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Mild Ovarian Stimulation for Infertility in Women with Polycystic Ovary Syndrome

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Objective: The aim of this study was to explore the effect of clomiphene citrate (CC) on the cycle characteristics and outcomes of women with polycystic ovarian syndrome (PCOS) undergoing ovarian stimulation. **Methods:** This is a cross sectional study, and it was conducted at the tertiary-care medical center. This study included 55 PCOS patients and 54 patients without PCOS undergoing ovarian mild stimulation. In the study group (n = 55), CC and human menopausal gonadotropin (HMG) were administered simultaneously beginning on cycle day 3, while in the control group without PCOS (n = 54) a differing protocol treatment was used. The primary outcome measure was the stimulation day, HMG dose, number of dominant follicles, serum E2, LH, P4 in trigger day and number of oocytes. Secondary outcomes included the number of top-quality embryos, maturation rate, fertilization rate, cleavage rate, incidence of premature LH surge, and OHSS, biochemical and clinical pregnancy rate. **Results:** The study group received obviously a lower total HMG dose [470.54 ± 304.5 (375–975) vs. 500.00 ± 287.59 IU, but similar HMG duration. While the antral follicle count (AFC) was higher in the study group, the number of oocytes retrieved and top-quality embryos was remarkably less [5 (0 – 30) vs. 13 (0 – 42), 2 (0 –14) vs. 3.5 (0 – 15), p = 0.003, respectively]. The mature oocyte rate was higher in the study group (p = 0.036). No significant differences were detected in fertilization rate and cleavage rate between the 2 groups. CC had a positive influence (higher oocytes retrieved and top-quality embryos) on cycle characteristics, but might be correlated with the impaired IVF outcomes (lower E2, lower implantation rate) in PCOS patients undergoing IVF, when CC + HMG was used simultaneously. **Conclusion:** In women with PCOS, mild CC stimulation resulted in increased oocytes and viable embryos compared with the control group. The study regimens had a low incidence of OHSS. The results of the CC combined regimen provide new insights into the development of a more patient-friendly protocol for women with PCOS. However, this study needs to be continued on more samples in the future.

Keywords: Mild Ovarian Stimulation, Clomiphene Citrate, Polycystic Ovary Syndrome

Introduction

Infertility is of increasing significance affecting almost 48.5 million couples around the world [1]. Anovulation is a major cause of infertility in women with polycystic ovary syndrome (PCOS) accounting for about 80 % of women with infertility. PCOS is an endocrine and reproductive disorder with a prevalence ranging from 5 % to 13 % in women of reproductive age [2 - 3]. PCOS is the primary cause of hyperandrogenism and oligo-anovulation at the reproductive age and is often associated with infertility as well as clinical and metabolic disorders [4 - 5].

It has been demonstrated that the prevalence of infertility in women with PCOS varies between 70 and 80 %. The evaluation of infertility in women with PCOS or other causes of subfertility should start after six months of attempting pregnancy without success if the couple has regular sexual intercourse (2 to 3 times/ week) without using contraceptive methods, according to the American Society for Reproductive Medicine [6]. Ultrasound morphological features of PCOS include the presence of 16 or more follicles measuring 2 - 9 mm in diameter, and/or an overall large ovarian volume of >10 mm^3 [7]. Approximately 74 % of women with PCOS seek pregnancy assistance, including induced ovulation, insemination or in vitro fertilization (IVF) [8 - 9]. However, PCOS women undergoing IVF treatment typically produce an increased number of oocytes, which are often of poor quality, leading to a lower fertilization rate and a higher miscarriage rate [10]. They also face a higher risk of moderate / severe ovarian hyperstimulation syndrome (OHSS) [11].

Treatment of PCOS is adapted based on the patient's presentation and desire for pregnancy. In order to optimize the efficacy of the treatment of infertile women with PCOS, several evaluations such as laparoscopy and semen analysis are mandatory before deciding on treatment. But it is also recommended that tubal patency evaluation (laparoscopy) may not be necessary prior to initiating clomiphene citrate (CC) treatment. However, if a patient is resistant to the CC or requires the use of gonadotropins, a tubal patency evaluation becomes mandatory prior to initiating the therapeutic treatment of infertility [12]. The clomiphene citrate has been a first-line drug for ovulation induction for anovulatory infertility and also has advantages including its oral route, low costs, and easy access compared to gonadotropins. CC is also used in GnRH antagonist protocols, and the combination of CC and GnRH antagonist is likely to reduce the risk of OHSS, medication costs, and gonadotropin duration compared to treatment without CC, but it is accompanied with an increased risk of premature LH surges [13 – 15].

