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Original article

# Association between insulin resistance and abnormal menstrual cycle in Saudi females with polycystic ovary syndrome

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ABSTRACT

*Background:* Polycystic ovary syndrome (PCOS) is an endocrine disorder experienced by women of reproductive age and is marked by insulin resistance (IR) and menstrual cycle abnormalities. In this study, we set out to assess how the level of menstrual abnormalities relates to the degree of IR in women with PCOS.

*Methods:* The participants in this study were 93 women diagnosed with PCOS and 100 controls with regular vaginal bleeding. Data was collected through blood samples, physical examinations, and medical histories. The primary outcome measures were body mass index (BMI), fasting glucose, fasting insulin, homeostatic model assessment for IR (HOMA-IR), and hormonal parameters.

*Results:* Values for BMI and HOMA-IR were higher in PCOS cases than in controls [(28.6 ± 1.9 vs. 23.7 ± 2.3) and (2.29 ± 2.87 vs. 1.48 ± 1.02), respectively]. Oligomenorrhea was documented in 79.4% of women with PCOS, with the others experienced vaginal bleeding intervals under 45 days. The greater the menstrual irregularity, the higher the levels of luteinizing hormone/follicle-stimulating hormone and testosterone. Among the PCOS group, those with vaginal bleeding intervals of above 90 days had a higher HOMA-IR values (2.46 ± 2.77), after adjustments for age and BMI, than the participants who went<45 days between periods (2.01 ± 2.14) and those whose interval was 45–90 days (2.09 ± 2.43).

*Conclusions:* Most of the participants with PCOS had obvious oligomenorrhea of at least 6 weeks between episodes of vaginal bleeding and had significantly higher insulin resistance than did the controls. This suggests that insulin resistance in PCOS cases may be predicted by the presence of clinically overt menstrual dysfunction.



## 1. Introduction

Polycystic ovary syndrome (PCOS), is a complex disorder with different phenotypes, involving metabolic, reproductive, and endocrine abnormalities and is among the most widespread such disorder in premenopausal women (Mumusoglu and Okan Yildiz, 2020). Its current prevalence is now estimated to be between 5.5 and 16.0% (Hatziagelaki et al., 2020), rates which vary according to geographic region in addition to characteristics of race and ethnicity (Wolf et al., 2018). A recent study conducted in Saudi Arabia found a 16% prevalence of PCOS in this region (Aldossary et al., 2020). There has been some indication in research that Middle Eastern women have a higher risk of PCOS than their Caucasian and Asian peers (Ding et al, 2017).

PCOS is implicated in an array of health conditions, including cardiovascular disease, hypertension and diabetes (Osibogun et al., 2020). Insulin resistance (IR) is common in women with PCOS, seen in 70% of cases, which may lead to additional reproductive and metabolic complications later on (Jeanes and Reeves, 2017, Wang et al., 2020). It is important, then, to identify clinical and/or biological markers of early IR in patients with PCOS, thereby helping to lower the rates of diabetes and other metabolic disorders and enhance the quality of life and long-term prognosis in these patients.

There is no firm definition of PCOS, with its varied expression of phenotypes, but oligomenorrhea and menstrual irregularities are key characteristics (Harris et al., 2017). Between 85% and 90% of PCOS cases experience oligoovulation and a lengthy gap between

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occurrences of vaginal bleeding (Harris et al., 2017, Hart et al., 2004). Amenorrhea in women with PCOS is diagnosed upon the cessation of menstruation for longer than three months. However, amenorrhea in such patients commonly goes unnoticed, so timely diagnosis and treatment does not occur. Moreover, PCOS is associated with miscarriages and other adverse pregnancy outcomes, especially in cases of amenorrhea (Yu et al., 2021), so it is imperative to diagnose and treat amenorrhea in women with PCOS at an early stage.

Research has shown a link between irregular and infrequent menstrual cycles and hyperinsulinemia (Wang et al., 2020). Abnormal hormone levels disrupt ovarian function, resulting in abnormal menstrual conditions like anovulation and amenorrhea (Abraham et al., 2021). Along with its implication in menstrual complications, IR significantly impacts women with PCOS, as measured by the homeostasis model assessment: insulin resistance (HOMA-IR) index (Li et al., 2022). As menstruation is affected by the secretions of sex hormones, IR interacts with estrogen levels. Elevated amounts of estrogen can intensify the secretion of luteinizing hormone (LH) and lower that of follicle stimulating hormone (FSH), leading in turn to follicular membrane cell and granulosa cell hyperplasia. In cases of PCOS, insulin makes the adrenal cortex more sensitive to the activation of adrenocorticotropic hormones, further raising androgen secretion and disrupting menstruation (Polak et al., 2017).

