Title

To freeze or not to freeze: decision regret and satisfaction following elective oocyte cryopreservation

Journal

Fertility and Sterility, 109(6)

ISSN

0015-0282

Authors

Greenwood, Eleni A
Pasch, Lauri A
Hastie, Jordan
et al.

Publication Date

2018-06-01

DOI

10.1016/j.fertnstert.2018.02.127

Peer reviewed

HHS Public Access

Author manuscript

Fertil Steril. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Fertil Steril. 2018 July 01; 110(1): 27–34. doi:10.1016/j.fertnstert.2018.03.009.

Insulin Resistance is Associated with Depression Risk in Polycystic Ovary Syndrome

Eleni A. Greenwood, M.D., M.Sc.[1], **Lauri A. Pasch, Ph.D.**[1], **Marcelle I. Cedars, M.D.**[1], **Richard S. Legro, M.D.**[2], **Esther Eisenberg, M.D., M.P.H.**[3], and **Heather G. Huddleston, M.D.**[1] **NICHD Reproductive Medicine Network**

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, CA

[2]Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey, PA

[3]Fertility and Infertility Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD

Abstract

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 (PPCOSII: NCT00719186)

Setting: Multicenter university-based clinical practice

Patients: 738 women with PCOS by modified Rotterdam criteria, seeking pregnancy, enrolled in a randomized clinical trial comparing clomiphene citrate versus letrozole (PPCOSII)

Interventions: The Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) was self-administered to identify depression using a validated algorithm at enrollment. Demographic and anthropometric data were collected, and serum assays performed. Insulin resistance was estimated using the Homeostatic Model of Insulin Resistance (HOMA-IR), with a cut-off of >2.2 considered abnormal.

Main Outcome Measures: Demographic, endocrine and metabolic parameters associated with depression

Results: In a univariate logistic regression analysis, elevated HOMA-IR was associated with 2.3-fold increased odds of depression (OR 2.32, 95% CI 1.28-4.21, p<0.01). This association

Correspondence to: Eleni Greenwood, M.D., M.Sc., Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California San Francisco School of Medicine, 499 Illinois Street, San Francisco, CA 94158-2519, eleni.greenwood@ucsf.edu, Phone: (415) 353-7475, Fax: (415) 353-7744.

Conflict of Interest Disclosures

EAG, LAP, MIC, RSL, EE, and HGH have nothing to disclose.

remained significant after controlling for age and BMI (adjusted odds ratio, aOR 2.23, 95% CI 1.11-4.46, p=0.02) and in a model including additional potential confounders (aOR 2.03, CI 1.00-4.16, p=0.05).

Conclusions: 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.

Capsule:

Insulin resistance is associated with depression risk in PCOS

Keywords

Polycystic Ovary Syndrome (PCOS); Depression; Insulin Resistance

Introduction

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 3 to 8-fold increased risk compared to 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 strongly associated with depression risk in PCOS. Some authors 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 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 non-fertility 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.

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 (PPCOSII: NCT00719186) (21). The Institutional Review Board at each center approved the study protocol, and each subject gave written, informed consent.

Subjects

The study population included 738 female patients, actively seeking pregnancy, ages 18-40, with PCOS diagnosed by modified Rotterdam criteria (2), defined as chronic ovulatory dysfunction plus hyperandrogenism or polycystic appearing ovaries, or both. Ovulatory dysfunction was defined as ≤8 menses per year, a spontaneous intermenstrual interval of ≥45 days, or chronic anovulatory bleeding indicated by midluteal serum progesterone of <3 ng/mL. Hyperandrogenism comprised clinical hirsutism as defined by modified Ferriman-Gallwey 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 which clinically imitate PCOS were excluded via measurement of TSH, prolactin 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 (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, were performed at the screening visit. Assessment of hirsustism was performed using modified Ferriman-Gallwey (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 hsCRP. Insulin was measured using the Immulite immunoassay

