

Polycystic ovary syndrome and depression: A neurobiological and biochemical correlation



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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a complex endocrinological disorder that commonly affects women during their early reproductive years. The wide spectrum of symptoms and associated hormonal imbalances often results in significant psychological distress, leading to increased incidence of depression, anxiety, and other mood disorders. **Aims and Objectives:** This study aims to assess the severity of depression using the Montgomery–Asberg depression rating scale (MADRS) in women newly diagnosed with PCOS, and to evaluate its correlation with glucose metabolism, metabolic syndrome, and hormonal dysregulation.

Materials and Methods: We conducted an observational cross-sectional study in which PCOS patients were stratified into mild, moderate, and severe depression categories based on their MADRS scores. Anthropometric, biochemical, and hormonal parameters were evaluated to identify the physical and clinical manifestations of PCOS. **Results:** Among the 69 PCOS patients studied, depression was classified as normal ($n = 38$), mild ($n = 17$), moderate ($n = 10$), and severe ($n = 4$) based on MADRS scores. The mean body mass index was elevated across all groups, indicating an overweight status (normal: 25.19 ± 6 , mild: 23.6 ± 4.14 , moderate: 24.8 ± 4.1 , and severe: 23.6 ± 3.8). Insulin resistance (IR), as indicated by homeostasis model assessment–IR, was also elevated in all categories of patients with depressive disorder (normal: 2.86 ± 1.8 , mild: 2.3 ± 0.72 , moderate: 2.89 ± 1.73 , and severe: 2.45 ± 0.84). The mean luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio was raised (normal: 2.55 ± 1.62 , mild: 1.35 ± 0.67 , moderate: 2.14 ± 0.99 , and severe: 2.4 ± 1.6), and serum testosterone levels were elevated in all groups (normal: 1.24 ± 0.83 , mild: 0.97 ± 0.76 , moderate: 0.93 ± 0.5 , and severe: 1 ± 0.63).

Conclusion: Dysregulation of the hypothalamic–pituitary–ovarian and hypothalamic–pituitary–adrenal (HPA) axes plays a central role in the pathogenesis of both PCOS and associated depression. Clinical manifestations such as hirsutism, infertility, and altered LH/FSH ratios may hyperactivate the HPA axis, contributing to mood disorders. IR, acting synergistically with LH, leads to hyperandrogenemia and impaired glucose uptake in brain regions that regulate mood, potentially exacerbating depressive symptoms.

Key words: Polycystic; Depression; Infertility; Hirsutism

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women during their early reproductive years. The primary complaints of women with PCOS include irregular

menstruation and prolonged amenorrhea. PCOS is frequently associated with features of metabolic syndrome, such as obesity, insulin resistance (IR), dyslipidemia, and hypertension, all of which contribute to an increased risk of cardiovascular diseases and type 2 diabetes mellitus. Endocrine dysfunction in PCOS is characterized by

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elevated levels of androgens and an altered luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio, typically showing a disproportionate rise in LH compared to FSH. These hormonal imbalances often result in clinical symptoms such as acne, alopecia, and hirsutism.¹

The global prevalence of PCOS is estimated to be around 9.2%,² while in India, it ranges from 3.7% to 22.5%.³ Women with PCOS often suffer from anovulatory infertility and may require assisted reproductive technologies to conceive.⁴ Even those who conceive spontaneously are at increased risk of complications such as miscarriage, gestational diabetes mellitus, and pre-eclampsia. These complications contribute to higher rates of infertility and cesarean section deliveries.⁴

The burden of PCOS and its associated symptoms often leads to significant psychological stress, with depression being a common comorbidity. Studies have shown that the prevalence of depression in women with PCOS is approximately 2.5 times higher than in women without the condition.⁵ According to Kanagarajan et al., the prevalence of depression in PCOS patients ranges from 11% to 93.5%.⁶ Recent meta-analyses and reviews suggest a threefold higher occurrence of depression among women with PCOS.⁷ As a result, screening for depression in every diagnosed PCOS patient is increasingly being recognized as a global standard.⁸

