

Correlation between phenotype and cortisol with anxiety status related to Polycystic Ovary Syndrome (PCOS)



Ummi Shulaeha^{1*}, Andi Mardiah Tahir^{1,2}, Nusratuddin Abdullah^{1,3}, Isharyah Sunarno^{1,4}

¹Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;

²Department of Obstetrics and Gynecology, Social Obstetrics and Gynecology Division, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;

³Department of Obstetrics and Gynecology, Endocrinology Fertility and Reproduction Division, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;

⁴Department of Obstetrics and Gynecology, Maternal Fetal Division, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia.

*Corresponding author:

Ummi Shulaeha;
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
ummishulaeha88@gmail.com

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Symptoms include irregular menstrual cycles, hirsutism, obesity, acne vulgaris, and infertility. PCOS is a stigmatized condition that affects women's identity and mental health, especially anxiety. In addition, increased cortisol is associated with increased anxiety. This study aims to determine the effect of phenotype and cortisol on anxiety status in polycystic ovary syndrome (PCOS) patients.

Methods: 40 patients diagnosed with polycystic ovary syndrome (PCOS) aged 18-40 years in Makassar. The Indonesian version of the Hamilton Anxiety Rating Scale (HAM-A) assesses anxiety. A blood sample is taken to check for cortisol (drip blood test). Cortisol levels were measured using the CMIA (Chemiluminescent microparticle Immunoassay) method. Data were analyzed using SPSS version 25.0 for Windows.

Results: The prevalence of phenotypes A, B, C, and D were 27.5%, 0%, 45%, and 45%, respectively. Phenotype C had a higher body mass index than the other phenotypes but was not significantly different. ($p > 0.05$). About 26.1% of patients with phenotype A were found to suffer from mild anxiety and 29.5% experienced moderate anxiety. Compared to phenotype C, 52.2% experienced mild anxiety and 35.5% experienced moderate anxiety; however, these results were not statistically significant. Higher cortisol levels were found in phenotype A compared to other phenotypes (phenotype C; 7.01 ± 3.12 and phenotype D; 6.37 ± 3.02) but not significantly different ($p > 0.05$).

Conclusion: The PCOS phenotype has no relationship with the anxiety status of PCOS patients and there is no relationship between the phenotype and serum cortisol levels in PCOS patients.

Keywords: Phenotype, PCOS, Cortisol, Anxiety.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common syndrome with a prevalence of around 2.5%-11.9% worldwide. The diagnosis of PCOS is based on menstrual irregularities, hyperandrogenism, and polycystic ovaries. It is a common cause of infertility in the reproductive age group.^{1,2} PCOS is characterized by excessive ovarian or adrenal androgen secretion or both. Intrinsic ovarian factors such as altered steroidogenesis and extra-ovarian factors such as hyperinsulinemia contribute to ovarian overproduction of androgens.³

Based on the National Institutes of Health (NIH) guidelines, a phenotypic approach is proposed to classify PCOS. Phenotype A includes hyperandrogenism (HA) (clinical or biochemical), ovulatory dysfunction (OD), and polycystic

ovaries (PCO).^{3,4} Phenotype B includes hyperandrogenism (HA) and ovulatory dysfunction (OD). Phenotype C includes hyperandrogenism (HA) and polycystic ovaries (PCO). Phenotype D includes ovulatory dysfunction (OD) and polycystic ovaries (PCO).⁴

In addition to all the long-term metabolic and endocrine outcomes, an increased prevalence of psychological disorders among women with PCOS has also been reported in several studies, including depression and anxiety.⁵⁻⁷ Most PCOS women who experience emotional disturbances reported 38%, depression 21-46%, and anxiety 34%.⁸ Women with PCOS tended to experience slightly increased anxiety and depression, on average, significantly more than women without PCOS. Women with PCOS with

a lower BMI tend to have slightly lower anxiety and depression scores, suggesting that having a lower BMI can reduce anxiety and depression.^{6,7}

Women with PCOS suffer from more mental distress than healthy women, with many reporting dissatisfaction with their body image or acne on their face or worry about their infertility. These factors associated with PCOS make these women more prone to feeling anxious and upset. Still, the specific causative factors, including sociological factors and molecular mechanisms, for anxiety/depressive-like behavior in these women with PCOS have not been fully elucidated.⁸⁻¹⁰

Clinical stressors such as anxiety can be measured through the hormone cortisol. Stress can increase cortisol levels, affecting

other endocrine functions, insulin resistance, and ovulation. Muharram et al. suggested a weak and positive relationship between personality type and cortisol in polycystic ovary syndrome. Cortisol levels were found to be higher in personalities who tend to be neurotic and psychotic compared to normal personalities who experience PCOS.^{11,12}

Based on those mentioned above, this study aims to investigate the effects of phenotype and cortisol on anxiety status in patients with polycystic ovary syndrome (PCOS).