(Siemens Diagnostics), with a range of 2.0 – 300 ulU/mL, and intra- and interassay coefficients of variation of 2.2% and 4.8%, respectively (24). Testosterone and androstenedione were measured by radioimmunoassay (RIA) (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 RIA 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 × fasting insulin in mIU/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 Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (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) (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 two weeks. A standardized scoring algorithm determines whether an individual has “major depressive syndrome” or “other depressive syndrome” on the basis of number of symptoms present on at least “more than half the days” (5+ versus 2-4 of 9 symptoms, respectively). Patients must report “little interest or pleasure in doing things” or “feeling down, depressed, or hopeless” or both, on at least “more than half the days” to meet criteria, in accordance with DSM-IV criteria. For the purposes of this study, all positive depression screens (i.e. “other” or “major” depressive syndrome) were considered together to constitute the “Depressed” group (28).

Statistical Analysis

Subjects meeting PRIME-MD PHQ scoring criteria for “major” or “other” depressive syndrome were classified as “Depressed.” Demographic, endocrine and metabolic parameters were compared between Depressed and Non-depressed groups using the two-sample Wilcoxon rank-sum test, chi-square or Fisher’s exact as indicated. Considering Depressed status as the outcome, univariate logistic regression analyses were performed to identify potential predictors for inclusion in the final multivariate logistic regression analyses. In the multivariate models assessing the relationship between elevated HOMA-IR and depression, we included age and BMI a priori. We further included all factors associated

with depression risk at the p<0.20 statistical significance level from univariate analyses. Select factors with substantial co-linearity with other variables in the model were excluded. Specifically, waist circumference was excluded due to co-linearity with BMI and HOMA-IR, our target outcome; sex hormone binding globulin was excluded due to co-linearity with insulin levels, a component of IR; fasting glucose was excluded due to its use in the calculation of HOMA-IR, and total cholesterol was selected as the representative parameter, excluding co-linear HDL and LDL cholesterol levels. The final model included the following co-variates: age, BMI, income, androstenedione, total testosterone, hirsutism, acne score, and total cholesterol.

To examine the impact of anti-depressant use on the relationship between insulin resistance and depression, the following sensitivity analyses were performed: 1) “antidepressant use” was added as a covariate to the final multivariate model, 2) all statistical analyses were repeated in the subgroup of patients not taking anti-depressants, and 3) all statistical analyses were repeated after reclassifying those patients taking anti-depressants as “Depressed.”

Statistical analyses were performed with STATA, version 14.2 (College Station, TX).

Results

Sixty-five of the 738 women (8.8%) met criteria for Depression on the basis of PRIME-MD PHQ, of whom 27 (3.7%) met criteria for “major” depressive syndrome and 38 (5.1%) for “other” depressive syndrome.

A summary of characteristics in Depressed and Not Depressed subjects is shown in Table 1.

Univariate regression analysis was used to examine the association between demographic, endocrine and metabolic parameters on Depressed status (Table 2). Elevated HOMA-IR, age, income, waist circumference and acne score were associated with depression (p<0.05). Education, androstenedione, hirsutism status, insulin, SHBG, and total, LDL and HDL cholesterol were associated with depression at the 0.05<p<0.10 level. Race, time attempting conception, history of prior live birth, substance use, triglycerides, IGF, and hsCRP were not associated with depression (Table 2).

The magnitude of the impact of elevated HOMA-IR on Depressed status was assessed by univariate logistic regression analysis (Table 3). Elevated HOMA-IR increased the odds of being depressed by 2.32 (95% CI 1.28-4.21, p<0.01). After controlling for age and BMI in a multivariate model, the adjusted odds ratio for depression for those with elevated HOMA-IR was 2.23 (95% CI 1.11-4.46, p=0.02). When demographic, endocrine and metabolic parameters were incorporated into the model, excluding select variables due to co-linearity (Model 3), elevated HOMA-IR levels increased risk of depression by 2.03 (95% CI 1.00-4.16, p=0.05).

