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REVIEW

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Medical therapy to treat obesity and optimize fertility in women of reproductive age: a narrative review

Janelle Duah[1*] and David B. Seifer[1]

Abstract

Background Overweight and obesity—chronic illnesses in which an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass resulting in adverse metabolic, biomechanical, and psychosocial health consequences—negatively impact female fertility. Adverse conception outcomes are multifactorial, ranging from poor oocyte quality and implantation issues to miscarriages and fetal health issues. However, with the advent of novel pharmacologic agents, significant weight loss can be achieved, improving the chances of healthy pregnancies, and their use should be considered during periconceptual counseling. There are currently 6 FDA-approved medications for weight loss: 2 GLP1-receptor agonists (GLP1-RAs) liraglutide and semaglutide, 1 dual GLP-1 and gastric inhibitory peptide agonist (GLP1-GIP) tirzepatide, Contrave (naltrexone/bupropion), Qsymia (phentermine/Topamax), and Xenical (orlistat). GLP1-RAs reduce food cravings, appetite, and "food noise" and improve insulin sensitivity and satiety, all of which lead to significant weight loss, ranging from 6 to 30% of starting total body weight or greater, depending on the specific agent used. Their efficacy and relative safety should make them first-line options for women seeking to lose weight in the year before trying to conceive. Contrave, the combination of naltrexone and bupropion, seems to work most significantly for weight loss by inhibiting the rewarding and reinforcing effects of food consumption. Clinical trials report ~ 6% loss of starting total body weight with use of Contrave, as well as improvement in metabolic health factors. It may also improve a woman's ability to conceive by mitigating the effects of PCOS and endometriosis and reducing the drive for alcohol and smoking. Qsymia, the combination of phentermine and topiramate, results in more weight loss than Contrave but cannot be used in the acute preconception period, as its topiramate component is a known teratogen. Orlistat is another FDA-approved medication for weight loss; however, it is currently used much less often than other anti-obesity drugs because of its relatively lower efficacy and significant side effects. Bariatric surgery, which can lead to significant weight loss (25–50%), was previously regarded as the most durable method for weight loss, before the advent of GLP1-RAs. Given the inherent risks of surgery, the development of vitamin (i.e. B12, folate, vitamin D) and mineral (i.e. iron, copper, zinc) deficiencies, that may impact the health of the mother and fetus, as well as the recommended delay of 1–2 years prior to attempting pregnancy, bariatric surgery should not be considered first-line therapy for obesity management in women of reproductive age, especially for women who are hoping to conceive quickly or are nearing advanced maternal age.

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Conclusion Clinically significant and meaningful weight loss is achievable with pharmacotherapy to help enhance fertility in women of reproductive age who are overweight or obese. Current research supports the use of weight loss medications for enhancing spontaneous conception and response to ovulation induction. Further research on the effects upon live birth rates are warranted. For meaningful weight loss, GLP1-RAs can be considered for use in the preconception period, as long as they are stopped at least 2 months before conception. Contrave can be considered as well, though resulting in less weight loss. Phentermine and Qsymia are teratogenic but can be used with contraception for weight loss before trying to get pregnant.

Keywords Overweight, Obesity, Infertility, Weight loss pharmacotherapy, GLP1-RAs

Introduction

The intersection of obesity and fertility in women of reproductive age presents a compelling yet complex field of study that has garnered significant attention in recent years. Obesity is not merely a condition of excess body weight; it is a profound systemic ailment that affects hormonal balance, metabolic function, and overall health [1]. Notably, obesity has been recognized by the American Medical Association as a disease, further highlighting its pervasive impact on numerous health parameters, including female reproductive health [2]. Recent studies have underscored the multifaceted nature of the impact of obesity on fertility, encompassing factors such as hormonal imbalances, ovulation irregularities, reduced efficacy of fertility treatments, and adverse pregnancy outcomes [3].

In examining the current medical therapies available to treat obesity and optimize fertility in women, this review draws from an array of recent research studies and expert opinion. The primary sources consulted included peer-reviewed journal articles, clinical guidelines, systematic reviews, and meta-analyses. These sources provide a robust framework for understanding the effects of various pharmacological treatments in tandem with dietary modifications and lifestyle changes on obesity and fertility outcomes. For example, studies indicate that even modest weight loss can significantly improve endocrine parameters, ovulation frequency, and menstrual cycle regularity, thereby increasing fertility prospects [3]. These findings are instrumental in affirming the importance of weight management as a precursor to, and in conjunction with, fertility treatments.

Several key questions drive this review: What are the core findings from recent research studies regarding the relationships among obesity, infertility, and the effectiveness of various medical therapies in optimizing fertility outcomes in women? How do different medical therapies compare in terms of safety, effectiveness, side effects, and suitability for different patient profiles? These questions are paramount in understanding the efficacy and applicability of various interventions in real-world clinical settings. The significance of psychological and emotional factors, such as stress, depression, and body image concerns, is also considered, given their profound impact on self-esteem, treatment adherence and success rates.

Ultimately, this literature review provides a comprehensive examination of medical therapies and interventions aimed at treating obesity and optimizing fertility in women of reproductive age. By critically analyzing recent research studies and expert guidelines, a nuanced understanding of the interconnected health concerns of obesity and infertility can be obtained. The goal is to highlight effective treatment strategies, identify gaps in current knowledge, and propose avenues for future research, thereby contributing to improved clinical outcomes for women afflicted by these complex conditions.

Search strategy

We conducted a thorough review of the literature, focusing on obesity, infertility, fertility, weight loss, and medical therapies for weight loss. The primary databases for our search included PubMed, Medline, and Google Scholar. Our initial search was broad, encompassing the terms obesity, overweight, weight management, fertility, infertility, weight loss pharmacotherapy, and bariatric surgery in women of reproductive age, including literature published in the English language. The selected studies encompassed a range of research designs, from retrospective analyses to prospective observational studies and meta-analyses. Each study was evaluated for its contribution to the understanding of the effects of overweight and obesity on fertility, the impact of weight loss in treating infertility, and the pharmacotherapeutic options for achieving weight loss.