The pathogenesis of PCOS is primarily characterized by a dysregulated hypothalamic–pituitary–ovarian (HPO) axis, which leads to abnormal gonadotropin-releasing hormone (GnRH) production, an altered LH/FSH ratio, immature ovarian follicle development, and an imbalance in estrogen and progesterone production. These changes result in ovarian dysfunction, abnormal androgen production, and infertility.⁹

The pathogenesis of depression is influenced by inflammation and imbalances in gamma-aminobutyric acid and serotonin neurotransmitters, as well as neurotrophic factors. The hypothalamic–pituitary–adrenal (HPA) axis also plays a crucial biological role in the development of depression. In PCOS, the HPA axis is activated due to underlying stress, leading to abnormal adrenocorticotrophic hormone (ACTH) secretion. ACTH stimulates both cortisol and adrenal androgen production, contributing to the development of depression.¹⁰

PCOS is a state of chronic inflammation. Obesity, IR, and the dyslipidemic metabolic state associated with PCOS further contribute to this inflammatory state. Inflammatory molecules such as tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 can cross the blood–brain barrier, causing

altered mood regulation, neurotransmitter metabolism, neuroendocrine function, and neural plasticity. This suggests that chronic inflammation plays a crucial role in the association between PCOS and depression.¹¹

Alterations in the gut microbiome – a component of the gut–brain axis – are also known to play a role in major depressive disorder. PCOS can cause disruptions in the gut microbiome, which may contribute to the onset of depressive symptoms in affected individuals.¹²

The etiology of depression in PCOS is multifactorial, involving genetic, biochemical, hormonal, inflammatory, and environmental factors.¹³ However, the exact mechanism linking PCOS and depression is not clear. Whether the wide range of distressing symptoms triggers depressive symptoms or whether metabolic, hormonal, or neurobiological factors play a primary role in the pathogenesis is still a matter of ongoing research.

Aims and objectives

This study aimed to assess the severity of depression in women newly diagnosed with polycystic ovary syndrome (PCOS) and the objectives of the study are to evaluate the association of PCOS with glucose metabolism, metabolic dysregulation, hormonal imbalance, and to establish the neurobiological and biochemical correlation between PCOS and depression.

MATERIALS AND METHODS

Study population and design

This descriptive cross-sectional study was conducted in collaboration with the Departments of Gynaecology, Psychiatry, and Biochemistry at the College of Medicine and Sagore Dutta Hospital, a tertiary care center in West Bengal, India.

The sample size was calculated as 65, based on a 93.5% prevalence of depression among women with PCOS reported in a previous study.⁶

The study population included women attending the gynecology outpatient department (OPD) who were diagnosed with PCOS based on the Rotterdam criteria. Systematic random sampling was done. Depressive symptoms were assessed by a psychiatrist using the MADRS.¹⁴ Of the 100 women diagnosed with PCOS, 31 did not attend the psychiatry OPD for further evaluation and were excluded. The remaining 69 women who attended the psychiatry OPD were evaluated and subsequently recruited for the study.

Inclusion criteria

All the menstruating women, irrespective of age, who did not have known endocrine disorders and were not currently on any medications such as hormonal, steroidal, and lipid-lowering drugs were included in the study.

Exclusion criteria

Women with any known chronic endocrine diseases that affect normal ovarian function and chronic systemic illness were excluded. History of severe stress, severe grief in the last 6 months was excluded from the study. The history of hormonal therapy, antidepressant medication, alcohol consumption, pregnancy, and lactation was also excluded.

The purpose and the significance of the study were explained thoroughly to all participating women, and written informed consent was obtained thereafter. The Institutional Ethics Committee approved the study protocol (vide: CMSDH/IEC/126/06-2018 dated June 23, 2018).

Procedure

Sociodemographic data were obtained, and women were evaluated based on menstrual, infertility, and obstetric history.