We performed three sensitivity analyses to examine the effect of anti-depressant use. Forty-nine of 704 (7%) women reported concomitant anti-depressant use. Forty-three of these women were classified as Non-Depressed while six fell into the Depressed group according

to symptom burden as measured by PRIME-MD. First, we added “anti-depressant use” as a co-variate to the multivariate model (model 3) and found that the relationship between elevated HOMA-IR and depression was essentially unchanged (aOR = 2.04, 95% CI 0.99-4.21, p =0.055). Second, we repeated the analyses excluding all patients using antidepressants and found the association between HOMA-IR and depression was sustained, even after adjustment for age and BMI (aOR = 2.27, 95% CI 1.10-4.68, p =0.03), and was only marginally altered upon further adjustment for all covariates in model 3 (aOR = 2.05, 95% CI 0.98-4.31, p =0.058). In a third analysis, all women reporting anti-depressant use, regardless of depression symptoms as measured by PRIME-MD, were categorized as “Depressed.” Here we found that the association between HOMA-IR and depression remained in the univariate model, but was attenuated upon adjustment for covariates (data not shown).

Discussion

In a large, rigorously characterized population of women with polycystic ovary syndrome, we found insulin resistance, as measured by HOMA-IR >2.2, was associated with more than twice the likelihood of depression. The effect was not explained by BMI or other potential confounders.

Data regarding the association between insulin resistance and depression in PCOS are limited and conflicting. Prior to our 2015 report (11), a total of six studies of depression in PCOS, in 657 women, reported metrics of insulin resistance (12, 13, 19, 20, 30, 31). Comparison across studies is limited by substantial heterogeneity, inconsistent classification for PCOS subjects, incongruent instruments and thresholds used to identify of depression, and discrepant metrics of insulin resistance.

In a recent investigation (11), we identified an independent relationship between HOMA-IR and depression risk using the Beck Depression Index Fast Screen, in a clinical population of 301 women with PCOS as defined by Rotterdam criteria (PCOS-Rotterdam), not seeking pregnancy. In that study, we reported a 7% increase in depression risk for each unit increase in HOMA-IR, after adjustment for confounders. In the current study, we chose to examine insulin resistance as a dichotomous predictor, to optimize clinical utility. The results of the present study corroborate and extend our earlier findings, in a different PCOS population, using a more rigorous psychological instrument. The PPCOSII population comprised women seeking fertility recruited from seven sites across the Unites States. The PRIME-MD PHQ instrument used in the present study interrogates clinical criteria per the DSM-IV. It has excellent sensitivity and specificity in diagnosing depression (73% and 96%, respectively) compared to the gold standard structured clinical interview by a mental health professional (28).

A prior analysis of 226 women with PCOS-Rotterdam recruited from a Turkish university (13) revealed findings consistent with our study results. BDI-II scores were correlated with HOMA-IR, as well as BMI, mFG and lipid parameters. In a multivariate regression model, HOMA-IR and mFG scores were independently associated with depression risk. An association between insulin resistance and depression risk has been reported in other,

smaller studies, as well (11, 31), however these studies did not adjust for possible confounders.

Other investigators have failed to detect an association between IR and depression in PCOS (19, 20, 30). Possible explanations reflect methodological limitations, such as inadequate power, or selection of psychological instruments or thresholds lacking discriminatory capacity. Depression is a heterogeneous disorder and the type and severity of depression analyzed may impact results. One study compared 73 women with self-reported PCOS with and without Major Depressive Disorder (MDD), determined by a structured clinical interview (20), and found no difference in markers of IR. This study was likely limited by power as well as self-report identification of PCOS, however we also hypothesize that distinct pathophysiologic mechanisms may play a role in the more severe psychiatric phenotypes such as MDD (11).

