Cognitive impairment and associated metabolic and hormonal factors in women with polycystic ovarian syndrome: a Montreal Cognitive Assessment-based case-control study

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women, frequently accompanied by metabolic dysfunction, hyperandrogenism, and psychological disturbances. Recent studies suggest possible links between PCOS and cognitive dysfunction, but evidence remains limited. We used the Montreal Cognitive Assessment (MoCA) to assess cognitive function in women with PCOS, and we investigated the interrelationships between hormonal dysregulation, metabolic dysfunction, and inflammatory status. A total of 120 women with PCOS (Rotterdam criteria) and 60 age-matched healthy controls underwent cognitive evaluation using MoCA. Demographic, anthropometric, hormonal, metabolic, and inflammatory markers and lipid profiles were assessed. PCOS patients demonstrated significantly lower total MoCA scores vs. controls (24.29 vs. 27.82, $p<0.001$). Cognitive impairment (MoCA<26) occurred in 34.16% of PCOS patients. Executive function, attention, language, and orientation domains were significantly impaired, while memory-related domains remained relatively preserved. Women with PCOS showed distinct cognitive vulnerability, particularly in executive, attention, language, and orientation domains. Cognitive dysfunction may represent an underrecognized PCOS aspect, warranting regular screening and future longitudinal studies.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine and metabolic disorders in women of reproductive age,[1] characterized by clinical and biochemical hyperandrogenism, chronic oligo-ovulation or anovulation leading to menstrual irregularities, and polycystic ovarian morphology on ultrasound.[2] Beyond reproductive features, PCOS is frequently accompanied by insulin resistance (IR),

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Informed consent: the aim of the study was explained to all participants in simple language (Arabic). The samples were collected from the individuals who agreed to participate in this study.

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obesity, dyslipidemia, and other metabolic abnormalities, conferring elevated risk of type 2 diabetes and cardiovascular disease.[1] Adverse mental health outcomes and reduced quality of life are also more common in PCOS, highlighting that its impact extends beyond gynecologic and metabolic domains.[3]

Recent attention has turned to PCOS potentially affecting cognitive function. Emerging evidence suggests women with PCOS could experience subtle cognitive deficits across multiple domains, including memory, attention, executive function, and visuospatial skills.[4] Several studies have reported poorer cognitive performance in PCOS patients compared to matched controls.[4,5] The etiology of these cognitive changes is not fully understood, but hormonal, metabolic, and inflammatory factors are thought to play a role.[4-6]

The Montreal Cognitive Assessment (MoCA) is a widely validated 30-point screening test assessing multiple cognitive domains.[7] Given its comprehensive coverage and brevity, MoCA has become standard for cognitive screening.

This study evaluated cognitive function in PCOS women using MoCA and investigated interrelationships between hormonal dysregulation, metabolic dysfunction, and inflammatory status.

Materials and Methods

This case-control study was conducted over a timeframe spanning from November 2023 to January 2025. The study recruited 120 female participants with PCOS diagnosed according to the 2003 Rotterdam criteria by a Specialist Gynecologist.[8] The study was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University (Order No. 20231013, Date 18/1/2024). All the participants gave their consent of approval.

PCOS with an age range between 20 to 50 years and a body mass index (BMI) of <35 kg/m^2 were included, while those with hypertension, ischemic heart disease, valvular heart disease, heart failure, fever, menopause, rheumatoid arthritis, autoimmune diseases, chronic infections, and those with BMI≥35 kg/m^2 were excluded. A total of 60 healthy women were recruited as controls, matched for age range (±5 years) and BMI (±3 kg/m^2). Controls were excluded if they had irregular menstrual cycles, hirsutism, or any endocrine disorders.

History and physical examination

This includes questions about age, smoking habits, educational level, and income, and measurement of weight, height, BMI, and waist-hip ratio.

