Int J Clin Exp Med 2020;13(8):5932-5940
www.ijcem.com /ISSN:1940-5901/IJCEM0113596

Original Article

The effect of modified erchen decoction on reproductive endocrine functions and glucose metabolism in patients with phlegm-dampness polycystic ovary syndrome complicated with insulin resistance

Wenjing Gong[1], Yanjing Mi[2], Yufeng Shi[3]

[1]Department of Gynecology of Traditional Chinese Medicine, South District of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China; [2]Department of Gynecology of Traditional Chinese Medicine, Binzhou Traditional Chinese Medicine Hospital, Binzhou, Shandong Province, China; [3]Department of Comprehensive Internal Medicine of Traditional Chinese Medicine, Shenzhen Bao'an Authentic TCM Therapy Hospital, Shenzhen, Guangdong Province, China

Received April 30, 2020; Accepted June 2, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Objective: To observe the effects of modified Erchen decoction on reproductive endocrine function and glucose metabolism in patients with phlegm-dampness type of polycystic ovary syndrome (PCOS) complicated with insulin resistance (IR). Methods: A total of 86 patients with PCOS complicated with IR were recruited in this prospective study and divided into two groups according to a random number table with 43 cases in each group. The patients in the control group were treated with a standard western medical recipe, and those in the treatment group were treated with modified Erchen decoction based in addition to the western medicine recipe. All patients received the treatment for 3 menstrual cycles. The observation indictors included traditional Chinese medicine (TCM) syndrome scale scores, serum lipid indicators (total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), insulin resistance indicators (fasting plasma sugar (FPG), fasting insulin (FINS) and homeostasis model assessment of insulin resistance (HOMA-IR)), sex hormone indicators (luteinizing hormone (LH), follicle stimulating hormone (FSH), E-diol (E_2) and testosterone (T)), ovulation and menstrual cycle before and after the treatment. The pregnancy outcomes of two groups were compared. Results: Compared with before treatment, the TCM syndrome scale scores, the levels of TC, TG, LDL-C, LH, FSH, T, FPG, FINS, HOMA-IR and menstrual cycle in both groups were decreased after treatment, and the levels of HDL-C, E_2 and ovulation rate were increased. All the above indicators of the treatment group were recovered to better levels than those of the control group ($P<0.05$). After 6 months of follow-up, the pregnancy rate in the treatment group was higher than that in the control group (72.09% vs. 51.16%, $P<0.05$). Conclusion: The combined use of modified Erchen decoction and standard western medicine for patients with phlegm-dampness PCOS and IR can significantly improve their clinical symptoms and insulin resistance, regulate lipid levels and improve the reproductive endocrine function.

Keywords: Modified erchen decoction, polycystic ovary syndrome, insulin resistance, endocrine function, glucose metabolism level, phlegm-dampness

Introduction

As a common endocrine disease in woman of childbearing age, polycystic ovary syndrome (PCOS) is characterized by polycystic ovaries (PCO), hyperandrogenemia and chronic anovulation. It mainly manifests as infertility, menstrual disorders, hirsutism and obesity, and is often accompanied by insulin resistance (IR) in various degrees [1]. According to an epidemiology study, about 50%-70% of PCOS patients were complicated with IR [2]. IR can aggravate the metabolic disorder of PCOS patients by inducing obesity, aggravating hyperandrogenemia and inhibiting follicular development, and then worsen their condition [3, 4]. To cope with PCOS complicated with IR, western medicine therapy has focused on reducing androgen, cor-

recting metabolic disorders, reducing insulin and inducing ovulation. In spite of effective alleviation of the clinical symptoms of patients, the clinical application of this treatment has some adverse reactions and poor prognosis of patients [5]. Lots of studies confirmed that traditional Chinese medicine (TCM) has obvious advantages in promoting follicular development and improving the menstrual disorders [6]. This study investigated the effects of modified Erchen decoction combined with standard western medicine recipe on reproductive endocrine function and glucose metabolism in patients with phlegm-dampness type of PCOS complicated with IR.

Materials and methods

General data

A total of 86 cases of patients with phlegm-dampness type of PCOS complicated with IR admitted to Shenzhen Bao'an Authentic TCM Therapy Hospital from August 2017 to March 2019 were enrolled in this prospective study and randomly divided into two groups according to a random number table, with 43 cases in each group. This study was approved by the medical Ethics Committee of Shenzhen Bao'an Authentic TCM Therapy Hospital.