Mechanisms by which insulin resistance impacts mood regulation are beginning to be elucidated in animal and human studies. The brain requires glucose as the obligate energy source; insulin receptors mediate brain metabolism in key brain regions (32, 33). In a rat model, inactivation of the insulin receptor in the hypothalamus results in systemic insulin resistance, dyslipidemia and depressive-like behavior (34); these changes are subsequently reversed by dietary restriction (35). In patients at risk for Alzheimer's disease, anatomic and physiological hippocampal abnormalities are identified on magnetic resonance imaging in association with insulin resistance (36, 37). Finally, pilot data from functional magnetic resonance imaging studies in insulin-resistant PCOS patients reveal alterations in limbic activation during emotional tasks, which normalize following metformin treatment (38). Taken together, these findings indicate that perturbations in insulin signaling impact structural and functional connectivity in key brain regions, adversely affecting mood (15).

Our findings corroborate a growing body of literature implicating impaired insulin signaling in the pathophysiology of depressed mood in the population at large. Diabetes diagnosis doubles the risk of depression (39). Large epidemiologic studies demonstrate a link between insulin resistance and depression in non-diabetic populations as well (16–18). Small clinical trials in diabetic (40) and non-diabetic (41) adults demonstrate an improvement in depression scores following treatment with insulin sensitizers. In one study, improvement in mood correlated with improvement in HbA1c (40). Suggesting potential bi-directionality between mood and metabolic health, treatment of depression using tricyclic antidepressants is associated with improved insulin sensitivity (42).

The use of anti-depressant medications by a small percentage of subjects adds complexity to the evaluation of mood disorders in this study population. Our sensitivity analyses examining anti-depressant use revealed that the association between insulin resistance use and depression remained robust after controlling for anti-depressant use in the multivariate model. Similarly, excluding women taking anti-depressant medications yielded results that mirror our original findings. In contrast, we found that reclassifying all women using anti-depressants as "Depressed," regardless of symptoms as measured by PRIME-MD, resulted in an attenuation of the insulin resistance – depression association in the multivariate models. This finding highlights an important area for future research. We hypothesize that

multiple pathways mediate depression risk; these processes may differ between women successfully treated with anti-depressant medications who are now relatively asymptomatic, compared to women experiencing symptoms of “metabolic depression” as postulated here. Alternatively, another hypothesis is that depression itself exacerbates insulin resistance, either via central and/or behavior mechanisms, and that the successful treatment of depression may lead to an improved metabolic profile.

The findings of our study linking insulin resistance and depression in PCOS may in part explain why women with PCOS are disproportionately impacted by mood disorders. Whether insulin resistance causes depression, or depressed mood results in insulin resistance via behavioral or central mechanisms is unknown. Given the emergence of insulin resistance as part of the core pathophysiology of PCOS early in the lifespan, one may speculate that insulin resistance precedes depression; however bidirectional mechanisms are likely present (43), perpetuating a vicious cycle.

Strengths and Limitations

An important strength of our study is the large, geographically diverse, and well-characterized population of women with PCOS. Use of a single research laboratory enables comparison of insulin values across the large number of subjects, negating the impact of assay variability. Our study has methodological limitations resulting from its ancillary design. The prevalence of depression in this PCOS cohort was 9%, substantially lower than prior reports ranging from 19-91%; median 37% (6). This may be a consequence of the strict PRIME-MD PHQ scoring algorithm used, or potentially reflect selection of motivated patients actively seeking pregnancy in a clinical trial context. In an analysis of a different randomized controlled fertility trial (OWL-PCOS), the depression rate by the PRIME-MD PHQ instrument was 11.4%, comparable to our data (44). Alternatively, the prevalence of depression using this instrument was 21% in an observational cohort study of women with PCOS, compared to 3% in control women (12). The PRIME-MD questionnaire is a screening tool constituting an initial step in the diagnosis of depression. While the DSM-IV (45), from which the PRIME-MD instrument was derived, has since been updated to the DSM-V (46), the core clinical symptoms comprising the depression diagnostic procedure remain unchanged in the newest iteration (46). Another limitation of our study is that we based our diagnosis of insulin resistance on a homeostatic test rather than a dynamic test of insulin action. However, our population excluded patients on diabetes medication or with poorly controlled glucose levels and thus is a largely normoglycemic population where the HOMA-IR has its best correlation with dynamic tests of insulin action (47). Causation cannot be inferred from the association between HOMA-IR and depression symptoms; the opposite possibility, that depression might impact insulin production or sensitivity, cannot be excluded. Finally, while the association between insulin resistance and depression remained robust in two sensitivity analyses investigating the role of antidepressant use, we found that classifying all women on anti-depressants as “Depressed” mitigated the linkage in the adjusted multivariate models. Future analyses are needed to establish the directionality of the insulin resistance-depression association and to disentangle the role of these medications in risk factor modulation.

