Original Article

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Association between Glucose Metabolism and Oral Combined Contraceptive Pills or Cyclic Progestin in Thai Women with Polycystic Ovary Syndrome: A 3-year Observational Study

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Abstract:

Objective: To measure the difference in fasting blood glucose (FBG) among Thai women with polycystic ovary syndrome (PCOS), having received either oral combined contraceptive pills (OCP) or cyclic progestin, during 3 years of treatment.

Materials and Methods: The data were collected by a retrospective chart review of women with PCOS, who had been treated at Siriraj Hospital before June 2019, backward to the year 2000. The patients were divided into two groups, according to their different treatments, namely: an OCP group and a cyclic progestin group. There were 44 cases in each group, and both groups had received complete hormonal treatment over 3 years.

Results: The patients' baseline characteristics showed a significantly lower body mass index (BMI) and waist circumference (WC) in the OCP group than in the cyclic progestin treatment group. After the 3-year period of treatment, the FBG differences in the OCP group and cyclic progestin treatment group were 3.4±8.4 and 3.6±8.5 mg/dL, respectively; which revealed no statistical significance. Additionally, the difference in the WC and metabolic profile between the studied groups after 3 years of treatment also revealed no significance. However, BMI presented a significant difference between the two hormonal regimens after 3 years of treatment (p-value=0.007), with higher differences in the OCP treatment group.

Conclusion: There was no statistically significant difference in FBG between the beginning and at the third year of treatment found in both regimens of hormonal treatment in Thai PCOS women.

Keywords: cyclic progestin, fasting blood glucose, oral combined contraceptive pills, polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a syndrome derived from abnormalities of the endocrine system. It is usually found in reproductive women; wherein the incidence rate is around 6%–20%[1]. At the Gynecologic Endocrinology Unit (GEU), Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital an incidence of approximately 5% is found[2]. Studies in Thai adolescents have reported the incidence of PCOS at an estimated 5.29%[3]. The important pathophysiology of PCOS includes chronic anovulation, insulin resistance and hyperandrogenism. The revised Rotterdam criteria 2003, are mostly used for the diagnosis of PCOS; whereby, the syndrome is diagnosed if at least two out of the following three criteria are met[4]: presence of oligomenorrhea and/or amenorrhea, hyperandrogenemia and/or hyperandrogenism and polycystic ovaries from pelvic ultrasonography. A differential diagnosis, considering other conditions with similar symptoms, is also necessary including, thyroid disorder, hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, adrenal tumor and ovarian tumor.

PCOS is usually associated with obesity, insulin resistance, dyslipidemia, and metabolic syndrome; albeit the mechanism has still not been clearly identified. The risk factors include genetics, environment, nutritional status and habits[5]. A previous study in the GEU, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital reported that the prevalence of an abnormal glucose tolerance test result in PCOS was 20%; wherein, impaired fasting glucose (IFG) accounted for 3.2%, impaired glucose tolerance (IGT) for 13.6%, and diabetes mellitus (DM) for 5.6% of cases[6,7]. Moreover, the incidence of metabolic syndrome was found to be increased in PCOS women. The previous study in the GEU, Siriraj Hospital, revealed that the prevalence of metabolic syndrome in PCOS was approximately 18.0%, 21.2%, and 21.2%; according to the NCEP ATP III, IDF and NHLBI/AHA definitions, respectively[8].

The goals in PCOS treatment are regulating the menstrual cycle to protect the endometrium from hyperplasia or neoplasm, improving the symptoms of androgen excess, infertility, and decreasing insulin insensitivity and metabolic syndrome. The medication mostly used is oral combined contraceptive pills (OCPs) and cyclic progestin. This is for the regulation of the menstrual cycle and for the prevention of endometrial hyperplasia and malignancy. Differences in the hormonal regimen might affect the differences in metabolic abnormalities[9]. High-dose oral contraceptives can increase insulin resistance, so sound advice is to avoid this kind of treatment in anovulatory and overweight women. A previous study reported that estradiol stimulates insulin secretion; similar to the insulinotropic effect of estradiol[10]. González et al. reported in their study that estradiol had an effect on the insulin receptor[11]. Ovarectomized rats showed decreasing insulin sensitivity, especially, at higher doses within the estradiol replacement group. The mechanism of progestin action on glucose metabolism might affect the pancreatic beta cells resulting in insulin regulation[12]. Moreover, androgenic progestin might have an "anti-insulin" effect, by increasing peripheral insulin resistance[13]. Presently, hormonal pills have been developed to decrease the dosage of estrogen and to lower the androgenic effect of progestin. This implies that the metabolic effect on hormonal treatment could be divergent in different treatment regimens. In Adeniji et al.'s study, statistical significance was found regarding the increase in fasting blood glucose after using OCPs in both the control and PCOS groups[14]. However, according to Mes-Krowinkel et al., no significant change was found in a homeostasis model assessment regarding insulin resistance (HOMA-IR) between OCP-used and OCP-omitted groups[15]. A systematic review and meta-analysis of OCP use, by Halperin et al., found no

