Check for updates

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

Alyse S. Goldberg, M.D.,[a] and Christina E. Boots, M.D., M.S.C.I.[b]

[a] Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; and [b] Center for Fertility and Reproductive Medicine, Northwestern University, Chicago, Illinois.

The objective of this narrative review is to advocate for improved comprehensive care of patients with obesity and infertility. Persons with an increased body mass index have less successful reproductive outcomes, and recently, new medications to treat neuroendocrine hormone imbalances are producing meaningful weight loss akin to surgical interventions. For the first time, obesity is publicly being recognized as a disease. These medications contain the newest generation of glucagon-like peptide 1 receptor agonists and deserve our attention for several reasons: regardless of body mass index, many patients will be using them; it is necessary to understand the mode of action, side effects, and implications for anesthetic procedures and pregnancy; and it is important to evaluate when they could be used to improve health outcomes and/or access to fertility care. (Fertil Steril® 2024;122:211–8. ©2024 by American Society for Reproductive Medicine.)

Key Words: Fertility, glucagon-like peptide 1 agonist, obesity, weight loss

The objective of this narrative review is to advocate for improved comprehensive care of patients with obesity and infertility. Persons with an increased body mass index (BMI) have less successful reproductive outcomes. This patient population presenting for infertility treatment is unique; they are motivated, compliant, educated, and eager to learn more. However, simply telling them to lose weight by "eating less and exercising more" is insufficient in addressing the obesity epidemic. No woman who has reached reproductive maturity and has not, at some point, attempted to modify her weight, which is why the new category of antiobesity medications has created a firestorm in society. For the first time, obesity is publicly being recognized as a disease because medications to treat neuroendocrine hormone imbalances are producing meaningful weight loss akin to surgical interventions. These medications contain the newest generation of glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) and deserve our attention for several reasons: regardless of BMI, many patients will be using them; it is necessary to understand the mode of action, side effects, and implications for anesthetic procedures and pregnancy; and it is important to evaluate when they could be used to improve health outcomes and/or access to fertility care.

PRECONCEPTION CARE

Weight loss may be one mechanism to improve reproductive outcomes; however, it is not the only tool in elevating the care provided to patients with obesity. Before initiating fertility care to any patient, enhanced preconception counseling should be conducted. This is perhaps even more important for patients with a higher BMI. They should be screened for comorbidities (i.e., diabetes, hypertension, and thyroid dysfunction), which extends beyond screening for overt disease to also the precursors of these diseases. For example, many of our young patients have early insulin resistance (diagnosed by a hemoglobin A1c [HbA1c] level of 5.7%–6.4% or abnormal fasting glucose or response to oral glucose load) but are not yet in the diabetic range (HbA1c level of >6.5%). Counseling patients on the spectrum of diseases and improving their trajectory are a unique and meaningful opportunity for preconception providers. Regardless of BMI, counseling on nutrition and physical activity should be performed. Although BMI can be predictive of poor lifestyle choices, normal and high BMIs can also be realized with poor and healthy habits, respectively. We should not assume that big equals bad or that lean equals good, or we will miss the opportunity to affect change.

In addition to optimizing physical health, screening mental health and well-being should also be a focus of the preconception conversation. Patients with obesity are at higher risk of depression, anxiety, and disordered eating, and these are only exacerbated

Received March 9, 2024; revised May 14, 2024; accepted May 22, 2024; published online May 27, 2024.
Correspondence: Christina E. Boots, M.D., M.S.C.I., Center for Fertility and Reproductive Medicine, Northwestern University, 259 East Erie, Suite 2400, Chicago, Illinois (E-mail: christina.boots@northwestern.edu).

Fertil Steril® Vol. 122, No. 2, August 2024 0015-0282/$36.00
Copyright ©2024 American Society for Reproductive Medicine, Published by Elsevier Inc.
https://doi.org/10.1016/j.fertnstert.2024.05.154

by adding the diagnosis of infertility. Screening for these mental health disorders and offering reliable referrals to mental health resources, including psychiatrists, psychologists, and peer groups specialize in perinatal mental health, are critical to providing excellent care (1).

