Putative role for insulin resistance in depression risk in polycystic ovary syndrome

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Objective: To evaluate whether insulin resistance is associated with depression risk in women with polycystic ovary syndrome (PCOS), independent of other factors, including body mass index (BMI).
Design: Cross-sectional.
Setting: Tertiary university center.
Patient(s): A total of 301 women, aged 14–52 years, with PCOS by Rotterdam criteria, consecutively examined between 2006 and 2013.
Intervention(s): Complete history and physical examinations, including endovaginal ultrasounds, dermatologic assessments, completion of Beck Depression Inventory Fast Screen (BDI-FS), and serum testing.
Main Outcome Measure(s): Scores >4 on BDI-FS indicated a positive screen for depression. Scores were further subdivided into mild (5–8), moderate (9–12), and severe (>12) depression risk. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).
Result(s): A total of 131 women (44%) were at risk for depression, determined by positive BDI-FS screening. These patients had higher BMI (32.3 vs. 28.5), and elevated insulin resistance, assessed by HOMA-IR (5.2 vs. 2.6), compared with patients with negative depression screening. In a stratified analysis by BMI category, obese women with positive depression screens had elevated HOMA-IR, compared with obese women with normal BDI-FS scores (7.4 vs. 4.1). In a multivariate logistic regression analysis, HOMA-IR was independently related to the odds of depression risk after controlling for age, ethnicity, BMI, and exercise (odds ratio: 1.07).
Conclusion(s): Depression is common in PCOS. After controlling for confounders in multivariate regression analyses, we found HOMA-IR to be significantly associated with depression risk. Our data suggest a complex interplay among insulin resistance, obesity, and depression in PCOS, warranting additional investigation. Mental health assessment is indicated in comprehensive care of patients with PCOS. (Fertil Steril® 2015;104:707–14. ©2015 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, depression, insulin resistance

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by anovulation, androgen excess, and polycystic ovaries (1–5). Insulin resistance is seen in 70% of women who have PCOS and is exacerbated by obesity, which is highly prevalent in those who have PCOS (6–10). Risk of depression is increased with PCOS, although the underlying mechanism is not known (11–13). Obesity is considered to be a major factor associated with depression risk, in both the general population (14, 15) and in women affected by PCOS (16, 17). However, analyses controlling for body mass index (BMI) continue to show an elevated depression risk in women who have PCOS, compared with women serving as controls (18, 19).

Several studies have reported an association between insulin resistance and depression in the general population (20–23). A recent meta-analysis of unadjusted data from 18 cross-sectional studies, including 25,847 adults, found a significant association between insulin resistance and depression, with a pooled effect size of 0.19 (95% confidence interval [CI] 0.11–0.27), which was attenuated somewhat in secondary

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analyses variably adjusted for BMI and other cofounders (24). In light of findings in the general population, the aim of this study was to determine whether insulin resistance and depression are associated in women who have PCOS. We hypothesized that depression risk would be associated with markers of insulin resistance in a PCOS cohort, independent of confounders, including BMI.

MATERIALS AND METHODS

This study was a cross-sectional cohort study of patients consecutively referred to the multidisciplinary PCOS clinic at our tertiary academic referral center between 2006 and 2013. Institutional review board approval was obtained from the University of California San Francisco Committee on Human Research. Patients were referred to the multidisciplinary clinic for evaluation of symptoms suggestive of PCOS. Prospective participants met with a study coordinator who obtained informed consent for their information to be included in the cohort study. During the study period, 80% of women seen in the PCOS clinic consented to participate; 136 women declined. Questionnaire, ultrasound, laboratory, and other clinical data were entered into the database for patients who consented to be included in the cohort.

Participants were included if they fulfilled the revised Rotterdam criteria for PCOS diagnosis, which are presence of 2 of the following 3 features (1) oligomenorrhea; (2) clinical and/or biochemical hyperandrogenism; and (3) polycystic ovaries (25). Oligomenorrhea was defined as <8 cycles per year during an extended period of time when not on oral contraceptive pills (OCPs). Clinical hyperandrogenism included hirsutism and/or significant acne warranting treatment. Biochemical hyperandrogenism included elevated total testosterone, free testosterone, or dehydroepiandrosterone sulfate (DHEAS).