Inclusion criteria: Patients who 1) met the diagnostic criteria of Guidelines for diagnosis and treatment of polycystic ovary syndrome in China, with homeostasis model assessment of insulin resistance (HOMA-IR)>2.69 [7, 8]; 2) met the diagnostic criteria of phlegm-dampness type in Guiding Principles for Clinical Study of New Chinese Medicines [9]; 3) aged between 18-40 years; 4) had signed the informed consent.

Exclusion criteria: 1) Patients complicated with diseases of fallopian tubes and ovarium; 2) patients with congenital and structural abnormalities of the reproductive system; 3) patients complicated with dysthyreosis, hyperprolactinemia and other endocrine diseases; 4) patients who were allergic to the drugs used in this study; 5) patients who had used hormone drugs or other drugs that may affect their therapeutic evaluation 3 months before entering the study; 6) patients with other causes of hyperandrogenemia; 7) patients with severe heart, liver and kidney dysfunctions; 8) patients with poor compliance and who could not cooperate with the research.

Therapeutic methods

Patients in the control group were treated with a standard western medicine recipe, including oral administration of metformin (Harbin Tongyitang Pharmaceutical Co., Ltd, 0.5 g/tablet) and cyproterone acetate (Shanghai Acebright Pharmaceuticals Group Co., Ltd, cyproterone acetate 2 mg/table, ethinyloestradiol 35 μg/tablet). The metformin was administrated 1 tablet/time, 3 times/day, non-stop during menstrual period. The cyproterone acetate was administrated after the 5th day of withdrawal of menses or end of the menstrual cycle, 1 tablet/time, 1 time/day, with 21 days as a cycle; and the next cycle began from the 5th day of the next menstruation.

The treatment group was treated with modified Erchen decoction. The recipe was comprised of: pinellia ternata 10 g, tangerine peel 10 g, Poria cocos 15 g, alisma rhizome 12 g, immature bitter orange 12 g, arisaema cum bile 6 g, rhubarb 10 g, epimeddium 15 g, tendril-leaved fritillary bulb 10 g, liquorice 5 g. The above herbs were decocted with water and the final volume of decoction was 400 mL. Patients orally took 200 mL of Erchen decoction in the morning and evening each day, non-stop during the menstrual period.

Patients in both groups were treated for 3 menstrual cycles.

Outcome measure

(1) TCM syndrome scale scores. TCM syndrome scale scores of all patients were evaluated before and after treatment according to the Guiding principles for clinical research of new Traditional Chinese Medicine. The items in this scale included menstrual cycle, the volume and the color of menstrual blood, distension of the abdomen and anorexia. The higher score indicates a more serious degree of disease.

(2) Serum lipid level. About 5 mL of fasting venous blood was taken from patients in the early morning before and after treatment. After centrifugation, total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol

Table 1. The comparison of the general data ($\bar{x}$ ± sd)

Groups	Age (years)	Course of disease (months)	BMI (kg/m^2)
Control group (n=43)	26.6±3.3	8.74±2.68	26.25±2.35
Treatment group (n=43)	26.4±3.0	8.32±2.51	26.59±2.43
t	0.325	0.750	0.660
P	0.746	0.455	0.511

Note: BMI: body mass index.

(HDL-C) levels in the serum, were detected by an automatic biochemical analyzer.

(3) Insulin resistance level. Before and after treatment, fasting plasma glucose (FPG), insulin and homeostasis model assessment of insulin resistance (HOMA-IR) levels were determined. FPG level was detected by the glucose oxidase method. Fasting insulin (FINS) level was determined by radio immunoassay. HOMA-IR = FPG * FINS/22.5 [10].

(4) Sex hormone level. The levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), E-diol (E_2) and testosterone (T) were determined by radio immunoassay before and after treatment.

(5) Ovulation and menstrual cycle. Before and during the treatment, the ovulation status was monitored by the color Doppler ultrasonic diagnostic apparatus. At first, the monitoring frequency was every other day until the dominant follicle reached 15 mm; and then it was adjusted to once a day until ovulation. The ovulation condition was counted and menstrual cycle changes were recorded.