Anthropometric measurements were performed following standard protocols. In this study, body mass index (BMI) values of 23–24.99 kg/m² and ≥25 kg/m² were considered overweight and obese, respectively.¹⁵

Biochemical analysis

Blood samples were collected for fasting blood glucose and lipid profile, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C), fasting insulin, thyroid-stimulating hormone (TSH), free thyroid hormone, testosterone, estrogen, and progesterone. All biochemical estimations were conducted in the Department of Biochemistry at the College of Medicine and Sagore Dutta Hospital. The calculation used for homeostasis model assessment–IR (HOMA-IR) was – fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. HOMA-IR value >2.5 denotes a state of IR.¹⁶

Statistical analysis

Data were analyzed using appropriate statistical tools. Means, standard deviations, and frequency distributions (percentages) were included in descriptive statistics. Normality of continuous variables was assessed by the Shapiro–Wilk test. For parametric data, the analysis of variance (ANOVA) test was employed. P<0.05 was considered statistically significant.

RESULTS ANALYSIS

Sociodemographic and depression risk factors (Table 1)

The mean age of the study population was 24±3.4 years. The mean age of menarche was 13.07±1.35 years. PCOS was higher (29%) in graduates. Students (40%) and housewives (44%) shared almost a similar percentage. 28.6% of women had hirsutism. Among the married women (48%), 27%, 8.6%, and 6.1% had primary infertility, secondary infertility, and a bad obstetric history. Menstrual irregularities ranged from 15 to 20 days (39.8%) to 2–3 months (60.2%), and the majority (32.7%) were suffering from PCOS for 1–3 years. Mean BMI and mean waist circumference (WC) were 24.68±5.12 and 85.11±13.43, respectively (Table 1).

All PCOS women were classified as normal (55.08%), mild (24.63%), moderate (14.5%), and severe depression (5.79%) based on MADRS (Table 2).

Analysis of serum lipid in PCOS with different grades of depression (Table 3)

A total of 69 PCOS women were grouped into normal (n=38), mild (n=17), moderate (n=10), and severe

Table 1: Demographic variables and depression risk factors within the PCOS group

Variables	PCOS women with depression n=69
Age (Mean±SD)	23.09±4.66
BMI	24.68±5.12
Waist circumference (Mean±SD)	85.11±13.43
Menarche (Mean±SD)	13.07±1.35
Occupation, (%)	
Student	40
Housewife	44
Not working women	12
Marital status, (%)	
Student	04
Married	48
Unmarried	52
Educational profile, (%)	
Preschool	17
Class 10	28
Class 12	04
Graduate	29
Paramedical students	09
Medical students	09
Nursing students	04
Primary infertility, (%)	27
Secondary infertility, (%)	8.6
Bad obstetric history, (%)	6.1
Delayed menstruation, (%)	
15–20 days	39.8
2–3 months	60.2
Duration of PCOS, (%)	
<1 year	31.6
1–3 years	32.7
4–7 years	28.6
>7 years	7.1
Hirsutism	28.6

PCOS: Polycystic ovary syndrome, SD: Standard deviation, BMI: Body mass index

(n=04) grades based on MADRS score. Lipid profile among the different groups of PCOS with depression showed no statistical difference ($P>0.05\%$ ANOVA for trend), but the mean value of TG was increased in the moderate group and reduced in the severe group (normal: 98.58 ± 37.69 , mild: 98.94 ± 43.26 , moderate: 112 ± 45.28 , and severe: 85.5 ± 15.54). TC concentration was higher in the normal group than the severe anxiety group (TC normal: Mean $\pm$ standard deviation (SD) 168.13 ± 28.6 ; confidence interval (CI) 158.73 – 177.53 , and TC severe: Mean $\pm$ SD 147.5 ± 22.15 ; CI 112.24 – 182.7). LDL-C mean values in all categories were below 100 mg/dL except the normal group (normal: Mean $\pm$ SD 106.13 ± 23.2). Almost the same HDL-C concentration was shared by different categories and was within the reference interval (Table 4).

It was revealed in our analysis mean BMI (normal 25.19 ± 6 , mild 23.6 ± 4.14 , moderate 24.8 ± 4.1 , severe 23.6 ± 3.8), mean WC (normal 85.58 ± 15 , mild 85.22 ± 9.8 , moderate 85.92 ± 13.2 , severe 82.2 ± 11.7), and mean HOMA-IR (minimal 2.86 ± 1.8 , mild 2.3 ± 0.72 , moderate 2.89 ± 1.73 , severe 2.45 ± 0.84) were high across the grading of depression but neither were significant (BMI =0.38, $P=0.76$; WC $F=0.18$, $P=0.9$; HOMA-IR $F=0.28$, $P=0.83$) (Table 5).