Laboratory analysis

The follicular stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone were analyzed using Cobas e411(Roche, Penzberg, Germany), and free testosterone was analyzed using enzyme-linked immunosorbent assay (Kayto, Zhejiang, China). Lipid profile, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very LDL (VLDL) was estimated by using Cobas c311 (Roche, Penzberg, Germany), and the C-reactive protein (CRP) was studied also and analyzed using Cobas c311 (Roche, Penzberg, Germany). The glycosylated hemoglobin (HbA1c) and insulin levels were measured using Cobas e411 (Roche, Penzberg, Germany). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was used to test for IR using the following equation: HOMA-IR = Glucose × insulin/405.

Montreal Cognitive Assessment test

The MoCA test scale of 30 items was used to assess the cognitive functions according to the domains of attention, language, memory, visuospatial, executive functions, and orientation, and scored accordingly from 0 to 30 with a cut-off value of 26. A score of 26 or above was considered normal cognitive function, while scores below 26 indicated cognitive impairment (CI), consistent with established MoCA validation studies.[9]

Statistical analysis

Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were compared using independent t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data. Categorical variables were analyzed using chi-square tests. Given the significant age difference between groups (p=0.002), age-adjusted analyses were performed using analysis of covariance (ANCOVA) for MoCA scores. Bonferroni correction was applied for multiple comparisons across cognitive domains. Multivariable linear regression was conducted to identify independent predictors of MoCA performance, adjusting for age, BMI, and education level. Statistical significance was set at p<0.05.

Results

Table 1 shows that PCOS women were significantly older (independent *t*-test, p=0.002) with higher weight and height (p<0.001, respectively) compared to the healthy controls (HCs). Fewer PCOS women have university and higher education levels relative to the HCs (p=0.004). However, BMI, waist-hip ratio, smoking history, and monthly income were not different between the two groups.

Due to the significant age difference between groups, subsequent cognitive analyses were adjusted for age as a covariate using ANCOVA.

Hormonal profile and C-reactive protein

As shown in Table 2, PCOS patients exhibited significantly lower FSH, higher LH, free and total testosterone, and serum C-reactive protein levels (p<0.001) relative to the HCs. Hormonal differences were analyzed using Mann-Whitney U tests due to non-normal distribution.

Diabetes-related parameters

The HbA1c and insulin levels and HOMA-IR were significantly higher in PCOS patients when compared to the

HCs (p<0.001), as indicated in Table 3. The percentage of PCOS patients classified as insulin resistant was significantly higher than HCs (p=0.024).

Lipid profile

Higher levels of TC and LDL were demonstrated in PCOS women compared to HCs (p=0.009; p<0.001, respectively) as indicated in Table 4. Conversely, HDL levels were significantly lower in the PCOS group than in the HCs (p<0.001). Although TG and VLDL levels were elevated in PCOS patients, these differences did not reach statistical significance.

Montreal Cognitive Assessment test

Table 5 illustrates the results of the MoCA test (different domains and total scores) of the study population.

Table 1. Population characteristics and baseline demographics.

Variables	Patients (n=120)	Controls (n=60)	p
Age, years			
Mean±SD	32.98±7.28	29.62±5.9	0.002
Range	20-48	20-47	
Weight, kg			
Mean±SD	70.61±9.49	64.13±8.31	<0.001
Range	51-91	49-84	
Height, m			
Mean±SD	1.6±0.07	1.53±0.06	<0.001
Range	1.44-1.75	1.43-1.67	
Body mass index, kg/m^2			
Mean±SD	27.64±3.51	27.25±3.02	0.470
Range	20.9-34.8	21.4-35.0	
Waist-hip ratio			
Mean±SD	0.82±0.1	.84±0.06	0.089
Range	0.65-1.05	00.72-0.97	
Smoking history, n (%)			
Never	111 (92.5)	57 (95)	0.388
Ex/current	9 (7.5)	3 (5)	
Education level, n (%)			
Primary school	3 (2.5)	1 (1.67)	
Intermediate school	46 (38.33)	11 (18.33)	
Secondary school	49 (40.83)	23 (38.33)	0.004
University	18 (15)	16 (26.67)	
Higher	4 (3.33)	9 (15)	
Income/month, n (%)			
Low	45 (37.5)	23 (38.33)	
Moderate	61 (50.83)	25 (41.67)	0.268
High	14 (11.67)	12 (20)	

SD, standard deviation.

