Correlation Luteinizing Hormone (LH)/Follicle Stimulating Hormone (FSH) Ratio with Low Density Lipoprotein (LDL)/ High Density Lipoprotein (HDL) Ratio in Polycystic Ovarium Syndrome (PCOS) Patients

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Abstract

The aim of this study is to analyze the correlation between the ratio of LH and FSH levels with LDL and HDL cholesterol in PCOS patients. This study is an observational cross-sectional study. The population in this study were women newly diagnosed with polycystic ovary syndrome who came to RSIA Ferina, RSIA Lombok 22, Elizabeth Clinic and RSIA Putri Surabaya and Clinical Pathology Laboratory of dr. Soetomo Surabaya. Examination of FSH, LH and LDL and HDL cholesterol levels on 27 specimens (stored frozen serum) using the ICT (Accurate Intan Madya®, VEDALAB) and enzymatic colorimetric (Dimension EXL®, Siemens) methods. Statistical analysis was performed using the Spearman and Pearson correlation test, with a significance level of $p < 0.05$. The results showed that there was a moderate positive correlation between FSH and LDL cholesterol ($r = 0.491$, $p = 0.009$). Phenotype D of PCOS (non-hyperandrogenic type) had a moderate negative correlation between the LH / FSH ratio and the LDL/HDL cholesterol level ratio ($r = -0.487$, $p < 0.05$). However, there was no relationship between the LH/FSH ratio and the ratio of LDL/HDL cholesterol levels in all SOPK patients in this study. This study showed that phenotype D PCOS patients (non-hyperandrogenic type) were less likely to have cardiovascular complications than other phenotypic PCOS patients. Insulin resistance has a role in the risk of dyslipidemia in non-hyperandrogenic PCOS patients.

Keywords: *PCOS, LH, FSH, LDL, HDL*

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that is most often found in women of reproductive age, with an incidence of 4-18% worldwide. Santoso and Irawan conducted a study in Surabaya to get the prevalence of PCOS in women of reproductive age by 4.5% in 2007. The prevalence of this disease has increased to 8-10% due to changes in people's lifestyles with a high calorie diet and sedentary life style.[1,2]

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The diagnosis of PCOS is determined by the presence of two of the three Rotterdam criteria, namely: oligomenorrhea or anovulation, clinical hyperandrogens, and polycystic ovary morphology on ultrasound evaluation. Many PCOS patients do not have clear clinical symptoms, and experience difficulty in diagnosis, especially in the Asian population. An increase in the ratio of LH/FSH was seen in PCOS patients. A disturbance in pulsatile GnRH causes an increase in LH levels but is not followed by an increase in FSH levels. However, other research states that only 30-90% of PCOS patients experience an increase in the LH/FSH ratio.[3]

PCOS patients often have a variety of endocrine and metabolic abnormalities. PCOS patients have increased levels of LDL cholesterol (LDL-C) and decreased levels of HDL cholesterol (HDL-C). The increase in LDL occurs due to insulin resistance and hyperinsulinemia which causes an increase in free fatty acids (FFA), and further induces the synthesis of very low-density lipoprotein (VLDL) and LDL-C. The decrease in HDL is caused by insulin resistance and the degradation of Apolipoprotein A1/HDL-C.[3]

Women with PCOS have a four times greater risk of developing metabolic syndrome than healthy population. According to NCEP (National Cholesterol Education Program) guidelines about 70% of women with PCOS have dyslipidemia. Rizzo's research reports that women with polycystic ovaries are more likely to have stenotic coronary heart disease detected by angiography than women with normal ovaries. This study aims to determine the correlation between the LH/FSH ratio and the ratio of LDL/HDL cholesterol levels in PCOS patients.[4,5]

Materials and Methods

This research is an observational analytic study with a cross sectional study approach. The research specimens were taken from samples of PCOS patients who came to RSIA Ferina, RSIA Lombok 22, Elizabeth Clinic and RSIA Putri from March to July 2019. Inclusion criteria included: PCOS patients diagnosed with 2 of the 3 Rotterdam criteria, age 18-40 years. Exclusion criteria were using hormonal contraception, suffering from heart disease, hypertension, insulin resistance/hyperinsulinemia, and endometriosis, also on statin medication.

Venous blood serum was taken from a population that met the criteria for the main study. The stored serum is used for checking the levels of FSH, LH, LDL-C and HDL-C in 2020. Specimens were stored at -80°C while waiting for the running process. Examination of FSH, LH using the AIM tool (Accurate Intan Medika) with the ICT method. The LDL-C and HDL-C tests used the RXL dimension (Siemens Healthineers, Germany).