Background

Obesity has been recently recognized as a chronic condition and, as such, has known negative consequences traversing many organ systems. According to the current guidelines from the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), a body mass index (BMI) of ≥25 kg/m2 is classified as overweight, a BMI of ≥30 kg/m2 is classified as obese, and a BMI of ≥40 kg/m2 is classified as severely obese [1]. Obesity, per the Obesity Medicine Association (OMA), is a "chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body

fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences." [2] Thus, we can recognize the profound impact that overweight or obesity can have on a person's health. 1 in 6 adults US are afflicted with this disease, and of the $3.3 trillion spent annually on medical care for chronic conditions, obesity alone is associated with $1.4 trillion or >42% of the total annual expenditure. According to the National Health and Nutrition Examination Survey (NHANES) data, 27.5% of US women over 20 years of age are overweight, with an additional 41.9% of women having obesity, including 11.9% who are severely obese [4].

Obesity and infertility

It is known that being overweight or obese increases one's risk of cardiovascular comorbidities such as hypertension, hyperlipidemia, obstructive sleep apnea, type 2 diabetes and stroke, but there is mounting evidence that these conditions can also result in impaired fertility, especially in women of reproductive age. As discussed by Amiri et al., the negative effects of female obesity on reproduction are due to a variety of ovarian and extra-ovarian factors [3]. In women who are overweight or obese, the time to conception is longer. Women with overweight or obesity also have a lower fertility rate, an increased need for gonadotropins, and higher rates of miscarriage. This difference seems to be due to a plethora of issues, such as menstrual irregularities, poorer oocyte quality, and abnormal endometrium resulting in implantation failure, compared with women of normal weight [3, 5–7]. Obesity also results in conditions that can increase health issues of both the mother and fetus during pregnancy, including the risk of gestational diabetes, hypertensive disease of pregnancy including preeclampsia, fetal growth abnormalities and congenital birth defects [5–8]. The effects of obesity are not limited to preconception or pregnancy. Indeed, beyond the immediate postpartum period, women struggling with obesity continue to have a higher prevalence of lifetime insulin resistance and cardiovascular disease [5–7].

Thus, when trying to become pregnant, women who are overweight or obese may have increased anxiety and/or depression, feeling as if the odds are against them in trying to create a healthy family. This can create a vicious cycle, as the psychological burden of obesity, including stress, depression, and body image dissatisfaction, can further impact self-esteem and reproductive health as well. Stress, a prevalent experience among individuals with obesity due to societal stigma and internalized weight bias and shame, can disrupt the hypothalamic–pituitary–adrenal (HPA) axis, which may adversely affect reproductive hormones and ovulatory function [8]. Additionally, depression and anxiety contribute to unhealthy eating behaviors and a sedentary lifestyle, further exacerbating obesity and its associated reproductive challenges. Poor body image can reduce the likelihood of seeking timely medical intervention and adhering to prescribed treatment regimens, thereby prolonging infertility [9]. Therefore, there is a unique opportunity to clinically address the option of weight loss in the preconceptual counseling period when women are most receptive to advice of how to optimize their chances of having a healthy child.

Sacha et al. evaluated prior weight loss experiences, attitudes toward future interventions, and willingness to delay fertility treatment for weight loss interventions in 148 women≤45 years old with infertility over the prior three months or who had suffered from recurrent pregnancy loss. Most of these women who were overweight or obese were attempting weight loss at the time of survey completion (69%). While 47% of these women reported interest in a supervised medical weight loss program, interestingly, 92% of overweight women and 84% of women with obesity were not willing to delay fertility treatment for more than 3 months to attempt weight loss [10]. Thus, women suffering from overweight and obesity do recognize the biopsychosocial effects of their weight on their fertility prospects and are looking for expeditious ways to lose weight to start the process of conception as soon as possible, especially when confronted with the effects of advancing age on fertility as well.

However, does weight loss actually improve fertility outcomes? The data regarding improvement in live births is currently controversial and likely incomplete. Large RCTs studying the effect of weight loss on live birth outcomes have generally included interventions based on diet, exercise, and the anti-obesity medication Orlistat, which is very rarely used currently due to its inefficacy. Smaller RCTs and observational studies have reported conflicting evidence for the benefit of lifestyle interventions on fertility outcomes, with most studies either being underpowered to detect a difference or demonstrating no effect on LBR. The highest weight loss achieved in these studies was ~22 lbs; however, recently introduced anti-obesity medications, such as GLP-1 receptor agonists, now enable more significant weight loss within 3–6 months. This faster weight reduction offers a new opportunity for short-term weight loss programs that can be implemented before starting fertility treatments. It may stand to reason that statistically significant improvements in live births haven't been seen with weight loss because the weight loss achieved and studied in these trials wasn't significant, focusing on medications and interventions that are outdated. While still mainly prescribed before pregnancy, these newer weight-loss medications are being incorporated into infertility treatment protocols [11]. If future studies confirm their safety in early

pregnancy, these drugs could play a key role in infertility treatments for many men and women facing obesity-related fertility challenges.

