Letter to "Treating obesity and fertility in the era of glucagon-like peptide 1 receptor agonists"

This narrative review from the August Views and Reviews by Goldberg and Boots (1) was extremely informative in presenting the mode of action and side effects of glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) and their efficacy and expectations for weight loss in patients with infertility and finally their implications for anesthetic procedures and pregnancy.

This letter cries for the need to create a clear delineation between polycystic ovary syndrome (PCOS), a condition associated with insulin resistance and metabolic syndrome, and non-PCOS state when evaluating the impact of the injectable GLP-1 RA on body mass index and fertility. The investigators stated that "to date, there is no human clinical data describing fertility impacts"; however, this is only accurate in non-PCOS state. They briefly mentioned the study by Salamun et al. (2) that showed an improvement in the embryo implantation rate after pretreatment with the GLP-1 RA liraglutide—a study performed in women with PCOS.

In women with PCOS, although it did not address assisted reproductive technology, a meta-analysis by Han et al. (3) of eight randomized trials found that GLP-1 RA was superior to metformin in improving natural conception and insulin sensitivity and reducing body mass index and abdominal circumference. As mentioned by Goldberg and Boots (1), the randomized open-label study by Salamun et al. (2) showed that the in vitro fertilization pregnancy rate per embryo transfer was significantly higher in the COMBI (metformin combined with low-dose liraglutide) group (85.7%) than in the metformin group (28.6%, $P=.03$) in obese women with PCOS who had poor response to first-line treatment (2). Another study by Nylander et al. (4) on women with PCOS showed a trend toward a decreased antimüllerian hormone level while taking liraglutide. Conversely, in the ovaries of mice with PCOS, GLP-1 served as a regulator of both proliferation and antiapoptosis in mural granulosa cells via mechanisms involving FoxO1.

Comparatively, in non-PCOS state, studies were only performed in animal models where GLP-1 RA administration resulted in a decrease in body and ovarian weights and delayed vaginal opening in animals. It had deleterious effects on granulosa cells and led to fewer developing follicles and a higher number of atretic follicles. Glucagon-like peptide 1 RA blocked the preovulatory luteinizing hormone surge by reducing the hypothalamic levels of *Kiss-1* and *Kiss-1r* expression, thus leading to a decrease in the serum follicle-stimulating hormone (FSH) and steroid levels. Glucagon-like peptide 1 also disrupted the FSH-induced progesterone production in rat granulosa cells and the FSH-induced cyclic adenosine monophosphate production, whereas it augmented the FSH receptor messenger ribonucleic acid expression in granulosa cells. Additionally, GLP-1 reduced the messenger ribonucleic acid levels of steroidogenic acute regulatory, P450scc, and 3-beta-hydroxysteroid dehydrogenase. As for the uterus, GLP-1 RA demonstrated a beneficial antifibrotic effect in the intrauterine adhesions model by significantly reducing the deposition of collagen fibers; however, it resulted in destruction of the luminal epithelium with shrinkage in muscle fiber indicating apoptosis.

It is agreeable that there are no human clinical data describing fertility impacts "in women without PCOS." The vulnerability of this infertility population, and the wealth of online and social media misinformation (such as "#ozempic-babies"), is causing a dramatic rise in the use of the quick-fix GLP-1 RA medications with their unknown reproductive consequences. The cry for understanding the impact of these GLP-1 RAs in these two distinct patient populations is clearly needed.

CRediT Authorship Contribution Statement

Zaher Merhi: Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of Interests

Z.M. has nothing to disclose.

Zaher Merhi, M.D.[a,b,c]

[a] Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Maimonides Medical Center, Brooklyn, New York; [b] Department of Biochemistry, Albert Einstein College of Medicine, Bronx, New York; and [c] Reproductive Endocrinology and Infertility, Rejuvenating Fertility Center, New York, New York

https://doi.org/10.1016/j.fertnstert.2024.08.314

REFERENCES

1. Goldberg AS, Boots CE. Treating obesity and fertility in the era of glucagon-like peptide 1 receptor agonists. Fertil Steril 2024;122:211–8.
2. Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. Eur J Endocrinol 2018; 179:1–11.
3. Han Y, Li Y, He B. GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. Reprod Biomed Online 2019;39:332–42.
4. Nylander M, Frøssing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. Reprod Biomed Online 2017;35:121–7.