(6) Pregnancy rate. Two groups of patients received telephone follow-up and outpatient follow-up for 6 months. During this period, the pregnancy rate in the two groups was counted.

Statistical analysis

SPSS 20.0 software was used for data analysis. The measurement data conformed to normal distribution were represented as mean ± standard deviation ($\bar{x}$ ± sd); independent sample t test was used for the comparison between the two groups, while paired t test was adopted in the intra-group comparison. The enumeration data were represented by percentage, and χ^2 test was used for the inter-group comparison. P<0.05 means the difference is statistically significant.

Results

Baseline data analysis

There were no that patients dropped out of the study nor were removed from follow-up during the trial. There was no significant difference in age, course of disease and body mass index between the two groups (P>0.05). See **Table 1**.

Erchen decoction improves TCM syndrome scale scores of PCOS patients complicated with IR

The scores of all items in the TCM syndromes scale in the two groups were decreased after treatment, and the TCM treatment group acquired a better improvement (P<0.001). The combination of standard western medicine and Erchen decoction can significantly improve the menstrual cycle, the quantity and color of menstrual blood, distension in the abdomen and anorexia of patients compared with standard western medicine alone. See **Table 2**.

Erchen decoction improves serum lipid levels of PCOS patients complicated with IR

After treatment, the levels of TC, TG and LDL-C in two groups were all decreased, while the levels of HDL-C were increased (P<0.001). After treatment, the levels of TC, TG and LDL-C in the TCM treatment group were significantly lower than that of control group, while the level of HDL-C was the opposite (P<0.001). See **Table 3** and **Figure 1**.

Erchen decoction improves the level of insulin resistance indicators of PCOS patients complicated with IR

After the treatment, FPG, FINS and HOMA-IR levels in two groups were all decreased, and their levels in the TCM treatment group were significantly lower than those in the control group (P<0.05). See **Table 4** and **Figure 2**.

Erchen decoction improves sex hormone levels of PCOS patients complicated with IR

After treatment, the LH, FSH and T levels in the two groups were decreased and the E_2 level

Table 2. The comparison of the TCM syndromes scores before and after treatment (($\overline{x}$ ± sd), score)

Groups	Menstrual cycle		Quantity and color of menstrual		Distension in the abdomen		Anorexia	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	4.25±1.36	3.32±1.04*	4.36±1.28	3.24±1.10*	3.98±1.13	3.01±0.97*	3.88±1.17	2.96±0.81*
Treatment group (n=43)	4.15±1.13	2.15±0.68*	4.47±1.22	2.24±0.96*	3.87±1.03	1.88±0.82*	4.03±1.20	1.85±0.59*
t	0.371	6.174	0.478	4.491	0.472	5.834	0.587	7.264
P	0.712	<0.001	0.684	<0.001	0.638	<0.001	0.559	<0.001

Note: Compared to this group prior treatment, *P<0.05. TCM: traditional Chinese medicine.

Table 3. Comparison of serum lipid indicator levels before and after treatment (($\overline{x}$ ± sd), mmol/L)

Groups	TC		TG		LDL-C		HDL-C	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	1.69±0.51	1.32±0.39***	4.98±0.95	4.54±0.59***	2.49±0.65	2.13±0.36***	1.26±0.52	1.59±0.48***
Treatment group (n=43)	1.62±0.53	1.14±0.36***	4.87±0.98	4.01±0.55***	2.44±0.57	1.76±0.32***	1.33±0.58	1.87±0.51***
t	0.624	2.224	0.529	4.309	0.379	5.037	0.589	2.622
P	0.534	0.029	0.599	<0.001	0.706	<0.001	0.557	0.010

Note: Compared with the group before treatment, ***P<0.001. TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: low density lipoprotein cholesterol.

