Insulin resistance is associated with depression risk in polycystic ovary syndrome

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Objective: To test the hypothesis that insulin resistance is associated with depression risk in polycystic ovary syndrome (PCOS).
Design: Secondary analysis of data from a multicenter randomized trial.
Setting: Multicenter university-based clinical practices.
Patient(s): Seven hundred thirty-eight women with PCOS by modified Rotterdam criteria seeking pregnancy enrolled in a randomized clinical trial comparing clomiphene citrate versus letrozole.
Intervention(s): The Primary Care Evaluation of Mental Disorders Patient Health Questionnaire was self-administered to identify depression using a validated algorithm at enrollment. Demographic and anthropometric data were collected, and serum assays were performed. Insulin resistance was estimated using the homeostatic model of insulin resistance (HOMA-IR), with a cutoff of >2.2 considered abnormal.
Main Outcome Measure(s): Demographic, endocrine, and metabolic parameters associated with depression.
Result(s): In a univariate logistic regression analysis, elevated HOMA-IR was associated with 2.3-fold increased odds of depression (odds ratio [OR] = 2.32; 95% confidence interval [CI], 1.28–4.21). This association remained significant after controlling for age and body mass index (adjusted OR [aOR] = 2.23; 95% CI, 1.11–4.46) and in a model including additional potential confounders (aOR = 2.03; 95% CI, 1.00–4.16).
Conclusion(s): Insulin resistance has a strong and independent association with depression in PCOS and may serve as a physiologic mediator. Our findings corroborate a growing body of evidence linking insulin resistance to depressed mood. The association between insulin resistance and depressed mood warrants further investigation to elucidate mechanisms and identify potential therapeutic targets. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome (PCOS), depression, insulin resistance

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy, affecting 10%–15% of reproductive age women (1). PCOS is typified clinically by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (2). Additionally, systemic insulin resistance is core to the pathophysiology of the disorder (3). Metabolic dysfunction is a consequence. Women with PCOS are at increased risk of diabetes, obesity, and metabolic syndrome (4, 5).

There is an increased prevalence of depression in PCOS, with an estimated magnitude of three- to eight-fold increased risk compared with controls (6). Depression increases the burden of the disorder for the women with PCOS and may negatively impact efforts at self-care, thus compounding metabolic consequences (7). The mechanisms underlying the disproportionate prevalence of depression in women with PCOS have not been fully elucidated. As a result, no targeted therapies exist.

A limited body of research has sought to elucidate the features most

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strongly associated with depression risk in PCOS. Some investigators have hypothesized that PCOS symptoms, including obesity, infertility, and cutaneous stigmata of hyperandrogenism, such as hirsutism and acne, are linked to depression (8, 9). More recently, biochemical factors, including elevated circulating testosterone (10) and insulin resistance (11–13), have been associated with depression in a small series of patients. In non-PCOS populations, emerging evidence suggests that metabolic disturbances act at the level of the central nervous system to disturb mood (14, 15). Specifically, insulin resistance has been implicated as a mediator of increased depression risk observed in a variety of clinical populations (16–18). Yet, while insulin resistance has been linked to depression, the causal relationship is unknown; impaired insulin signaling might perturb mood, or conversely, depressed mood might cause insulin resistance via behavioral or central mechanisms.

The evidence regarding the association between insulin resistance and depression in PCOS is sparse and conflicting (12, 13, 19, 20). Previously, we identified a putative role for insulin resistance in mediating depression risk in a cohort of women with PCOS seeking consultation for nonfertility indications at a single university center (11). The objective of the present study was to investigate whether the association between insulin resistance and depression was present within another large population of women with anovulatory PCOS seeking fertility treatment in a multicenter clinical trial.

MATERIALS AND METHODS

This is a secondary analysis of a multicenter, double-blind, prospective randomized trial of clomiphene citrate versus letrozole in the treatment of infertility in women with PCOS (the Pregnancy in Polycystic Ovary Syndrome II study [PPCOSII]: NCT00719186) (21). The Institutional Review Board at each center approved the study protocol, and each subject gave written, informed consent.

