

INTRODUCTION

The definition of Polycystic Ovary Syndrome (PCOS) most used today are NIH Criteria and Rotterdam Criteria. It is a leading cause of infertility and is also associated with an increased risk of metabolic syndrome (MBS), diabetes mellitus type 2, cardiovascular disease, and endometrial cancer.

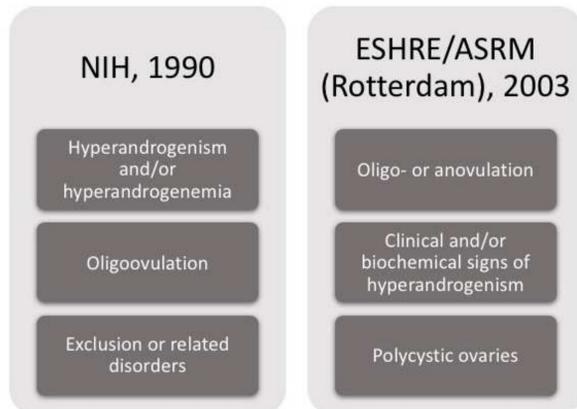


Figure 1. NIH and Rotterdam Criteria for PCOS

PCOS is an endocrine and metabolic dysfunction characterized by hyperandrogenism and abnormal insulin resistance (IR) in relatives of women with PCOS are heritable. PCOS is an endocrine and metabolic dysfunction and is strongly associated with obesity. Insulin resistance is usually associated with obesity. But 20% of women with PCOS are thin or at a normal weight and found 3 -10% incidence of a missed diabetes diagnosis. However, lean women with PCOS may be at an increased risk of developing insulin resistance despite not being overweight. It is estimated that between 6 and 22 percent of normal-weight women with PCOS are insulin resistant or have hyperinsulinemia. On the other hand, the connection between insulin and PCOS is not yet well understood. Therefore we evaluate the correlation between the methylation level of the IRS-1 gene and its mRNA expression in lean PCOS patients.

METHODS

This cross-sectional study was undertaken among Yasmin Clinic Dr. Cipto Mangunkusumo General Hospital, Jakarta between October 2018 until August 2019. This study received ethical approval from the Ethics Review Committee of Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, with an ethical clearance number of 0449/UN2.F1/ETIK/2018. A total of 10 women with lean PCOS by Rotterdam Criteria were included in this study. Ten normal lean women with Body Mass Index (BMI) < 23 were used as a control group. The hormonal level of testosterone, sex hormone binding globulin (SHBG), and free androgen index (FAI) were measured using ELISA. The methylation status of the IRS-1 gene was analyzed using MSP, and mRNA expression was investigated using qPCR. All data obtained from each subject were recorded and analyzed using Statistical Package for Social Services (SPSS) version 22.