These findings agree with those from a cross-sectional study of PCOS cases, where intervals between vaginal bleeding of at least 35 days were linked to elevated homeostatic model assessment for IR (HOMA-IR), indicating a possible correlation between IR and the degree of oligomenorrhea (Brower et al., 2013). This research suggests that menstrual irregularity may play a role in screening for metabolic disorders in PCOS cases. The focus of these studies, however, was the link between irregular menstruation and type 2 diabetes mellitus. Where research is not as robust is investigating the link between the level of clinically overt menstrual dysfunction in women with PCOS and their level of IR. If such an association does exist, menstrual irregularity could be employed as a basic clinical indicator in patients to detect those with the most risk of metabolic dysfunction.

Although some research has focused on the connection between IR and menstruation in PCOS, weaknesses in study design or lack of control for important confounders limit the findings. For example, PCOS patients with oligomenorrhea were excluded in some studies, while others grouped oligomenorrheic with amenorrheic patients with no distinction, resulting in incomplete associations between IR and menstrual dysfunction. Bias and confounding also occurred in some studies, where the role of hormones such as testosterone was not taken into consideration. In others, multivariate analysis was not carried out to compare HOMA-IR values among the PCOS patients with eumenorrhea, oligomenorrhea and amenorrhea, so a significant increasing trend of HOMA-IR scores in these patients was not reported. To help fill this research gap, we carried out a cross-sectional study to assess the correlation between the extent of menstrual irregularity and impaired glucose metabolism in women with PCOS.

## 2. Materials and methods

### 2.1. Ethical considerations

Institutional ethical approval was obtained as was written informed consent from all women before the beginning of the study. All procedures were in line with the principles of the Declaration of Helsinki for research on human subjects.

### 2.2. Diagnostic criteria

Using the Rotterdam 2003 criteria, PCOS cases were diagnosed when two of these three conditions were present: 1) oligo- or anovulation, 2) biochemical and/or clinical markers of hyperandrogenism, and 3) evidence of polycystic ovarian morphology on ultrasonographic examination (Rotterdam Diagnostic Criteria, 2004). A PCOS diagnosis was established only after the exclusion of related disorders. A measurement of 12 or more 2–9 mm-cysts in one or both ovaries and/or a volume above 10 ml of either ovary was used to diagnose polycystic ovarian morphology (Rotterdam Diagnostic Criteria, 2004).

Controls were diagnosed if they had a long-standing history of normal menstrual cycles, had no evidence of hirsutism [modified Ferriman-Gallwey (mFG) score $\leq 3$] or polycystic ovarian morphology, as determined by ultrasonography (Wu et al., 2003).

### 2.3. Selection of the study population

Patients newly diagnosed with PCOS were selected from the endocrine clinic at King Abdullah Medical City, in Makkah, in western Saudi Arabia. Patients at this outpatient clinic presented with principal complaints of abnormal menstruation, acne, hirsutism, and problems with fertility. Of the 124 patients assessed for eligibility, 21 were excluded. Of those remaining 103, 100 agreed to participate, but incomplete questionnaires limited the final number of cases to 97. With the help of a gynecologist, women of reproductive age who visited the OB/GYN department of King Abdullah Medical City were selected at random and asked to participate as controls. Of the 114 women eligible, 109 agreed to participate, but insufficient data limited that number to 100 controls.

Participants in the PCOS cohort were grouped into three sets based on the time between episodes of vaginal bleeding: <45 days, 45–90 days, and more than 90 days. Some of the women whose intervals were more frequent than every 45 days had normal menstruation, so ovulatory function was assessed by the amount of progesterone present in days 22–24 of menses. Those with amounts of progesterone under 4 ng/ml were deemed anovulatory, with the remainder considered ovulatory (Brower et al., 2013).