Hormonal analysis in PCOS with different grades of depression (Table 6)

Mean LH-FSH ratios were increased (normal 2.55 ± 1.62 , mild 1.35 ± 0.67 , moderate 2.14 ± 0.99 , severe 2.4 ± 1.6)

Table 2: Distribution of PCOS patients based on the severity of depression

Depression	n	Percentage
Normal	38	55.08
Mild	17	24.63
Moderate	10	14.5
Severe	04	5.79
Total	69	100

PCOS: Polycystic ovary syndrome

among all the grades of depression, though their differences were not statistically significant with reference to the severity of depression ($F=1.7$, $P=0.16$ ANOVA for trend). Similarly, the mean serum testosterone was elevated (normal 1.24 ± 0.83 , mild 0.97 ± 0.76 , moderate 0.93 ± 0.5 , and severe 1 ± 0.63) in all categories of PCOS with depression, but not significant ($F=0.73$, $P=0.53$). Serum estradiol concentration was low in contrast to serum progesterone concentration across the PCOS with depression group compared to the reference interval (Table 4), but neither was significant ($P>0.05$ ANOVA for trend). TSH concentration remained normal among all PCOS with depression categories (Table 7).

DISCUSSION

In our study, the mean age of participants was 23.09 ± 4.66 years, with ages ranging from 14 to 38 years. Notably, 93% of the women were within the 14–30-year age group, whereas only 7% were older than 30. This indicates that PCOS predominantly affects women in the early reproductive years, potentially contributing to significant psychological and emotional stress.

Among the 48% of participants who were married, the incidence of primary infertility was the highest at 27%, compared to secondary infertility (8.6%) and adverse obstetric history (6.1%). These findings are consistent with a review by Collée et al., which reported that PCOS is a leading cause of infertility, affecting approximately 15% of women.¹⁷ Thus, PCOS imposes an additional reproductive burden beyond other causes of infertility.

Almost all participants reported irregular menstrual cycles, with 60.2% experiencing cycles as long as 2–3 months. The average age of menarche in our study was 13.07 ± 1.35 years, which is consistent with the established secular trend observed among Indian women.¹⁸ However, a Mendelian randomization study by Ma et al. found that a later age

Table 3: Distribution of serum lipid among the different grades of depression level in the PCOS patients (n=69)

Parameters	Normal (n=38) (Mean $\pm$ SD) CI-95%	Mild (n=17) (Mean $\pm$ SD) CI-95%	Moderate (n=10) (Mean $\pm$ SD) CI-95%	Severe (n=04) (Mean $\pm$ SD) CI-95%	F-test $P\leq0.05$
TG (mg/dL)	98.58 ± 37.69 88.19–110.97	98.94 ± 43.26 76.7–121.19	112 ± 45.28 79.6–144.4	85.5 ± 15.54 60.76–110.24	0.5 0.68
TC (mg/dL)	168.13 ± 28.6 158.73–177.53	150.53 ± 31.5 134.33–166.7	151.9 ± 23.5 135.08–168.72	147.5 ± 22.15 112.24–182.7	2.1 0.09
LDL-C (mg/dL)	106.13 ± 23.2 98.5–113.76	96.35 ± 25.23 83.38–109.33	96.4 ± 18.78 82.97–109.83	92.5 ± 16.98 65.48–119.52	1.17 0.32
HDL-C (mg/dL)	47.16 ± 11.71 43.31–51.01	46.71 ± 13.99 39.51–53.9	46.8 ± 6.28 42.30–51.3	50.25 ± 5.73 41.12–51.38	0.1 0.95

PCOS: Polycystic ovary syndrome, SD: Standard deviation, CI: Confidence interval, TG: Triglyceride, TC: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol

at menarche (15–18 years) may be associated with a lower risk of developing PCOS, partially supporting our observations.¹⁹

