Polycystic ovarian syndrome, obesity, and insulin resistance: intertwined comorbidities that impact assisted reproductive technology success

Polycystic ovarian syndrome (PCOS), a common endocrine condition affecting reproductive-age women, is often, but not always, associated with obesity and insulin resistance (IR) (1). Obesity has been established as a risk factor for poor outcomes in each step of assisted reproductive technology (ART) treatment, including lower pregnancy and live birth rates and higher miscarriage rates compared with normal weight counterparts (2). As obesity rates continue to rise worldwide, it has become increasingly important to examine the impact of obesity and its comorbidities, such as IR, on patients with infertility, particularly patients with PCOS who, because of oligo- or anovulation, may require ART to conceive.

Liang et al. (3) present the results of a single-center, retrospective cohort study including 282 women diagnosed with infertility, PCOS, and IR who underwent frozen embryo transfer (FET) between January 2020 and August 2023. Polycystic ovarian syndrome was diagnosed using the 2003 Rotterdam criteria. Insulin resistance was calculated using the homeostasis model assessment insulin resistance index (HOMA-IR). The patients were divided into body mass index (BMI) quartiles. They performed a linear regression analysis to elicit the relationship between BMI and embryo implantation rate. A multivariate analysis was used to examine the relationship between BMI and biochemical, clinical, and ongoing pregnancies after adjusting for confounding variables. The investigators demonstrated a linear association between BMI and clinical pregnancy outcomes (P for nonlinearity $>.05$). They showed that each 1 kg/m^2 increase in BMI was associated with a 2% decrease in embryo implantation rate ($P<.05$), 11% decrease in positive β-human chorionic gonadotropin, "biochemical pregnancy" ($P<.05$), and 9% decrease in clinical and ongoing pregnancy rates ($P<.05$). Liang et al. (3) conclude that increasing BMI in women with both PCOS and IR significantly impacts measures of ART success and ongoing pregnancy.

Insulin resistance has a well-established impact on fertility, contributing to anovulation, decreased oocyte quality, and reduced embryo implantation rates (4). Although HOMA-IR is a direct measure of IR, hemoglobin A1c is more commonly used by reproductive centers as a screening and diagnostic tool for IR and diabetes. Liang et al. (3) included patients with a diagnosis of IR at an HOMA-IR value $\geq$ 2.69. There was, however, no further stratification of patients based on the degree of IR. Future studies may also consider incorporating hemoglobin A1c levels that may translate into clinically useful counseling tools.

Additionally, Liang et al. (3) cited significant differences ($P<.001$) in the endometrial preparation used for FET, introducing selection bias as the type of protocol chosen may reflect underlying differences in patient characteristics. Preparation protocols included natural cycle, modified natural cycle with letrozole, hormone replacement treatment (HRT) cycles, and HRT cycles with leuprolide acetate downregulation. The HRT regimens were most frequently used, particularly at the lowest and highest BMI quartiles (86.7% and 85.2%, respectively), compared with an average of 66.7% for the entire study population. It is unclear whether the endometrial preparation and residual bias between preparation groups impacted outcomes.

A notable limitation of this study is the generalizability of its population. The small retrospective cohort of 282 is drawn from a single center. The highest BMI category included patients $\geq$ 28 kg/m^2 and only comprised 9.9% of the study population. The World Health Organization and the Centers for Disease Control and Prevention both define obesity as a BMI $\geq$ 30 kg/m^2 and obesity rates in populations such as the United States are significantly higher than those analyzed by the investigators. There is also no data presented on ethnicity/race, which has been shown to impact ART outcomes (5).

Despite the study's limitations, Liang et al. (3) provide a useful metric for patient counseling; small increases in BMI can impact ART success, potentially in a somewhat linear fashion. Through their multivariate analysis, the investigators demonstrated that BMI independently affected outcomes. These data can be useful in counseling patients with PCOS about the impact of preconception weight loss on fertility and ongoing pregnancy. The synergistic relationship between obesity, IR, and PCOS can make weight loss particularly difficult for patients. Individualized treatment plans that incorporate realistic goals and interventions are important in optimizing fertility and pregnancy outcomes in this population. Furthermore, because of the known deleterious impact of aging on fertility, not all patients have the luxury of taking the significant amount of time required to achieve weight loss before attempting conception. New therapies, including glucagon-like peptide-1 (GLP-1) agonists, may provide a possible solution or adjunct to diet and lifestyle modification. In a systematic review of the impact of GLP-1 agonists on patients with PCOS, the combination of metformin and GLP-1 agonists was noted to have a significant effect on weight loss and endocrine and metabolic parameters, including IR (6). However, more long-term data are necessary to establish the ongoing safety of these therapies.

As reproductive endocrinologists, our patients with PCOS with IR and obesity provide a unique challenge. There is an important balance between advocating for preconception weight loss, optimizing fertility, pregnancy, and obstetric health outcomes, and avoiding the deleterious impact of aging on fertility treatment success. There is likely a patient-specific "sweet spot" that balances weight loss goals and moving forward with fertility treatment. In some situations, optimization of outcomes may involve embryo cryo-

preservation before weight goals are met with subsequent weight loss and eventual FET.

CRediT Authorship Contribution Statement

Katarina Smigoc: Writing – review & editing, Writing – original draft, Conceptualization. **Jennifer Fay Kawwass:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Interests

K.S. has nothing to disclose. J.F.K. has nothing to disclose.

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REFERENCES

1. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. J Clin Endocrinol Metab 2021;106:e1071–83.
2. Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States. Fertil Steril 2016;106:1742–50.
3. Liang H, Li N, Li R. Preovulation body mass index and pregnancy after first frozen embryo transfer in patients with polycystic ovary syndrome and insulin resistance. Fertil Steril 2025;123:105–14.
4. Di Carlo C, Cimini C, Belda-Perez R, Valbonetti L, Bernabo N, Barboni B. Navigating the intersection of glycemic control and fertility: a network perspective. Int J Mol Sci 2024;25:9967.
5. Ethics Committee of the American Society for Reproductive Medicine. Electronic address asrm@asrm.org. Disparities in access to effective treatment for infertility in the United States: an ethics committee opinion. Fertil Steril 2021;116:54–63.
6. Bader S, Bhatti R, Mussa B, Abusanana S. A systematic review of GLP-1 on anthropometrics, metabolic and endocrine parameters in patients with PCOS. Womens Health (Lond) 2024;20:17455057241234530.