### 2.4. Exclusion and inclusion criteria

Exclusion of PCOS-related conditions was accomplished by measuring amounts of TSH to rule out thyroid dysfunction, levels of prolactin to exclude hyperprolactinemia, and amounts of 17-hydroxyprogesterone to rule out 21-hydroxylase-deficient nonclassic adrenal hyperplasia. When clinically warranted, examination to rule out Cushing's syndrome and androgen-secreting neoplasms was conducted. Further exclusion criteria included pregnancy at the time of the study or in the previous year, use of oral contraceptives or other medications impacting the hypothalamic–pituitary–ovarian axis within the last 6 months, any major systemic disease, such as an autoimmune disease, malignancy, central nervous system disorder, or prior treatment with chemotherapy or immunosuppressive agents. Exclusion criteria were incomplete or missing information on menstrual cycle length or use of hormonal medication within the previous three months. All women for whom main outcome measurements were collected were included if they met the criteria for either PCOS or controls.

### 2.5. Acquisition of parameters

Demographic and medical history data were collected by having all participants fill out a questionnaire. Data included personal information, relevant family history, menstrual history, skin

conditions linked to hyperandrogenism (hirsutism, acne), and metabolic disease. A complete medical evaluation was carried out on each subject including taking height, weight, waist and hip dimension, and conducting a transvaginal pelvic ultrasound for antral follicle counting. Fasting baseline blood samples were drawn to measure biochemical and hormonal parameters at the follicular or preovulatory stage of the menstrual cycle (days 2–4) or randomly for subjects with no menstrual bleeding. Subjects were instructed to abstain from everything but water for at least 8 h prior to sampling. Glucose and lipid markers including total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were assessed by colorimetric reflectance spectrophotometry, using the VITROS 250 Clinical Chemistry Auto-analyzer (Ortho-Clinical Diagnostics Inc., Rochester, NY, US). Insulin levels were determined by sandwich chemiluminescent immunoassay (CLIA), using the LIAISON auto-analyzer. The homeostatic model for the assessment of insulin resistance (HOMA-IR) was calculated using this formula: [fasting glucose (in mmol/L) × fasting insulin (μU/mL)] / 22.5. A HOMA-IR value above 2.5 was used to indicate IR (Matthews et al., 1985). The follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were measured using CLIA (Ortho-Clinical Diagnostics Inc., Rochester, NY, US).

### 2.6. Statistical analysis

Descriptive statistics were expressed as mean ± standard error. Mean values between groups were compared using the ANOVA test. We used the chi-square and Fisher's exact tests to investigate the relationship between categorical variables and stepwise multiple regression analysis for comparison of the mean HOMA-IR in controls with each menstrual cycle length group, controlling for BMI and age. A P-value of < 0.05 was deemed statistically significant. All data underwent analysis using SPSS ver. 21.0 (SPSS, Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Characteristics of the studied groups

Data from 97 PCOS patients newly diagnosed with PCOS and 100 controls seen at King Abdulaziz Medical City from January 2020 to 2021 were analyzed for this study. Characteristics of the two groups of women can be seen in Table 1. Overall, significantly higher BMI, LH/FSH, and testosterone levels were found in PCOS cases than in controls. Participants with PCOS also had elevated amounts of fasting glucose, fasting insulin, HOMA-IR, TC, TGs, HDL, and LDL. Control women were slightly younger than their counterparts in the PCOS group, although this difference was not of statistical significance.

**Table 1**
Characteristics of controls and PCOS women.

| Variable | Control group (N = 100) | PCOS group (N = 97) | *P*-value |
|---|---|---|---|
| Age (years) | 26.7 ± 6.5 | 27.5 ± 6.03 | 0.455 |
| BMI (kg/m$^2$) | 23.7 ± 2.3 | 28.6 ± 1.9 | <0.05 |
| WHR (cm) | 0.80 ± 0.2 | 0.84 ± 0.11 | <0.05 |
| Fasting glucose (mmol/L) | 4.53 ± 0.6 | 5.76 ± 0.6 | <0.05 |
| Fasting insulin (μU/mL) | 7.2 ± 2.3 | 9.01 ± 3.5 | <0.05 |
| HOMA-IR | 1.48 ± 1.02 | 2.29 ± 2.87 | <0.05 |
| TC (mmol/L) | 4.60 ± 1.1 | 4.99 ± 0.89 | <0.05 |
| HDL (mmol/L) | 1.50 ± 0.5 | 1.65 ± 0.6 | <0.05 |
| LDL (mmol/L) | 2.28 ± 0.73 | 2.86 ± 0.82 | <0.05 |
| TGs (mmol/L) | 1.0 ± 0.60 | 1.48 ± 0.94 | <0.05 |
| LH/FSH | 0.60 ± 0.51 | 1.69 ± 1.21 | <0.05 |
| Testosterone (nmol/L) | 1.4 ± 0.5 | 2.5 ± 0.7 | <0.05 |