The data normality test was performed using the Shapiro-Wilk test. Data that is normally distributed are expressed in mean values, while data that are not normally distributed are expressed in the mean value. The correlation of LH and FSH ratios with the ratio of LDL and HDL cholesterol levels in PCOS patients was analyzed by doing the Pearson correlation test (if the data were normally distributed) or the Spearman (if the data were not normally distributed)

Results and Discussion

The number of subjects who participated in this study were 27 patients PCOS. Data on the characteristics of research subjects included age, body mass index and fenotipe (Table 1). The results of this study are in line with the research of Wahyuni et al, which shows that obesity is more likely to experience PCOS, namely 50.5%.[6] Tavares and Barros state that the highest prevalence of patients with metabolic syndrome in each PCOS phenotype in Brazil has a BMI>30 kg/m^2 (obese). Obesity will cause chronic hyperinsulin or insulin resistance, and can aggravate hormonal and metabolic disorders in PCOS patients. This may be one reason obese patients sought treatment more frequently in this study.[7]

The Rotterdam criteria divides PCOS patients into 4 phenotypes. Phenotype A is PCOS patients with classic symptoms (hyperandrogen triad, anovulation, and polycystic ovary). Phenotype B has symptoms of hyperandrogens and polycystic ovaries. Phenotype C has symptoms of hyperandrogens and anovulation. Phenotype D had symptoms of anovulation and polycystic ovaries without symptoms of hyperandrogens. Wiweko's research in Indonesia, Daan N, et al in the Netherlands, showed that phenotype A and D populations were the largest phenotypes. The Rotterdam criterion uses the Ferriman-Gallwey score, where a score of more than 8 is used to diagnose hyperandrogens. This score is probably lower in PCOS patients in Asia, so that the sensitivity decreases.[8,9,10] The combination of the higher incidence of polycystic ovary morphology compared to European patients and the sensitivity of this low Ferriman-Gallwey

score could explain phenotypes A, B, C only slightly compared to phenotype D in this study

Table 1. Characteristics of PCOS patients (n=27).

	n (%)	Mean ± std	Median ± std
Age (years)		29.93 ± 4.323	29 (24 – 39)
BMI (kg/m^2)	27	29.91 ± 3.097	30.1 (21.2 – 35.5)
Phenotypes (Rotterdam)			
A	5 (18.5%)		
C	2 (7.4%)		
D	20 (74.1%)		

Description: BMI, Body Mass Index; n, the number of cases

The age range of research subjects was 24-39 years. This study sample (60%) was obese (BMI >30 kg/m^2) with a mean BMI of 29.91 kg / m2 (overweight). This study also showed that phenotype D was more than phenotype A and phenotype C.

Table 2. Comprehensive Results of lipid and hormonal profile of PCOS patients (n=27).

Parameters	Mean ± std	Median ± std
LH (mIU/mL)	16.23 ± 7.305	16 (5 – 29.5)
FSH (IU/L)	7.94 ± 2.683	7.3 (5 – 18.3)
LDL (mg/dL)	86.93 ± 21.870	90 (31 – 127)
HDL (mg/dL)	36.04 ± 15.073	35 (4 – 68)

Description: LH, Luteinizing Hormone; FSH, Follicle-Stimulating Hormone; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; n, the number of cases.

The population of this study shows that there is an imbalance in LH and FSH production, as in table 2. Based on the mean of LH and FSH, it is found that LH / FSH > 2. In the past, this ratio served as the gold standard for clinical diagnosis of PCOS in addition to the Rotterdam criteria. However, LH / FSH levels have become controversial after a number of studies have reported a variable prevalence of this ratio (30-90%) among women with PCOS.[11] A disturbance in pulsatile GnRH causes an increase in LH levels but is not followed by an increase in FSH levels. The hyperandrogenic state causes an increase in estrogen levels by the aromatase enzyme activity. Estrogen will inhibit FSH production from the anterior pituitary.[12]

Table 3. Correlation of Lipid and hormonal profile in PCOS patients (n=27).

