A Comparative Study of LDL-C Levels in Polycystic Ovary Syndrome Women with Different Cardiovascular Risks According to American Heart Association Criteria

Yada Tingthanatikul MD*, Saranthorn Sripilaipong MD*, Orawin Vallibhakara MD*, Areepan Sophonsritsuk MD, PhD*, Sawaek Weerakiet MD*, Sakda Arj-Ong Vallibhakara MD, PhD**

* Reproductive Endocrinology and Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
** Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Objective: To compare metabolic parameters including low-density lipoprotein cholesterol (LDL-C) levels between polycystic ovary syndrome (PCOS) women with the different cardiovascular disease risks (CVD), and to study the frequency of PCOS women in each risk category who need treatment for the target LDL-C levels according to the recommendation by the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS).

Material and Method: This was a retrospective comparative study. Data from the medical records and electronic forms of the 208 PCOS women, who consecutively attended the Reproductive between February 2004 and December 2010 were analyzed. According to the recommendation of the AE-PCOS society, the subjects were classified into three groups of CVD risk.

Results: There were 22, 129, and 57 women being at optimal risk, at risk, and at high-risk groups, respectively. There were significant differences in all metabolic factors between the different CVD classifications according to the AE-PCOS society. Furthermore, the PCOS women at high-risk had higher rates of the most significant parameters than those at risk. However, the LDL-C levels were not different between PCOS women at high-risk and at risk. Interestingly, 56%, 90.7%, and 100% of PCOS women at risk, at high-risk, and at high-risk plus other risks, respectively, had LDL-C levels above the target goals, which needed to be lower for the primary CVD prevention according to the AE-PCOS society recommendation.

Conclusion: There were differences in all metabolic factors between the different CVD classifications, but LDL-C levels were not different between PCOS women at high-risk and at risk. To get target goal for the primary CVD prevention, 91% and 100% of PCOS women at high-risk and at high-risk plus other risks need to lower LDL-C levels.

Keywords: CVD risk classification, LDL-C level, Metabolic parameters, Polycystic ovary syndrome

Correspondence to:
Sophonsritsuk A; Reproductive Endocrinology, Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.
Phone: +66-2-2011412, Fax: +66-2-2011416
E-mail: areepan.sop@mahidol.ac.th

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women(1). Women with PCOS commonly present with chronic anovulation, hyperandrogenism, and/or polycystic ovaries(1). Insulin resistance (IR) and its compensatory hyperinsulinemia are the significant pathophysiology of PCOS(1,2). With this regard, women with PCOS are at increased risk of metabolic abnormalities including glucose intolerance, hypertension, dyslipidemia, and metabolic syndrome (MS)(1). These metabolic disturbances promote atherosclerosis leading to cardiovascular disease (CVD)(3,5). Although evidence for CVD event is limited, PCOS women have more sub-clinical disease and more CVD risk factors when compared to the non-PCOS women(6). The Committee of the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society have recommended all PCOS women should be screened for CVD risk factors aimed to classify the women at risk and to consider primary prevention(6).

Treatments to control all risk factors for women at risk of CVD have been recommended by the American Heart Association (AHA)(7,8). The low-density lipoprotein cholesterol (LDL-C), one of the important risk factors, is the primary target for lipid-lowering treatment according to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)(9). The ideal levels of LDL-C are different between groups depending on the severity of the CVD risk(7,9). The AHA and the American College of Cardiology (ACC) have categorized CVD risks in women into 3 groups as at optimal risk, at risk, and at high-risk(7,8). Based on the AHA guideline(7,8), the
AE-PCOS society has also recommended that PCOS-related CVD risk has been classified as: at optimal risk, at risk, and at high-risk\(^6\). The target treatment LDL-C levels are 130 mg/dl or less for PCOS women at optimal risk and at risk women, while the level is 100 mg/dl or less for those at high-risk\(^6\).

The present study primarily aimed to compare metabolic parameters, especially LDL-C levels, between PCOS women with the different CVD risks categorized by the AE-PCOS society. The second objective was to study how many PCOS women in each category need to be treated to get the targeted LDL-C levels according to the recommendation of the AE-PCOS society.