Data expressed as mean ± SD; BMI = Body mass index; FPG = Fasting plasma glucose; HOMA-IR = homeostasis model assessment of insulin resistance; TC = Total cholesterol; HDL = High density lipoprotein; LDL = Low density lipoprotein; TG = Triglyceride; FSH = Follicle stimulating hormone; LH = Luteinizing hormone. $P < 0.05$ versus normal controls.

### 3.2. PCOS parameters of different menstrual cycle length

Participants with PCOS were classified into three groups based on the time between occurrences of vaginal bleeding (Table 2). Overall, 79.4% of PCOS patients had evident oligomenorrhea, with at least 45 days between episodes of vaginal bleeding. Women with bleeding intervals between 45 and 90 days made up 50.5% of the PCOS cohort, 20.6% had bleeding intervals of under 45 days, and the remainder (28.9%) of the PCOS women went more than 90 days between menstrual periods.

The three groups did not vary significantly with respect to age, BMI, WHR, and fasting glucose. However, levels of LH/FSH and testosterone rose as the duration of interval between vaginal bleeding increased. Similarly, levels of circulating insulin and HOMA-IR increased significantly as intervals of vaginal bleeding increased. After controlling for age and BMI, we found PCOS women with a menstrual cycle longer than 90 days had the most elevated HOMA-IR values; additionally, these subjects had the most elevated total cholesterol, LDL, and TGs and the lowest amount of HDL, though these differences were not of statistical significance (Table 2).

## 4. Discussion

In our investigation, we confirmed significantly higher levels of IR and androgen in women with PCOS than in women without PCOS. Additional breakdown of women by duration of interval between vaginal bleeding showed a significant association between the severity of menstrual irregularity and that of IR.

More than half of the PCOS cases in our cohort had menstrual cycle intervals between 45 and 90 days, whereas 20.6% and 28.9% had cycle intervals below 45 days and above 90 days, respectively. As a whole, then, over three-quarters of the subjects with PCOS had overtly irregular vaginal bleeding (oligomenorrhea). The elevated prevalence of these cycle irregularities in these PCOS patients recruited from an endocrine clinic may be attributed to this group of women having a more severe phenotype of PCOS, which motivated them to seek medical attention (Louwers and Laven, 2020).

An increasing body of research points to a link between PCOS and IR, with the risk of IR development higher in obese patients with PCOS (Wu et al., 2003, Kałużna et al., 2022). An IR incidence of about 65% has been reported in normal-weight women with PCOS, a figure which reaches as much as 95% in obese PCOS cases (Carmina and Lobo, 2004). In our study, we recorded a significantly higher BMI in participants with PCOS than in controls, although their BMI did not meet the criteria to be diagnosed as obese (Table 1). Hyperandrogenism, IR-induced hyperinsulinemia, and alterations in intrafollicular paracrine signaling can impair normal follicular development and ovulation (Dumesic and Richards, 2013, Polak et al., 2017). Research has shown a potential link between IR and the impaired growth of oocytes and embryo quality, further linking IR to lower than normal fertilization and implantation rates in women with PCOS (Nikbakht et al., 2021). Establishing clinical indicators that can effectively detect IR early in PCOS cases may result in improved pregnancy outcomes for these women.

In our study, an association was found between abnormalities in the menstrual cycle and severity of IR, findings in line with those of previous studies (Brower et al., 2013, Ezeh et al., 2021). This