Table 2. Hormonal profile and C-reactive protein of the study population.

Variables	Patients (n=120)	Controls (n=60)	p
FSH, mIU/mL			
Mean±SD	6.49±0.67	8.34±2.38	<0.001
Range	4.17-8.24	4.02-12.29	
LH, mIU/mL			
Mean±SD	13.55±0.78	8.08±2.25	<0.001
Range	11.36-16.21	3.89-11.80	
Total testosterone, ng/mL			
Mean±SD	0.92±0.28	0.34±0.11	<0.001
Range	0.47-1.90	0.09-0.54	
Free testosterone, ng/mL			
Mean±SD	2.95±0.47	1.3±0.4	<0.001
Range	2.10-4.72	0.17-1.90	
C-reactive protein, mg/L			
Mean±SD	3.09±1.05	2.2±1.2	<0.001
Range	1.1-4.8	0.5-4.6	

SD, standard deviation; FSH, follicular stimulating hormone; LH, luteinizing hormone.

The scores of executive processing, sustained attention, language, and spatiotemporal orientation domains were significantly lower in PCOS patients in comparison to the values of HCs (p<0.001), whereas scores of naming, abstract thinking, and delayed recall domains were not different between the two groups. Additionally, patients with PCOS demonstrated significantly lower total MoCA scores (p<0.001) compared to HCs. Overall, CI was indicated by the scores of 34.16% of PCOS patients. Correlation analysis revealed several significant associations with total MoCA scores (Table 6). The strongest negative correlation was observed with HOMA-IR (r=-0.564, p<0.001), indicating that higher IR was associated with poorer cognitive performance. Similarly, insulin level demonstrated a strong negative correlation with MoCA scores (r=-0.523, p<0.001). Age showed a moderate negative correlation (r=-0.504, p<0.001), consistent with expected age-related cognitive decline. HbA1c levels also negatively correlated with cognitive performance (r=-0.490, p<0.001), suggesting that even subclinical glycemic disturbances may impact cognition. Conversely, education level showed a positive correlation with MoCA scores (r=0.293, p<0.001), indicating a protective effect of higher educational attainment on cognitive function.

MoCA domain comparisons used ANCOVA with age adjustment. Multivariable linear regression analysis was performed to identify independent predictors of cognitive performance (Table 7). The overall model was highly significant (F=44.944, p<0.001) and explained 50.7% of the variance in total MoCA scores (R^2=0.507, adjusted R^2=0.495). Three variables emerged as significant independent predictors: age [β=-0.209, 95% confidence interval (95% CI): -0.262 to -0.155, p<0.001], education level (β=1.138, 95% CI: 0.763 to 1.514, p<0.001), and HOMA-IR (β=-0.708, 95% CI: -1.164 to -0.252, p=0.003). Notably, PCOS group status was not a significant independent predictor when controlling for these variables (β=0.068, 95% CI: -0.988 to 1.124, p=0.899), suggesting that the cognitive differences observed between groups are mediated through age, educational, and metabolic factors rather than PCOS diagnosis per se.

Age-adjusted analysis using ANCOVA revealed that PCOS patients had significantly lower MoCA scores compared to controls, even after controlling for age differences (adjusted means: PCOS 25.66 *vs*. control 27.70, difference = -2.05 points, p<0.001) (Table 8).

Table 3. Diabetes-related parameters of the study population.