**Material and Method**

This retrospective comparative study was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital. Data from the medical records and electronic forms of 208 women with PCOS consecutively attended the Reproductive Endocrinology and Infertility Unit, Department of Obstetrics and Gynecology, Ramathibodi Hospital, Mahidol University between February 2004 and December 2010 were analyzed.

**Subjects**

The criteria of the Rotterdam European Society for Human Reproduction & Embryology/ the American Society for Reproductive Medicine-sponsored PCOS consensus workshop group\(^6\) were used for the diagnosis of PCOS. All PCOS women had at least two of three components of the diagnostic criteria: 1) oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (absence of menstrual cycles in the past 6 months), 2) any sign of clinical hyperandrogenism such as acne, seborrhea and hirsutism (Ferriman-Gallwey score greater than 8)\(^10\) or biochemical hyperandrogenism, and 3) typical ultrasonic appearance of polycystic ovary established by at least one ovary demonstrates an ovarian volume greater than 10 cm\(^3\) and/or 12 or more follicles of 2 to 9 mm in diameter.

The diseases which mimic to PCOS such as hyperprolactinemia, thyroid dysfunction, hypothalamic amenorrhea, congenital adrenal hyperplasia (CAH), and hormone-producing ovarian neoplasia were ruled out using prolactin, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), fasting 17-hydroxyprogesterone (17-OHP) levels, and ultrasonography.

**Procedures**

In accordance with our protocol, all women confirmed the diagnosis of PCOS underwent a review of cigarette smoking, family history of diabetes mellitus (DM) and CVD. Anthropometric and metabolic measurements were also performed. Body weight and height were measured with participants in light clothing without shoes\(^11\). Waist circumference (WC) was measured with a soft tape on standing subjects midpoint between the lower margin of the last palpable rib and the top of the iliac crest\(^11\). Hip circumference was measured at the widest portion of the buttocks\(^11\). Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Waist-to-hip ratio (WHR) was calculated as WC in centimeters divided by hip circumference in centimeters. Blood pressure was measured on the right arm of women in a sitting position after 30 minutes rest using a manual mercury sphygmomanometer. The first and fifth Korotkoff phases were used to define systolic and diastolic blood pressures. Two blood pressure recordings at 5 minutes interval were obtained and the average value was calculated.

A 75-g glucose tolerance test (OGTT) was performed after three days on a diet containing 300 g carbohydrate/day and an overnight fast of at least 10 to 12 hours Blood samples for plasma glucose levels were obtained at 0 and 120 minutes. Blood samples for fasting LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, and cholesterol were also obtained. According to NCEP ATP III\(^12\), the diagnosis of MS is made if there are any three or more of the following findings: 1) elevated WC: greater than 80 cm, 2) elevated triglycerides: 150 mg/dl or more, 3) reduced HDL-cholesterol: less than 50 mg/dl, 4) elevated blood pressure: systolic blood pressure 130 mmHg or greater and/or diastolic blood pressure 85 mmHg or greater, and 5) elevated fasting glucose: 100 mg/dl or greater.

The definitions of glucose intolerances are as follows\(^13\): 1) impaired fasting glucose (IFG): FG 100 mg/dl or greater and less than 126 mg/dl, 2) impaired glucose tolerance (IGT): 2-hour post-load glucose 140 mg/dl or greater and less than 200 mg/dl, and 3) type 2 DM: FG FG 126 mg/dl or greater and/or 2-hour PG 200 mg/dl or greater.

According to the AE-PCOS society recommendation, the categories of PCOS-related CVD risk are optimal risk, at risk, and at high-risk\(^6\). The Androgen Excess and the Polycystic Ovary Syndrome Panel Committee\(^6\) has recommended the target LDL-C levels for primary prevention of CVD...
depended on the risk categories as follows: 1) PCOS women at optimal risk, LDL-C target level 130 mg/dl or less, 2) PCOS women at risk, LDL-C target level 130 mg/dl or less, 3) PCOS women at high-risk, LDL-C target level 100 mg/dl or less, and 4) PCOS women at high-risk plus other risk or DM, LDL-C target level 70 mg/dl or less.