**Table 2**
Characteristics of PCOS parameters among groups of varying menstrual cycle length.

| Variable | < 45 days (N = 20) | 45–90 days (N = 49) | > 90 days (N = 28) | *P*-value |
|---|---|---|---|---|
| Age (years) | 27.8 ± 6.20 | 27.4 ± 6.03 | 27.6 ± 5.80 | 0.457 |
| BMI (kg/m$^2$) | 27.71 ± 1.10 | 27.75 ± 1.72 | 27.68 ± 1.76 | 0.936 |
| WHR (cm) | 0.82 ± 0.11 | 0.83 ± 0.11 | 0.84 ± 0.11 | 0.304 |
| Fasting glucose (mmol/L) | 5.19 ± 0.59 | 5.13 ± 0.54 | 5.09 ± 0.51 | 0.157 |
| Fasting insulin (μU/mL) | 8.7 ± 2.9 | 9.2 ± 3.7[c] | 10.9 ± 4.2[b] | <0.05 |
| HOMA-IR | 2.01 ± 2.14 | 2.09 ± 2.43[c] | 2.46 ± 2.77[b] | <0.05 |
| TC (mmol/L) | 4.96 ± 0.95 | 4.97 ± 1.0 | 5.03 ± 0.89 | 0.487 |
| HDL (mmol/L) | 1.66 ± 0.56 | 1.67 ± 0.52 | 1.64 ± 0.55 | 0.802 |
| LDL (mmol/L) | 2.78 ± 0.82 | 2.78 ± 0.76 | 2.93 ± 0.84 | 0.192 |
| TGs (mmol/L) | 1.81 ± 0.81 | 1.89 ± 1.0 | 1.92 ± 1.2 | 0.468 |
| LH/FSH | 1.49 ± 1.45[c] | 1.68 ± 1.01 | 2.02 ± 1.30[a] | <0.05 |
| Testosterone (mmol/L) | 2.10 ± 0.96 | 2.34 ± 1.05 | 2.65 ± 0.97 | <0.05 |

[a] P < 0.05 in comparison with < 45-day group.
[b] P < 0.05 in comparison with 45–90-day group.
[c] P < 0.05 in comparison with greater than 90-day group.

positive correlation between length of vaginal bleeding interval and HOMA-IR, with the longest intervals having the highest HOMA-IR, suggests that determining the extent of menstrual irregularity as a straightforward clinical parameter may be a valuable predictor of the severity of metabolic and endocrine disorders (Li et al., 2022).

Oligomenorrhea has been associated with hyperandrogenism (Harris et al., 2017). In our study, we observed elevated testosterone levels in subjects with PCOS, levels that increased with longer vaginal bleeding intervals. Prior investigations have established a positive correlation between amounts of serum androgen in women both with and without PCOS and the number of follicles, with research also showing the effectiveness of anti-androgen therapy in PCOS cases to decrease the number and size of ovarian cysts (Dumesic et al., 2001). Researchers have postulated that the development of PCOS follicles is initially affected by hyperandrogenism, with elevated follicular androgen levels boosting the recruitment of small follicles, an excess of which will subsequently hinder the follicle selection process (Jonard and Dewailly, 2004, Gervásio et al., 2014). Thus, hyperandrogenism in PCOS cases may cause menses disruption by damaging normal follicular growth. In our PCOS subgroup analysis, we noticed that hyperandrogenic subjects in vaginal bleeding interval groups of both 45–90 days and 90 days or more had more severe IR, suggesting that hyperandrogenism may worsen the degree of IR in PCOS patients. Our findings reinforce those of a previous study, in which an independent association was found between hyperandrogenism and the likelihood of developing type 2 diabetes and obesity (Persson et al., 2021), the potential mechanism being that hyperinsulinemia stimulates ongoing excessive production of androgen (Garzia et al., 2022).

There were some limitations to this investigation. First, the smaller sample size could have impacted the findings, as could its observational design and some reliance on patient self-reporting. Additionally, the participants were recruited from just one clinic, so the study population and results may not be representative of most women experiencing PCOS. However, having all patients from the same clinic means a more homogenous pool of subjects, so there may be fewer confounding factors related to differences in socioeconomic class or other variables. Certainly, the homogeneity in age and marital status between cases and controls is a strong point. Another strength is that clinical exams and hormone measurements were used to confirm menstrual patterns.

Metformin, used to enhance insulin sensitivity, has shown promise as treatment for IR in patients with PCOS (Rashid et al., 2022). Future research should extend this work by assessing the effect of treatment with metformin in a longitudinal study. The representativeness of the data may also be improved through cluster sampling.

## 5. Conclusion

Our findings demonstrate the preponderance of women of PCOS with oligomenorrhea (menstrual cycles greater than 45 days) in PCOS cases seen clinically. The degree of dysfunction in androgen metabolism in PCOS patients increased with worsening oligomenorrhea, and the severity of IR correlated positively with the time between vaginal bleeding. This suggests that the evident menstrual irregularity signaled by the duration of a menstrual cycle may serve as a valuable predictor of IR in women who have PCOS.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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