METHODS

This observational study with a cross-sectional design examines the relationship between phenotype and cortisol and anxiety status in polycystic ovary syndrome (PCOS) patients. This research was conducted at RSUP Dr. Wahidin Sudirohusodo and other network hospitals. The study sample included all female patients diagnosed with polycystic ovary syndrome (PCOS) aged 18-40. All subjects who met the inclusion criteria were included in the study until the number of subjects was sufficient.

The inclusion criteria included: women of reproductive age (18-40 years); diagnosed with polycystic ovary syndrome using the Rotterdam criteria; not currently taking medication, such as anti-anxiety and anti-depressant drugs; and willing to participate in the research. Exclusion criteria for pregnant and lactating women, patients diagnosed with anxiety disorders, congenital adrenal hyperplasia, or other kidney disorders, and refused to participate in this study.

Before conducting the research, informed consent was carried out in which the research subjects explained the aims and objectives of the study. The research subjects were also informed that obtained data from the examination would be recorded in the questionnaire sheet (subjective complaints, physical examination history, risk factors, anxiety status using the Hamilton Anxiety Rating Scale and hormonal analysis examination).

The diagnosis of polycystic ovary syndrome was then made based on the Rotterdam Consensus confirming the diagnosis of polycystic ovary syndrome

must meet the three following criteria: oligo-anovulation, clinical signs and biochemical signs of hyperandrogenaemia (excluding other symptoms of hirsutism, such as congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome, thyroid disease, hyperprolactinemia); and the presence of polycystic ovaries on ultrasound examination. Phenotypic clustering was performed based on the NIH consensus; Phenotype A includes hyperandrogenism (HA) (clinical or biochemical), ovarian dysfunction (OD), and polycystic ovaries (PCO). Phenotype B has HA and OD. Phenotype C has HA and PCO. Phenotype D has OD and PCO

A general physical examination and vital signs were carried out, which included blood pressure, pulse, respiration, temperature and body mass index. The Indonesian version of the Hamilton Anxiety Rating Scale (HAM-A) assesses anxiety. A blood sample is taken to check cortisol (blood test).

The research data obtained is recorded in a specific form and processed electronically using software designed to calculate statistically with SPSS version 25.0 for Windows. The Chi-Square test will be performed if the independent and dependent variables are presented in the categorical form and consist of two groups. The interpretation of the results using the degree of significance α (p-alpha) of 5% (0.05).

RESULTS

In our study, there were 40 cases of PCOS, with the most common phenotype being phenotype C (45%). The proportion of patients with phenotypes A and D was 27.5%, phenotype C was 45.0%, and no phenotype B. Basic characteristics, occupation, and relevant family history of the women studied are shown in Table 1. Based on age, most PCOS phenotypes A and D were <30 years old, whereas phenotype C was mostly ≥ 30 years old. There was no significant difference between the three PCOS phenotype groups based on age ($p > 0.05$) (Table 1).

The results of the analysis of the relationship between anxiety status and cortisol levels with the PCOS phenotype are presented in Table 2. The Hamilton

rating scale for anxiety is used to assess the severity of each condition. From the 11 phenotype A patients studied, 26.1% suffered from mild anxiety, and 29.5% experienced moderate anxiety. Compared with phenotype C, 52.2% experienced mild anxiety, and 35.5% experienced moderate anxiety. Although the highest level of anxiety was found in phenotype C compared to groups A and D. This result was insignificant.

In this study, we also analyzed the cortisol levels for each phenotype. Visible cortisol levels were higher in phenotype A compared to other phenotypes (phenotype C and phenotype D; 6.37 ± 3.02 mcg/dL) but not significantly different ($p > 0.05$) (Table 2).

The Hamilton rating scale for anxiety was used to rate the severity of each condition among those who experienced it. The Hamilton rating scale comprises 14 symptoms-defined elements and caters to psychological and somatic symptoms. Each item is assessed with a basic numerical score of 0 (none) to 4 (severe): $>17/56$ is considered mild anxiety; 25-30 is considered moderate-severe. In this study, there was no significant difference between phenotype and anxiety (Hamilton's indicator score) in PCOS patients ($p > 0.05$) (Table 3).