Moreover, although weight loss interventions in fertility treatment trials have generally not shown a significant improvement in live birth rates (LBR), some studies have indicated a reduction in pregnancy-related complications and increase in rates of spontaneous conception and response to ovulation induction. After losing weight, notable increases in the rates of spontaneous conception, as well as a significant improvement in the response to ovulation induction and in vitro fertilization have been observed [12–15]. In addition, the Danish National Birth Cohort study of 2,374 women revealed that those who were overweight or obese and had lost weight had, on average, 5.5 fewer days to pregnancy for each 1 kg decrement in weight [3, 16]. How much weight loss is necessary to reap these benefits? Five randomized controlled trials, each with sample sizes of >100 women, revealed higher rates of spontaneous conception and improved ovulation in the setting of ovulation induction in women with overweight or obesity who had lost ~ 7% of their starting body weight, translating to 9–20 lbs lost [17]. Thus, while we await large RCTs studying the impact of weight loss from newer medications on live birth rates, powered to detect such difference, the implementation of weight loss interventions for those seeking to enhance their risks of unassisted conception as well as to enhance ovulation rates in response to ovulation induction can still be recommended. In fact, weigh loss before conception is deemed so important that both the American College of Obstetricians and Gynecologists and British Fertility Society recommend that women should aim for a normal BMI (i.e. <25 kg/m2) before starting any form of fertility treatment. They also recommend that treatment should be deferred until the BMI is less than 35 kg/m2, although in those who are younger (e.g., less than 37 years old with normal day 3 serum FSH), a weight reduction to a BMI of less than 30 kg/m2 is preferable [18, 19].

Pharmacotherapies for weight management and their effects on fertility

With many women of reproductive age suffering from overweight or obesity, which negatively impacts their fertility outcomes, weight loss is key in helping to improve their chances of becoming pregnant and having healthy births. However, with so many new and effective FDA-approved medications for weight loss, which ones might be best? Clinicians and patients need to consider the amount of weight loss to be targeted as well as the anticipated fertility treatment required and the timeline of when a patient wants to start such treatment when deciding upon the best individualized weight loss strategy. Clinicians and patients are encouraged to act quickly to avoid unnecessary delays [12, 16]. The newest class of drugs directed to weight loss are the GLP1-receptor agonists (GLP1-RAs) and likely represent the future cornerstone of medical therapy for weight loss.

GLP1-RAs

Glucagon-like peptide (GLP1) is a naturally occurring hormone produced in the body by three main organs, but mostly from the L-cells of the small intestine [20]. When nutrients, especially carbohydrates, are ingested, L-cells release GLP-1 into the intestinal capillaries within minutes. GLP-1 is also secreted in smaller quantities by the pancreas as well as the brain and other parts of the central nervous system. This peptide binds its receptors, which are located in the brain, pancreas, heart, and GI tract, to cause a few different but synergistic effects which favor weight loss. When it binds to receptors in the pancreas, it causes the pancreas to release insulin. This insulin can then work more effectively, as GLP1-RAs also increase the number of glucose transporters on the membranes of receiving cells, allowing them to more efficiently respond to insulin and take in more sugar, increasing insulin sensitivity [21]. Activating receptors in the GI tract leads to slowing stomach emptying and increased satiety. Binding receptors in the brain causes increased feelings of fullness, thus leading to reduced food intake [22]. However, these peptides have very short half-lives in the human body. GLP1-receptor agonists (GLP1-RAs) are synthetic molecules that mimic the structure of these peptides and bind their receptors for much longer, potentiating these effects. Research has shown that these molecules have even more positive effects on our brains, reducing cravings for sweet or heavy foods, reducing "food noise" or obsessive, intrusive thoughts about food and reducing cravings for alcohol, cigarettes, as well as other illicit substances [21].

There are three GLP1-RAs that are FDA-approved for weight loss: liraglutide (Saxenda), semaglutide (Wegovy), and tirzepatide (Zepbound). Zepbound is actually a combination of GLP1-RA and gastric inhibitory peptide (GIP) agonist, creating better efficacy than its previously mentioned predecessors. These three different GLP1-RAs differ in dosing, administration frequency, and potency. Saxenda is a daily injection. Dosing starts at 0.6 mg injected daily subcutaneously and can be increased to a maximum of 3.0 mg. When taken as prescribed, patients can lose about 6% of their starting total body weight in 56 weeks [22]. Wegovy, on the other hand, is a weekly injection that can lead to an average of 14.9–17.9% loss of total body weight at 68 weeks, as seen in the rigorous "Semaglutide Treatment Effect in People with Obesity" (STEP) 1–8 and subsequent trials [23–27]. Doses range from 0.25 mg injected subcutaneously to 2.4 mg. Zepbound, the newest agent, is also a weekly injection but

can lead to average of 22.9% loss of starting total body weight in approximately one year, as evidenced in the SURMOUNT 1–4 and successive trials [28, 29]. This profound efficacy occurs because of the addition of the GIP molecule, which has the same effects of GLP-1s plus the additional effect of increasing adipose/fat metabolism, with chronic stimulation of its receptors, leading to their desensitization. This synergism between GLP1 and chronic GIP stimulation works so well that anecdotally, some patients have reported more than 40% total body weight loss.

Interestingly, we recently have learned that GLP1-receptors are also located in the reproductive tract of most mammals [30]. GLP-1 may have anti-inflammatory and antifibrotic effects on the gonads and the endometrium, which are affected by obesity, diabetes, and polycystic ovary syndrome (PCOS). It also seems that GLP-1 RAs can reverse polycystic ovary morphology and decrease serum concentrations of androgens as well as decrease their bioavailability in women with PCOS [30]. Elkind-Hirsch et al. illustrated enhanced menstrual regularity and improved rates of conception in women suffering from overweight or obesity with PCOS treated with GLP-1 RAs in the preconception period [31]. Another small randomized open-label pilot study of 28 women with obesity and PCOS reported that 12 weeks of preconception treatment with low-dose liraglutide (1.2 mg QD) in combination with metformin (1000 mg BID) was more beneficial than metformin alone in increasing IVF pregnancy rates as well as spontaneous pregnancies in patients who had been previously resistant to lifestyle modification and first-line reproductive treatment (clomiphene citrate, letrozole, and/or ovarian drilling) [14, 32]. The pregnancy rate per embryo transfer was significantly greater in the liraglutide plus metformin group (COMBI) than in the metformin alone group (85.7% versus 28.6%, respectively, $P=0.03$). The cumulative pregnancy rate at 12 months was 69% in the COMBI group and 36% in the MET group. Thus, improvement in fertility outcomes with the use of GLP1-RAs may be due to more than just mere weight reduction and may include direct positive impact on the female reproductive system itself. Notably, these anti-inflammatory effects may occur not only in the reproductive tract but also in the cardiovascular and renal systems. Wegovy was recently approved by the FDA for the reduction of cardiovascular events in patients with coronary artery disease, prior heart attack, and/or prior stroke [33, 34]. Emerging evidence shows a reduction in renal events in patients with chronic kidney disease treated with semaglutide as well [35].