FERTILITY CARE

The relative risks of poorer reproductive outcomes are higher in patients with an increased BMI, whereas the absolute risks are generally low. To date, there are no high-quality prospective studies showing that acute weight loss improves fertility treatment outcomes. For these 2 reasons, BMI alone should not be used to restrict access to fertility care (2), and instead, our field should be working to improve the care for patients in higher BMI ranges. Although BMI alone should not restrict access to fertility care, it should be considered when an individualized care plan is created. This care plan should consider how BMI may be associated with difficult visualization of the ovaries and/or increased complexity of procedures such as saline ultrasound examinations, intrauterine inseminations, and embryo transfers. There may also be a role for higher medication dosing during ovarian stimulation and/or altered administration techniques, such as intramuscular vs. subcutaneous trigger medications (3, 4). Anesthesia colleagues have set strict BMI limits in an effort to predict airway complications during monitored anesthesia care, and often, this is the BMI that ultimately limits access to in vitro fertilization (IVF) (5, 6). It is possible that airway prediction may be improved with additional variables (i.e., neck circumference or previous anesthesia events) beyond BMI alone. Further discussion about expanding IVF access to a higher BMI is in the third article of this Views and Reviews. When restrictions are limited beyond our specialty, our focus should be on the following: referrals to IVF centers with advanced anesthesia options; improving other non-IVF aspects of fertility care; and, for some patients, helping them achieve a BMI that both improves health and increases their access.

WEIGHT LOSS

Weight loss may be the "right" answer for some patients as part of their infertility treatment plan. The treatment plan should consider the patients' age, ideal family size, other aspects of their health, and their desire for and commitment to weight loss. Maternal age and its influence on oocyte quality remain the overarching predictor of fertility success, and thus, pausing fertility treatments to focus on weight loss and improved health should balance the risks of reproductive aging and consider the ideal number of children (7). The mechanisms of weight gain and obesity are vast and complex, as well as the weight loss strategies. However, these strategies are routed in 5 tenets: nutrition; physical activity; behavioral therapy; medications; and bariatric surgery. When weight loss is recommended, education, resources, and ongoing support should be offered to both increase effectiveness and ensure that the weight loss is achieved safely.

To properly counsel patient about weight loss, it is important to have a solid and up-to-date understanding of the evidence surrounding weight loss and fertility (8). Recent large prospective studies have mostly not demonstrated an increased live birth rate (Table 1) (9–13). Five randomized controlled trials, each with sample sizes of >100 women, have explored whether acute weight loss before fertility treatment improves success (9–13). In these studies, the weight loss interventions were successful in achieving the goal of approximately 7% loss (i.e., 9–20 lb on average) using caloric restriction, sometimes with increased physical activity, and/or antiobesity medications. The intervention groups had higher rates of spontaneous conception and improved ovulation in the setting of ovulation induction. However, in the general infertility and unexplained infertility population, weight loss did not improve the live birth rates. In 3 of the studies, the weight loss intervention was associated with a nonsignificant increase in the miscarriage rates. Although the lack of statistical significance should be noted, the trend suggests caution and a potential increased risk of miscarriage for some patients.

There are no prospective studies on bariatric surgery and subsequent fertility outcomes; however, in the setting of anovulation, resumption of menses has been documented after the weight loss associated with bariatric surgery (14, 15). A recent large retrospective study compared IVF outcomes in patients who had previously undergone bariatric surgery with those in age- and BMI-matched controls (16). There was no difference in the cumulative live birth rates; however, those who underwent bariatric surgery retrieved fewer oocytes and had fewer frozen embryos and lower birth weights. Additional evidence showing worse obstetric outcomes has cautioned that conception should not happen within at least 1 year of surgery (14, 15).

Finally, there is a new class of antiobesity medications on the market that is demonstrating effective and meaningful weight loss—GLP-1 RAs, such as semaglutide (17) and tirzepatide (18). A landscape of medical interventions to aid in weight loss before pregnancy have been recently reviewed (19, 20). The approval of GLP-1 RA agents to treat obesity irrespective of diabetes has led to an increase in uptake of these medications and raises concerns about heightened prenatal exposure (21). Although there are no studies correlating weight loss achieved with these medications with improved fertility outcomes, we anticipate seeing data in the near future. Several trials are registered; however, data have not yet been published. The remainder of this article focuses on these new medications that reproductive endocrinologists will be seeing more of and, we would argue, should be using as the most effective, least invasive means of weight loss.

GLP-1 AND GASTRIC INHIBITORY POLYPEPTIDE RAS IN FERTILITY CARE

Implementing obesity management into a reproductive endocrinology practice is realistic in both academic settings and private practice. Most reproductive endocrinologists have experience treating polycystic ovary syndrome and, thus, have managed similar medications with similar side effects, such as metformin. Additionally, as infertility specialists, we are familiar with prescribing medications that require specialty pharmacies and insurance prior authorizations.

TABLE 1

Randomized controlled trials investigating weight loss and fertility treatment outcomes.

