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Reproduction and Anti-Obesity Medications: A Review of Current Evidence

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ABSTRACT

Obesity, typified by the disproportionate accumulation of body fat, constitutes a burgeoning global health dilemma with far-reaching impacts on numerous facets of human well-being, prominently inclusive of reproductive health. The pervasive effects of this worldwide health predicament are both direct and indirect, having a compelling influence on fertility, thus underlining the exigency for efficacious therapeutic interventions. FDA-approved anti-obesity pharmaceuticals, comprising metformin, orlistat, phentermine, and glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide and semaglutide, have been substantiated to facilitate weight loss and enhance metabolic indices. However, despite their promising roles in mitigating obesity, the extent of our understanding of these drugs' implications for reproductive health remains inadequate.

This thorough review endeavors to aggregate and scrutinize the present corpus of evidence relating to the influence of these anti-obesity drugs on fertility. By exploring the prospective direct and indirect impacts of these pharmaceuticals on reproductive health, we aspire to illuminate their multifunctional roles extending beyond the sphere of weight regulation. In the female population, obesity has been correlated with menstrual abnormalities, infertility, and complications during gestation, frequently concurrent with an increased incidence of Polycystic Ovary Syndrome (PCOS). In the male counterpart, obesity has been associated with compromised semen quality and erectile function, often compounded by Metabolic Syndrome (MetS) and hormonal disequilibrium.

This exhaustive analysis seeks to equip physicians with a framework for refining their therapeutic approaches, appreciating the intricate interplay between obesity treatment and reproductive health. We aim to afford a broader and more nuanced comprehension of the complex interrelations between obesity, anti-obesity medications, and reproductive well-being. The intention is to empower healthcare practitioners with the insights necessary to deliver bespoke care strategies to those grappling with obesity and attendant fertility complications. Ultimately, this initiative augments our evolving understanding of the complex mechanisms operating at the juncture of obesity and fertility, thereby paving the way for future investigations in this critical field of study.

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MANUSCRIPT

1. Introduction

Overweight and obesity, characterized by excessive body fat accumulation, pose significant health risks. According to the World Obesity Federation in 2019, 13% of the global adult population were obese, 39% were overweight, and five million deaths were linked to obesity[1]. These conditions are the leading preventable causes of premature death worldwide and enhance the likelihood of developing chronic diseases such as hypertension, cardiovascular disease, dyslipidemia, and diabetes. In Mexico, a particularly concerning situation exists with 36.9% of adults being obese and 38.3% overweight. Furthermore, the prevalence of abdominal obesity in individuals aged 20 or older is 81.0%. Obesity is 45% more likely in women than men and 1.7 times higher in adults aged 40-59 than in the 20-39 age group. In adults with abdominal obesity, chronic diseases like diabetes, hypertension, dyslipidemia, and cardiovascular disease are more prevalent[2]. Among American countries, Mexico has the fifth-highest obesity prevalence. In recent years, overweight and obesity have become significant public health challenges in Mexico, affecting the population's well-being and the country's development. To address this epidemic, efforts need to intensify to ensure access to and availability of healthy food, promote healthier lifestyles, improve professional health training on overweight and obesity care, develop comprehensive interventions with a people-centered and planetary sustainability vision, enhance educational and awareness campaigns, foster environments promoting active lifestyles, and safeguard prevention and control efforts from conflicts of interest[3].

Obesity exerts a substantial impact on reproductive health in both males and females. In women, obesity has been associated with menstrual irregularities, infertility, and pregnancy complications. This excess adiposity has been linked to a higher prevalence of Polycystic Ovary Syndrome (PCOS), a commonly misunderstood endocrine disorder that results in ovulatory dysfunction, insulin resistance, and hyperandrogenism. In men, obesity can lead to diminished semen quality and erectile function. Beyond this, Metabolic Syndrome (MetS) marked by excessive adipose tissue is often associated with hormonal imbalances that can exacerbate infertility. Overarching these gender-specific effects, obesity can also disrupt hormonal production, thereby influencing overall reproductive function. It's worth noting that these conditions are not immutable; interventions such as weight loss, dietary changes, exercise, and pharmacological or surgical treatments have demonstrated the potential to restore hormonal balance, enhance semen quality, and improve sexual function. Nevertheless, the medical examination and history-taking of patients with obesity often overlook their reproductive health, indicating an urgent need for more comprehensive approaches in clinical practice. As a consequence of these reproductive challenges and their potential reversibility, obesity's impact on fertility underscores the need for more inclusive patient care and intensifying efforts in public health strategies aimed at combating obesity[4,5].