With such promising results, why aren't more people prescribed these medications? First, there are contraindications to their usage, as there are with any medication. A personal or family history of medullary thyroid cancer or MEN2 syndrome prohibits use, as does a prior history of pancreatitis or biliary disease [34]. Second, some patients may experience quality of life-affecting side effects, which are dose dependent, tend to get better with time, and are generally limited to the GI tract. These include nausea (16–44%), diarrhea (9–30%), constipation (3–24%), and abdominal pain (6–20%). Other less frequent side effects include insomnia, hypoglycemia, headache, and fatigue [36]. Additionally, with their ever-growing popularity, these medications may go out of stock or be on back order, leading to problems with consistent access due to supply chain issues. One practical deterrent to being able to take this medication may be that a person's insurance may not cover the cost. The out-of-pocket costs for a 1-month supply can reach ~$1425 [37] and may not be financially sustainable for many patients, especially if they are already embarking on costly fertility treatments. However, some insurances may allow if a provider submits appeals through prior authorizations, letters of medical necessity, and/or peer-to-peer appeals.

There are also concerns about the safety of GLP1-RAs to the fetus in the first trimester, during pregnancy, in the postpartum period, and during breastfeeding/lactation. Since 2015, pharmacotherapies have been classified by the FDA via the Pregnancy and Lactation Labeling Rules [38]. The PLLR requires manufacturers to replace pregnancy letter categories with narrative summaries of risks associated with using a drug during pregnancy and lactation, and in females and males of reproductive potential. As of May 31, 2016, the Novo Nordisk safety database recorded 271 cases of liraglutide exposure during pregnancy. Outcomes included 45.9% live births without congenital abnormalities, 1.8% live births with congenital abnormalities, 34.2% fetal losses, and 18% pregnancy terminations. These results were consistent with outcomes observed in pregnancies where mothers received a placebo. While clinical trials reported cases of fetal loss in Saxenda-treated patients, similar occurrences in the placebo group make it impossible to establish a drug-associated risk. The current labeling for other liraglutide-containing products states that there is no data in pregnant women available to determine a risk for major birth defects or miscarriage [39].

Animal reproduction studies suggest that semaglutide exposure during pregnancy may pose risks to the fetus. The compound was administered to rats, rabbits, and cynomolgus monkeys during organogenesis at doses at or below the maximum recommended human dose (MRHD). These studies observed embryofetal mortality, structural abnormalities, and growth alterations. During an April 29, 2021, labeling meeting, the DDLO Nonclinical Team indicated that these findings in animals were likely linked to weight loss experienced by

the test subjects, raising uncertainty about their clinical relevance. Human data on semaglutide exposure during pregnancy remain limited, based on both clinical studies and the applicant's pharmacovigilance database. Per Wegovy and Zepbound labeling, data is currently insufficient to determine if there is a drug associated risk of maternal or fetal adverse reactions. There are efforts to collect further data via the Pregnancy Registry, but manufacturers hypothesize that it will take years before to get enough data to provide a concrete assessment of the safety of their use in pregnancy [40, 41]. For now, the only way to truly confer no risk is to limit use to only the preconception period. The manufacturers of semaglutide and liraglutide recommend a washout period based on their respective half-lives. Semaglutide and tirzepatide have a half-life of around 1 week. This means it takes 5–7 weeks for them to be eliminated from the system after the last dose. Complete washout requires 8–10 weeks [42]. Thus, the manufacturers of semaglutide and tirzepatide currently advises stopping treatment 2 months before conception [34]. Liraglutide has a half-life of ~ 13 h; it has been recommended that liraglutide be stopped 10–14 days before conception [22]. However, these recommendations may be overly conservative and essentially out of an abundance of caution. The safety profile of GLP1-RA use during the first trimester of pregnancy is starting to be investigated in recent studies, which have not yet revealed an elevated risk of major birth defects [17, 44]. In a prospective multicenter observational study, Dao et al. examined 168 pregnant women exposed to a GLP1-RA during the first trimester of pregnancy, alongside two reference groups (pregnant women diagnosed with diabetes mellitus and pregnant women with overweight or obesity). No specific pattern of birth defects was identified. The rates of major birth defects, excluding genetic or chromosomal anomalies and those associated with intrauterine infections, were similar in both the GLP1-RA exposed group and the reference group with diabetes (2.6% and 2.3%, respectively). The rate of preterm births was almost doubled in the group with diabetes (15.1%) and in the group with overweight or obesity (14.5%) compared with the GLP1-RA group (8.0%). Interestingly, however, there was a greater incidence of elective terminations for personal reasons in the GLP1-RA group than in both reference groups. The authors surmised that this may be indicative of both a greater number of unplanned pregnancies and anxiety related to the unknown risks of GLP1-RA medication for the fetus, indicating the need for more research on this topic [45].