Lipid Profile	LHa	FSHb	LH/FSHa
LDLa	r =-0.277; p=0.161	r =0.491; p=0.009	
HDLa	r =0.085; p= 0.673	r =-0.172; p=0.390	
LDL/HDLb			r=-0.232; p=0.244

[a]Normal distribution and Pearson correlation, [b]Non-Normal and spearman correlation, significant value <0.05* (P-value represents significance from Pearson and Spearman correlation statistical analysis). Description: LH, Luteinizing Hormone; FSH, Follicle-Stimulating Hormone; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; n, the number of cases

The results of the correlation test between FSH levels and LDL cholesterol levels showed a positive correlation 0.491, the strength of the relationship was moderate, which was significant (p = 0.009) (Table 3). This means that there is a significant relationship between FSH and LDL cholesterol (p <0.05). The results of the correlation test between FSH levels and HDL cholesterol levels showed a negative correlation of -0.172, which was not significant (p = 0.390). This means that there is no significant relationship between FSH and HDL cholesterol (p> 0.05). These results are in accordance with the results of research by Arshad F, et al. (2019) in Pakistan which showed that FSH had a significant correlation with LDL (p = 0.01, r = 0.36) while FSH had no significant correlation with HDL (r = -0.152, p = 0.323)

Table 4. Correlation of Lipid and hormonal profile in PCOS patients based on phenotypes (n=27).

Parameter	**LDL/HDL[a]** Hyperandrogen types (Phenotype A+C)	**LDL/HDL[a]** Non-hyperandrogen types (Phenotype D)
LH/FSH[b] Hyperandrogen types (Phenotype A+C)	r =-0.357;p=0.432	-
LH/FSH[b] Non-hyperandrogen types (Phenotype D)	-	r =-0.487; p=0.029

[a]Normal distribution and Pearson correlation, [b]Non-Normal and spearman correlation, significant value <0.05* (P-value represents significance from Pearson and Spearman correlation statistical analysis). Description: LH, Luteinizing Hormone; FSH, Follicle-Stimulating Hormone; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; n, the number of cases

The correlation of the LH and FSH ratios with the LDL and HDL cholesterol ratios in phenotype D (Table 4) is in accordance with the explanation of several previous studies. Women with hyperandrogenic PCOS differed significantly from women with non-hyperandrogenic PCOS regarding most of the endocrinological and cardiometabolic parameters. Women with hyperandrogenic PCOS have worse

cardiometabolic profiles, including higher BMI, higher LDL cholesterol and lower HDL cholesterol. Another study showed that the significantly lower prevalence of metabolic syndrome (6.5%) and hypertension (11.8%) in non-hyperandrogenic women was consistent with the prevalence previously reported in a population of normal (non-PCOS) women with age, BMI, and the same ethnic background. Overweight or obesity (28.5%) and lipid disorders (increased LDL-C, 52.2%) were relatively common among young women with PCOS phenotype D compared with non-PCOS.[9,13]

Based on the case finding in this study, it was found that phenotype D was the largest phenotype in the subjects of this study. The subjects of this study were taken consecutively, based on patients who came to several hospitals and clinics in Surabaya. This indirectly illustrates that phenotype D is the most common PCOS phenotype in the East Java region, which turns out to be consistent with research conducted in Asia. The correlation of LH and FSH ratios with the ratio of LDL and HDL cholesterol to phenotype D is in accordance with the explanation of several previous studies, indicating that insulin resistance has a role in the risk of dyslipidemia in non-hyperandrogenic PCOS patients. SOPK patients have impaired tissue insulin resistance. This will trigger the release of excess insulin as a form of compensation. This hyperinsulinemia condition will cause increased activation of the Insulin Growth Factor-1 (IGF-1) receptor. Ovarian theca cell abnormalities in SOPK patients also cause a decrease in aromatase so that estrogen decreases. This decrease in estrogen causes the synthesis of G protein coupled estrogen receptor to decrease, resulting in an increase in circulating LDL-C due to decreased LDL receptors. This imbalance of LDL-C and HDL-C cholesterol causes an increase in the ratio of circulating LDL-C to HDL-C. Lipids that accumulate in these blood vessels will cause atherosclerosis. [14]

Conclusion

The negative correlation of the LH and FSH ratios with the LDL and HDL cholesterol ratios in phenotype D. Women with hyperandrogenic PCOS have worse cardiometabolic profiles, including higher BMI, higher LDL cholesterol and lower HDL cholesterol. Overweight or obesity and lipid disorders were relatively common among young women with PCOS phenotype D compared with non-PCOS. Insulin resistance still has a role in the risk of dyslipidemia in non-hyperandrogenic PCOS patients

Conflict of Interest: The author declare that they have no conflict of interest.

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Ethical Approval

This research was carried out when it had received ethical clearance from the ethical committee of the Faculty of Medicine, Airlangga University, Surabaya, Indonesia has agreed and stated that this research is ethical, with ethical clearance number 125/EC/KEPK/FKUA/2020. Respondents included in the inclusion criteria determined in the study were given informed consent and a statement to be willing to participate in this study. If the respondent is not willing, it will be excluded and not included in the study.

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