The phenotype of the PCOS greatly varies depending on life stage, genotype, ethnicity and environmental factors. Especially, it has been demonstrated that PCOS has strong interactions with the obesity prevalence worldwide due to the worsening of the PCOS features induced by the insulin resistance. Teede et al. showed that modest weight loss of 5 % to 10 % of initial body weight has been demonstrated to improve many of the features of PCOS [16]. Another study conducted by Barnard et al. also revealed that women with PCOS had lower quality of life (QoL) on all seven factors of the modified PCOSQ (emotional disturbance, weight, infertility, acne, menstrual symptoms, menstrual predictability and hirsutism). Weight was the largest contributor to poor QoL for women taking and not taking AA medication [17]. Further, recent study on the relationship between zinc-α2-glycoprotein (ZAG) and androgen excess with insulin resistance in PCOS women showed significantly lower circulating ZAG and M-value in PCOS women than in the controls. In all population, overweight/obese subjects had significantly lower circulating ZAG levels than lean individuals. Moreover, multivariate logistic regression analysis showed that circulating ZAG was significantly associated with PCOS even after controlling for anthropometric variables, blood pressure, lipid profile and hormone levels [18].

The pathogenesis of PCOS are still not fully understood. Numerous studies suggest different factors that are associated with PCOS. Some studies revealed that the high prevalence of the PCOS can be explained by some genetic factors. Others suggested that obesity maybe involved in the pathogenesis, because obesity, particularly abdominal obesity, aggravates the reproductive and metabolic dysfunction. Nevertheless, there is need of a reproducible, accurate marker which can be predictor for PCOS which in turn would support the clinical management. The aim of this study was to explore the effect of clomiphene citrate CC on the cycle characteristics and outcomes of women with PCOS undergoing ovarian stimulation.

Materials and Methods

Research design

This is a hospital based retrospective case-control study. The 109 surveyed participants, 55 with PCOS and 54 without PCOS, and patients that met the entry criteria were divided in three groups according to the received stimulation protocol.

Study participants

Among all infertile women with PCOS referred to our Reproductive Unit for couple infertility from January 2019 to June 2021, we observed and evaluated those who satisfied the following entry criteria: having received a mild stimulation protocol with clomiphene citrate plus human menopausal hormone (hMG) or with hMG alone in a GnRH antagonist co-treated timing with ovulation and intrauterine insemination (IUI), invitro fertilization\ Intracytoplasmic sperm injection (IVF / ICSI) cycle, and having received metformin in the preceding three to six months. Diagnosis of PCOS was based on the ESHRE / ASRM 2003 criteria. None had a previous IVF cycle. Indication to IVF is displayed. Since the IUI cycles were performed in other centers before metformin pre-treatment, we did not take into account the previous response to gonadotropin treatment when setting the HMG starting dose. Before being enrolled for the treatment program, all patients received a three to six months pre-treatment with metformin extended release 1000 – 2000 mg daily, in order to reduce the risk of ovarian hyperstimulation syndrome (OHSS) and to suppress the excessive ovarian production of androgens. Obese patients were invited to lose weight by following a hypocaloric low glycemic index diet and exercise. Patients whose BMI remained higher than 30 were excluded by the study. In order to assess eligibility to three group, all patients underwent a careful physical examination, including height and weight measurement. Antral follicle count (AFC) was evaluated in the early follicular phase (day 2 – 5) by transvaginal ultrasound. Blood tests were performed on day 2 or 3 to assess basal FSH, LH, Estradiol (E2) and Antimullerian hormone (AMH) serum levels. Endometrial thickness was evaluated by ultrasound.