significant change in insulin level, blood sugar level, or HOMA-IR[16]. Additionally, another systematic review, by Glisic et al., found that cyclic progestin did not increase the risk of cardiovascular disease, nor did it affect the metabolic profile[17].

However, there is still no definitive conclusion on how OCPs and cyclic progestin effects carbohydrate metabolism, fasting blood glucose, and other metabolic profiles. Based on data from the GEU, both treatment groups could be observed; with about 50% of PCOS patients being obese, and 20% of them having insulin insensitivity[7]. Therefore, physicians should choose the appropriate treatment for their patients by considering not only insulin resistance but also their fasting blood glucose level as well as other metabolic profiles. In this research, the researcher aimed to observe the differences in fasting blood glucose levels after 3-year treatment programs with two hormonal regimens: oral combined contraceptive pills and cyclic progestin.

Material and Methods

This research was a retrospective chart review study, in which the sample size was calculated based on the data from a pilot study of PCOS patients at the GEU, Siriraj Hospital. The required number was calculated to be 44 cases in both the PCOS women treated with the OCPs group and in the cyclic progestin group. The inclusion criteria were: patients aged between 18 and 45 years old; diagnosed with PCOS by the revised Rotterdam 2003 criteria, having a normal 75-gram oral glucose tolerance test, and were receiving treatment at the GEU, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital; under continuous hormonal treatment for at least 3 years. The data were collected before June 2019, backward to the year 2000. Exclusion criteria were: incomplete data, a change in the hormonal treatment during the 3-year follow-up, laboratory tests not performed at Siriraj Hospital, and those receiving medication that could affect their glucose metabolism.

For PCOS, the revised Rotterdam 2003 criteria were used for the diagnosis. PCOS was diagnosed in cases where at least two out of the following three criteria were met: the presence of oligomenorrhea and/or amenorrhea, hyperandrogenemia and/or hyperandrogenism, and polycystic ovaries. After gaining ethical approval, from the Institutional Review Board, Faculty of Medicine, Siriraj Hospital (Certificate of Approval, Number Si 395/2019), the patients' data were collected at the first visit and three years after treatment for both treatment groups. The demographic data collected included: age, parity, waist circumference and blood pressure. In addition, data to create the metabolic profile were also collected, i.e., fasting blood glucose, 75-gram oral glucose tolerance test and lipid profile.

Statistical analysis was performed using the SPSS statistics 21 program. Descriptive analysis was used to describe the patients' characteristics. The Student-t test was used to analyze the continuous data. The data are shown as the mean value for the difference±standard deviation (mean S.D.).

Results

After the medical chart review had been completed, 88 cases of PCOS patients were included in the study. These were divided into two groups of 44 cases each: first, the group of those who had received OCPs and second, the group of those who had received cyclic progestin. Patients in the OCP group received various regimens comprising of: 0.03 mg ethinyl estradiol, plus 3 mg drospirenone for 20 women; 0.02 mg ethinyl estradiol, plus 0.15 mg desogestrel for 16 women; 0.035 mg ethinyl estradiol, plus 2 mg cyproterone acetate for 5 women; 0.02 mg ethinyl estradiol, plus 3 mg drospirinone for 2 women; and 0.03 mg ethinyl estradiol, plus 2 mg chlormadinone acetate for 1 woman. In the cyclic progestin group, the regimens involved receiving medroxyprogesterone acetate, norethisterone, and dydrogesterone for 28, 11, and 5 women, respectively (data not shown in the table). The baseline characteristics of the

patients in both groups are shown in Table 1. Regarding the OCP treatment group, it showed a lower body mass index (BMI) and waist circumference (WC) than in the cyclic progestin treatment group; with statistical significance (BMI 22.03.7 kg/m^2 and 26.87.1 kg/m^2, p-value<0.001; WC 74.8±7.6 cm and 83.0±16.7 cm, p-value=0.030). Moreover, the 2-hour oral glucose tolerance test values in the OCP treatment group were found to be significantly lower than those found in the cyclic progestin treatment group. In contrast, the cholesterol and high density lipoprotein (HDL) levels in the OCP treatment group were found to be higher than those found in the cyclic progestin treatment group.