Conclusions

In conclusion, we report an independent association for insulin resistance and depression in PCOS. Whether treating insulin resistance will improve depressive symptoms in PCOS is poorly understood. Further investigation is required to elucidate mechanisms mediating the association of insulin resistance and depression, and to identify potential therapeutic targets for this high-risk population.

Acknowledgments

Support

PPCOSII

Supported by grants from the NICHD (U10 HD27049, U10 HD38992, U10HD055925, U10 HD39005, U10 HD38998, U10 HD055936, U10 HD055942, U10 HD055944, and U54-HD29834); and by the National Center for Research Resources and the National Center for Advancing Translational Sciences through an NIH grant (UL1 TR000127)

References

1. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Human reproduction (Oxford, England). 2010;25(2):544–51.
2. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human reproduction (Oxford, England). 2004;19(1):41–7.
3. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. Human reproduction (Oxford, England). 2016;31(11):2619–31.
4. Rubin KH, Glintborg D, Nybo M, Abrahamsen B, Andersen M. Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome. The Journal of clinical endocrinology and metabolism. 2017;102(10):3848–57. [PubMed: 28938447]
5. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update. 2010;16(4):347–63. [PubMed: 20159883]
6. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction (Oxford, England). 2017;32(5):1075–91.
7. Devarajooh C, Chinna K. Depression, distress and self-efficacy: The impact on diabetes self-care practices. PLoS One. 2017;12(3):e0175096. [PubMed: 28362861]
8. Elsenbruch S, Hahn S, Kowalsky D, Offner AH, Schedlowski M, Mann K, et al. Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. The Journal of clinical endocrinology and metabolism. 2003;88(12):5801–7. [PubMed: 14671172]
9. Adali E, Yildizhan R, Kurdoglu M, Kolusari A, Edirne T, Sahin HG, et al. The relationship between clinico-biochemical characteristics and psychiatric distress in young women with polycystic ovary syndrome. The Journal of international medical research. 2008;36(6):1188–96. [PubMed: 19094426]
10. Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. Psychosomatic medicine. 2004;66(3):356–62. [PubMed: 15184695]
11. Greenwood EA, Pasch LA, Shinkai K, Cedars MI, Huddleston HG. Putative role for insulin resistance in depression risk in polycystic ovary syndrome. Fertility and sterility. 2015;104(3): 707–14.e1. [PubMed: 26054555]