Trial name	Lead investigator	Publication year	Study site	Study population	Study duration	Intervention 1	Intervention 2	Control	Fertility treatment	Weight loss	Live birth rate	Miscarriage rate
OWL-PCOS	Legro et al. (9)	2015	United States, multicenter	PCOSAge, 18–40 y; BMI, 27–42 kg/m^2	16 wk	Caloric restriction with meal replacements, medication (sibutramine or orlistat), and increased physical activity	Both intervention 1 and OCP	OCP alone	Ovulation induction with timed intercourse for 4 cycles	−6.2% and −6.4% −1.0% *P* < .001	Intervention: 25.0% (12/48) and 25.5% (12/47) Control: 8.5% (4/47)	20% (3/15) and 14.3% (2/14) 42.9% (3/7)
	Mutsaerts et al. (10)	2016	The Netherlands	InfertilityAge, 18–38 y; BMI, >29 kg/m^2	6 mo	Caloric restriction, increased physical activity, and coaching	None	Direct to fertility treatment	Standard of care Dependent on indication	−4.4 kg −1.1 kg *P* < .001	Intervention: 43.9% (123/280) Control: 53.9% (153/284) RR, 0.82; 95% CI, 0.69–0.97	23.4% (41/175) 14.5% (27/186) RR, 1.54; 95% CI, 0.98–2.43
	Einarsson et al. (11)	2017	Sweden, Denmark, and Iceland	InfertilityAge, 18–38 y; BMI, 30–35 kg/m^2	12 wk of weight loss2–5 wk of weight stabilization	Strict low-calorie liquid formula diet	None	Direct to fertility treatment	1 cycle of IVF	−9.44 ± 6.57 kg +1.19 ± 1.95 kg *P* < .00001	Intervention: 29.6% (45/152) Control: 27.5% (42/153) 95% CI, 12.9 to −8.6; *P* = .77	30.3 (20/66) 23.2% (13/56) Not significant
	Wang et al. (12)	2021	China	InfertilityAge, 20–40 y; BMI, >25 kg/m^2	4–12 wk	Orlistat (weight loss medication) plus recommendations for low-fat diet and high-quality physical activity	None	Placebo medication plus recommendations for low-fat diet and high-quality physical activity	1 cycle of IVF	−2.49 kg −1.22 kg *P* .005	Intervention: 25.5% (112/439) Control: 25.6% (92/438) RR, 1.0; 95% CI, 0.8 −1.25; *P* = .98	19.4% (27/139) 15% (20/133) RR, 1.29; 95% CI, 0.76–2.19
FIT-PLESE	Legro et al. (13)	2022	United States, multicenter	Unexplained infertilityAge, 18–40 y; BMI, >30 kg/m^2	16 wk	Caloric restriction with meal replacements, orlistat, and increased physical activity	None	Increased physical activity without weight loss goals	Ovarian stimulation with intrauterine insemination for 3 cycles	−6.6 ± 5.4% −0.3 ± 3.2% *P* < .001	Intervention: 12.2 % (23/188) Control: 15.2% (29/191) RR, 0.81; 95% CI, 0.48–1.34; *P* = .40	33.3% 14/59)23.7% (21/63) RR, 1.40; 95% CI, 0.79 −2.50

Note: BMI = body mass index; CI = confidence interval; OCP = oral contraceptive pill; PCOS = polycystic ovary syndrome; RR = relative risk.

Goldberg. Treating obesity and fertility with GLP1a. Fertil Steril 2024.

TABLE 2

Summary of the 2 newest medications containing glucagon-like peptide 1 receptor agonist.

Name	Mechanism of action	Weight loss efficacy after 1 y (placebo-subtracted)	Dose titration	Safety concerns/ contraindications	Duration to stop before anesthesia	Duration to stop before pregnancy
Semaglutide	GLP-1 receptor agonist that suppresses appetite and delays gastric emptying	−14.9% (−12.5%)	0.25 mg weekly × 4 wk and then 0.5 mg; can increase to 1, 1.7, or 2.4 mg as needed	Family or personal history of medullary thyroid cancer or MEN2 syndrome and pregnancy	At least 1 wk per anesthesia guidelines	At least 2 mo before conception per manufacturer
Tirzepatide	GIP/GLP-1 dual agonist that suppresses appetite and delays gastric emptying	−15% (−11.9%) at 5 mg −19.5% (−16.4%) at 10 mg−20.9% (−17.8%) at 15 mg	2.5 mg × 4 wk and then increase to 5 mg; can increase by 2.5 mg every 4 wk to a maximum dose of 15 mg as needed	Family or personal history of medullary thyroid cancer or MEN2 syndrome and pregnancy	At least 1 wk per anesthesia guidelines	At least 1 mo before conception per manufacturer

GLP-1 = glucagon-like peptide 1; MEN2 = multiple endocrine neoplasia type 2.