Inclusion criteria

According to the Rotterdam's criteria definition, the diagnosis of PCOS / D is justified when at least two of the stated three inclusion parameters are fulfilled. Infertility is defined as trying to get pregnant (with frequent intercourse) for at least a year with no success, anovulatory infertility women.

Exclusion criteria

Women age over 45 years; infertility diagnosis and treatment information are incomplete; women with functional cysts on the ovaries. BMI > 30 kg/cm^2, thyroid dysfunction, pituitary tumors, congenital adrenal hyperplasia, adrenal tumors, Cushing syndrome, androgen-secreting tumors, moderate-to-severe endometriosis.

Stimulation protocol

Group 1 comprised 59 patients who received ovulation timing with Clomiphene citrate 50 - 150 mg daily starting from day 3 through day 6 of the menstrual cycle, plus hMG, Cetrotide 0.25 mg administered at a fixed - dose of 150 IU starting from day 3 to day 6 with further dose adjustments. Group 2 patients comprised 33 women whose IUI cycle was individualized, with Clomiphene citrate 50 - 150 mg daily starting from day 3 through day 6 of the menstrual cycle, plus hMG, and Cetrotide 0.25 mg administered at a fixed - dose of 150 IU starting from day 3 to day 6 with further dose adjustments. Group 3 comprised 17 patients who received IVF treatment with Clomiphene citrate 50 mg daily starting from day 2 through day 6 of the menstrual cycle, plus hMG, and Cetrotide 0.25 mg administered at a fixed-dose of 150 IU starting from day 3 to day 6 with further dose adjustments. Regimen starting from day 3 onwards, the starting dose being set according to a nomogram based on patients age, AFC and AMH. All patients from group 1 gave written informed consent to the off - label use of clomiphene citrate in IVF. In both groups a GnRH antagonist was started once the leading follicle(s) reached 14 mm in diameter. Serial ultrasound examination and evaluation of serum E2 levels were used to assess follicular maturation and endometrial thickness. Human chorionic gonadotropin (hCG) 6.500 to 10.000 IU s.c. was administered when at least two follicles reached a mean diameters of 18 mm. Progesterone level was assessed at hCG day. Timing ovulation was performed after 36 hours injected by hCG. IUI was performed after 36 hours injected by hCG. IVF or ICSI was performed as clinically appropriate, with embryo transfer performed either in day 3 or in day 5, since no superiority of blastocyst compared to cleavage-state embryo transfer has been demonstrated. Patients were eligible for frozen embryo transfer

when serum progesterone (P) level was higher than 1.75 ng/ml and/or E2 level was higher than 3500 pg/ml on hCG day. Luteal phase was supported by vaginal micronized progesterone 600 mg/day.

Statistical analysis

An unpaired t-test was caried out for continuous variables to compare the mean between two groups. For categorical variables, Pearson Chi-square test was conducted. Multiple logistic regression was carried out for identifying the factors influencing PCOS. Statistical significance was determined at a p-value lower than 0.05. STATA 14 program was used for statistical analysis.

Ethical statement

The study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences (No.2019/3-01). All patients provided written informed consent before participating in this study. The study was approved by the Institutional Ethical Committee of National Center for Maternal and Child Health, Ulaanbaatar, Mongolia.

Results

The study included 112 women who had not been pregnant for 12 months or more and were infertile between the ages of 21 and 42 as 58 women diagnosed by Rotterdam's criteria infertility, and 54 women with chronic anovulatory infertility cycle as a control group. Clinical observations were conducted. The survey was conducted from Jan 2019 to June 2021, based on the Infertility and Reproductive Center (IRC) of the Obstetrics and Gynecology Hospital (MSM) of the National Center for Maternal and Child Health (NCMCH).

A total of 112 women was participated in this study, and the average age of women with PCOS was 29.79 ± 4.25, without PCOS was 34.29 ± 4.24. BMI of participants were 25.18 ± 4.19 and 24.61 ± 2.85, respectively in each group. There were significant differences in characteristics such as gonadotropins,

Table 1. General characteristics of study participants.