Several pharmaceutical agents have received approval for the management of obesity, and they have shown demonstrable efficacy in facilitating weight loss and ameliorating metabolic parameters. These pharmaceuticals encompass a wide array of mechanistic classes, including metformin, a biguanide that decreases hepatic glucose production; orlistat, a lipase inhibitor that reduces dietary fat absorption; and phentermine, a sympathomimetic amine that suppresses appetite. Moreover, the advent of glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and semaglutide, have revolutionized obesity treatment due to their dual action in reducing appetite and inducing weight loss, in addition to their beneficial effects on glycemic control[6-10].

Nevertheless, despite their validated effectiveness in managing obesity, the investigation into these drug's direct and indirect impacts on reproductive function remains insufficiently thorough. Given the profound influence of obesity on reproductive health, the pressing need for rigorous exploration of these effects is starkly highlighted. It is essential not only to clarify these drug's roles in promoting weight loss but also to expand the research focus to encompass their potential effects on individual's reproductive capacities.

Considering this significant knowledge gap and the profound implications of obesity on reproductive health, the primary objective of this review article is to synthesize the available evidence regarding the effects of anti-obesity pharmacotherapy on fertility. By providing a comprehensive analysis of current data and identifying areas necessitating further research, we aim to foster a more integrative approach in the management of obesity, one that concurrently addresses weight reduction and fertility concerns. This approach will equip physicians with personalized, holistic care strategies, improving patient management and ultimately enhancing our understanding of the interconnected mechanisms of obesity and fertility.

2. Anti-obesity drugs and fertility

2.1 Metformin

Metformin is a pharmaceutical drug belonging to the biguanide class, and it is one of the most widely used oral antidiabetic agents globally. Metformin was first isolated in 1922, but it was not until 1957 that it was introduced in the United Kingdom for the treatment of type 2 diabetes mellitus (T2DM), and finally, in 1995, it was approved by the United States Food and Drug Administration (FDA) for the same purpose. This drug is derived from Galega officinalis, also known as "goat's rue" or "French lilac," a plant that has been used in traditional European medicine for centuries to treat various conditions, including the polyuria associated with diabetes[11].

Metformin, a widely prescribed treatment for type 2 diabetes mellitus, primarily operates by reducing hepatic glucose production and enhancing insulin sensitivity, leading to lower blood glucose levels. This is achieved not through the previously assumed inhibition of complex I activity, but rather via the inhibition of complex IV activity at clinically relevant concentrations. This inhibition prompts an increase in the cytosolic redox state, leading to a selective inhibition of glycerol-derived hepatic gluconeogenesis. Concurrently, at the cellular level, metformin activates AMP-kinase (AMPK), an enzyme pivotal to cellular energy homeostasis. The activation of AMPK results in a further decrease in hepatic gluconeogenesis and promotes glucose uptake by skeletal muscles. Consequently, these combined actions contribute to the glucose-lowering effects observed with metformin usage[12].

In addition to its approved use in the treatment of T2DM, metformin is also used off-label in various conditions such as polycystic ovary syndrome (PCOS), cancer, T1DM, anti-anging and some forms of insulin resistance. Regarding its use in managing obesity, metformin has shown to have a modest effect on weight loss in obese individuals, both diabetic and non-diabetic. Although weight loss is not its primary indication, it has been observed that metformin can promote weight loss by improving insulin sensitivity, which could have a feedback effect on reducing appetite and, therefore, caloric intake. Additionally, metformin may also have an effect on modulating the gut microbiota, which could play a role in regulating body weight. However, despite these positive effects, metformin is not officially approved for weight loss, and its use for this purpose should be carefully considered by a healthcare professional [13].

Metformin, a central agent in managing type 2 diabetes mellitus, is also known for its broad implications in reproductive health. It plays a significant role in both female and male reproductive physiology. In the context of Polycystic Ovary Syndrome (PCOS), a common disorder affecting 5-20% of women of reproductive age, metformin has been shown to improve ovarian cyclicity, mitigating the risk of gestational diabetes [14].

However, the effectiveness of metformin in improving hirsutism in adult PCOS women, particularly those with a Body Mass Index (BMI) of 25 kg/m^2 to 30 kg/m^2, may be less than oral contraceptive pills (OCPs). The certainty around this difference in effectiveness is less clear in BMI groups under 25 kg/m^2 and over 30 kg/m^2 [15].

Metformin's impact on hormonal profiles and ovarian function in PCOS is comparable to myo-inositol, as per findings by Azizi Kutenaei et al., they suggest that myo-inositol might improve fertility outcomes by moderating hyperandrogenism. Agrawal et al., 2019 concluded that the combination of metformin and myo-inositol is more effective in inducing ovulation in infertile PCOS women, resulting in significantly higher live birth rates[16,17].

In non-obese PCOS women, metformin usage is associated with a slight increase in clinical pregnancy rates compared to placebo, as discovered by Magzoub R et al., 2022. They also found metformin comparable to clomiphene citrate in terms of clinical pregnancy rates, though it has a higher risk of miscarriage. In addition, metformin may help preserve ovarian function and fertility during cyclophosphamide-based chemotherapy, which can cause severe gonadotoxicity, as suggested by Huang CC et al[18].