Polycystic ovaries were defined as the presence of ≥ 12 antral follicles, and/or an ovarian volume >10 mL in ≥ 1 ovaries. Patients were excluded if other etiologies for their clinical presentations were identified through routine laboratory screening, including: thyroid-stimulating hormone (TSH) to assess for thyroid dysfunction; prolactin to assess for hyperprolactinemia; 17-hydroxyprogesterone to assess for congenital adrenal hyperplasia; and follicle-stimulating hormone and estradiol to assess for hypogonadotropic hypogonadism and premature ovarian insufficiency. Screening for Cushing's syndrome was performed if clinically indicated through history and physical examination.

Study participants completed a comprehensive intake questionnaire addressing various aspects of their demographics, medical history, health behaviors including exercise, and psychological adjustment. Subjects were asked to identify their primary concern regarding PCOS. Participants were asked to discontinue OCPs, metformin, and antiandrogenic medications for ≥ 1 month before completing laboratory work, and to not restart these drugs until they had been evaluated in the clinic. Laboratory tests were typically completed 1–2 months before the initial visit.

Participants completed the Beck Depression Inventory Fast Screen (BDI-FS). The BDI-FS is a 7-item version of the standard Beck Depression Inventory intended for use in clinic populations with coexisting medical issues. Derived from the 21-item Beck Depression Inventory (BDI-II), developed by Beck et al. (26), the scale includes items that emphasize dysphoria and anhedonia, and those shown to have a high impact on the cognitive aspects of depression in prior factor analyses (27).

Participants are asked to choose 1 statement for each item that best describes the way they have been feeling in the past 2 weeks. Each item is rated on a 4-point scale ranging from 0 to 3. Total scores are computed as the sum of the score for all 7 items, and range from 0 to 21. This scale has been validated in a series of studies of family practice and internal medicine patients, published in the BDI-FS manual (27). Subsequent studies have validated its use for various diseases, including multiple sclerosis (28), chronic pain (29), end-stage renal disease (30), and sleep disorders (31). We considered BDI-FS scores as a linear scale and across 4 categories. The following recommended categories were considered: ≤ 4: not depressed; 5–8: at risk for mild depression; 9–12: at risk for moderate depression; ≥ 13: at risk for severe depression (27, 32).

Fasting serum was obtained. Metabolic testing included measurement of fasting lipid levels, and a 75-g, 2-hour oral glucose tolerance test (OGTT). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated by multiplying fasting plasma insulin (μIU/mL) by fasting plasma glucose (mg/dL), and dividing by the constant 405, as described by Matthews et al. (33). The HOMA-IR correlates well with the glucose clamp test, which is the gold standard of measurement of insulin resistance, in mild diabetics (34). Serum values were obtained predominantly at the University of California San Francisco laboratory and 2 commercial laboratories, based on individual insurance plans, to facilitate affordability. Liquid chromatography/tandem mass spectrometry and electrochemiluminescence immunoassay were variably utilized by these laboratories to measure insulin values.

Testosterone (T) and sex hormone–binding globulin (SHBG) were uniformly measured in a subset of our patients who were not taking OCPs, using banked specimens ($n = 126$) at the University of Virginia Center for Research in Reproduction Ligand Assay and Analysis Core. Testosterone was measured by radioimmunoassay (Coat-a-Count Kit; Siemens Healthcare Diagnostics; assay sensitivity 0.2–180 nmol/L; intra-assay coefficient of variation [CV] = 4.4%; interassay CV = 6.4%). Sex hormone–binding globulin was measured using Immulite (L2KSH2 Kit; Siemens Healthcare Diagnostics; assay sensitivity 6.1–1,500.0 ng/dl; intra-assay CV = 2.8%; interassay CV = 6.5%). Free T was calculated using the following equation derived from the law of mass action (35, 36):

$$[fT] = ([T] - (N \times [fT]))/(KsT\{[SHBG] - [T] + N[fT]\})$$

where [T] = total testosterone concentration, KsT = affinity constant of SHBG for T, [SHBG] = SHBG concentration, N = KaTCa + 1, KaT = affinity constant of albumin for T, and Ca = albumin concentration, considered as equal to 43 g/L.