Characteristics	PCOS with (n = 58)	PCOS without (n = 54)	Total (n = 112)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	29.79 ± 4.24	34.29 ± 4.24	31.96 ± 4.44	0.000
BMI (kg\m^3)	25.18 ± 4.19	24.61 ± 2.85	24.91 ± 3.61	0.397
	N (%)	N (%)	N (%)	
Pregnant count				
Never	34 (58.6)	20 (37.0)	54 (48.2)	0.036
One or more	24 (41.4)	34 (63.0)	58 (51.8)	
Having child				
Yes	47 (81.0)	32 (59.3)	79 (70.5)	0.020
No	11 (19.0)	22 (40.7)	33 (29.5)	
Menstrual regulation				
Regular	15 (25.9)	49 (90.7)	64 (57.1)	0.000
Oligomenorrhea	40 (69.0)	5 (9.3)	45 (40.2)	
Amenorrhea	3 (5.1)		3 (2.7)	
Semen analysis				
Normozoospermia	53 (91.4)	46 (85.2)	99 (88.4)	
Oligozoospermia	5 (8.6)	6 (11.1)	11 (9.8)	
Astenozoospermia		2 (3.7)	2 (1.8)	
Number of cycles				
One	38 (65.5)	39 (72.2)	77 (68.7)	
Two	11 (19.0)	14 (26.0)	25 (22.3)	
Three	9 (15.5)	1 (1.8)	10 (9.0)	

Table 2. Comparison of variables in those with and without PCOS.

Characteristics	PCOS with (n = 58)	PCOS without (n = 54)	Total (n = 112)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Uterine volume	42.93 ± 18.84	42.09 ± 16.97	42.62 ± 18.01	0.829
AFC in right ovary	14.26 ± 3.91	4.46 ± 2.13	9.54 ± 5.86	0.000
AFC in left ovary	14.29 ± 4.41	3.91 ± 2.29	2.29 ± 6.30	0.000
Clomiphene citrate dose (mg)	94.83 ± 40.22	104.62 ± 38.87	99.55 ± 39.70	0.193
Duration of infertility year	3.88 ± 2.44	4.93 ± 3.09	4.39 ± 2.81	0.052
Ferrimane Galvey score	8.10 ± 4.01	3.07 ± 1.33	5.68 ± 3.94	0.000
Right ovarian volume (ml)	8.11 ± 3.26	3.54 ± 2.73	6.63 ± 3.76	0.000
Left ovarian volume (ml)	6.74 ± 2.81	2.73 ± 1.66	5.44 ± 3.12	0.000
Endometrial thickness day	0.03 ± 4.94	0.35 ± 0.18	0.70 ± 3.55	0.304

Table 3. The results of treatment of ovulation stimulation.

Characteristics	PCOS with (n = 58)	PCOS without (n = 54)	Total (n = 112)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
HMG duration day	1.48 ± 0.50	1.68 ± 0.47	1.58 ± 0.49	0.030
Trigger day on menstruation	13.16 ± 2.04	12.19 ± 1.44	12.66 ± 1.82	0.007
AMH ng\ml	6.47 ± 3.41	1.64 ± 0.87	5.04 ± 3.64	0.000
Basal LH (IU\L)	7.98 ± 3.81	5.81 ± 2.06	7.01 ± 3.32	0.000
Basal FSH (IU\L)	6.27 ± 1.74	7.61 ± 3.01	6.88 ± 2.48	0.007
Basal E2 (pg\ml)	45.43 ± 36.11	44.99 ± 27.02	45.23 ± 32.21	0.943
Day 8-11 LH (IU\L)	12.44 ± 8.97	9.01 ± 5.70	10.74 ± 7.69	0.019
Trigger day progesterone (ng\ml)	1.36 ± 5.00	0.35 ± 0.39	0.87 ± 3.62	0.142
Trigger day E2 (pg\ml)	617.83 ± 609.02	849.33 ± 496.62	731.39 ± 566.16	0.034
Follicles > 14 mm on trigger day (n) in RO	1.51 ± 1.92	1.74 ± 1.05	1.62 ± 1.56	0.432
Follicles > 14 mm on trigger day (n) in LO	1.17 ± 1.89	1.19 ± 1.05	1.18 ± 1.54	0.965
Follicles > 14 mm on trigger day (n)	2.67 ± 3.55	2.93 ± 1.60	2.79 ± 2.77	0.623
Right dominant size cm	1.79 ± 0.33	1.77 ± 0.27	1.78 ± 0.30	0.731
Trigger day endometrial thickness (cm)	0.84 ± 0.25	0.78 ± 0.20	0.81 ± 0.23	0.156
Trigger day dominant follicle's size (cm)	1.67 ± 0.41	2.63 ± 5.35	2.18 ± 3.90	0.261
Mature oocyte count	6.00 ± 2.83	4.00 ± 2.15	4.25 ± 2.24	0.493
Viable embryo count	5.00 ± 2.83	3.43 ± 2.38	3.63 ± 2.39	0.572
Transferred embryo count	2.5 ± 0.71	2.14 ± 1.03	2.19 ± 0.98	0.606
Implantation rate of embryo	50.0 ± 19.81	66.67 ± 25.82	64.29 ± 24.40	0.452

