2.52	0.001	0.048	0.35	<0.001
GN duration (d)	11.74±2.84	9.33±1.97	11.47±2.62	<0.001	<0.001	<0.001	0.41
GN dose (iu)	1963.40±821.33	1545.51±653.38	1688±746.15	<0.001	0.001	0.30	0.005

after the intramuscular injection of human chorionic gonadotrophin (hCG). Fertilized oocytes were evaluated 20 hours after insemination in terms of the appearance of 2 pronuclei. Four grades were determined according to cell counts and percentage of fragmentation. No more than 2 top-quality embryos were transferred on day 2 to day 5, we tested for β-human chorionic gonadotropin (β-hCG) levels in the blood for confirmation of pregnancy at day 12 to 14 day after embryo transfer.

Data collection

Data were collected including age, body mass index (BMI), hormones: basal follicle stimulating hormone (FSH), LH, and testosterone level on day 2 before downregulation; the quantity of oocytes obtained, mature oocytes scalar, and number of grade 3 (top-quality) embryos were compared among the 3 groups.

The co-primary endpoints were the number of eggs, the oocyte maturation rate, the high-quality embryo rate, and the clinical pregnancy rate (CPR) after fresh embryos transfer. Subordinate endpoints included the quantity of embryos transferred, and the abortion rate which was defined as the number of natural miscarriage before 20 weeks of gestation out of all known pregnancies.

Different grades and severity categories grades of OHSS were present in the classification system, which graded OHSS into minor, moderate, and severe categories when patients presented with typical clinical symptoms with or without biological and ultrasound signs asking for regular monitoring and initiation of specific treatment. This was considered a moderate or severe grade of OHSS.

Statistical analysis

SPSS23.0 software was used for all statistical analysis in the study. Results were presented as mean ± standard deviation or percentage (%). Measured data were compared with analysis of variance. Enumeration data were performed with chi-square test. $P<0.05$ was considered statistically significant.

Results

General information

The BMI in the OC long-term regimen group (OC-L group) was the highest ($P<0.05$), but there was no significant difference between the GnRH antagonist regimen group and the follicular phase long-term regimen group ($P>0.05$). Basal LH level in OC-L group was the highest, but there was no significant difference between OC-L group and the follicular phase long-term regimen group; basal FSH level in the GNRH antagonist regimen group was the lowest. There was no significant difference in age and basal E_2 level among the 3 groups (Table 1).

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Table 2. The comparison of laboratory data (χ±s).

	C1	Gn-ant	OC	P	P1: 2	P2: 3	P1: 3
No. of oocytes retrieved	17.49±7.17	12.85±7.26	12.38±5.43	<0.001	<0.001	0.69	<0.001
No. of mature oocytes	14.33±7.03	10.63±6.45	10.19±4.88	<0.001	<0.001	0.70	<0.001
No. of fertilized oocytes	11.82±5.92	8.512±5.46	8.16±4.31	<0.001	<0.001	0.72	<0.001
No. of cleaved embryos	8.58±7.13	8.14±5.13	7.77±4.18	0.55	0.65	0.74	0.29
No. of embryo transferred	2.12±3.21	1.461±0.74	1.79±0.62	0.22	<0.001	0.03	<0.001
No. of embryo frozen	6.80±4.45	3.20±3.74	3.31±2.61	<0.001	0.12	0.49	0.31

Table 3. The comparison of clinical outcomes (%).

	C1	Gn-ant	OC	P
Clinical pregnancy rate (%)	53.92	40.00	37.36	<0.05
Incidence rate of OHSS (%)	7.85	6.17	14.28	<0.05
Abortion or ectopic pregnancy rate (%)	10.58	8.75	13.18	<0.05

IVF outcomes of patients in the 3 groups

The number of eggs, oocyte maturation rate, and high-quality embryo rate in the super-long downregulation group were significantly higher than those in the other 2 groups. The fertilization rate and cleavage rate of the 3 groups was not significantly different. After fresh embryo transplantation, the pregnancy rate of the super-long downregulation group was significantly higher than that of other groups (Table 2).

Clinical outcomes of patients in the 3 groups

The patients had a higher risk of OHSS in group 1 (OC-L protocol) (P<0.001), but no remarkable differences were found in other 2 groups (Table 3).

Discussion

Studies have shown that the incidence rate of PCOS is 5–10%, accounting for 30–60% of anovulatory infertility [12]. In the past 20 years, GnRH agonists have been the "National Guideline" protocol in PCOS, and the majority of IVF/intracytoplasmic sperm injection treatment cycles performed. In recent studies, GnRH agonist with oral contraceptive pill (OCP) protocol requires more OHSS preventive measures owing to a significantly higher risk of moderate to severe OHSS (with a consequent need for hospitalization) compared with other protocols [13,14]. Thus, no optimal protocol has been determined for PCOS patients [15]. Christine et al. found that despite the similarity in oocyte and embryo quality, significantly lower clinical pregnancy rates and ongoing pregnancy rates in the OCP group could be observed. As primary IVF protocol for PCOS patients, extended duration of OCP pretreatment actually does not ameliorate the oocyte and embryo quality [16]. In our research, we found a significantly higher clinical pregnancy rate, higher number of oocytes retrieved, mature oocytes and fertilized oocytes in the C_1-protocol.

OHSS is a rare iatrogenic complication occurring in women who take fertility medication to stimulate egg growth. Particularly severe OHSS threaten lives. Xiao et al. compared GnRH agonist protocol with GnRH antagonist protocol, finding that patients had lower OHSS rate using GnRH antagonist protocol [17]. However, no effective therapy could be determined to eliminate the risk of OHSS completely when gonadotropins are used. The study of Zou et al. [18] found that the fertilization rate of the antagonist group was lower than that of the long-term regimen group, and there was no advantage for improving the clinical pregnancy rate. The study of Li [19] also found that the clinical pregnancy rate and implantation rate in the antagonist group were lower than those in the long-term luteal regimen group. Li et al. [20] found that in GnRH-antagonist regimen, drug adjustment led to a decrease in E_2, while spontaneous E_2 decline in early follicular phase predicted a poor outcome of IVF. In our study, higher risk incidence of OHSS happened in the OC-L group as compared with the other 2 groups, the number of eggs, oocyte maturation rate, and high-quality embryo rate in the super-long downregulation group were significantly higher than those in other 2 groups; the fertilization rate and cleavage rate of the 3 groups had no significant difference.

In addition, it has been suggested that LH measurement should be removed from the diagnostic criteria according

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to the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group [21]. However, high levels of LH often couple with intrafollicular endocrinological disturbances, thus, high LH might have side effects on IVF treatment [22]. Tarlatzis et al. found that the baseline LH/FSH ratio >3 weakened follicular up-growth, oocyte maturation, as well as increased risk of miscarriage [23,24]. In our study, higher risk incidence of abortion or ectopic incidence happened in the OC-L group as compared with the other 2 groups.

In summary, despite the advantages and disadvantages of each of the 3 regimens, our study showed that the long follicular phase modulation regimen had a satisfactory effect in ovulation induction, a satisfactory clinical pregnancy rate, and the OHSS rate was lower than other groups. Therefore, the protocol of super-long down regulation in the follicular phase should be considered the first intention IVF therapy for PCOS patients. A multi-center research study with a large-scale population data is required to confirm these observations.

Conclusions

This study showed that the super-long downregulation in follicular phase regimen has the advantages of simple treatment process, high oocyte maturation rate, and high-quality embryo rate and pregnancy rate. It is a good choice for PCOS patients to promote ovulation during IVF.

Conflict of interest

None.

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