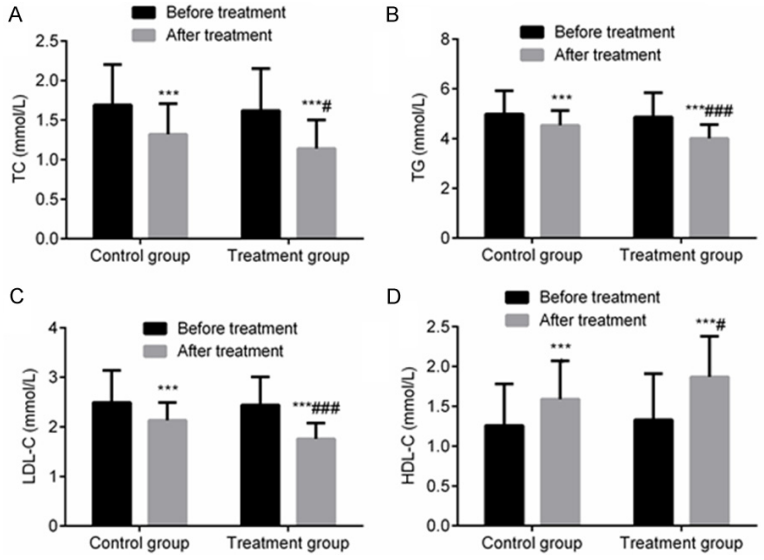

Figure 1. The comparison of serum lipid indicator levels before and after treatment. A: TC level; B: TG level; C: LDL-C level; D: HDL-C level. Compared with this group before treatment, ***P<0.001; compared with control group after treatment, #P<0.05, ###P<0.001. TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: low density lipoprotein cholesterol.

was increased (P<0.001). Compared to the control group, the TCM treatment group showed significantly lower LH, FSH and T levels but significant higher E_2 level (P<0.01). See **Table 5**.

Erchen decoction improves ovulation rate and menstrual cycle of PCOS patients complicated with IR

After treatment, the ovulation rates of the two groups were both increased, and the menstrual cycles were shortened (P<0.001). The ovulation rate of the TCM treatment group was higher than that of control group, and the menstrual cycle of the TCM treatment group was shorter than that of control group (P<0.05). See **Table 6**.

Erchen decoction improves pregnancy rate of PCOS patients complicated with IR

After follow-up for 6 months, the pregnancy rate of the TCM treatment group was higher than that of the control group (72.09% vs. 51.16%, P=0.046). See **Table 7**.

Adverse reactions

All the patients completed the treatment and received follow-up for 6-months, with no miss of a follow-up. No serious adverse reactions and complications occurred during the treatment.

Discussion

PCOS is a common disease of gynecological endocrine disorder with abnormal glucose and lipid metabolism. With the incidence increasing, it has become a frequently encountered disease in the gynecological clinic and a serious threat to female health. IR is one of the main pathophysiological mechanisms of PCOS, and an important factor of ovarian function change and hyperandrogenemia of PCOS patients [11, 12]. Hyperandrogenemia can not only promote the synthesis of ovarian androgens, but also directly act on the pituitary or hypothalamus to increase the LH concentration, so as to increase the secretion of ovarian androgens and result in the dysgenesis of follicular development [13]. Hyperinsulinemia can inhibit the liver to synthesize sex hormone binding proteins, to improve the sensitivity of pituitary gonadotropic hormones, and further to promote the secretion of androgens [14-16]. Thus, IR and IR-induced hyperinsulinemia may be important factors in the development of PCOS [17]. Western medicine has a certain effect on PCOS complicated with IR, but it falls short in the improvement of endocrine function and glucose metabolism, failing to obtain a favorable prognosis [18, 19]. Therefore, how to treat PCOS complicated with IR is a difficult problem in clinical work.

In recent years, TCM has been gradually applied to the clinical treatment of PCOS complicated with IR. It can not only effectively alleviate the clinical symptoms of patients, but also improve the endocrine function and glucose metabolism in a safe and non-toxic way [20]. Instead of a disease named as “PCOS complicated with IR”, TCM mainly classifies it into “delayed menses”, “hypomenorrhea”, “amenorrhea”, “dysgenesia” and “metrorrhagia” according to the clinical manifestations of patients [21]. TCM

Table 4. Comparison of the level of insulin resistance indicators before and after treatment ($\overline{x} \pm sd$)

Groups	FPG (mmol/L)		FINS (mIU/L)		HOMA-IR	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	5.78±0.82	5.06±0.45***	25.36±4.33	18.67±3.27***	4.12±1.34	3.56±1.06***
Treatment group (n=43)	5.74±0.75	4.55±0.47***	25.10±5.03	12.87±3.64***	4.22±1.38	2.32±1.14***
t	0.236	6.147	0.257	7.773	0.341	5.224
P	0.814	<0.001	0.798	<0.001	0.734	<0.001

Note: Compared with this group before treatment, ***P<0.001. FPG: fasting plasma sugar; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance.