Moreover, 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 [23–27]. 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 [17]. Finally, a 2023 review of a noninsulin antidiabetic medication in the Journal of the American Medical Association revealed that 461 individuals filled GLP-1 RA prescriptions in their first trimester of pregnancy. There was no statistically significantly increased risk of malformations [43]. Thus, the data are reassuring that first trimester exposure to GLP1-RA therapy, specifically semaglutide, does not seem to have any adverse effects on the fetus.

Women who stop GLP1-RA therapy during pregnancy may be eager to restart after giving birth. However, there are no conclusive data concerning whether these molecules can enter breast milk and affect the child. Moreover, the reduction in appetite and significant weight loss that can occur with use can cause a reduction in milk supply, which can adversely affect the baby's nutrition and growth. It thus stands to reason that women planning on breastfeeding should not (re)-initiate GLP1-RA use until after the baby has weaned.

Of note, there is a chance of experiencing weight regain when stopping GLP1-RAs, as with all anti-obesity medications. Per STEP 1 extended trial data, people regained ~ 2/3 of the weight they had lost within a year after stopping [46]. To reduce weight regain as much as possible, most obesity specialists advocate tapering off and strict adherence to optimal lifestyle habits, including following a high protein and fiber diet and performing 250 min of moderate intensity exercise per week.

Contrave

Another FDA-approved option for weight loss is the oral medication Contrave. This medication, which combines the active ingredients naltrexone and bupropion, has garnered attention for its dual-action mechanism targeting appetite regulation and metabolic pathways. Naltrexone, an opioid antagonist, is commonly used for alcohol use disorder and opioid use disorder. It also plays a pivotal role in the neurochemical pathways associated with appetite regulation and food intake. It functions by blocking mu-opioid receptors in the brain, thereby inhibiting the rewarding and reinforcing effects of food consumption. Additionally, naltrexone's action in the hypothalamus contributes to enhanced control over hunger signals, modulating the physiological drive to consume food [47, 48]. This results in fewer cravings and a reduction in compulsive eating behaviors, which can often be associated with obesity. Moreover, there is emerging, though limited, data concerning the use of low-dose naltrexone (LDN) for medical conditions such as PCOS, endometriosis, and insulin resistance. This might make it an appropriate choice for women of reproductive age struggling

with overweight or obesity and infertility caused by these conditions.

Bupropion, an aminoketone antidepressant, is commonly prescribed for tobacco use disorder and depression, and as an adjunct for the management of ADD/ADHD. It inhibits the reuptake of dopamine and norepinephrine, which are neurotransmitters integral to mood regulation and the mesolimbic reward system [46–48]. By enhancing neural dopaminergic and noradrenergic activity, bupropion not only improves mood but also increases energy levels and reduces appetite. This makes bupropion particularly effective in addressing obesity-related lifestyle behaviors such as overeating and sedentariness, and promotes enhanced overall physical activity.

The combination of naltrexone and bupropion in Contrave leverages the synergistic effects of both components, resulting in a compounded impact on weight loss beyond their individual pharmacological actions. Naltrexone's ability to inhibit mu-opioid receptors and block reward pathways complements the enhancement of neural dopaminergic and noradrenergic activity by bupropion, thereby amplifying overall appetite suppression and craving reduction. Clinical studies have demonstrated that this synergism leads to more significant weight loss and improved metabolic health markers than the effects of each drug used independently [47, 48]. These findings substantiate the rationale for using a combination medication such as Contrave, which targets multiple pathways involved in obesity management, thereby offering a more comprehensive and effective treatment option for patients struggling with weight-related issues, especially if they are rooted in emotional eating, stress eating, binge eating, comfort eating, boredom eating, nighttime eating syndromes or physical inactivity.

Although Contrave is a very promising drug, there must be consideration for the patient population for whom this medication would not be safe. Contrave is not recommended for individuals with uncontrolled hypertension, seizure disorders, bulimia, anorexia nervosa, or those undergoing abrupt discontinuation of alcohol, benzodiazepines, or antiepileptic drugs. It is also contraindicated in patients using chronic opioids, other bupropion-containing products, or MAOIs within the last 14 days [49].

The dosage and administration of Contrave follow a structured escalation schedule to optimize its tolerability and efficacy. Initially, patients are prescribed one tablet (8 mg naltrexone/90 mg bupropion) in the morning during the first week. The dosage is then increased to one tablet in the morning and one in the evening during the second week, two tablets in the morning and one in the evening during the third week, and finally two tablets twice daily starting from the fourth week onward [47, 49]. This gradual increase helps mitigate the side effects associated with the medication. Common adverse reactions include nausea, constipation, headache, vomiting, dizziness, and dry mouth [49], which generally occur during the initial stages of treatment and tend to subside over time as patients adjust to the medication. However, more severe side effects such as elevated blood pressure, heart rate changes, hepatotoxicity, and the risk of seizures, emphasize the need for patient-specific risk assessment and regular monitoring [49].

The clinical efficacy of Contrave is well-documented in a series of randomized, double-blind, placebo-controlled trials, called the COR trials [50–52]. Subjects treated with Contrave exhibited a mean percent body weight loss of -5.4% compared with −1.3% in placebo-treated subjects over a period of 56 weeks. Moreover, the impact of Contrave was found to extend beyond mere weight reduction. Participants in clinical studies also displayed improvements in obesity-associated comorbidities, such as lowered triglycerides, enhanced glycemic control in type 2 diabetes patients, and improved cholesterol ratios. These results suggest that Contrave not only aids in weight loss but also contributes to an overall healthier metabolic profile. Additionally, owing to the effects of the individual components, patients may also experience improved mood, better focus and concentration, and less desire to drink alcohol and smoke cigarettes—all of which may improve fertility. However, we do not observe any direct effects of Contrave, whether positive or negative, on female fertility.