Among the 100 women diagnosed with PCOS, 69 patients attended the psychiatry OPD for evaluation. These patients were assessed for depression using the MADRS and

categorized as normal (55.08%), mild (24.63%), moderate (14.63%), and severe depression (5.79%). Thus, nearly half (45%) of the PCOS patients show some degree of depression. This is in line with findings by Dybciak et al., who reported that depression is 2.5 times more prevalent in women with PCOS compared to non-PCOS counterparts.⁵ According to the World Health Organization (2025) estimates, 70% of PCOS cases remain undiagnosed, suggesting that PCOS may silently contribute to the global burden of depression. To get rid of the hidden burden, it is absolutely necessary to diagnose PCOS in all adolescents and adult women and subsequently screen them for depression.

In our study, women of all categories of PCOS with depression were overweight. This observation aligns with the well-documented characteristics of PCOS.¹ However, keen observation revealed that BMI gradually decreases as the depression progresses. Lipid profile in all categories remains normal compared to the reference level (Table 3), but in severe depressive patients, values are slightly lower

Table 4: Reference interval of blood biochemistry

Parameter	Reference interval
FBG	70–100 mg/dL
T-CHO	<200
TG	<150
LDL-C	<100
HDL-C	40–59
HOMA-IR	≤2.5
TSH	0.27–4.2 µIU/mL
FT4	0.93–1.7 ng/dL

FBG: Fasting blood glucose, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, T-CHO: Total cholesterol, TG: Triglycerides, TSH: Thyroid-stimulating hormone, FT4: Free tetraiodothyronine, HOMA-IR: Homeostasis model assessment-insulin resistance

Table 5: Distribution of HOMA-IR in different grades of depression level in PCOS patients (n=69)

Parameters	Normal (n=38) (Mean±SD) CI-95%	Mild (n=17) (Mean±SD) CI-95%	Moderate (n=10) (Mean±SD) CI-95%	Severe (n=04) (Mean±SD) CI-95%	F-test P≤0.05
HOMA-IR	2.86±1.8 2.16–3.5	2.3±0.72 1.6–3	2.89±1.73 1.89–3.8	2.45±0.84 1.56–3.34	0.28 0.83
BMI	25.19±6 23.1–27	23.6±4.14 20.4–26.7	24.8±4.1 22.4–27.1	23.6±3.8 20.8–26.3	0.38 0.76
WC	85.58±15 80.5–90.6	85.22±9.8 77.6–92.7	85.92±13.2 78.2–93.5	82.2±11.7 73.8–90.5	0.18 0.9

PCOS: Polycystic ovary syndrome, SD: Standard deviation, CI: Confidence interval, HOMA-IR: Homeostasis model assessment-insulin resistance, BMI: Body mass index, WC: Waist circumference

Table 6: Distribution of serum hormones among the different grades of depression in PCOS patients (n=69)

Parameters	Normal (n=38) (Mean±SD) CI-95%	Mild (n=17) (Mean±SD) CI-95%	Moderate (n=10) (Mean±SD) CI-95%	Severe (n=04) (Mean±SD) CI-95%	F-test P≤0.05
LH (IU/mL)	12.46±7.18 10–14.8	8.17±4.6 4.6–11.73	11.6±5.7 8.2–14.9	10.45±6.7 5.59–15.3	1.12 0.3
FSH (IU/mL)	5.2±1.7 4.69–5.86	6.4±2.48 4.54–8.36	5.57±1.62 4.64–6.5	4.4±0.95 3.7–5	5.0 0.003
LH/FSH (Ratio)	2.55±1.62 2–3	1.35±0.67 0.8–1.8	2.14±0.99 1.5–2.7	2.4±1.6 1.25–3.55	1.7 0.16
PRL (ng/mL)	17.5±9.19 14.39–20.6	15.9±8.1 9.6–22.1	12.66±6.3 9–16.3	16.15±6.15 11.7–20.54	0.74 0.53
Testosterone (ng/mL)	1.24±0.83 0.96–1.5	0.97±0.76 0.43–1.8	0.93±0.5 0.57–1.15	1±0.63 0.58–1.39	0.73 0.53
Estradiol (pg/mL)	23.36±18.28 17.35–29.37	22.95±16.9 14.26–31.65	21.24±12.83 12.05–30.42	32.38±32.23 18.9–42.2	0.37 0.77
Progesterone (pg/mL)	1.73±3.4 0.6–2.8	1.38±1.5 0.61–2.1	1.37±1 0.63–2.1	1.85±0.69 0.74–2.9	0.09 0.96
TSH (µIU/mL)	3±1.7 2.44–3.6	3.73±2.2 1.7–3.7	1.7±1.3 1.07–3.65	2.8±1.2 1.41–4.5	0.36 0.77
FT4 (ng/mL)	1.25±0.13 1.2–1.3	1.26±0.8 0.97–1.9	1.49±0.9 1.24–1.4	1.26±0.17 1.07–1.52	0.49 0.68