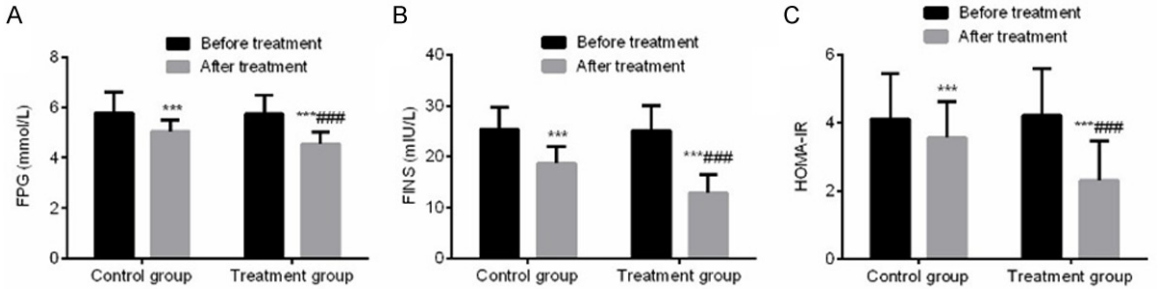

Figure 2. Comparison of the level of insulin resistance indicators before and after treatment. A: FPG level; B: FINS level; C: HOMA-IR level. Compared with this group before treatment, ***P<0.001; compared with control group after treatment, ###P<0.001. FPG: fasting plasma sugar; FINS: insulin; HOMA-IR: homeostasis model assessment of insulin resistance.

believes that PCOS complicated with IR is characterized by spleen-kidney-yang deficiency in essence with phlegm-dampness as manifestations. Due to long-term poor diet and spleen deficiency, the spleen qi is impaired and spleen dysfunction occurs, which further results in phlegm and dampness. The spleen deficiency is not cured and blood loss due to menstruation further aggravates this, leading to delayed menses and amenorrhea. Therefore, the treatment should be focused on drying dampness to eliminate phlegm. Our results show that the levels of TCM syndromes scale scores, TC, TG, LDL-C, LH, FSH, T, FPG, FINS, HOMA-IR levels and the menstrual cycles were all decreased in two groups after the treatment, while the levels of HDL-C, E_2 and ovulation rates increased. All the above indexes in the TCM treatment group were better improved than those in control group. After 6-month follow-up, the higher pregnancy rate was reported in the TCM treatment group in comparison to the control group. All these findings indicate that using modified Erchen decoction to treat phlegm-dampness PCOS complicated with IR can significantly alleviate the clinical symptoms, reduce the serum lipid levels, improve the insulin resistance condition, decurtate the menstrual cycle, and improve sex hormones and pregnancy rate.

The possible reasons may be that in the prescription of modified Erchen decoction, pinellia tuber has the efficiencies of disintegrating masses and dispersing accumulation, as well as dry damping and eliminating phlegm; Tangerine peel helps to drying damp and eliminating phlegm, in addition to regulating qi and invigorating the spleen; Poria cocos is beneficial to induce diuresis to alleviate edema while invigorating the spleen; Alisma rhizome also contributes to removing dampness and promoting diuresis, as well as detumescence and heat release; Immature bitter orange functions in breaking the stagnant qi and eliminating glomus; Arisaema cum bile is useful in expelling endogenous wind to relieve convulsion and drying dampness to eliminate phlegm; Rhubarb aids to eliminate stasis and restoring menstrual flow, results purgation, and helps heat-clearing and fire-purging; Epimeddium can invigorate the kidney yang, and dispel wind and dampness; Tendril-leaved fritillary bulb possesses the function of clearing away heat and dispersing phlegm, in addition to eliminating the mass and relieving swelling; Licorice root is capable of invigorating the spleen and replenishing qi, expelling phlegm to arrest coughing and importantly it can be a coordinator of the drug actions in a prescription. In the combina-

Table 5. The comparison of sex hormone levels before and after treatment ($\overline{x}$ ± sd)