Goldberg. Treating obesity and fertility with GLP1a. Fertil Steril 2024.

Referrals to clinics that specialize in weight loss management can be a great resource to our patients. However, several patients will not have efficient access to this resource because of geographic, financial, or wait time constraints. Thus, once a patient with obesity and infertility presents to a fertility office, we either would ideally have expedient referrals to multidisciplinary practices or should provide this care as part of our comprehensive reproductive treatment plan. Let us walk through a patient scenario.

A 32-year-old woman presents with 1 year of primary infertility. Her cycles are every 32–38 days, and the BMI and antimüllerian and HbA1c levels were 41 kg/m^2, 5 ng/mL, and 5.9%, respectively. After thorough preconception testing and a fertility evaluation determined no clear etiology for her fertility, her reproductive endocrinology and infertility specialist offers comprehensive treatment options. First, we assess the patient's potential and willingness to improve lifestyle and mental health status. We discuss the basic concepts and importance of nutrition and mental health. Online resources and a referral to a dietician and psychologist are provided. Second, we discuss the role BMI may play on infertility and briefly review the data on weight loss, ovulatory function, and the fertility treatment, such as IVF. After further discussion, the patient describes several years of weight loss attempts with various calorie-restrictive diets and the inability to sustain meaningful weight loss. Given her good ovarian reserve and relatively young reproductive age, she is motivated to pursue weight loss again before fertility treatment and is particularly excited to consider one of the new antiobesity medications that she has heard so much about.

Medication choice

To select the right medication, we need to better understand GLP-1 and gastric inhibitory polypeptide (GIP) (Table 2). Glucagon-like peptide 1 and GIP are 2 incretin hormones that are secreted by L-cells in the gut after food intake (22). They bind to their respective receptors to stimulate insulin secretion in a glucose-dependent manner. Glucagon-like peptide 1 and GIP RAs mimic the effects of incretin by binding the receptor of GLP-1 or GIP, leading to prolonged physiologic actions. Both have central effects to reduce appetite and decrease gastric emptying to increase satiety, which can lead to reduced food intake and lowering of body weight (23). In addition to influencing multiple organs such as the brain, pancreas, skeletal muscle, and kidneys, GLP-1 RA can increase glucose uptake and lipolysis in white adipose tissue and thermogenesis in brown adipose tissue (22).

Short-acting (daily administration) GLP-1 RAs, such as exenatide (Byetta), liraglutide (Victoza), and dulaglutide (Trulicity), are approved for use in diabetes. After approval for glucose control, liraglutide was approved and commercialized for weight loss (marketed as *Saxenda*). The newest generation of these medications is longer acting (weekly administration). Semaglutide is a GLP-1 RA and is marketed as *Ozempic* for diabetes use and approved at higher doses, under the name Wegovy, for chronic weight management. The enhanced efficacy of the weekly administration of GLP-1 RA (17) compared

with its predecessors has caught media attention and catapulted its popularity. Most recently, a medication that combines the dual stimulation of both GLP-1 and GIP receptors received Food and Drug Administration approval. Tirzepatide leads to further improvement in both glucose reduction and weight loss in patients with and without type 2 diabetes compared with semaglutide (18). Tirzepatide for the treatment of diabetes is marketed as Mounjaro and received Food and Drug Administration approval for weight loss in patients without diabetes in late 2023 under the name Zepbound. Given that semaglutide and tirzepatide are the most effective and most common at the time of this publication, our recommendation to our hypothetical patient is to start with tirzepatide.

Prescribing

Semaglutide and tirzepatide are subcutaneous injections that are administered weekly by the patient at home. The medication is started at a low dose and then titrated at the manufacturer's recommended schedule. The starting dose of semaglutide is 0.25 mg for 4 weeks and then increased to 0.5 mg. Depending on clinical response and side effects, the dose can be gradually increased to 1, 1.7, or 2.4 mg and then maintained.

Tirzepatide is also a subcutaneous weekly injection. Dosing principles start at 2.5 mg, increasing to 5 mg weekly after 4 weeks. Further titration by 2.5 mg every 4 weeks depends on the response as well as the ability to tolerate the adverse gastrointestinal symptoms. If losing weight, then the dose does not need to be increased. There is no specific biochemical monitoring recommended for either medication. When initiating tirzepatide, patients should be counseled regarding the potential reduction in efficacy/absorption of oral contraceptives (24). Thus, women are advised to use nonoral contraception for 4 weeks after each dose escalation. This has not been noted by manufacturers when prescribing semaglutide (25).