The data from Table 2 represents the metabolic profile between the first visit and after three years of treatment; according to the adjusted BMI and WC analysis. There was no significant change in FBG after three years of treatment between the two groups. Moreover, the cholesterol, triglycerides, HDL, and low density lipoprotein (LDL) values were not significantly different between the two groups.

Anthropometric measurements at the first visit and after three years of treatment for both groups with oral combined pills treatment and cyclic progestin treatment are shown in Table 3. There was no significant difference in WC among the participants in both treatment groups during the three years of treatment; however, there was a significantly higher difference in BMI after the three year treatment in the OCP group.

Table 1 Baseline characteristics and metabolic profiles in the oral combined pills (OCP) treatment group and the cyclic progestin treatment group

Characteristics	OCP treatment group (n=44)	Cyclic progestin treatment group (n=44)	p-value
Age (years old)	25.0±4.5	26.8±6.3	0.130
Body mass index (kg/m^2)	22.0±3.7	26.8±7.1	<0.001
Waist circumference (cm)	74.8±7.6	83.0±16.7	0.030
Systolic blood pressure (mmHg)	111.0±14.0	116.5±14.1	0.080
Diastolic blood pressure (mmHg)	69.9±9.5	72.6±12.2	0.260
Fasting blood glucose (mg/dL)	82.4±5.6	85.1±0.5	0.070
2 hours oral glucose tolerance test (mg/dL)	94.8±18.5	107.7±23.3	0.020
Cholesterol (mg/dL)	203.9±50.4	185.3±31.2	0.040
Triglyceride (mg/dL)	79.8 ±58.1	99.5±6.2	0.120
High density lipoprotein (mg/dL)	64.9±16.0	55.41±3.2	0.003
Low density lipoprotein (mg/dL)	123.0±50.6	110.0±29.2	0.150

Note: The data are presented as the mean S.D.

Table 2 Metabolic profile between the first visit and after three years of treatment in the oral combined pills (OCP) and the cyclic progestin treatment groups

	OCP treatment group (n=44)			Cyclic progestin treatment group (n=44)			p-value†
	1st visit	3rd year	Difference	1st visit	3rd year	Difference	
FBG (mg/dL)	82.4±5.6	85.8±8.9	3.4±8.4	85.1±7.5	87.9±9.5	3.6 ±8.5	0.93
Cholesterol (mg/dL)	203.9±50.4	190.8±35.2	-13.1±44.7	185.3±31.2	188.5±35.5	3.5±27.2	0.082
Triglyceride (mg/dL)	79.8±58.1	106.8±46.1	27±47.2	99.5±56.2	95.1±43.8	-4.5±44.0	0.06
HDL (mg/dL)	64.9±16.0	70.2±20.9	5.3±16.2	55.4±13.2	58.7±16.7	2.6 ±10.2	0.44
LDL (mg/dL)	122.9±50.6	98.8±29.1	-24.2±41.3	110.0±29.2	110.7±29.1	1.8±27.8	0.55

Note: The data are presented as the mean S.D.
†Adjusted BMI and waist circumference
FBG=fasting blood glucose, HDL=high density lipoprotein LDL=low density lipoprotein

Table 3 Anthropometric measurement at the first visit and after three years of treatment in the oral combined pills (OCP) and the cyclic progestin treatment groups

Parameter	OCP treatment group (n=44)			Cyclic progestin treatment group (n=44)			p-value†
	1st visit	3rd year	Difference	1st visit	3rd year	Difference	
BMI (kg/m^2)	21.9±3.7	22.3±3.9	0.4±1.2	26.8±7.1	25.1±6.5	-0.5±1.0	0.007
WC (cm)	74.8±83.0	74.4±9.9	-0.2±4.8	83.2±16.7	80.7±13.9	-0.1±3.9	0.980