PCOS: Polycystic ovary syndrome, SD: Standard deviation, CI: Confidence interval, LH/FSH: Luteinizing hormone/follicle-stimulating hormone, PRL: Prolactin, TSH: Thyroid-stimulating hormone, FT4: Free tetraiodothyronine

Table 7: Reference ranges of serum hormones (Follicular phase)

Hormone (follicular phase)	Reference interval
LH (mIU/mL)	2.4–12.5
FSH (mIU/mL)	3.5–12.5
TT (ng/mL)	0.2–0.8
E2 (pg/mL)	30–100
Prog (ng/mL)	0.15–0.7
PRL (ng/mL)	4.79–23.3

LH: Leutinsing hormone, FSH: Follicle-stimulating hormone, TT: Total testosterone, E2: Estradiol, Prog: Progesterone, PRL: Prolactin

than other categories (Table 5). Although the number of women under each category was very low for comments, it gave us a reflection of the acute state of depression in PCOS women. FSH concentration was low compared to LH concentration, altered LH-FSH ratio, hyperandrogenemia, and increased IR across the four categories of depression, favoring the established biochemical diagnosis of PCOS (Tables 4 and 6) and consistent with previous research, including that of Fatemeh et al.,²⁰ prolactin level remained normal.

A key factor in the development of PCOS is the impaired functioning of the HPO axis. Under normal conditions, pulsatile secretion of GnRH from the hypothalamus regulates LH and FSH release from the pituitary. LH promotes ovulation, while FSH facilitates follicular maturation.⁹ Estrogen and progesterone produced by developing and ruptured follicles regulate this system via negative feedback.⁹

In PCOS, this feedback mechanism is dysregulated, leading to sustained GnRH stimulation, excess LH secretion, and an altered LH/FSH ratio. This hormonal imbalance enhances androgen production, reduces estrogen synthesis, and ultimately impairs follicular development and ovulation, resulting in cyst formation, menstrual irregularities, and infertility.⁹

The HPA axis plays a crucial role in managing the body's physiological response to stress. In response to stress, corticotropin-releasing hormone is secreted from the hypothalamus, stimulating the release of ACTH from the pituitary and cortisol from the adrenal cortex. The HPA axis is tightly regulated through a negative feedback loop and is central to emotional and psychological well-being.²¹

Women with PCOS in our study experienced emotional stressors such as infertility (35%), obesity (100%), and hirsutism (28%), all of which may hyperactivate the HPA axis, resulting in chronic cortisol elevation and androgen excess. These hormonal changes interfere with emotional

regulation and contribute to the onset of depressive symptoms. Benjamin et al. and Gonzalez-Iglesias and Freeman both support the role of HPA axis dysregulation in PCOS-related depression.^{10,22}

Attia et al. reported that IR, when combined with elevated LH, promotes increased androgen synthesis from theca cells.²³ Hyperinsulinemia also hinders follicular maturation and ovulation. Moreover, PCOS is intrinsically associated with both androgen excess and peripheral IR, creating a vicious cycle that perpetuates metabolic and reproductive dysfunction.²⁴ Beyond its metabolic implications, IR is increasingly recognized as a key contributor to depression in PCOS. Brain regions involved in mood regulation – such as the amygdala, ventral tegmental area, and raphe nuclei – contain insulin receptors.²⁵ IR is linked to impaired neuroplasticity and neurotransmission, altered insulin-mediated glucose uptake, and disruption in neuronal signaling pathways. These effects can adversely impact emotional regulation, thereby increasing vulnerability to depression.²⁶

Our study lacked the biochemical parameters of inflammation, such as IL-6 and C-reactive protein. We did not culture the gut microbiome in our study. Chronic inflammation and gut-brain-axis alteration in PCOS provide other evidence on the neurobiological connection between PCOS and depression. This area remained open for future direction of research.