Groups	LH (U/L)		FSH (U/L)		E_2 (pg/mL)		T (ng/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	13.36±2.03	8.87±1.61***	5.98±1.57	5.03±1.38***	39.85±8.69	49.88±10.69***	0.51±0.23	0.40±0.19***
Treatment group (n=43)	12.98±3.11	6.68±1.74***	5.82±1.65	4.15±1.24***	40.67±9.26	60.35±12.13***	0.48±0.21	0.29±0.14***
t	0.671	6.058	0.461	3.110	0.423	4.259	0.632	3.056
P	0.504	<0.001	0.646	0.003	0.673	<0.001	0.529	0.003

Note: Compared with this group before treatment, ***P<0.001. LH: luteinizing hormone; FSH: follicle stimulating hormone; E_2: E-diol; T: testosterone.

Table 6. The comparison of ovulation and menstrual cycles before and after treatment ($\bar{x} \pm sd$)

Groups	Ovulation rate (%)		Menstrual cycle ($\bar{x} \pm sd$)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	17 (39.53)	27 (62.79)***	50.25±9.65	43.25±6.25***
Treatment group (n=43)	19 (44.19)	36 (83.72)***	50.96±10.13	36.28±5.27***
t/χ^2	0.191	4.806	0.333	5.591
P	0.662	0.028	0.740	<0.001

Note: Compared with this group before treatment, ***P<0.001.

Table 7. The comparison of pregnancy (n (%))

Groups	Pregnancy	Without pregnancy
Control group (n=43)	22 (51.16)	21 (48.84)
Treatment group (n=43)	31 (72.09)	12 (27.91)
χ^2	3.983	
P	0.046	

tion of the above herbs, the main function can be deduced as depriving the evil wetness and eliminating sputum, regulating qi and normalizing function of the stomach and spleen.

However, this is a single center study with a small sample size and ashort follow-up time. Thus, there may be some bias in the results. Therefore, a multicenter study with more cases and longer follow-up time are needed in the future to make a better exploration.

In conclusion, modified Erchen decoction in addition to standard western medicine can significantly improve the clinical symptoms and the insulin resistance and accommodate the serum lipid levels, decurtating the menstrual cycle, thus improving the pregnancy rate of phlegm-dampness type of PCOS patients complicated with IR.

Disclosure of conflict of interest

None.

Address correspondence to: Yufeng Shi, Department of Comprehensive Internal Medicine of Traditional Chinese Medicine, Shenzhen Bao'an Authentic TCM Therapy Hospital, No.99 Lai'an Road, Xixiang Street, Bao'an District, Shenzhen 518100, Guangdong Province, China. Tel: +86-010-6028-3775; E-mail: shiyufeng99ba@163.com

References

[1] Qi J, Wang W, Zhu Q, He Y, Lu Y, Wang Y, Li X, Chen ZJ and Sun Y. Local cortisol elevation contributes to endometrial insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 2018; 103: 2457-2467.

[2] Kordestani F, Mazloomi S, Mortazavi Y, Mazloomzadeh S, Fathi M, Rahmanpour H and Nazarian A. Preliminary study showing no association between G238A (rs361525) tumor necrosis factor-alpha (TNF-alpha) gene polymorphism and its serum level, hormonal and biochemical aspects of polycystic ovary syndrome. BMC Med Genet 2018; 19: 149.

[3] Daghestani MH, Daghestani M, Daghistani M, El-Mazny A, Bjorklund G, Chirumbolo S, Al Saggaf SH and Warsy A. A study of ghrelin and leptin levels and their relationship to metabolic profiles in obese and lean Saudi women with polycystic ovary syndrome (PCOS). Lipids Health Dis 2018; 17: 195.

[4] Majid H, Masood Q and Khan AH. Homeostatic model assessment for insulin resistance (HOMA-IR): abetter marker for evaluating insulin resistance than fasting insulin in women with polycystic ovarian syndrome. J Coll Physicians Surg Pak 2017; 27: 123-126.

[5] Jahromi BN, Dabbaghmanesh MH, Bakhshaie P, Parsanezhad ME, Anvar Z, Alborzi M, Zarei A and Bakhshaei M. Assessment of oxytocin level, glucose metabolism components and cut-off values for oxytocin and anti-mullerian hormone in infertile PCOS women. Taiwan J Obstet Gynecol 2018; 57: 555-559.