The question of whether long-term use of Contrave can adversely affect female fertility remains largely unexplored in human studies. However, animal studies indicate potential concerns. For example, high doses of the combination of naltrexone and bupropion have been associated with increased fetal loss and some developmental anomalies in animal models [49]. These findings necessitate a cautious approach in interpreting the potential effects on human fertility. Given known risks in pregnancy, women who are planning to become pregnant are advised to discontinue the medication and allow for a washout period as recommended by their healthcare providers, usually at least 2 weeks, due to the half-life of its metabolites being ~ 37 h [54]. It is noted that if a woman becomes pregnant while on Contrave, the medication should be discontinued immediately [49].

If a woman is considering starting or restarting Contrave in the postpartum period, then careful consideration about plans to breastfeed must be weighed. The excretion of naltrexone and bupropion into breast milk introduces potential risks to nursing infants, despite limited data on exact concentrations and effects. Both components are known to be excreted in breast milk, necessitating a conservative approach when prescribing Contrave to breastfeeding women [49]. Thus, given

the scarcity of rigorous studies detailing the safe exposure limits for nursing infants, the recommendation is to avoid using Contrave while breastfeeding.

Interestingly, no research exists on the potential weight regain that occurs when stopping Contrave. However, anecdotally, people who have stopped this medication do experience weight regain, with most people returning to their starting weight within 2 years, some as soon as within 3 months [55, 56]. Thus, it may be prudent to start working on conception earnestly and urgently after the washout period, before they regain all their weight that was lost.

Qsymia

Qysmia has become a notable option in the pharmacological management of obesity, combining phentermine, a sympathomimetic amine anorectic, and topiramate, an anticonvulsant, to promote weight loss through a unique dual mechanism. This combination targets the central nervous system and affects multiple neurotransmitter pathways, ultimately suppressing appetite and reducing food cravings. Phentermine primarily increases the release of norepinephrine, increasing satiety and energy expenditure, whereas topiramate modulates gamma-aminobutyric acid (GABA) receptors and AMPA receptors to mitigate cravings and increase feelings of fullness [57–60]. A pivotal 56-week double-blind, placebo-controlled study, called CONQUER, involving more than 2,400 participants suffering from overweight or obesity, confirmed significant weight loss in the Qsymia-treated groups [61]. The patients who received higher doses of Qsymia (15 mg/92 mg) experienced an average weight loss of 10.9% from their baseline body weight, compared with 1.6% in the placebo group. This evidential support has positioned Qsymia as effective for long-term weight management, provided that it is complemented by a reduced-calorie diet and increased physical activity. Despite its efficacy, Qsymia is not free from contraindications or risks. This medication is not to be used in patients with hyperthyroidism or glaucoma. Common adverse reactions include paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. More severe risks include cognitive impairment, mood disorders, metabolic acidosis, tachycardia, and teratogenicity [62]. This risk of teratogenicity makes this a nonoptimal option for weight management in women with overweight or obesity who are hoping to conceive. This risk is mostly due to the topiramate component. Topiramate has been shown to cause fetal malformation, including cleft lip and/or cleft palate, and reduced fetal weights at dosages that are regularly used clinically [60, 62]. Moreover, the modulation of neurotransmitter pathways by topiramate and its impact on GABA receptors could interfere with normal ovulatory cycles, egg quality, and implantation, as observed in rat models, thus reducing fertility outcomes [61]. Additionally, the presence of phentermine and topiramate in human milk raises concerns about their potential effects on breastfeeding infants, further complicating decisions around the use of Qsymia before conception [60]. Clinical guidelines and recommendations highlight the necessity of pregnancy testing before initiating Qsymia and continuing monthly tests throughout treatment to prevent unintended exposure during early pregnancy. Most providers also request their female patients to sign contracts confirming the use of contraceptives during the use of Qsymia. Thus, measures are actively taken to ensure that a person does not become pregnant while taking this medication.

Notably, phentermine itself does not seem to confer as much risk to fertility and the fetus but is not approved by the FDA for long-term weight management strategies longer than 12 weeks. Chang et al. reported the efficacy of a short-term phentermine-based intervention, albeit in a small study. Following phentermine use, 33 of the 55 patients (60%) achieved pregnancy by the end of the study period. The total live birth rate was 49%. The median time to conception after cessation of phentermine was 187 days Nearly half (16 of 33 women) conceived within 6 months of stopping phentermine, and 23 women (70%) conceived within 12 months of stopping phentermine. The remaining 10 women conceived after 12 months of phentermine discontinuation. Most patients only lost ~ 5% of their starting weight [63]. This may mean that phentermine alone could be useful as an option in patients who are overweight and do not have much weight to lose or who are looking for a fast, short-term intervention.

Orlistat

Orlistat is another option for weight management, although it is currently rarely used given its relatively lower efficacy than the agents previously mentioned. It inhibits both gastric and pancreatic lipases, preventing the absorption of ~ 30% of all ingested fat. This results in the excretion of these unabsorbed fats, essentially reducing caloric intake. It is available over the counter under the name Alli and as a prescription, branded as Xenical. In the XENDOS (XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial, the largest randomized controlled trial (RCT) that evaluated the effect of orlistat in 3,305 patients, orlistat was found to cause a total body weight loss of 2.4% after 4 years, which, admittedly, may be of questionable clinical significance [64]. However, it was found to have significant effects on overall metabolic health, reducing the risk of developing type 2 diabetes, and improving blood pressure, insulin sensitivity, and lipid profiles. Importantly, the use of orlistat has high rates of attrition, owing to significant side effects. These

include oily stools, flatulence, and frequent bowel movements. Additionally, deficiencies in vitamins A, D, E, and K are common and necessitate the use of daily supplementation of these nutrients while on Orlistat. As such, this medication is contraindicated for use in people who already have malabsorptive syndromes such as ulcerative colitis or Crohn's disease. Additionally, Orlistat is not to be used in patients with cholestasis.