Finally, there are 2 other considerations when prescribing these medications: cost and medication shortages. Several insurance companies require prior authorization for these medications. A significant administrative burden is placed on the clinical office to submit this and often resubmit with alternative brands if the first request is denied. However, fertility offices have some familiarity with this process given the need for authorization for several fertility medications and procedures. Because of their popularity and manufacturer delays, several patients have difficulty accessing these medications, especially at certain doses. Delay of doses often causes delay of results, and these medications may need to be retitrated. Additionally, there are no clear guidelines about switching between these medications and whether starting at the lowest dose and titrating from the beginning are necessary. The lack of generic formulations keeps the cost of these medications high, and without insurance coverage or special coupons, monthly costs can be thousands of dollars in the United States. Given the limited data on safety and efficacy, the use of compounded agents is not recommended.

Efficacy and expectations

The efficacy of semaglutide has been studied in the Semaglutide Treatment Effect in People with Obesity (STEP) trials. The last study, STEP 8, described a mean weight loss of 15.8% in 338 subjects after 68 weeks. Most participants were women (78.4%) (26). Tirzepatide use in individuals without diabetes but with a BMI of >30 kg/m^2 was evaluated in the SURMOUNT-1 trial (18). The mean changes in weight after 72 weeks with 5-, 10-, and 15-mg doses were 15%, 19.5%, and 20.9% loses, respectively (vs. placebo, −3.1%). Extension trials from STEP 1 and SURMOUNT documented utility in the longer use of GLP-1 and GIP RAs. The STEP 4 extension trial illustrated that weight loss plateaued around week 60 of semaglutide use with a total expected weight loss of 17.4% (26). When tirzepatide use was extended (SURMOUNT-4), the weight loss continued until week 76 and averaged 25.8% until the trial was stopped at week 88 (27). *Excitingly, more than 30% of patients lost >25% of their body weight, which is approaching the estimated rate of approximately 30% after bariatric surgery* (28). There are no current guidelines on the standard interval and frequency of monitoring visits. General recommendations would be to offer check-ins every few months with increasing intervals over time. These check-ins should be to assess the pace of weight loss, offer support in cases of side effects, encourage healthy nutrition and continued exercise, and monitor mental health. These visits could be in person or virtual and could be provided by the physician or other clinical providers, such as nurses, pharmacists, and/or nurse practitioners.

Side effects and contraindications

Semaglutide and tirzepatide medications have similar adverse reaction profiles predominantly manifesting as gastrointestinal symptoms such as nausea, vomiting, and constipation, which can be severe at times (17). As noted in the phase 3 trials, these symptoms were daily for some people. Over-the-counter medications, such as antinausea or antacid medications, can be used to manage these side effects. Reports of gallstones have been documented (25), and rare, serious instances of gastroparesis have been postulated to be associated with semaglutide (29). Long-term implications associated with weight loss, including reductions in lean muscle mass (17) and/or the development of osteoporosis, are areas of concern (30).

The only clear contraindications to using these medications are pregnancy, lactation, and individuals with a known genetic predisposition to medullary thyroid cancers or associated syndromes (e.g., multiple endocrine neoplasia type 1). Caution is also advised against the use of these medications if there is a personal history of pancreatitis.

Glucagon-like peptide 1 RAs are considered class C for use in pregnancy and are not recommended. Manufacturers of semaglutide recommend abstaining from the medication for 8 weeks before pregnancy because of observed teratogenicity in animals treated with semaglutide. Manufacturers of tirzepatide recommend abstaining for 4 weeks before pregnancy in the Canadian product guidelines; however, the US product guidelines do not provide a recommended amount of time between discontinuation and conception (24). Preclinical animal studies suggest a higher risk of early pregnancy loss, reduced fetal weight, and increased skeletal and visceral malformations. However, the challenge lies in differentiating whether observed fetal outcomes result from an energy deficit or specific drug effects, given that pregnancy should not be a hypocaloric state.