Limitations of the study

The study was cross-sectional in nature, which restricts the ability to establish causal relationships between PCOS, depression, and biochemical parameters. Longitudinal studies are needed to assess the directionality and progression of these associations over time.

CONCLUSION

Our study attempts to elucidate the neurobiological and biochemical links between PCOS and depression. While our findings demonstrate important trends and correlations, limited sample size and the absence of key hormonal data – such as cortisol and dehydroepiandrosterone sulfate (DHEAS) levels – restrict the ability to draw definitive conclusions. We recommend that future studies incorporate a more comprehensive hormonal profile, including testosterone, DHEAS, and cortisol, to better understand the bidirectional relationship between PCOS and mental health. An interdisciplinary approach, integrating gynecology, psychiatry, and endocrinology, is essential for the holistic evaluation and management of PCOS.

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REFERENCES

- Campbell RE. Beyond the ovary: Rewiring our perspective on polycystic ovary syndrome. *Nat Rev Endocrinol*. 2024;20(5):257. <https://doi.org/10.1038/s41574-024-00963-3>
- Salari N, Nankali A, Ghanbari A, Jafarpour S, Ghasemi H, Dokaneheifard S, et al. Global prevalence of polycystic ovary syndrome in women worldwide: A comprehensive systematic review and meta-analysis. *Arch Gynecol Obstet*. 2024;310(3):1303-1314. <https://doi.org/10.1007/s00404-024-07607-x>
- Chaudhari AP, Mazumdar K and Mehta PD. Anxiety, depression, and quality of life in women with polycystic ovarian syndrome. *Indian J Psychol Med*. 2018;40(3):239-246. https://doi.org/10.4103/ijpsym.ijpsym_561_17
- Bahri Khomami M, Shorakae S, Hashemi S, Harrison CL, Piltonen TT, Romualdi D, et al. Systematic review and meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Nat Commun*. 2024;15(1):5591. <https://doi.org/10.1038/s41467-024-49749-1>
- Dybczak P, Raczkiewicz D, Humeniuk E, Powrózek T, Gujski M, Małacka-Massalska T, et al. Depression in polycystic ovary syndrome: A systematic review and meta-analysis. *J Clin Med*. 2023;12(20):6446. <https://doi.org/10.3390/jcm12206446>
- Kanagarajan SS, Varshney P, Ganjekar S, Muralidhar A and Desai G. Psychiatric comorbidities among Indian women with polycystic ovary syndrome: A scoping review. *J Psychiatry Spectr*. 2023;2(1):7-15.
- Yin X, Ji Y, Chan CL and Chan CH. The mental health of women with polycystic ovary syndrome: A systematic review and meta-analysis. *Arch Womens Ment Health*. 2021;24(1):11-27. <https://doi.org/10.1007/s00737-020-01043-x>
- Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod Oxf Engl*. 2018;33(9):1602-1618. <https://doi.org/10.1093/humrep/dey256>
- Ma L, Shen W and Zhang J. The life cycle of the ovary. In: Wang S, editor. *Ovarian Aging*. Singapore: Springer Nature; 2023. p. 7-33. https://doi.org/10.1007/978-981-19-8848-6_2
- Benjamin JJ, MaheshKumar K, Radha V, Rajamani K, Puttaswamy N, Koshy T, et al. Stress and polycystic ovarian syndrome-a case control study among Indian women. *Clin Epidemiol Glob Health*. 2023;22:101326.
- Aydogan Kirmizi D, Baser E, Onat T, Demir Caltekin M, Yalvac ES, Kara M, et al. Sexual function and depression in polycystic ovary syndrome: Is it associated with inflammation and neuromodulators? *Neuropeptides*. 2020;84:102099.