Orlistat does not seem to have a positive effect on fertility. Currently, only 6 studies investigating the use of Orlistat in the preconception period are available. Wang et al. found that there were no differences between the Orlistat and placebo groups regarding live births, conception, clinical pregnancy, or pregnancy loss. The only statistically significant difference ascertained was in weight loss [65]. Similarly, the FIT-PLESE study concluded that in women experiencing obesity and inexplicable infertility, an intensive preconception lifestyle intervention including orlistat, though resulting in an average weight loss of 7% of starting total body weight, did not improve the rate of live birth, pregnancy rates, or time to pregnancy compared with an activity-based intervention that did not itself result in any weight loss. Thus, even with weight loss, orlistat had no positive effects on fertility outcomes [66]. Indeed, there was a nonsignificant trend toward higher rates of miscarriage in the orlistat group. It was noted to occur after implantation and attributed by the authors to decreased long-chain polyunsaturated fatty acid absorption. The development of vitamin D deficiency with Orlistat may also play a role, as studies have shown that women with normal vitamin D levels are more likely to conceive, including those with IVF and experience improved implantation and a decreased risk of pregnancy-related complications for both mothers and fetuses [67].

Special consideration - metformin

Of note, metformin is not currently FDA-approved for weight loss but has long been used for weight management in special populations, including in women with PCOS and people with antipsychotic-associated weight gain. Further research is needed to substantiate its use as a primary intervention for weight loss.

Impact of medical therapy compared to bariatric surgery

Bariatric surgery is widely recognized as an effective, long-term solution for sustained weight loss, especially for individuals with higher BMIs who are unlikely to achieve the required weight loss through pharmacotherapy alone to attain significant health benefits. The most commonly performed bariatric procedure, the gastric sleeve, typically results in ~60–70% of their excess weight [68], which can be on par with semaglutide and tirzepatide therapy. According to the American Society for Metabolic and Bariatric Surgery, bariatric surgery should be considered for individuals with a BMI > 35, regardless of the presence of comorbidities, or > 30 with any obesity-related conditions [69, 70]. There are a few reported case–control and cohort studies that show improved fertility in women who lose weight after bariatric surgery compared with women with severe obesity, owing in part to reduced absorption and thus efficacy of oral contraceptives, and a reduced risk of obstetrical complications, including gestational diabetes, macrosomia and hypertensive disorders of pregnancy [71, 72], . However, it is unclear whether this is solely due to significant weight loss, which can now be accomplished via nonsurgical means with GLP1-RAs or through possible direct effects on the female reproductive tract itself.

Moreover, other studies have shown negative effects on conception and other fertility outcomes. The incidence of intrauterine growth restriction (IUGR) appears to be increased in women who have undergone bariatric surgery in the preconception period. Operative complications are not uncommon with bariatric surgery, and several cases have pointed to an increased risk for intestinal hernias and nutritional deficiencies in subsequent pregnancies. Deficiencies in iron, vitamin A, vitamin B12, vitamin K, folate and calcium can result in both maternal complications, such as severe anemia, and fetal complications, such as congenital abnormalities, IUGR and failure to thrive [73].

Most recommendations advise waiting 1–2 years after bariatric surgery to attempt conception to allow for maximum preconception weight loss and to identify and treat concomitant nutritional deficiencies [72, 73]. Given these risks and wait time, this may not be an option for women of advanced age or women with low age-specific AMH consistent with diminished ovarian reserve who wish to conceive in a short period of time.

As of now, there is just one study available comparing the effectiveness and cost efficiency of bariatric surgery and GLP1-RA medical therapy [74]. Haseeb et al. evaluated the cost-effectiveness viability of semaglutide compared with endoscopic sleeve gastroplasty (ESG) over 5 years for individuals with class II obesity. Of note, ESG is a newer minimally invasive procedure whereby a suturing device is placed down the patient's throat and used to suture the stomach to make it smaller. This is a different surgery than the more commonly known traditional sleeve gastrectomy. Their study suggests that endoscopic sleeve gastroplasty is cost saving compared with semaglutide in the treatment of class II obesity. On price threshold analyses, a 3-fold decrease in the price of semaglutide would be needed to achieve non-dominance. However, no such data exists about other bariatric surgeries including sleeve gastrectomy and Roux-en-Y gastric bypass,

about tirzepatide, over longer than a 5-year period, or in other patient populations outside of those with class 2 obesity i.e. overweight, class 1 or class 3 obesity.

Medications in the pipeline

As the global struggle with obesity intensifies, new medications are emerging that offer fresh hope for those looking to manage their weight. These groundbreaking treatments, currently in the pipeline, could revolutionize the way we approach weight loss, providing more effective, sustainable options for individuals who have struggled with traditional methods. Possible upcoming treatments include oral GLP1-RAs (orflorglipron, danuglipron) and various combination medications. Some of these combinations include dual GLP-1 and amylin receptor agonists (amycretin, CamiSegra), dual GLP-1 and glucagon receptor agonists (mazdutide, survodutide), and triple action GLP-1, GIP, and glucagon receptor agonists (retatrutide). Even cannabinoid-receptor inverse agonists medications like monalubant are on the horizon [75].