Variables	Patients (n=120)	Controls (n=60)	p
HbA1c, %			
Mean±SD	5.81±0.48	5.23±0.27	<0.001
Range	4.8-7.2	4.6-5.9	
Insulin level mlU/mL			
Mean±SD	29.34±4.84	11.61±3.89	<0.001
Range	18.32-44.92	5.32-24.1	
HOMA-IR			
Mean±SD	3.15±1.01	2.28±0.82	<0.001
Range	0.83-5.86	0.74-4.18	
Insulin resistance, n (%)			
No	46 (76.67)	55 (91.67)	0.024
Yes	14 (23.33)	5 (8.33)	

SD, standard deviation; HbA1c, glycosylated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

Table 4. Lipid profile of the study population.

Variables	Patients (n=120)	Controls (n=60)	p
Cholesterol, mg/dL			
Mean±SD	182.49±24.09	172.84±13.28	0.009
Range	139.9-255.8	142.8-204.6	
TG, mg/dL			
Mean±SD	125.29±28.14	119.78±22.64	0.228
Range	91.1-211.5	79.6-161.7	
HDL, mg/dL			
Mean±SD	35.96±4.42	40.30±3.87	<0.001
Range	24.40-44.3	30.1-47.2	
LDL, mg/dL			
Mean±SD	121.13±19.06	107.20±7.53	<0.001
Range	82.8-180.2	87.4-126.6	
VLDL, mg/dL			
Mean±SD	24.56±6.22	23.78±4.40	0.435
Range	12.9-42.3	15.9-31.9	

SD, standard deviation; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Table 5. Montreal Cognitive Assessment test in patients and controls.

Variables	Patients (n=120)	Controls (n=60)	p
Executive function			
Mean±SD	4.54±0.69	4.90±0.30	<0.001
Range	2-5	4-5	
Naming			
Mean±SD	2.95±0.21	2.95±0.22	1.00
Range	2-3	2-3	
Sustained attention			
Mean±SD	4.75±0.96	5.92±0.28	<0.001
Range	3-6	5-6	
Language			
Mean±SD	2.48±0.69	2.83±0.38	<0.001
Range	1-3	2-3	
Abstract thinking			
Mean±SD	1.89±0.31	1.95±0.22	0.197
Range	1-2	1-2	
Delayed recall			
Mean±SD	3.58±1.02	3.63±0.80	0.700
Range	1-5	2-5	
Spatiotemporal orientation			
Mean±SD	5.26±0.63	5.93±0.25	<0.001
Range	4-6	5-6	
Total score			
Mean±SD	25.45±3.28	28.12±0.78	<0.001
Range	16-30	27-30	

SD, standard deviation.

Table 6. Correlation analysis with the total Montreal Cognitive Assessment score.

Variable	Correlation coefficient (r)	p
HOMA-IR	-0.564	<0.001***
Insulin level	-0.523	<0.001***
Age	-0.504	<0.001***
HbA1c	-0.490	<0.001***
Education level	0.293	<0.001***

HbA1c, glycosylated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; *p<0.05, **p<0.01, ***p<0.001.

Table 7. Multivariable linear regression analysis predicting total MoCA score.

Variable	β Coefficient	Standard Error	t-statistic	p	95% confidence interval
Age (years)	-0.209	0.027	-7.693	<0.001*	(-0.262, -0.155)
Education level	1.138	0.190	5.977	<0.001*	(0.763, 1.514)
HOMA-IR	-0.708	0.231	-3.064	0.003	(-1.164, -0.252)
PCOS group status	0.068	0.535	0.127	0.899	(-0.988, 1.124)
Intercept	31.189	0.814	38.298	<0.001	(29.582, 32.796)

HOMA-IR, Homeostasis Model Assessment of Insulin Resistance Model Statistics; PCOS, polycystic ovarian syndrome.
Model statistics: R2=0.507 (50.7% of variance explained); adjusted R2=0.495; F-statistic=44.944, p < 0.001; sample size=180 (120 PCOS, 60 controls); RMSE=2.094. Significance levels: *p<0.05, **p<0.01, ***p<0.001

Table 8. Age-adjusted Montreal Cognitive Assessment analysis (analysis of covariance).