pregnancy count, and menstrual cycle between the PCOS and the non-PCOS group of patients (Table 1).

In the Table 2, we shown antral follicle counts. Uterine volume and endometrial thickness were not significant different in each group, however other characteristics were diverse in each group. For example, AFC in right and left ovaries were significantly higher (14.26 ± 3.91 and 14.29 ± 4.41) in PCOS group, while the non-PCOS group had the values of 4.46 ± 2.13 and 3.91 ± 2.29, respectively. Also, right and left ovarian volume was also higher (8.11 ± 3.26 and 6.74 ± 2.81) than that in the non-PCOS groups (3.54 ± 2.73 and 2.73 ± 1.66).

In the Table 3, we have shown the endometrial thickness of the patients. HMG duration and Cetrotide dose was not different between PCOS and non - PCOS groups. On the other hand, AMH, basal LH, basal FSH was significantly different in each group. Trigger day on menstruation was 13.16 ± 2.04 in

Table 4. Reproductive history of the participants.

Characteristics	PCOS with (n = 58) N (%)	PCOS without (n = 54) N (%)	Total (n = 112) N (%)	p-value
Biochemical pregnancy				
Yes	11 (19.0)	11 (20.4)	22 (19.6)	0.999
No	47 (81.0)	43 (79.6)	90 (80.4)	
Clinical pregnancy				
Yes	11 (19.0)	10 (18.5)	21 (18.8)	0.814
No	47 (81.0)	44 (81.5)	91 (81.2)	
Live birth				
Yes	11 (19.0)	9 (16.7)	20 (17.9)	0.943
No	47 (81.0)	45 (83.3)	92 (82.1)	
OHSS				
Yes	2 (3.4)	-	2 (1.8)	
No	56 (96.6)	54 (100)	110 (98.2)	
Other cycle pregnancy				
Yes	2 (3.4)	3 (5.6)	5 (4.5)	0.091
No	56 (96.6)	51 (94.4)	107 (95.5)	

Table 5. Multivariate analysis on risk factors for PCOS.

Characteristics	OR	95 % CI	p-value
Age, years	0.05	(0.03 - 0.86)	0.000
BMI, kg	0.03	(0.01 - 0.36)	0.047
Menstrual	0.47	(0.93 - 0.85)	0.000
Uterine volume	0.34	(0.13 - 0.77)	0.098
FGS	0.04	(0.00 - 0.62)	0.000
Ovarian volume right	0.05	(0.02 - 0.59)	0.002
Ovarian volume left	0.02	(-0.01- 0.40)	0.126
AFC left	0.03	(0.02 - 0.52)	0.101
AFC right	0.02	(-0.02 - 0.23)	0.199
Endometrial thickness	0.09	(-0.00 - 0.14)	0.789
Having child			
Yes	1.00	Reference	
No	0.26	(0.19 - 0.66)	0.011
Intrauterine insemination			
No	1.00	Reference	
Yes	0.26	(-0.00 - 0.16)	0.011
IVF ICSI			
Yes	1.00	Reference	
No	0.61	(0.04 - 0.89)	0.000
Biochemical pregnancy			
Yes	1.00	Reference	
No	0.51	(0.42 - 0.96)	0.637

Continued

Clinical pregnancy			
Yes	1.00	Reference	
No	0.16	(-0.06 - 0.91)	0.731
OHSS			
Yes	0.29	Reference	
No	1.00	(-0.13 - 0.94)	0.361
Other cycle pregnancy			
Yes	1.00	Reference	
No	0.13	(-0.01- 0.28)	0.547

the PCOS group and 12.19 ± 1.44 in the non - PCOS group. Moreover, used metformin was higher in the PCOS group (1.47 ± 0.50) than that in the non - PCOS group of patients (1.09 ± 0.29).