**Statistical analysis**

All analyzes were performed using Statistical Package for the Social Sciences version 21. Descriptive statistics, baseline characteristics were described with mean ± standard deviation (SD) for the continuous data and frequency (%) for the categorical data. To compare variables between multiple groups, the ANOVA with post-hoc test and Chi-square test were used where appropriate. A p-value of <0.05 was considered statistically significant.

**Results**

Total number of PCOS women enrolled in the present study was 208. These women were non-smoker, and their family had no history of CVD. There were 22, 129, and 57 women being at optimal risk, at risk, and at high-risk groups, respectively. The characteristic of all three groups were shown in Table 1. The BMI, WC, and all metabolic parameters were similar, but cholesterol and LDL-C were higher in women at high-risk than those at risk and at optimal risk. When compared between women at risk and at optimal risk, obesity, and all lipid parameters were greater in the risk group, while there were no differences in diastolic pressure and glucose levels (Table 1). Triglyceride level was greater and HDL-C level was lesser in women at high-risk (170.21±78.04 mg/dl vs. 100.25±62.15 mg/dl vs. 50.90±13.86 mg/dl, p<0.001, and 38.39±8.47 mg/dl vs. 38.39±8.47 mg/dl vs. 38.39±8.47 mg/dl, p<0.001, respectively). Interestingly, LDL-C and cholesterol levels were not different compared between PCOS women at risk and at high-risk (Table 1).

Table 2 showed prevalence of PCOS women with metabolic parameters. Most but not all abnormal metabolic parameters were greater in the high-risk than the risk groups. Both groups had the same frequencies of abnormal cholesterol and LDL-C (p = 0.838 and 0.761, respectively).

Table 3 showed numbers and frequencies of women who needed to treat to get target LDL-C levels according to the AE-PCOS society recommendation. All of PCOS women (100%) in high-risk group with MS and other risk factors or type 2 DM had LDL-C level (70 mg/dl or greater) above its target level. The remaining high-risk PCOS women had LDL-C level greater than 100 mg/dl in 39 out of 43 (90.7%). Women at risk who need to have LDL-C level 130 mg/dl or less were found in 72 out of 129 (55.8%).

**Discussion**

Many studies of metabolic parameters which are CVD risk factors in PCOS women have been reported. Most of studies were conducted to compare between PCOS women and controls. Some studies aimed to depict metabolic parameters in PCOS women with different characters, for example, IR vs. non-IR, overweight vs. normal weight, and different ethnicities. We conducted a comparative study to compare cardiovascular metabolic risk factors between PCOS women with different CVD risks. The CVD risk classification used in the current study has originally provided by the AHA. The AE-PCOS society has implemented this classification for PCOS women aimed to categorize these women as being at optimal risk, at risk, or at high-risk for CVD.

However, there are some differences between two classifications. For example, IGT is a risk factor classified in PCOS women at risk for CVD, but it is not mentioned in the AHA classification. Most importantly, MS is classified as a high-risk factor for PCOS women, whereas only is a risk factor according to the AHA classification. In fact, MS is composed of three or more CVD risk factors and is more prevalent both in American and Asian PCOS women. Accordingly, MS has been categorized as the criterion at high CVD risk for PCOS women.