12. Hollinrake E, Abreu A, Maifeld M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertility and sterility. 2007;87(6):1369–76. [PubMed: 17397839]
13. Cinar N, Kizilarslanoglu MC, Harmanci A, Aksoy DY, Bozdag G, Demir B, et al. Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome. Human reproduction (Oxford, England). 2011;26(12):3339–45.
14. McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CW, Miranda A, et al. Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"? Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2007;19(4):257–64. [PubMed: 18058283]
15. Rasgon NL, McEwen BS. Insulin resistance-a missing link no more. Molecular psychiatry. 2016;21(12):1648–52. [PubMed: 27698431]
16. Adriaanse MC, Dekker JM, Nijpels G, Heine RJ, Snoek FJ, Pouwer F. Associations between depressive symptoms and insulin resistance: the Hoorn Study. Diabetologia. 2006;49(12):2874–7. [PubMed: 17066302]
17. Pearson S, Schmidt M, Patton G, Dwyer T, Blizzard L, Otahal P, et al. Depression and insulin resistance: cross-sectional associations in young adults. Diabetes Care. 2010;33(5):1128–33. [PubMed: 20185745]
18. Timonen M, Laakso M, Jokelainen J, Rajala U, Meyer-Rochow VB, Keinänen-Kiukaanniemi S. Insulin resistance and depression: cross sectional study. BMJ (Clinical research ed). 2004;330(7481):17–8.
19. Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS). Fertility and sterility. 2010;94(1):357–9. [PubMed: 19896652]
20. Annagur BB, Tazegul A, Uguz F, Kerimoglu OS, Tekinarslan E, Celik C. Biological correlates of major depression and generalized anxiety disorder in women with polycystic ovary syndrome. Journal of psychosomatic research. 2013;74(3):244–7. [PubMed: 23438716]
21. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. The New England journal of medicine. 2014;371(2):119–29. [PubMed: 25006718]
22. Legro RS. RMN Amigos Protocol V. 6.0 2011 [Available from: http://c2s2.yale.edu/rmn/resource/AMIGOS_Protocol_v6.0_246516_284_24481.pdf.
23. Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. American journal of obstetrics and gynecology. 1981;140(7):815–30. [PubMed: 7258262]
24. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Alvero R, et al. The Pregnancy in Polycystic Ovary Syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial. Fertility and sterility. 2014;101(1):258–69.e8. [PubMed: 24156957]
25. Legro RS, Schlaff WD, Diamond MP, Coutifaris C, Casson PR, Brzyski RG, et al. Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. The Journal of clinical endocrinology and metabolism. 2010;95(12):5305–13. [PubMed: 20826578]
26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9. [PubMed: 3899825]
27. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care. 2000;23(1):57–63. [PubMed: 10857969]
28. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. Jama. 1999;282(18):1737–44. [PubMed: 10568646]

29. Hahn SRKK, Spitzer RL, Williams JBW. . The PRIME-MD instrument In: Maruish ME, ed. The Use of Psychological Testing for Treatment Planning and Outcome Assessment. 2nd ed. Hillsdale, NJ: Laurence Erlbaum Associates; 1999.
30. Rahiminejad ME, Moaddab A, Rabiee S, Esna-Ashari F, Borzouei S, Hosseini SM. The relationship between clinicobiochemical markers and depression in women with polycystic ovary syndrome. Iranian journal of reproductive medicine. 2014;12(12):811–6. [PubMed: 25709638]
31. Rasgon NL, Rao RC, Hwang S, Altshuler LL, Elman S, Zuckerbrow-Miller J, et al. Depression in women with polycystic ovary syndrome: clinical and biochemical correlates. Journal of affective disorders. 2003;74(3):299–304. [PubMed: 12738050]
32. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends in neurosciences. 2013;36(10):587–97. [PubMed: 23968694]
33. Hopkins DF, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabetic medicine : a journal of the British Diabetic Association. 1997;14(12):1044–50. [PubMed: 9455932]
34. Grillo CA, Piroli GG, Kaigler KF, Wilson SP, Wilson MA, Reagan LP. Downregulation of hypothalamic insulin receptor expression elicits depressive-like behaviors in rats. Behavioural brain research. 2011;222(1):230–5. [PubMed: 21458499]
35. Grillo CA, Mulder P, Macht VA, Kaigler KF, Wilson SP, Wilson MA, et al. Dietary restriction reverses obesity-induced anhedonia. Physiology & behavior. 2014;128:126–32. [PubMed: 24518861]
36. Rasgon NL, Kenna HA, Wroolie TE, Kelley R, Silverman D, Brooks J, et al. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiology of aging. 2011;32(11):1942–8. [PubMed: 20031276]
37. Kenna H, Hoeft F, Kelley R, Wroolie T, DeMuth B, Reiss A, et al. Fasting plasma insulin and the default mode network in women at risk for Alzheimer's disease. Neurobiology of aging. 2013;34(3):641–9. [PubMed: 22770543]
38. Marsh CA, Berent-Spillson A, Love T, Persad CC, Pop-Busui R, Zubieta J-K, et al. Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study. Fertility and sterility. 2013;100(1):200–7.e1. [PubMed: 23557757]
39. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24(6):1069–78. [PubMed: 11375373]
40. Guo M, Mi J, Jiang QM, Xu JM, Tang YY, Tian G, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clinical and experimental pharmacology & physiology. 2014;41(9):650–6. [PubMed: 24862430]
41. Rasgon NL, Kenna HA, Williams KE, Powers B, Wroolie T, Schatzberg AF. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. TheScientificWorldJournal. 2010;10:321–8.
42. Okamura F, Tashiro A, Utumi A, Imai T, Suchi T, Tamura D, et al. Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism: clinical and experimental. 2000;49(10):1255–60. [PubMed: 11079812]
43. Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L. Metabolic syndrome and major depression. CNS spectrums. 2014;19(4):293–304. [PubMed: 24103843]
44. Dokras A, Sarwer DB, Allison KC, Milman L, Kris-Etherton PM, Kunselman AR, et al. Weight Loss and Lowering Androgens Predict Improvements in Health-Related Quality of Life in Women With PCOS. The Journal of clinical endocrinology and metabolism. 2016;101(8):2966–74. [PubMed: 27253669]
45. American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC.
46. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders, 5th ed. . Washington, DC.
47. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes care. 2004;27(6):1487–95. [PubMed: 15161807]