As shown in Table 4, there were significant between-group differences in intrauterine insemination ($p = 0.020$), and IVF \ ICSI ($p = 0.001$).

The multivariate logistic analysis shown in Table 5 indicates that the independent risk factors for PCOS include age ($p = 0.000$, OR 0.05), BMI ($p = 0.047$, OR 0.03), menstrual cycle ($p = 0.000$, OR 0.47), FGS ($p = 0.000$, OR 0.04), ovarian volume right ($p = 0.002$, OR 0.05), having child ($p = 0.011$, OR 0.26), and intrauterine insemination ($p = 0.011$, OR 0.26) as well as IVF \ ICSI ($p = 0.000$, OR 0.61).

Discussion

PCOS is the most common cause of infertility in women, as manifested frequently during adolescence. PCOS is primarily characterized by ovulatory dysfunction and hyperandrogenism [19 - 21]. The clinical features of the PCOS spectrum include hirsutism, acne, menstrual irregularity as well as obesity and insulin resistance. Depending on these spectra, 6 % to 20 % of reproductive aged women are affected with PCOS and these symptoms arise during the teenage years. Experimental and clinical data suggest that there are several hallmarks of women with PCOS. In detail, abnormal secretion of gonadotropin, impaired insulin secretion, abnormal adipose tissue function is described mainly as pathophysiology of PCOS. A recent study of Azziz represented that women with PCOS have increased gonadotrophin secretion of luteinizing hormone (LH) as well as increased LH pulse amplitude and frequency. When secretion of the LH increased, it leads to the stimulation of increased androgen production in the ovarian theca cells, which in turn results to hyperandrogenism in PCOS patients [22]. Another study of Tosatti et al. showed lower TNF levels, and decreased TNF/IL-6, TNF/IL-2, and TNF/IL-4 ratios in PCOS patients compared to the control group ($p < 0.05$). An imbalance between pro - and anti-inflammatory cytokines, with prominent counter-regulatory cytokine production may be important in explaining the phenotypes present in PCOS and to direct better interventions for patients with this syndrome [24]. Non-alcoholic fatty liver disease (NAFLD) also has been suggested as a risk factors related to PCOS. When a total of 188 PCOS patients treated in Shengli Oilfield Central Hospital (Dongying, China) were retrospectively analyzed, the levels of LH, follicle stimulating hormone, testosterone, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) index in the PCOS group were higher than those in normal control group. The prevalence rate of NAFLD in PCOS group (44.68 %) was significantly higher than that in control group (24.62 %) and NAFLD patients had more obvious metabolic abnormalities [high BMI, WHR, FBG, FINS, HOMA-IR index, total cholesterol (TC) and triglyceride (TG), and low high-density lipoprotein HDL [23].

PCOS is a complex disorder and significantly different due to ethnicity. Numerous studies have shown that ethnicity has an impact on the prevalence and clinical manifestations of PCOS. Engmann et al. demonstrated that Hispanic women with PCOS had a significantly higher prevalence of hirsutism (93.8 vs. 86.8 %), abnormal free androgen index (FAI) (75.8 vs. 56.5 %), abnormal homeostasis model assessment (HOMA) (52.3 vs. 38.4 %) and hyperglycemia (14.8 vs. 6.5 %), as well as lower sex hormone binding globulin compared to non-Hispanic