[6] Yildirim E, Karabulut O, Yuksel UC, Celik M, Bugan B, Gokoglan Y, Ulubay M, Gungor M and Koklu M. Echocardiographic evaluation of diastolic functions in patients with polycystic ovary syndrome: a comperative study of diastolic functions in sub-phenotypes of polycystic ovary syndrome. Cardiol J 2017; 24: 364-373.

[7] Group of Endocrinology and Guidelines Expert Group, Chinese Medical Association Gynaecology and Obstetrics Branch. Guidelines for Chinese diagnosis and treatment of polycystic ovary syndrome. Chin J Obstet Gynecol 2018; 53: 2-6.

[8] Insulin Resistance Section, Diabetes Branch and Chinese Medical Association. Expert guidance on methods and applications of insulin

resistance assessment. Chin J Diabet 2018; 10: 377-385.
[9] Zhen XY. Guiding principle for clinical research on new drugs of traditional Chinese medicine. Edited by Zhen XY, Beijing, China Medical Science Press, 2002, pp. 239.
[10] Wiweko B, Indra I, Susanto C, Natadisastra M and Hestiantoro A. The correlation between serum AMH and HOMA-IR among PCOS phenotypes. BMC Res Notes 2018; 11: 114.
[11] Seyam E and Hefzy E. Evaluation of the correlation between insulin like factor 3, polycystic ovary syndrome, and ovarian maldescent. Gynecol Endocrinol 2018; 34: 481-488.
[12] Pergialiotis V, Konstantopoulos P, Prodromidou A, Florou V, Papantoniou N and Perrea DN. Management of endocrine disease: the impact of subclinical hypothyroidism on anthropometric characteristics, lipid, glucose and hormonal profile of PCOS patients: a systematic review and meta-analysis. Eur J Endocrinol 2017; 176: R159-r166.
[13] Zhang J, Hu J, Zhang C, Jiao Y, Kong X and Wang W. Analyses of risk factors for polycystic ovary syndrome complicated with non-alcoholic fatty liver disease. Exp Ther Med 2018; 15: 4259-4264.
[14] Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raee MJ and Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: arandomized double-blind placebo controlled clinical trial. Phytother Res 2018; 32: 276-283.
[15] Seyyed Abootorabi M, Ayremlou P, Behrooz-Lak T and Nourisaeidlou S. The effect of vitamin D supplementation on insulin resistance, visceral fat and adiponectin in vitamin D deficient women with polycystic ovary syndrome: a randomized placebo-controlled trial. Gynecol Endocrinol 2018; 34: 489-494.
[16] Greenwood EA, Pasch LA, Cedars MI, Legro RS, Eisenberg E and Huddleston HG. Insulin resistance is associated with depression risk in polycystic ovary syndrome. Fertil Steril 2018; 110: 27-34.
[17] Afshar Ebrahimi F, Foroozanfard F, Aghadavod E, Bahmani F and Asemi Z. The effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress, and gene expression related to inflammation in polycystic ovary syndrome: a randomized controlled clinical trial. Biol Trace Elem Res 2018; 184: 300-307.
[18] Nekoonam S, Naji M, Nashtaei MS, Mortezaee K, Koruji M, Safdarian L and Amidi F. Expression of AKT1 along with AKT2 in granulosa-lutein cells of hyperandrogenic PCOS patients. Arch Gynecol Obstet 2017; 295: 1041-1050.
[19] Patlolla S, Vaikkakara S, Sachan A, Venkatanarasu A, Bachimanchi B, Bitla A, Settipalli S, Pathiputturu S, Sugali RN and Chiri S. Heterogenous origins of hyperandrogenism in the polycystic ovary syndrome in relation to body mass index and insulin resistance. Gynecol Endocrinol 2018; 34: 238-242.
[20] Noroozzadeh M, Ramezani Tehrani F, Bahri Khomami M and Azizi F. A comparison of sexual function in women with polycystic ovary syndrome (PCOS) whose mothers had PCOS during their pregnancy period with those without PCOS. Arch Sex Behav 2017; 46: 2033-2042.
[21] Cooney LG, Lee I, Sammel MD and Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2017; 32: 1075-1091.