In the current study, the PCOS women at high-risk had significantly greater central obesity, FG, blood pressure, and triglyceride, and had significantly lesser HDL-C than those at risk and at optimal risk. This phenomenon could be explained by the fact that PCOS women at high-risk are those with MS and/or type 2 DM, and all these factors are the components of MS. As a result, the levels of these CVD factors were mostly different between groups. A study from China compared between PCOS women with (n = 159) and without MS (n = 674) also demonstrated the similar results. IR and obesity are most likely to be etiological causes of severity of these factors. Dukrast et al. had also demonstrated IR was greater in PCOS with MS than those without MS. Most recently, BMI has been shown to be a predictor for MS in PCOS women with OR of 1.420. In the current study IR and obesity are also likely to be the causes of...
increased CVD risk. Although IR parameters were not shown, acanthosis nigricans, which are strongly associated with IR\(^{(28,29)}\) were more prevalent in the PCOS at high-risk than those at risk and at optimal risk. In addition, BMI, and WC were significantly higher in the PCOS women at high-risk.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCOS (n = 208 cases)</th>
<th>Comparison group</th>
<th>Post-hoc p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimal risk (n = 22)</td>
<td>At risk (n = 129)</td>
<td>At high-risk (n = 57)</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>27.32±5.78</td>
<td>28.59±5.58</td>
<td>30.86±6.69</td>
</tr>
<tr>
<td>Waist-Hip ratio(^a)</td>
<td>0.80±0.07</td>
<td>0.82±0.07</td>
<td>0.87±0.05</td>
</tr>
<tr>
<td>Waist circumference (cm)(^a)</td>
<td>67.04±5.70</td>
<td>76.79±9.86</td>
<td>95.36±13.09</td>
</tr>
<tr>
<td>BMI (kg/m(^2))(^a)</td>
<td>19.76±1.58</td>
<td>24.20±4.21</td>
<td>33.80±6.64</td>
</tr>
<tr>
<td>Systolic BP (mmHg)(^a)</td>
<td>108.41±9.65</td>
<td>115.65±9.45</td>
<td>132.49±12.06</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)(^a)</td>
<td>70.14±6.84</td>
<td>74.32±6.66</td>
<td>85.72±10.30</td>
</tr>
<tr>
<td>Oligomenorrhea(^b)</td>
<td>14 (63.64)</td>
<td>58 (44.96)</td>
<td>27 (47.37)</td>
</tr>
<tr>
<td>Amenorrhea(^b)</td>
<td>8 (36.36)</td>
<td>64 (49.61)</td>
<td>25 (43.86)</td>
</tr>
<tr>
<td>Family history of DM(^b)</td>
<td>8 (36.36)</td>
<td>33 (25.58)</td>
<td>24 (42.11)</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)(^a)</td>
<td>85.00±5.47</td>
<td>86.97±6.89</td>
<td>104.00±27.47</td>
</tr>
<tr>
<td>75g OGTT at 2-hour (mg/dl)(^a)</td>
<td>93.41±20.51</td>
<td>115.69±28.58</td>
<td>171.04±65.14</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)(^a)</td>
<td>57.32±15.20</td>
<td>100.25±62.15</td>
<td>170.21±78.04</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)(^a)</td>
<td>178.00±16.69</td>
<td>207.09±35.11</td>
<td>210.42±38.70</td>
</tr>
<tr>
<td>LDL (mg/dl)(^a)</td>
<td>104.27±18.20</td>
<td>135.08±34.99</td>
<td>137.67±33.92</td>
</tr>
<tr>
<td>HDL (mg/dl)(^a)</td>
<td>62.84±8.59</td>
<td>50.90±13.86</td>
<td>38.39±8.47</td>
</tr>
<tr>
<td>Non HDL (mg/dl)(^a)</td>
<td>115.16±16.69</td>
<td>156.19±33.47</td>
<td>172.04±37.70</td>
</tr>
</tbody>
</table>

PCOS = polycystic ovary syndrome; BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; OGTT = oral glucose test; LDL = low-density lipoprotein; HDL = high density lipoprotein

1, 2, and 3 represent optimal risk, at risk, and at high-risk groups, respectively

\(^a\) Values are expressed as mean ± SD, \(^b\) Values are expressed as number and percentage [n (%)], \(^c\) p-value was calculated by ANOVA, \(^d\) p-value was calculated by Chi-square test
High LDL-C level is the important risk factor of CVD\(^{30,31}\). Combination of high LDL-C level with other metabolic factors was associated with increased risk of CVD\(^{30}\). LDL-C has been interested and observed for decades in PCOS women\(^{32,33}\). However, there were contradicting data of LDL-C levels compared between PCOS and control women. Some studies showed that LDL-C level was significantly greater in PCOS women than controls \(^{34,35}\), but some studies did not \(^{26,36}\). An increase in LDL-C level in PCOS women may be related to hyperandrogenemia\(^6\) and ethnics\(^{20}\), but not to IR\(^{22}\) and BMI\(^{36}\). A study from China showed no difference in LDL-C levels between PCOS women with and without MS\(^{26}\). Similarly, it was not different in the LDL-C level between PCOS women at high-risk and at risk in the present study. Nevertheless, LDL-C remains the primary target for lipid-lower interventions to prevent CVD in women\(^7\) including PCOS women\(^{36}\).