- Lee S, Tejesvi MV, Hurskainen E, Aasmets O, Plaza-Díaz J, Franks S, et al. Gut bacteriome and mood disorders in women with PCOS. *Hum Reprod Oxf Engl*. 2024;39(6):1291-1302. <https://doi.org/10.1093/humrep/deae073>
- Kowalczyk M, Kowalczyk E, Galita G, Majsterek I, Talarowska M, Popławski T, et al. Association of polymorphic variants in Argonaute genes with depression risk in a polish population. *Int J Mol Sci*. 2022;23(18):10586. <https://doi.org/10.3390/ijms231810586>
- Snaith RP, Harrop FM, Newby DA and Teale C. Grade scores of the montgomery-asberg depression and the clinical anxiety scales. *Br J Psychiatry J Ment Sci*. 1986;148:599-601. <https://doi.org/10.1192/bjp.148.5.599>
- Aziz N, Kallur SD and Nirmalan PK. Implications of the revised consensus body mass indices for Asian Indians on clinical obstetric practice. *J Clin Diagn Res JCDR*. 2014;8(5):OC01-OC03. <https://doi.org/10.7860/jcdr/2014/8062.4212>
- Owei I, Umekwe N, Provo C, Wan J and Dagogo-Jack S. Insulin-sensitive and insulin-resistant obese and non-obese phenotypes: Role in prediction of incident pre-diabetes in a longitudinal biracial cohort. *BMJ Open Diabetes Res Care*. 2017;5(1):e000415. <https://doi.org/10.1136/bmjdr-2017-000415>
- Collée J, Mawet M, Tebache L, Nisolle M, Brichant G. Polycystic ovarian syndrome and infertility: Overview and insights of the putative treatments. *Gynecol Endocrinol*. 2021;37(10):869-874. <https://doi.org/10.1080/09513590.2021.1958310>
- Meher T and Sahoo H. Secular trend in age at menarche among Indian women. *Sci Rep*. 2024;14(1):5398. <https://doi.org/10.1038/s41598-024-55657-7>
- Ma Y, Cai J, Liu LW, Hou W, Wei Z, Wang Y, et al. Age at menarche and polycystic ovary syndrome: A Mendelian randomization study. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2023;162(3):1050-1056. <https://doi.org/10.1002/ijgo.14820>
- Fatemeh B, Shahideh JS, Negin M. Health related quality of life and psychological parameters in different polycystic ovary syndrome phenotypes: A comparative cross-sectional study. *J Ovarian Res*. 2021;14(1):57. <https://doi.org/10.1186/s13048-021-00811-2>
- Bellavance MA and Rivest S. The HPA - immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Front Immunol*. 2014;5:136. <https://doi.org/10.3389/fimmu.2014.00136>
- Gonzalez-Iglesias AE and Freeman ME. Brain Control over Pituitary Gland Hormones. In: *Neuroscience in the 21st Century*. Cham: Springer; 2022. p. 2291-2344. Available from: https://link.springer.com/rwe/10.1007/978-3-030-88832-9_58 [Last accessed on 2025 Aug 02].
- Attia GM, Almouteri MM and Alnakhli FT. Role of metformin in polycystic ovary syndrome (PCOS)-related infertility. *Cureus*. 2023;15(8):e44493. <https://doi.org/10.7759/cureus.44493>
- Chen W, Pang Y. Metabolic syndrome and PCOS: Pathogenesis and the Role of metabolites. *Metabolites*. 2021;11(12):869. <https://doi.org/10.3390/metabo11120869>
- E Silva NM, Lam MP, Soares CN, Munoz DP, Milev R and De Felice FG. Insulin resistance as a shared pathogenic mechanism between depression and type 2 diabetes. *Front Psychiatry*. 2019;10:57.

<https://doi.org/10.3389/fpsyt.2019.00057>

26. Fernandes BS, Salagre E, Enduru N, Grande I, Vieta E and Zhao Z. Insulin resistance in depression: A large meta-analysis

of metabolic parameters and variation. *Neurosci Biobehav Rev.* 2022;139:104758.

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