Table 1.

Characteristics of non-depressed versus depressed PCOS subjects

	Overall N=738	Non-depressed N=673	Depressed N=65	p
Demographics				
Age, yrs N=738	29.0 (4.2)	29.0 (4.2)	27.0 (4.6)	<0.01
BMI, kg/m^2 N=738	35.1 (9.3)	35.0 (9.4)	36.3 (7.6)	0.10
Waist circumference, cm N=737	107 (20.5)	107 (20.6)	111 (18.5)	0.05
Caucasian, % N=738	79	79	77	0.64
Education, %				0.07
≤Some high school	5	5	6	
High school graduate	18	17	23	
Some college	36	35	45	
College or Graduate degree	41	43	26	
N=738				
Income, %				<0.01
<$25,000	11	10	22	
$25,000 - $74,999	56	57	48	
>$75,000	20	21	11	
Wish to not answer	15	13	20	
N=738				
Time trying to conceive, months N=705	24 (37.9)	24 (37.6)	28 (41.1)	0.78
Prior live birth, % N=738	20%	20%	23%	0.52
Current cigarette smoking, % N=738	15%	14%	17%	0.58
Current alcohol use, % N=738	63%	63%	60%	0.60
Current antidepressant use, % N=704	7%	7%	10%	0.36
Androgen status				