Human gestational exposure to long-acting GLP-1 RA is limited in the published literature. Muller et al. (31) summarized 26 records of exposure of short-acting GLP-1 RA (liraglutide or exenatide) during pregnancy or lactation, and Minis el al. (32) reported 2 cases of exposure to liraglutide up to 13 weeks' gestation and dulaglutide up to 15 weeks. After cessation of the medication and initiation of insulin, no fetal malformations, comorbidities, or maternal complications were reported, and neonatal weight was appropriate for gestational age. In the original drug application trials for semaglutide (SUSTAIN 1–6 and STEP 1–5 and 8), 46 pregnancies were exposed to the drug for a short duration until pregnancy was confirmed. There was a single report of a congenital anomaly of the external ear. All semaglutide-treated women had healthy children with no pregnancy losses or confirmed teratogenicity (25). In 2023, Skov et al. (33) reported a case where semaglutide was discontinued at 3 weeks and 4 days of gestation. The pregnancy resulted in an infant with macrosomia, and the investigators attributed the infant size to the "rebound weight gain" because the patient did not have gestational diabetes. Finally, a 2023 review of a noninsulin antidiabetes medication in the *Journal of the American Medical Association* found that 461 individuals filled GLP-1 RA prescriptions in the first trimester. There was no statistically significantly increased risk of malformations (21).

There are no clinical trials or case reports regarding tirzepatide use in pregnant patients. Studies in animals (i.e., rats and rabbits) have shown harm to fetal development when there was maternal weight loss (24).

In a patient with infertility, a crucial consideration would be the use of these medications before procedures requiring anesthesia, such as an oocyte retrieval or hysteroscopy. The American Society of Anesthesiologists Consensus currently recommends discontinuing the long-acting GLP-1 and/or GIP RA 7 days before the procedure, regardless of the indication of the medication, procedure being performed, or type of anesthesia being planned (intravenous sedation and general anesthesia both require 1-week abstinence) (34). This recommendation is due to the known delay in gastric emptying and, thus, increased risk of aspiration.

Medication discontinuation

Weight regain is commonly observed after a reduction in BMI whether achieved through medical or lifestyle modifications. Weight regain after discontinuation of GLP -RA is anticipated because of the resurgence of physiologic response to weight loss and adaptations in gut hormones aimed at maintaining weight homeostasis. This observation has been documented in the extension of the STEP 1 trial (35). One year after stopping semaglutide 2.4 mg, participants had regained two thirds of their weight loss. Furthermore, the STEP 4 study compared those who stopped semaglutide 2.4 mg after 20 weeks with those continuing for an additional 48 weeks. Those who continued the medication had sustained weight loss, whereas those who switched to placebo experienced weight gain to less than their baseline weight. However, the weight regain had not yet plateaued at week 68 when the study was concluded (36). Similar observations were described in the SURMOUNT-4 study, where withdrawal of tirzepatide led to regain of lost weight and continued treatment maintained or progressed weight loss (27).

When GLP-1 RAs are discontinued before conception, it is imperative to assess possible ramifications of acute and possibly rapid weight regain before and in early gestation, as well as the resulting untoward influence on mental health. As observed in 1 case report (33), weight regain can manifest in an overshoot effect leading to potentially higher than expected weight gain in pregnancy. The profound return of hunger cues has been reported and will require psychological management. Potential consequences of excessive preconception weight gain or "weight cycling" are excess gestational weight gain and associated negative outcomes including early pregnancy loss, gestational diabetes, preeclampsia, and nonelective cesarean delivery (37). It is crucial, but challenging, to mitigate the risk of weight cycling through strategies including counseling on behavioral changes and nutritional support and physical activity. The adoptions of multidisciplinary and multifaceted approaches, when available, are highly recommended for the best chance of long-term weight management (38).

The optimal recommendations on how to stop semaglutide or tirzepatide are not known. Weaning the dose of the medication may have less obvious appetite stimulation than an abrupt cessation. However, this has not been studied. A preliminary unpublished study (39) suggested that bridging with metformin offered some improvement in weight regain, although improved cardiometabolic parameters did revert toward baseline once semaglutide was switched back to metformin or no medication.

Specific considerations of GLP-1 RA in fertility treatment

There are nuances to using this medication around the time of fertility treatment. Notably, the recommendations currently encourage discontinuation before conception; however, the preconception use of this medication may have important benefits and possible repercussions. The reproductive effects of GLP-1 RA are not well understood. Although it has been suggested that GLP-1 receptors exist in the reproductive system (40), to date, there is no human clinical data describing fertility impacts. The benefits of using these medications preconception include improved insulin sensitivity and other

metabolic parameters associated with higher BMIs, such as blood pressure and inflammation. In a single prospective study of 27 participants, an improved embryo implantation rate after pretreatment with a short-acting GLP-1 RA (liraglutide) before IVF was reported. The investigators hypothesized that the anti-inflammatory properties of this medication may positively affect the endometrium and enhance receptivity and implantation (41).