DISCUSSION

In this study, PCOS was more common in our 30s. Mostly, women learned they had PCOS in their 20s and 30s because of the difficulty conceiving. However, PCOS can occur at any age after puberty. Our study involved both obese and non-obese PCOS, and there was no significant association between obesity and the PCOS phenotype. This study agrees with previous studies, which found no independent effect of high BMI on oligomenorrhea rate, antral follicle count, ovarian volume, or serum androgens.¹³ Our study suggests that women with PCOS are more likely to have missed periods. It has been shown that late menarche has higher androgen levels, as in primary amenorrhea. Girls with primary amenorrhea have higher androgen levels and are overweight, exacerbating hyperandrogenemia.^{14,15}

We found that PCOS patients had mild status anxiety (57.5%) and 42.5% had

Table 1. Baseline characteristic of respondents based on phenotypes

Characteristic	A (n= 11)		C (n= 18)		D (n=11)		Total		P
	n	%	n	%	n	%	n	%	
Age (Years)									
< 30	8	72.7	8	44.4	9	81.8	25	62.5	0.093
≥ 30	3	27.3	10	55.6	2	18.2	15	37.5	
Education (Years)									
≤ 9	1	9.1	5	27.8	2	18.2	8	20.0	0.467
> 9	10	90.9	13	72.2	9	81.8	32	80.0	
Occupation									
Employed	9	81.8	15	83.3	6	54.5	30	75.0	0.183
Unemployed	2	18.2	3	16.7	5	45.5	10	25.0	
Body Mass Index									
Obese	3	37.3	10	55.6	6	54.5	19	47.5	0.288
Non-obese	8	72.7	8	44.4	5	45.5	21	52.5	
The age of menarche (Years)									
< 12	2	18.2	1	5.6	0	0.0	3	7.5	0.247
≥ 12	9	81.8	17	19.4	11	100.0	37	92.5	
Family history of PCOS									
Yes	3	27.3	0	0.0	0	0.0	3	7.5	0.014*
No	8	72.7	18	100.0	11	100.0	37	92.5	

*Statistically significant if p-value less than 0.05

Table 2. Relationship between anxiety levels and cortisol levels with PCOS phenotypes

Variable	Phenotype (n=40)			P
	A (n=11)	C (n=18)	D (n=11)	
Anxiety Level, n (%)				
Mild	6 (26.1)	12 (52.2)	5 (21.7)	0.519 ^a
Severe	5 (29.5)	6 (35.5)	6 (35.3)	
Cortisol levels (mcg/dL) (Mean±SD)	8.07±2.51	7.01±3.12	6.37±3.02	0.399 ^b

^aChi Square Test; ^bAnova Test; *Statistically significant if p-value less than 0.05

moderate anxiety status. The results of our study are similar to those of a previous study that studied 70 women (18–45 years) diagnosed with PCOS according to the Rotterdam criteria and without a pre-existing psychiatric illness who were clinically interviewed for anxiety and depression disorders.^{15,16} It was found that mild, moderate, and severe anxiety were 62.90%, 29.60%, and 7.40%, respectively. Previous studies also reported a similar result, with a prevalence of mild anxiety of 39%, moderate anxiety of 18%, and severe anxiety of 14% in PCOS patients.^{16,17}

In this study, more than half of women with phenotype C PCOS experienced anxiety symptoms, of which 52.2% experienced mild anxiety, and 35.5% experienced moderate anxiety. A possible explanation for the prevalence of anxiety in women PCOS is a physical manifestation of their condition. Phenotype C includes PCO and hyperandrogenism, such as

acne, obesity, and hirsutism, which lead to negative self-image and low self-esteem. In addition, they may also experience fear and concerns about the future and their ability to conceive.¹⁸

Previous studies have reported that PCOS patients with phenotype A have higher anxiety than phenotypes B, C, and D. Although the specific causes and mechanisms are still unclear, this can be hypothesized due to the effects of hyperandrogenism which causes hirsutism and acne, as well as potential factors such as obesity, insulin resistance.¹⁹ Specific causal factors, including sociological factors and molecular mechanisms, for anxiety-like behavior in women with PCOS are not fully understood. Chaudhry et al. reported that the biological mechanism of the association between PCOS symptoms and anxiety can be explained based on hyperandrogenism and insulin resistance. Anxiety increases in parallel with the

gradual development of hyperinsulinemia and hyperandrogenism, characteristic features of PCOS. A parallel relationship with anxiety is also found in cases of hormonal disorders in persons with PCOS.^{16,17,20}