	Overall N=738	Non-depressed N=673	Depressed N=65	p
Total Testosterone, mg/dL N=737	49.5 (28.8)	48.7 (28.8)	54.9 (29.0)	0.11
Androstenedione, mg/dL N=737	4.0 (1.7)	3.9 (1.7)	4.2 (2.2)	0.07
SHBG, nmol/L N=737	27.0 (23.2)	27.4 (23.7)	24.5 (15.4)	0.09
MFG score N=738	17 (8.6)	16 (8.6)	18 (7.7)	0.08
Hirsutism, % N=738	87%	87%	94%	0.12
Acne score N=738	3 (16.1)	2 (15.8)	5 (19.3)	0.04
Metabolic Parameters				
Total cholesterol, mg/dL N=737	178 (36.5)	179 (36.2)	169 (38.7)	0.09
LDL, mg/dL N=737	119 (33.1)	119 (33.1)	114 (32.4)	0.11
HDL, mg/dL N=737	37 (37.9)	37 (10.8)	36 (9.3)	0.11
Triglycerides, mg/dL N=737	102 (57.7)	101 (57.9)	113 (55.8)	0.19
Glucose, mg/dL N=737	85.9 (11.8)	86.0 (12.0)	85.5 (9.3)	0.63
Insulin, mg/dL N=737	14.7 (19.5)	14.2 (19.6)	19.7 (17.6)	<0.01
IGF1 N=737	174 (69.5)	173.0 (68.6)	189.5 (76.9)	0.15
HOMA-IR N=737	3.12 (4.8)	2.97 (4.9)	4.28 (3.6)	<0.01
Diabetes diagnosis, % N=738	1.4%	1.2%	3.1%	0.22
H/o metformin, % N=738	41%	40%	43%	0.69

	Overall N=738	Non-depressed N=673	Depressed N=65	p
hsCRP, mg/L N=737	4.3 (7.0)	4.2 (7.1)	5.7 (6.2)	0.26

Median (SD), or % as indicated

P-values compare Non-depressed versus Depressed, and are calculated from Wilcoxon Rank Sum Test or chi-square as appropriate

Abbreviations: MFG, modified Ferriman-Gallwey score; HOMA-IR, homeostatic model assessment of insulin resistance

Table 2.

Demographic, endocrine and metabolic parameters associated with depression risk in PCOS by statistical significance level in univariate logistic regression models

p<0.05	**0.05<p<0.10**	**0.10<p<0.20**
Elevated HOMA-IR	Education	BMI
Age	Androstenedione	Total testosterone
Income	Hirsutism	Glucose
Waist circumference	Insulin	
Acne score	Total cholesterol	
	LDL cholesterol	
	HDL cholesterol	
	SHBG	

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance

Table 3.

Logistic regression models of association between insulin resistance and depression risk in PCOS

	Model 1		Model 2		Model 3	
	Univariate OR (95% CI)	**p**	**Multivariate OR (95% CI)**	**p**	**Multivariate OR (95% CI)**	**p**
Abnormal HOMA-IR	2.32 (1.28-4.21)	<0.01	2.23 (1.11-4.46)	0.02	2.03 (1.00-4.16)	0.05
Age, yrs	0.92 (0.86-0.98)	<0.01	0.92 (0.86-0.98)	0.01	0.95 (0.89-1.02)	0.18
BMI, kg/m^2	1.02 (0.99-1.25)	0.14	1.00 (0.97-1.04)	0.84	1.00 (0.97-1.04)	0.89
Income						
<$25k	Referent				Referent	
$25k - $74,999	0.38 (0.19-0.75)	<0.01			0.38 (0.19-0.77)	<0.01
≥$75k	0.23 (0.09-0.61)	<0.01			0.35 (0.13-0.94)	0.04
Wish to not answer	0.69 (0.30-1.56)	0.30			0.67 (0.29-1.57)	0.36
Androstenedione, mg/dL	1.18 (1.03-1.34)	0.02			1.11 (0.93-1.33)	0.24
Total testosterone, mg/dL	1.01 (1.00-1.01)	0.16			1.00 (0.99-1.01)	0.74
Hirsute	2.38 (0.85-6.72)	0.10			2.04 (0.71-5.91)	0.19
Acne score	1.01 (1.00-1.02)	0.03			1.01 (1.00-1.02)	0.07
Total cholesterol, mg/dL	0.99 (0.99-1.00)	0.08			0.99 (0.99-1.00)	0.13

Model 1: unadjusted odds ratios

Model 2: controls for age and BMI, selected a priori

Model 3: includes all variables associated with depression risk at p<0.20 on univariate logistic regression analyses, while excluding select co-linear variables

HOMA-IR: Homeostatic model assessment of insulin resistance, cut-off >2.2 considered elevated