Reply of the authors: a call for metabolic stratification within obesity research and an urgent need for human, reproductive translational research with glucagon-like peptide 1 receptor agonists

We appreciate the letter in response to our narrative review (1). The objectives of this review were primarily to provide a clinical introduction to this new medication that has rapidly entered our subspecialty and make a call to our colleagues to elevate the care we provide to all patients with obesity. Your letter provides an excellent opportunity to highlight additional topics that we were unable to include, specifically the need to better stratify risk and benefit profiles among patients with obesity.

It is critical to emphasize that body mass index (BMI) is an oversimplification of health, and addressing obesity clinically needs to be individualized. As the letter investigators articulated, polycystic ovary syndrome (PCOS) should be studied and interpreted differently among patients with obesity. Additionally, specific phenotypes within PCOS, such as insulin resistance, polycystic ovarian morphology/ovarian reserve, hyperandrogenism, and ovulatory dysfunction, should *each* be considered when making decisions about medications, weight loss, and fertility treatment modalities. Polycystic ovary syndrome, by its very nature of being a "syndrome," is heterogeneous, and not all individuals diagnosed with PCOS exhibit insulin resistance, which is also true in obesity (2). However, PCOS, or even hyperandrogenism, is often thought of as a surrogate marker for future metabolic complications because the presence of these conditions may "unmask" a predisposition to metabolic syndrome. By focusing on glycemic status, blood pressure, metabolic biochemical abnormalities (i.e., liver enzymes, hemoglobin A1C, fasting glucose, and triglycerides), clinicians may better identify the individuals with (and without) PCOS who are most likely to benefit from glucagon-like peptide 1 receptor agonist (GLP1-RA) interventions in terms of both fertility outcomes and achieving healthy gestational outcomes.

Our research should be doing the same. As research into the role of GLP1-RA in individuals with PCOS advances, it would be beneficial to consider risk stratification based on metabolic screening rather than solely on BMI. Rather than lumping all obesity together and all PCOS together, ideal studies would analyze variables individually—ovulatory dysfunction, hyperandrogenism, insulin resistance, and BMI—and only after these variables are inputted should we thoughtfully create composite variables, such as PCOS-phenotype A or metabolically healthy obesity (3). This approach could offer more precise guidance for therapeutic interventions.

Lastly, the letter investigators cite the limited number of animal models studying and demonstrating an effect of GLP1-RA's on reproductive outcomes. Given the quick acceptance of GLP1-RA's into clinical practice, there is an urgent need for translational research on these effects to human granulosa cells and folliculogenesis.

CRediT Authorship Contribution Statement

Christina E. Boots: Writing – review & editing, Writing – original draft, Conceptualization. **Alyse S. Goldberg:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Interests

C.E.B. has nothing to disclose. A.S.G. reports lecture honoraria from Biosyent.

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