Group	Unadjusted mean	Age-adjusted mean	Difference	p
PCOS	25.45 ± 3.28	25.66	-2.05	<0.001***
Control	28.12 ± 0.78	27.70		

PCOS, polycystic ovarian syndrome; *p<0.05, **p<0.01, ***p<0.001.

Discussion

Our research indicated that PCOS women were older and of higher weight and height. Previous studies indicate PCOS symptoms may worsen with age due to cumulative metabolic and hormonal burden.[10,11] Although age does not directly cause PCOS, it enhances clinical expression through increased IR and hyperandrogenism.[10] The significant age difference between groups, despite attempts at matching, represents a study limitation. However, age-adjusted analyses were performed to minimize this confounding effect. Elevated weight among PCOS patients aligns with the literature documenting high prevalence of overweight and obesity, even with comparable BMI to non-PCOS counterparts.[12]

PCOS women achieved lower higher and university education compared to HCs. Literature links lower educational achievement with reduced health literacy, leading to delayed specialized medical access and delayed health diagnoses in PCOS-affected women.[13]

Women with PCOS typically show elevated LH, total and free testosterone, and lower FSH levels. Previous research consistently reports this profile, relating it to hypothalamic-pituitary-ovarian axis dysregulation.[14,15] Higher CRP levels in PCOS patients indicate a chronic low-grade inflammatory condition.[16]

Women with PCOS had significantly higher insulin concentration, HbA1c level, and HOMA-IR, emphasizing the well-documented correlation between PCOS and impaired glucose metabolism, supporting PCOS classification as a condition with strong metabolic mechanisms.[17,18] Although PCOS patients were not diabetic, raised HbA1c levels within prediabetic thresholds indicate premature glycemic homeostasis disturbance. This supports evidence demonstrating women with PCOS have an increased risk of advancing to type 2 diabetes mellitus over time.[19]

A classic dyslipidemic profile was demonstrated in women with PCOS in the current study, characterized by elevated TC, increased LDL, and decreased HDL levels, whereas TG and VLDL levels were not different. These findings align with a growing body of evidence indicating that lipid disturbances are a prominent metabolic feature of PCOS.[20,21]

However, not all studies concur on the extent of TG and VLDL changes. Some earlier research in lean or young PCOS populations found no significant difference in TG or TC levels compared to controls, with PCOS subjects differing mainly in having lower HDL and higher LDL.[22] Such discrepancies are often attributed to variations in sample characteristics (*e.g.*, age, adiposity, ethnicity) and the criteria used to define PCOS.

Montreal Cognitive Assessment test

Women with PCOS scored lower on executive function tasks (which include planning, problem-solving, and visuospatial-executive tasks), indicating that many PCOS patients failed one or more executive items (*e.g.*, trail-making or clock-drawing). These findings align with other human studies reporting poorer executive performance and mental flexibility tasks in PCOS,[4,23] but contradict other who found no such finding.[24] These discrepancies suggest that executive cognitive effects in PCOS may be moderate and influenced by confounders like metabolic health and sample characteristics.

In contrast to executive skills, naming ability (which includes identifying familiar animals) was preserved in PCOS. This suggests that PCOS does not impair semantic memory retrieval or basic language function required for object naming, and they could name common objects just as accurately as healthy women, indicating intact lexical access and memory for learned concepts. This preservation suggests that the neural substrates responsible for semantic memory and language processing, primarily located in the temporal lobes, remain unaffected by the hormonal and metabolic disturbances characteristic of PCOS.[25,26]

A pronounced deficit in sustained attention (which includes digit span, vigilance tapping, and serial subtraction) was demonstrated by women with PCOS, denoting difficulty in maintaining focus and performing continuous mental operations. Multiple studies corroborate attention impairments in PCOS even in midlife.[23,27] Even neurophysiological studies, such as the event-related potentials, have objectively indicated attention dysfunction in PCOS, reflected as longer latencies in cognitive processing.[28] On the reverse, one interventional study observed no immediate change in attention task performance between PCOS and controls.[24]