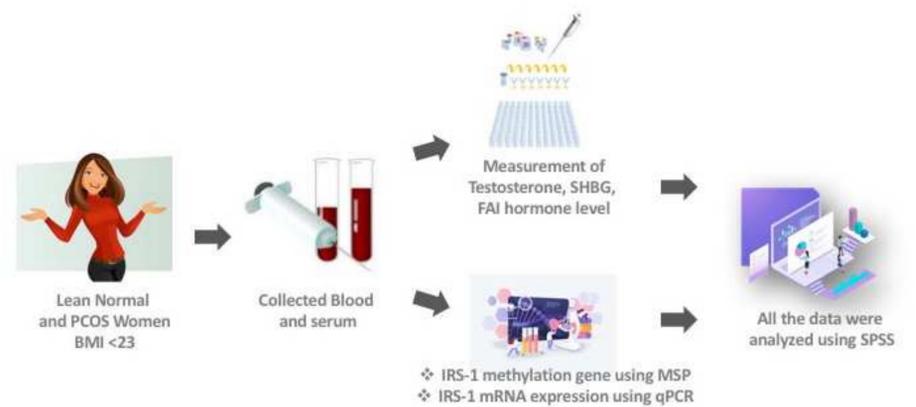


Figure 2. Research Work Flow

RESULT AND DISCUSSION

Twenty women of reproductive age with BMI <23, were recruited as a participant. Those women were divided into two groups, the lean PCOS group, and the normal lean group. The mean age of those two groups is 28.62 ± 1.11 and 23.75 ± 0.88 years old (Lean PCOS VS normal Lean) with p=0.004. The BMI were 21.05 ± 0.54 vs 20.85 ± 0.48 kg/m². Which was classified as obese according to WHO Asia Pacific BMI Classification. In this study, we found that there were significant differences in Age (p=0.004) and SHBG level (p=0.022) between Lean PCOS compared to control.

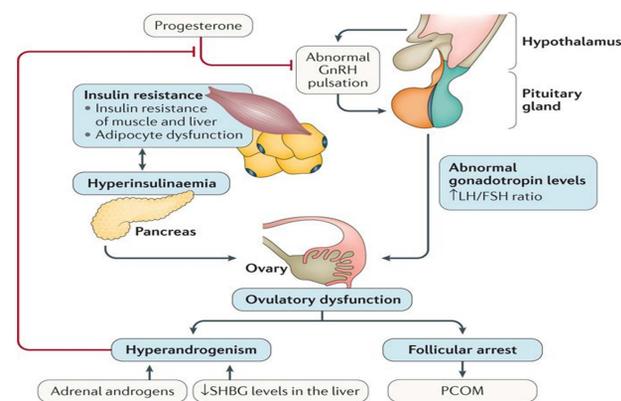
Table 1. Data Distribution

Variable	PCOS Lean	Control Lean	p
Age (year)	28.62 ± 1.11	23.75 ± 0.88	0.0004
Body Mass Index (kg/m ²)	21.05 ± 0.54	20.85 ± 0.48	0.477
Testosterone (nmol/L)	0.77 ± 1.44	1.09 ± 0.24	0.265
FAI (%)	4.96 ± 1.15	4.98 ± 1.15	0.987
SHBG (nmol/L)	57.54 ± 6.53	84.15 ± 8.04	0.022
IRS mRNA expression	1.48E-8 (7.61E-11 – 6.37E-8)	1.57E-8 (1.25X10 ⁻⁹ – 1.19X10 ⁻⁷)	0.600
Methylation	3.04 (0.87-107.63)	4.71 (0.53-11.17)	0.753
Unmethylation	97.04 (48.16-99.13)	96.61 (89.95-99.48)	0.753

CONCLUSION

We conclude that the epigenetic mechanism of IRS-1 is not associated with the risk of lean PCOS. Further studies with a large number of the sample are needed to give a better result. More investigation including dietary intact, nutrition, and UV exposure are needed to identify, not only in the lean but also in obese PCOS patients.

We also found that the methylation of the IRS-1 gene was not correlated with mRNA expression in lean PCOS (p>0.05). Insulin resistance (IR) plays an important role in the pathogenesis of polycystic ovary syndrome (PCOS). Current evidence suggests that IRS-1/2-mediated activation of phosphatidylinositol 3-kinase (PI3-kinase) controls insulin-mediated glucose transport and carbohydrate metabolism.



From previous study, mRNA expression of the IRS-1 gene was found to be significantly higher in obese subjects compared to the lean ones. This finding corroborates with the results from previously conducted studies which found that IRS-1 expression was 3.3 times higher in the

obese population compared to the lean population. In PCOS patients, this expression was found to be as much as 6.2 times higher in obese patients compared to the lean ones. These results indicate that aside from insulin function, IRS-1 expression was also influenced by an individual's body composition.

REFERENCES

- Aziiz J Clin Endocrinol Metab (2006) 91(3): 781–785; Wang and Mol Human Reproduction (2017) 32(2): 261–264; Goyal and Dawood J Hum Reprod Sci (2017) 10(3): 154-161; Ruan et al Endocrine Journal (2012) 59(7): 601-609; Dunaif Fertil Steril (2006) 86(1): s13-S14; Villuendas Hum Reprod (2015) 20(11): 3184-91