Serum cortisol levels, while all PCOS phenotypes are within the range of cortisol levels normal serum. This is in line with the previous study that serum cortisol levels in PCOS patients were still within the normal range of $10.38 \pm 0.80 \mu\text{g/dL}$.¹¹ PCOS patients with various phenotypes had transient serum cortisol levels that were not significantly different. Our data show that the PCOS phenotype does not reflect differences in serum cortisol levels. PCOS pathological conditions with various phenotypes are not associated with changes in cortisol secretion. A previous study also found that higher cortisol in PCOS patients according to phenotype severity is a marker of stress-induced

Table 3. Phenotype relationship with Hamilton's anxiety indicator score for PCOS patients

Hamilton anxiety symptom indicators	Phenotype (n=40)			p
	A(Mean±SD)	C(Mean±SD)	D(Mean±SD)	
Anxious	3,27 ± 0,78	3,22 ± 0,73	3,00 ± 0,77	0,827
Tension	2,81 ± 0,75	2,55 ± 0,51	2,54 ± 0,52	0,363
Fears	1,27 ± 0,47	1,27 ± 0,46	1,45 ± 0,68	0,977
Insomnia	1,36 ± 0,67	1,38 ± 0,50	1,36 ± 0,50	0,959
Intellectual	1,45 ± 0,93	1,33 ± 0,76	1,54 ± 1,12	0,826
Depressed mood	1,18 ± 0,40	1,22 ± 0,43	1,45 ± 0,52	0,798
Somatic (muscular)	1,09 ± 0,30	1,11 ± 0,32	1,09 ± 0,30	0,865
Somatic (sensory)	0,91 ± 0,30	0,94 ± 0,23	1,00 ± 0,00	0,720
Cardiovascular symptoms	0,36 ± 0,50	0,55 ± 0,51	0,81 ± 0,60	0,324
Respiratory symptoms	0,63 ± 0,50	0,72 ± 0,46	0,91 ± 0,83	0,634
Gastrointestinal symptoms	0,91 ± 0,31	1,00 ± 0,34	1,27 ± 0,65	0,470
Genitourinary symptoms	1,18 ± 0,40	1,05 ± 0,41	0,73 ± 0,64	0,431
Autonomic symptoms	1,09 ± 0,30	0,83 ± 0,38	1,00 ± 0,00	0,072
Behavior at interview	0,45 ± 0,52	0,38 ± 0,50	0,45 ± 0,52	0,732

Kruskal Wallis Test; *Statistically significant if p-value less than 0.05

hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis, which can accentuate adrenal androgen excess and lead to severe PCOS.²¹ The role of cortisol in the pathogenesis of PCOS was reported with inconsistent results in which increased cortisol secretion in the morning and evening was found in women with PCOS. In contrast, other studies reported no significant difference in cortisol levels.¹⁹⁻²⁴

This study is limited by a cross-sectional design where only status anxiety was moderate and mild gains, and there were no cases with severe anxiety where the effects on cortisol levels were not comparable. We examined status anxiety using a questionnaire, which could bias the results due to the subjective measurement. We also measure serum cortisol intermittently, preferably in the morning when cortisol levels peak. Nevertheless, we investigated the variance of the PCOS phenotype associated with cortisol and anxiety status, as previous studies have only shown an association between PCOS being related to cortisol and status anxiety.

CONCLUSION

Based on the analysis of the data obtained from this study, it can be concluded that the PCOS phenotype is not related to the anxiety status of PCOS patients and there is no relationship between the phenotype and serum cortisol levels in PCOS patients. Further research is needed

on other factors related to anxiety and the PCOS phenotype.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this manuscript.

ETHICS CONSIDERATION

The Ethics Committee for Health Research, Faculty of Medicine, Universitas Hasanuddin (No: 799/UN4.6.4.5.31/PP36/2021) has examined and approved all research designs.

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AUTHOR CONTRIBUTIONS

Ummi Shulaeha conceived and designed the analysis, collected the data, contributed data or analysis tools, and wrote the original paper. Andi Mardiah Tahir and Nusratuddin Abdullah conceived and designed the analysis, contributed data or analysis tools, and validated the final paper. Isharyah Sunarno contributed data or analysis tools and performed the analysis.

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