Conclusions

In summary, overweight and obesity—chronic illnesses in which an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences—negatively impact female fertility. Adverse conception outcomes are multifactorial, ranging from poor oocyte quality and implantation problems to miscarriages and fetal health issues. However, with the advent of new and novel pharmacologic agents (see Table 1 for a summary), weight loss can help improve the chances of healthy pregnancies and may be most considered during periconceptual counseling. GLP1-RAs mimic naturally occurring peptides to cause satiety, reduce food cravings, appetite, and "food noise" that leads to significant weight loss, ranging from 6 to 40% or even greater, depending on the specific agent used. There is also some evidence that GLP1-RAs improve the function of the female reproductive system in ways independent of weight loss and thus may be the first-line option for weight loss and improved fertility outcomes in women of reproductive age with obesity. Emerging research has not revealed any untoward effects on the fetus when there has been inadvertent exposure in the first trimester, but the manufacturers out of an abundance of caution recommend stopping usage 2 months prior to trying to conceive. These recommendations are data dependent and could change in the future. Concerns to keep in mind with GLP1-RAs use include contraindications, side effects, access, availability, insurance coverage, cost, and the desire to breastfeed. Contrave, consisting of naltrexone and bupropion, has a unique dual-action mechanism that not only regulates appetite but also addresses neurochemical pathways associated with reward-driven eating behaviors. This combination of pharmacologic actions makes Contrave a potent adjunct to diet and exercise in the management of obesity. Clinical trials reported ~ 5–6% loss of starting total body weight as well as improvement in metabolic health factors. It may improve a woman's ability to conceive by helping PCOS and endometriosis and reducing the drive for alcohol and smoking. However, there are no data supporting Contrave's ability to directly improve fertility, and it may cause harm to the growing fetus and nursing infant. Contrave should be stopped at least 2 weeks before trying to conceive or as soon as a person becomes pregnant and should not be used while breastfeeding. Qsymia results in more weight loss than Contrave but cannot be used in the acute preconception period, as its topiramate component is a known teratogen. Its teratogenicity is such that women on this medication must take monthly pregnancy tests and attest to using contraceptives while on it. Its other component, phentermine, may be used without concern for ill effects but only for short periods of time, as it is currently only FDA approved for up to 12 weeks of continuous use. Indeed, studies have shown that phentermine on its own improves fertility outcomes, and thus may be a good option for women suffering from overweight or lower classes of obesity who desire modest weight loss quickly before conception. Orlistat is another FDA-approved medication for weight loss; however, it is currently used much less often than other anti-obesity drugs because of its relatively lower efficacy and significant side effects. Moreover, orlistat itself has not been shown to have any positive effects on fertility and may lead to higher miscarriage rates, possibly due to issues with fatty acid synthesis and vitamin D deficiency. Metformin, which is widely used to increase fertility in women of reproductive age with PCOS, is not approved by the FDA for weight loss, although it may result in weight loss in certain populations. Bariatric surgery, which can lead to significant weight loss, was previously regarded as the most durable method for weight loss, before the advent of GLP1-RAs. Given the risks inherent in surgery and the development of vitamin deficiencies that can impact the health of both the mother and fetus as well as the recommended delay of 1–2 years prior to attempting pregnancy, bariatric surgery should not be considered first-line for obesity management in women of reproductive age looking to conceive in a timely fashion.

Table 1 Comparison of FDA-approved agents for weight loss

Agent	GLP1-RA	Contrave (naltrexone and bupropion)	Qsymia (phentermine and topiramate)	Orlistat
Mechanism of action	Activates GLP1 receptors throughout the body for a wide variety of effects including enhanced insulin sensitivity, increased satiety, less cravings, and anti-inflammatory effects in the reproductive tract itself [20–22]	Naltrexone: blocks mu-opioid receptors in the brain, thereby inhibiting the rewarding and reinforcing effects of food consumption Bupropion: enhances neural dopaminergic and noradrenergic activity, thus increasing energy levels and reducing appetite [48, 49]	Phentermine: primarily increases the release of norepinephrine, increasing satiety and energy expenditure, Topiramate: modulates gamma-aminobutyric acid (GABA) receptors and AMPA receptors to mitigate cravings and increase feelings of fullness [57, 58]	Lipase inhibitor, preventing absorption of up to 30% of all ingested fat, thus reducing caloric intake [64]
Method of administration	SQ Injection [36]	Oral [50]	Oral [57, 61]	Oral [64]
Dosing frequency	Saxenda (liraglutide): daily [22] Wegovy (semaglutide): weekly [23] Zepbound (tirzepatide): weekly [28, 29]	BID [50]	QD [57]	TID [64]
Total % loss of body weight	Saxenda (liraglutide): 6% [22] Wegovy (semaglutide): 14.9–17.9% [23–27] Zepbound (tirzepatide): 22.9% [28, 29]	5.4% [51]	10.9% [57]	2.4% [64]
Contraindications	Personal or family history of medullary thyroid cancer or MEN2 syndrome, prior history of pancreatitis or biliary disease [34]	Uncontrolled hypertension, seizure disorders, bulimia, anorexia nervosa, use of other bupropion-containing meds, chronic opioids, and/or MAOIs in the past 14 days, and those undergoing abrupt discontinuation of alcohol, benzodiazepines, or antiepileptic drugs [50]	Glaucoma, hyperthyroidism, use of MAOIs in the past 14 days, CAD [61]	Malabsorptive syndromes, cholestasis [64]
Side effects	Nausea, vomiting, abdominal pain, acid reflux, constipation, diarrhea [36]	Nausea, constipation, headache, vomiting, dizziness, dry mouth, elevated blood pressure, elevated heart rate, hepatotoxicity, risk of seizures [50]	Cognitive dysfunction, paresthesias, dizziness, dysgeusia, constipation, kidney stones [61]	Abdominal cramping, oily fecal incontinence, flatus, deficiencies in fat soluble vitamins, risk of oxalate kidney stones [64]
Independent effect on fertility	Liraglutide: yes, positive [14, 32] Semaglutide: yes, positive [30] Tirzepatide: unknown	No [48]	No, and teratogenic [62]	No [65]
How long to stop before trying to conceive	Liraglutide: 2 weeks [22] Semaglutide: 2 months [34] Tirzepatide: 2 monhs [41]	2 weeks [52]	ASAP, must be using contraception while taking [61]	N/A, rarely used now [65]

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