Note: The data are presented as the mean S.D.
†Adjusted BMI and waist circumference
BMI=body mass index, WC=waist circumference

Discussion

The prevalence of obesity in PCOS women was found to be about 30%–75%[18]. The study from the GEU, Siriraj Hospital, revealed that 57% of Thai PCOS women were obese and central obesity was at 49%[19]. The presence of obesity can effectively lead to further metabolic abnormalities, such as, DM, dyslipidemia, hypertension, metabolic syndrome and cardiovascular disease[20]. Moreover, the risk of thromboembolic events is also increased in obese women. Hormonal treatment should be provided to PCOS women to regulate menstruation to aid in preventing endometrial hyperplasia and/or cancer. The use of OCPs provides more benefits than cyclic progestin; such as, contraception and anti-androgenic effects. A meta-analysis of 35 studies reported there was no association of OCP use with clinically significant adverse metabolic consequences[16];

however, oral combined contraceptive pills may deteriorate carbohydrate metabolism[21]. This effect might be primarily through the activity of progestin. However, modern low-dose OCP preparations, with the new generation of progestin, have a less metabolic impact than the high-dose and old regimens[21]. Previous studies have shown that the estradiol and androgenic effects of progestin may affect carbohydrate metabolism and also cause a decrease in insulin sensitivity. However, data regarding the long-term effect of hormonal contraceptives on carbohydrate metabolism are still unclear[22]. A recent systematic review reported no significant differences in carbohydrate profiles between different hormonal contraceptives pills in healthy women[23]. The effect of progestin on carbohydrate metabolism depends on the type of progestin. In one study, levonorgestrel presented the highest deterioration of glucose and insulin response after oral glucose tolerance tests[24]. The new generation of progestins such as dienogest and cyproterone have shown lesser effects on metabolic profiles while at the same time reducing the androgenic effect[25]. According to previous studies, it is likely that the use of OCPs in combination with ethinyl estradiol with progestin types of gonanes; such as desogestrel and gestodene, may cause an increase in insulin resistance[26]. This study revealed the same results as found in previous studies; in which there was no significant difference in glucose metabolism in either the OCP or cyclic progestin treatment groups. These results might be due to the various hormonal regimens of OCPs and cyclic progestin. Carbohydrate metabolic effects were, however, found to be affected, depending on either the type or the dose of estrogen and progestin. Also, it is important to note that the baseline characteristics of the participants between the two groups were different. Regarding anthropometric measurement in the previous study by Manzoor et al., a worsening profile in the OCP group was found[27]. The finding in that first study was different from that of this study, in which no difference was reported. In this study, patients in the OCP group had a thinner anthropomorphism and better metabolic profile than those in the cyclic progestin group. This was because the physicians sought to avoid thrombotic risk from OCP treatment in obese women. This study showed no statistically significant difference in FBG, lipid profile or WC changes after OCP and cyclic progestin treatments among the Thai PCOS women (after BMI and WC adjustment). The cyclic progestin treatment group showed a difference in BMI after treatment, however, the WC did not show any significant difference. This may be due to the changes of fat in other areas; such as, in the upper/lower arm, , thigh or lower leg (in the peripheral areas of the body). The contributive strength of this trial is the development of an initial database of Thai PCOS women for comparing the differences in FBG between OCP and cyclic progestin treatment regimens. However, there are a number of study limitations to note including, being a retrospective study, the various hormonal doses and regimens used, many conditions affecting weight, and glucose metabolism, the time constraint of only covering a three-year follow-up period as well as the different baseline characteristics of the participants between the two groups.

Further data could not be collected over a longer term, because of the changing hormonal regimens due to the contraceptive and anti-androgenic effects as well as the related risk of thromboembolism. In the future, a better, more controlled study should be conducted; involving a randomized controlled trial, a larger population, sampling with the same hormonal regimen and a longer follow-up period. The implications that could be achieved from a well-conducted study may provide more information for appropriately choosing the right hormonal regimen, with a lower effect on glucose metabolism; especially in obese PCOS women.

Conclusion

There were no differences in fasting blood glucose, anthropometry or lipid profile among the PCOS female patients in the two studied groups; namely the OCP and cyclic progestin groups, after the 3-year treatment.

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Conflict of interest

The authors declare they have no conflicts of interest with any private company and received no honorarium budget from any institute regarding this study.

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