The language domain of MoCA (encompassing verbal fluency and sentence repetition) was significantly lower in PCOS patients, indicating reduced performance in tasks like word generation and perhaps sentence repetition or articulating complex phrases. Prior research has consistently noted that PCOS women underperform on tests of verbal fluency and verbal memory relative to HCs,[23,27,29] supporting the notion that PCOS appears to subtly impair certain language functions, especially those requiring quick and flexible word generation. Contrary to these findings, Schattmann and Sherwin did not observe changes in verbal memory or vocabulary after manipulating sex hormones in PCOS women, implying that short-term androgen level shifts may not acutely affect language.[30]

Abstract reasoning (assessed by MoCA's similarities questions) did not significantly differ between PCOS and HCs, as both scored 1.9 out of 2 points. This suggests that the ability to understand abstract relationships and analogies (*e.g.*, identifying how two objects are alike) is largely intact in PCOS. There is a scarcity in the literature on abstract thinking in PCOS but the result of the present study aligns with the general finding that global intelligence and reasoning remain normal.[5,30]

Surprisingly, delayed recall of words was not significantly different between PCOS and HCs in this research, indicating both groups could recall a similar number of items. The absence difference in recall may be due to the relatively younger age of participants (mostly in their 20s and 30s) and the short, structured memory task in MoCA. Some prior studies that found memory deficits did so in more demanding or sensitive tests, or in older women.[5,23,31]

Regarding spatiotemporal orientation, women with PCOS showed a significant deficit in orientation (identifying the current date, month, place, *etc*.). This suggests subtle issues in awareness of time or place in the PCOS group, though the majority were still well-oriented. Yet even a small difference in orientation is notable, given that these items are generally easy for unimpaired adults.

PCOS-related metabolic and hormonal abnormalities provide plausible mechanisms for CI. IR – prevalent in PCOS – is known to impair frontal lobe metabolism, cognitive flexibility, and attentional capacity.[4] IR signaling in the brain is important for memory consolidation, and impairment of this pathway (common in PCOS) may lead to subtle memory issues over time. Chronic hyperglycemia or dysglycemia can accelerate memory decline; indeed, higher HbA1c was linked to worse memory performance in PCOS and control women alike.[25]

Additionally, concentration and executive attention can be impaired by mood disturbances (fatigue, anxiety, depression), which are common in PCOS.[4,32,33] These cognitive domains are integral to maintaining temporal orientation. Indeed, improvements in PCOS mood symptoms correlate with improved executive task scores.[6,26] Furthermore, PCOS is associated with sleep apnea and poor sleep quality, leading to confusion or daytime cognitive fog.[34]

The multivariable regression analysis revealed that cognitive differences between PCOS patients and controls are primarily mediated through age, educational attainment, and IR rather than PCOS diagnosis directly. Age showed the strongest effect (standardized β=-0.490), consistent with normal cognitive aging. Education level demonstrated a protective effect (standardized β=0.359), highlighting the importance of cognitive reserve. Importantly, HOMA-IR emerged as an independent predictor of cognitive performance (standardized β=-0.282), supporting the hypothesis that metabolic dysfunction contributes to CI in PCOS. The finding that PCOS group status became non-significant when controlling for these factors suggests that the cognitive effects of PCOS are mediated through its associated metabolic and demographic characteristics.

Conclusions

Women with PCOS exhibit significantly lower cognitive performance on the MoCA, suggesting mild CI. This extends understanding of PCOS beyond metabolic and reproductive features, indicating subtle neurocognitive consequences. These results highlight the importance of comprehensive PCOS management by incorporating cognitive screening tools like MoCA into routine assessment to facilitate early detection of neurocognitive dysfunction. Early identification could enable timely interventions such as lifestyle modifications, metabolic control, or cognitive rehabilitation to potentially improve cognitive outcomes and quality of life

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