There has been no report how many PCOS women need treatment to lower LDL-C level. The present study has shown that most PCOS women with any CVD risk had higher LDL-C levels than the target ones. Fifty-six percent, 90.7%, and 100% of PCOS women at risk, at high-risk, and at high-risk plus other risks, respectively, needed lowering LDL-C levels to less than 130, less than 100, and less than 70 mg/dl, respectively, according to the recommendations\(^6,7\). These prevalence rates seem to be higher than those of the general population\(^{37}\). A study from French population with a mean age of 65.75 years showed an elevated LDL-C level in 27.7% for all subjects and in 51.0% for those at high-risk\(^{37}\). For these patients, some interventions for controlling risk factors and LDL-C have been recommended\(^7\). Lipid-lowering pharmacologic therapy should be considered to achieve the LDL-C target goal in addition to those baseline interventions including life-style modification and medical treatments for other risk factors\(^6,7\).

Limitation of the present study was that we did not run sub-clinical examinations, coronary artery calcification (CAC) for example, for these PCOS women. We would not include the women with CAC into the risk group. However, the women with MS and its components were associated with CAC\(^{38}\), it is most possible that PCOS women with any risks in the current study had CAC occurred already in any groups, at risk or at high-risk.

In conclusion, we have demonstrated that PCOS women showed the differences in all metabolic factors compared between the different CVD classifications according to AE-PCOS society.
Furthermore, the PCOS women at high CVD risk had more prevalence rates of most but not all metabolic parameters than those at risk. By contrast, the LDL-C levels were not different compared between PCOS women at high-risk and at risk. Interestingly, 56%, 90.7%, and 100% of PCOS women at risk, at high-risk, and at high-risk plus other risks, respectively, had LDL-C levels above the targeted goals which needed lowering for the primary CVD prevention according to the AE-PCOS society recommendation.

What is already known on this topic?
PCOS was diagnosed in women with two out of three of the following symptoms, that is, chronic anovulation, hyperandrogenism, and polycystic ovaries. Not only have hyperandrogenism and abnormal menstrual regularities but women with PCOS are also at increased risk of metabolic abnormalities and CVD. LDL-C is the significant atherogenic factor for CVD. The target level of LDL-C levels for primary prevention of CVD women with PCOS are already known and suggested.

What this study adds?
Although the target for lowering LDL have been published depending on the risk categories by AE-POS, at optimal risk, at risk, and at high-risk, the differences of metabolic parameters including LDL-C levels have not been widely reported. In the present study, the metabolic parameters between PCOS women with the three different CVD risks categorized by the AE-PCOS society were reported. Moreover, more than 90% of PCOS women who classified at high-risk or higher needed to lower LDL-C to the level less than target according to the recommendations.

Potential conflicts of interest
None.

References


การศึกษาเปรียบเทียบระดับ LDL-C ในสตรีกลุ่มอาการรังไข้เมื่อมีความเสี่ยงต่อโรคหัวใจและหลอดเลือดในระดับที่แตกต่างกันตามเกณฑ์ของ American Heart Association

ญาดาติงธนาธิกุล, ศรัณย์ธรศิริพิไลพงศ์, อรวินวัลลิภากร, อารีย์พรรณโสภณสฤษฎิสุข, เสวกวีระเกียรติ, ศักดาอาจองค์, วัตถุประสงค์: เพื่อเปรียบเทียบค่าตัวแปรทางเมแทบอลิซึมรวมทั้งระดับ LDL-C ระหว่างสตรีที่มีภาวะ PCOS ที่มีความเสี่ยงต่อการเกิดโรคหัวใจและหลอดเลือดที่แตกต่าง และเพื่อศึกษาถึงจำนวนของสตรีที่มีภาวะ PCOS ในแต่ละกลุ่มความเสี่ยงที่จำเป็นต้องรักษา

วัตถุประสงค์: เพื่อเปรียบเทียบค่าตัวแปรทางเมแทบอลิซึมรวมทั้งระดับ LDL-C ระหว่างสตรีที่มีภาวะ PCOS ที่มีความเสี่ยงต่อการเกิดโรคหัวใจและหลอดเลือดที่แตกต่าง

ผลการรักษา: กลุ่ม optimat risk 129 และกลุ่ม high-risk 35.