However, detrimental effects could be postulated as well. Nutritional deficits and the altered metabolism noted during acute weight loss may affect pregnancy and neonatal outcomes. Perhaps, similar to the randomized controlled trials using lifestyle and other weight loss medications, acute weight loss may be associated with improved ovulation rates and spontaneous conceptions but not with assisted reproductive technology outcomes. We need to carefully monitor the rates of miscarriage, and similar to the results noted after bariatric surgery, we need to carefully monitor birth weights and the metabolic health of children. The rate of preconception weight loss should be monitored, and thoughtful nutritional counseling to ensure nutritional adequacy should be provided to persons taking this medication preconception. Although not yet identified, there may benefits to assessing nutritional status before conception by taking a dietary history, ensuring prenatal vitamin adherence, and considering screening the serum levels for common vitamin deficiencies (iron, vitamin D, and vitamin B12) and anemia.

Before initiating these medications, mental health support should be provided, and screening for disordered eating behaviors should be performed. Weight loss, especially required weight loss, can trigger new events for several persons who have struggled with body image, weight, and food. Ensuring that they have specialized support during this time is important to providing comprehensive and compassionate care to our patients.

One of the most compelling uses for these medications is for those undergoing ovarian stimulation for planned oocyte or embryo cryopreservation. There is currently a lack of data regarding the use of GLP-1 RA medication during oocyte stimulation. Data collection is ongoing. One of the primary advantages of continuing this medication around the time of ovarian stimulation in the setting of required weight loss is to access this treatment. As shown in the data earlier, weight regain is common after discontinuation of the medication, and for persons just under the BMI cutoffs, prolonged time without the medications incurs the risk of not meeting these restrictions before their first cycle or in the event of needing a second or third cycle. Finally, counseling regarding the anesthesia recommendation to discontinue long-acting GLP-1 RA is critical to ensuring that this process is completed in a timely and safe manner.

CONCLUSION

Reproductive endocrinology and infertility specialists should consider integrating obesity management into the care of our patients with appropriate collaboration and resources.

As compassionate and comprehensive caregivers, it is our responsibility to ensure that patients with high BMIs are receiving unbiased, evidenced-based treatment. This is most likely to occur using a multidisciplinary approach. For any patients considering or already taking antiobesity medications, we should be offering nutritional counseling and mental health support and ensuring that they discontinue appropriately before conception and/or procedures requiring anesthesia.

Weight loss before pregnancy in some persons living with obesity may restore ovulation and improve maternal and fetal outcomes. However, long-term data are not yet available, and thus, careful attention to ongoing, upcoming research is needed.

CRediT Authorship Contribution Statement

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

Declaration of Interests

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

REFERENCES

1. Treatment and management of mental health conditions during pregnancy and postpartum: ACOG clinical practice guideline No. 5. Obstet Gynecol 2023;141:1262–88.
2. Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: a committee opinion. Fertil Steril 2021;116:1266–85.
3. Matorras R, Meabe A, Mendoza R, Prieto B, Ramón O, Mugica J, et al. Human chorionic gonadotropin (hCG) plasma levels at oocyte retrieval and IVF outcomes. J Assist Reprod Genet 2012;29:1067–71.
4. Shah DK, Missmer SA, Correia KF, Ginsburg ES. Pharmacokinetics of human chorionic gonadotropin injection in obese and normal-weight women. J Clin Endocrinol Metab 2014;99:1314–21.
5. Romanski PA, Farland LV, Tsen LC, Ginsburg ES, Lewis EI. Effect of class III and class IV obesity on oocyte retrieval complications and outcomes. Fertil Steril 2019;111:294–301.e1.
6. Liang T, Ruetz K, Haakman O, Vilos A, Vilos G, Abu-Rafea B. Impact of class III obesity on outcomes and complications of transvaginal ultrasound-guided oocyte pickup. F S Rep 2020;1:270–6.
7. Goldman RH, Farland LV, Thomas AM, Zera CA, Ginsburg ES. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019;221:617.e1–13.
8. Vitek WS, Hoeger KM. Worth the wait? Preconception weight reduction in women and men with obesity and infertility: a narrative review. Fertil Steril 2022;118:447–55.
9. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, et al. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:4048–58.
10. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, et al. Randomized trial of a lifestyle program in obese infertile women. N Engl J Med 2016;374:1942–53.
11. Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlström PO, et al. Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Hum Reprod 2017;32:1621–30.
12. Wang Z, Zhao J, Ma X, Sun Y, Hao G, Yang A, et al. Effect of orlistat on live birth rate in overweight or obese women undergoing IVF-ET: a randomized clinical trial. J Clin Endocrinol Metab 2021;106:e3533–45.
13. Legro RS, Hansen KR, Diamond MP, Steiner AZ, Coutifaris C, Cedars MI, et al. Effects of preconception lifestyle intervention in infertile women with obesity: the FIT-PLESE randomized controlled trial. PLOS Med 2022;19:e1003883.
14. Pathak MM, Shekhar KV, Meshram RJ. A narrative review on effects of maternal bariatric surgery on offspring. Cureus 2023;15:e48513.