Patients

The study population included 738 female patients, actively seeking pregnancy, ages 18–40, with PCOS diagnosed by the modified Rotterdam criteria (2), defined as chronic ovulatory dysfunction plus hyperandrogenism or polycystic appearing ovaries or both. Ovulatory dysfunction was defined as eight or fewer menses per year, a spontaneous intermenstrual interval of $\geq$45 days, or chronic anovulatory bleeding indicated by midluteal serum P of $<$ 3 ng/mL. Hyperandrogenism comprised clinical hirsutism as defined by modified Ferriman-Gallwey (mFG) score $>$8, or elevated serum testosterone or free androgen index, as defined by center-specific screening lab cutoffs. Polycystic appearance of ovaries on transvaginal ultrasound was identified with the presence of 12 or more antral follicles measuring 2–9 mm in diameter or an increased ovarian volume ($>$10 cm^3) of either ovary. Other disorders that clinically imitate PCOS were excluded via measurement of TSH, PRL, and 17-hydroxyprogesterone.

Subjects were otherwise healthy and were not taking insulin sensitizers or sex steroid medications. Patients with poorly controlled glucose (defined as a glycohemoglobin level $>$ 7.0%) were excluded. Further details regarding subject eligibility criteria for the trial are publicly available (22). Subjects (n =738) who completed the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) at the screening visit were included in this analysis.

Anthropomorphic Measurements and Serum Testing

Comprehensive histories and physical examination, including waist circumference and body mass index (BMI), were performed at the screening visit. Assessment of hirsutism was performed using mFG scoring (23). Standard acne lesion assessments were performed, noting counts and types of lesions.

Serum was assayed at a central laboratory (Ligand Core Laboratory, University of Virginia) for hormonal and metabolic parameters. Tests included serum androgens (total testosterone and androstenedione), sex hormone–binding globulin (SHBG), fasting glucose, fasting insulin, fasting lipids, and high sensitivity C-reactive protein (hsCRP). Insulin was measured using the Immulite immunoassay (Siemens Diagnostics), with a range of 2.0–300 μIU/mL and intra- and interassay coefficients of variation of 2.2% and 4.8%, respectively (24). testosterone and androstenedione were measured by radioimmunoassay (Siemens Diagnostics). For testosterone, the assay sensitivity is 10 ng/dL, and intra- and interassay coefficients of variation are 4.0% and 7.1%, respectively; assay sensitivity for androstenedione is 0.1 ng/dL, and intra- and interassay coefficients of variation are 4.7% and 7.2%, respectively (24). The precision of the radioimmunoassay assay is comparable to liquid chromatography–tandem mass spectrometry methods (25).

Homeostatic assessment of insulin resistance (HOMA-IR) was calculated from fasting insulin and glucose by the following equation: HOMA-IR = fasting glucose in mg/dL $\times$ fasting insulin in μIU/ml/405 (26). HOMA-IR correlates with the gold standard glucose clamp test for measuring insulin resistance (27). Insulin resistance was defined using a HOMA-IR threshold of $>$2.2.

Psychological Measurements

Depression was assessed via the PRIME-MD PHQ (28). All eligible participants were asked to complete this questionnaire at the time of the screening visit, at the intended clinical site. The PRIME-MD PHQ is a validated, patient-administered questionnaire derived from the original PRIME-MD clinician-administered instrument. PRIME-MD was the first tool designed to diagnose specific mental disorders in the primary care setting, in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (28, 29). Using PRIME-MD PHQ, subjects are queried about nine symptoms of clinical depression and asked to indicate whether the symptom has bothered them “not at all,” “several days,” “more than half the days,” or “nearly every day” over the prior 2 weeks. A standardized scoring algorithm determines whether an individual has “major depressive syndrome” or “other depressive syndrome” on the basis of number of