Whites. Non-Hispanic Black women had a significantly lower prevalence of metabolic syndrome (24.5 vs. 42.2 %) compared with Hispanic women, and lower serum triglyceride levels compared to both Hispanics and non-Hispanic Whites (85.7 ± 37.3 vs. 130.2 ± 57.0 vs. 120.1 ± 60.5 mg/dL, $p < 0.01$), with a markedly lower prevalence of hypertriglyceridemia (5.1 vs. 28.3 vs. 30.5 %, $p < 0.01$) compared to the other two groups [24]. Meta-analysis of the prevalence of PCOS in different continents suggested the lowest prevalence in Chinese women (2003 Rotterdam criterion: 5.6 % 95 % interval: 4.4 – 7.3 %), and then in an ascending order for Caucasians (1990 NIH criterion: 5.5 % 95 % interval: 4.8 – 6.3 %), Middle Eastern (1990 NIH 6.1 % 95 % interval: 5.3 – 7.1 %; 2003 Rotterdam 16.0 % 95 % interval: 13.8 – 18.6 %; 2006 AES 12.6 % 95 % interval: 11.3 – 14.2 %), and Black women (1990 NIH: 6.1 % 95 % interval: 5.3 – 7.1 %) [25]. Another study by Sendur et al. also demonstrated that, after screening 2264 studies, compared with White women with PCOS (wPCOS), East Asian women with PCOS (eaPCOS) were less hirsute, whereas Hispanic women with PCOS (hPCOS), South Asian women with PCOS (saPCOS) and Middle Eastern women with PCOS (mePCOS) were more hirsute. saPCOS had higher androgen and lower sex hormone-binding globulin (SHBG) concentrations, mePCOS had higher DHEAS concentrations, and hPCOS and Black women with PCOS (bPCOS) had lower SHBG and DHEAS measures than wPCOS. Menstrual disturbances were more frequent in eaPCOS. Both saPCOS and eaPCOS had lower body mass index with increased central adiposity. hPCOS and bPCOS were more obese. saPCOS, mePCOS, hPCOS and bPCOS had a higher prevalence of insulin resistance than wPCOS [24].

The results of this study demonstrated that, among total of 1340 infertile women enrolled in this study, there was significant difference in AFC between women with or without PCOS, mostly influenced by BMI. Recent retrospective study of Wiser et al. showed that the rate of decline in AFC among women with PCOS was linear, while in those with non - PCOS, it was exponential until 30 years of age, and then became similar to that of PCOS. The rate of follicle loss per year was significantly slower in PCOS women compared with that in non-PCOS women [26]. In the study of Sun et al. AFC demonstrated a strong correlation with OHSS, with a cutoff value of 24 in patients with PCOS. A total of 19.5 % of the patients had mild OHSS, while 80.5 % had moderate OHSS. However, BMI and AFC were not different between the mild and moderate OHSS groups [27]. Further, it also been reported that serum anti-Mullerian hormone (AMH) levels, the mean ovarian volume (MOV) and AFC were significantly higher in the PCOS group than in the control group ($p < 0.05$). Moreover, the AMH levels revealed a significant positive correlation with AFC values, ($r = 0.74$, $p = 0.001$) and negative correlation with the serum follicle-stimulating hormone FSH levels ($r = - 0.37$, $p = 0.001$) [28]. This observation was consistent with our study.

Our study has some limitations. First, in the present study, we did not include lifestyle intervention, which is a common phenomenon in PCOS patients. Numerous systematic reviews demonstrated that inappropriate diet, low physical activity, alcohol consumption as well as psychosocial stressors are significantly associated with high prevalence of PCOS. Second, studies suggested that PCOS is associated with low-grade systemic inflammation. It has been confirmed that elevation of multiple markers of inflammation such as C-reactive protein, interleukin-18, monocyte chemoattractant protein-1 and white blood count as well as endothelial dysfunction and increased oxidative stress are potent marker of PCOS. Thus, in the future studies, these factors should be assessed with regard to PCOS development stage. Moreover, our present study had a relatively small sample size with insufficient power on order to compare the incidence of PCOS, therefore a large sample trial is needed to confirm our conclusions.

Conclusion

In women with PCOS, mild CC stimulation resulted in increased oocytes and viable embryos compared with the control group. The study regimens had a low incidence of OHSS. The results of the CC combined regimen provide a new insight into the development of a more patient-friendly protocol for women with PCOS. However, this study needs to be continued on more samples in the future.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this study.

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