15. Samarasinghe SNS, Woods C, Miras AD. Bariatric surgery in women with polycystic ovary syndrome. Metabolism 2024;151:155745.
16. Nilsson-Condori E, Mattsson K, Thurin-Kjellberg A, Hedenbro JL, Friberg B. Outcomes of in-vitro fertilization after bariatric surgery: a national register-based case-control study. Hum Reprod 2022;37:2474–81.
17. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989–1002.
18. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
19. Goldberg AS, Dolatabadi S, Dutton H, Benham JL. Navigating the role of anti-obesity agents prior to pregnancy: a narrative review. Semin Reprod Med 2023;41:108–18.
20. Nuako A, Tu L, Reyes KJC, Chhabria SM, Stanford FC. Pharmacologic treatment of obesity in reproductive aged women. Curr Obstet Gynecol Rep 2023;12:138–46.
21. Cesta CE, Rotem R, Bateman BT, Chodick G, Cohen JM, Furu K, et al. Safety of GLP-1 receptor agonists and other second-line antidiabetics in early pregnancy. JAMA Intern Med 2024;184:144–52.
22. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol 2017;13:605–28.
23. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242–51.
24. U.S. Food and Drug Administration. Mounjaro (tirzepatide) injection, for subcutaneous use. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf. Accessed February 24, 2024.
25. Ozempic (semaglutide) injection, for subcutaneous use. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf. Accessed February 24, 2024.
26. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. J Am Med Assoc 2022;327:138–50.
27. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. J Am Med Assoc 2024;331:38–48.
28. Palumbo P, Banchelli F, Miloro C, Toschi PF, Mecheri F, Gabriele S, et al. Weight loss trend after bariatric surgery in a population of obese patients. Clin Nutr ESPEN 2023;57:58–64.
29. Kalas MA, Galura GM, McCallum RW. Medication-induced gastroparesis: a case report. J Investig Med High Impact Case Rep 2021;9:23247096211051919.
30. Herrou J, Mabilleau G, Lecerf JM, Thomas T, Biver E, Paccou J. Narrative review of effects of glucagon-like peptide-1 receptor agonists on bone health in people living with obesity. Calcif Tissue Int 2024;114:86–97.
31. Muller DRP, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. Front Endocrinol (Lausanne) 2023;14:1215356.
32. Minis E, Stanford FC, Mahalingaiah S. Glucagon-like peptide-1 receptor agonists and safety in the preconception period. Curr Opin Endocrinol Diabetes Obes 2023;30:273–9.
33. Skov K, Mandic IN, Nyborg KM. Semaglutide and pregnancy. Int J Gynecol Obstet 2023;163:699–700.
34. Joshi GP, Abdelmalak BB, Weigel WA, Soriano SG, Harbell MW, Kuo CI, et al. American Society of Anesthesiologists consensus-based guidance on preoperative management of patients (adults and children) on glucagon-like peptide-1 (GLP-1) receptor agonists. Available at: https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative. Accessed July 2, 2023.
35. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. Diabetes Obes Metab 2022;24:1553–64.
36. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. J Am Med Assoc 2021;325:1414–25.
37. Piccinini-Vallis H, Woolcott C, Miller L, Snelgrove-Clarke E, Cahill S. The relationship between pre-pregnancy attempts to lose weight and gestational weight gain: an exploratory primary care prospective cohort study. J Obstet Gynaecol Can 2021;43:337–43.e1.
38. Wharton S, Lau DCW, Vallis M, Sharma AM, Biertho L, Campbell-Scherer D, et al. Obesity in adults: a clinical practice guideline. Can Med Assoc J 2020;192:E875–91.
39. Jensterle M, Ferjan S, Goricar K, Janez A. The maintenance of long-term weight loss after semaglutide withdrawal in obese women with PCOS treated with metformin: a 2-year observational study. Endocr Abstr 2023;90:RC10.3.
40. Jensterle M, Janez A, Fliers E, DeVries JH, Vrtacnik-Bokal E, Siegelaar SE. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. Hum Reprod Update 2019;25:504–17.
41. 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.