The study from Notaro, concluded that metformin is a suitable adjuvant medication for ovulation induction/stimulation in assisted reproduction therapies of both low and high complexity for PCOS women. The side effects are mainly mild, and there is no teratogenicity risk[19].

Metformin's effects also extend to male reproductive health, improving sperm concentration, motility, and morphology, particularly in obese individuals. Its treatment has shown to mitigate obesity-induced sperm abnormalities and improve serum testosterone and luteinizing hormone pulsatility in these individuals[20].

While metformin holds promising potential for both male and female fertility, it's essential to weigh potential risks and benefits individually. The safety of metformin during pregnancy remains controversial. Further research is needed to fully understand the complex interactions of metformin within the reproductive system and ascertain its long-term safety, especially during pregnancy.

2.2 Orlistat

Orlistat, is an anti-obesity drug that was first introduced into the market in 1998 by the pharmaceutical company Roche. It is a synthetic derivative of lipostatin, a molecule produced by the bacterium Streptomyces toxytricini, which exhibits an inhibitory effect on pancreatic and gastric lipases. Its mechanism of action focuses on the inhibition of these lipases, enzymes responsible for the breakdown of triglycerides in the intestine. By blocking this process, orlistat prevents the absorption of approximately one-third of the dietary fat, thereby favoring the reduction of total caloric intake[21].

The side effects of orlistat are directly related to its mechanism of action and include gastrointestinal discomfort, abdominal pain, flatulence, fatty diarrhea, and deficiencies in fat-soluble vitamins (A, D, E, and K) due to decreased fat absorption. The standard dose for adults is 120 mg three times a day, taken with meals[22].

Clinical studies have shown that orlistat can be effective in weight loss and in maintaining weight loss. A long-term 4-year study demonstrated that 37% of patients taking orlistat lost more than 5% of their initial body weight, and 19% lost more than 10%[23].

It is important to highlight that orlistat should be administered as part of a comprehensive weight loss program that includes diet, exercise, and behavior control, as it does not produce significant results on its own. Despite its widespread use for weight reduction, little is known about the effect of orlistat on reproductive health. In the following section, we will discuss the available studies on the relationship between orlistat use and fertility in both men and women.

Few studies have investigated the effects of Orlistat on fertility, primarily in overweight and obese women undergoing fertility treatments, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), as well as in overweight and obese men.

One such study, conducted by Tong et al., involved 29 patients in the Orlistat group who completed 37 embryo transfer cycles. It was found that Orlistat intervention in overweight/obese infertile women undergoing IVF/ICSI increased the clinical pregnancy rate (59.46%) compared to the control group (39.47%). However, there was no significant difference in the live birth rate between the two groups[24].

A randomized controlled trial designed by Li et al., 2018, is currently underway to evaluate if preconception Orlistat treatment for 1-3 months can improve the live birth rate in overweight and obese women undergoing IVF and embryo transfer[25].

In a broader perspective, the FIT-PLESE trial, led by Legro et al., 2022, studied 379 women with obesity and unexplained infertility who underwent preconception lifestyle modifications. The results indicated that intensive lifestyle intervention and orlistat for weight loss did not improve fertility or birth outcomes compared to an exercise intervention without targeted weight loss[26].

As for male fertility, a study conducted by Suleiman JB et al., 2020, observed that Orlistat reversed infertility in obese male rats by targeting testicular lactate metabolism and sexual behavior, thereby suggesting that Orlistat may preserve the fertility potential in obese men[27]. Further investigation by the same group of researchers demonstrated that Orlistat attenuated the decline in steroidogenesis and spermatogenesis by up-regulating steroidogenic genes, indicating its potential to improve fertility in overweight/obese men[28].

Despite the positive results from these studies, it should be noted that the findings are not universally consistent, indicating that further research is needed to definitively determine the effects of Orlistat on fertility in both men and women.

2.3 Phentermine

Phentermine is a centrally acting stimulant and anorectic agent that is primarily used as a short-term adjunct in the management of obesity. It was first approved by the FDA in 1959 and has since been widely used in the United States and Mexico, retaining its place in the market due to its efficacy and safety profile, despite the emergence of various new weight loss drugs[29].

Phentermine works by stimulating the release of neurotransmitters in the brain, specifically norepinephrine, dopamine, and serotonin, leading to an increase in levels of these substances. This action results in appetite suppression and a feeling of fullness, thus decreasing food intake and promoting weight loss. It targets the hypothalamus, the part of the brain that controls hunger and satiety, effectively acting on the hunger axis[30].

While it has proven effective for weight loss when combined with a low-calorie diet and regular physical activity, phentermine can come with several mild and self-limiting side effects, which are well tolerated by patients, do not necessitate drug discontinuation. These may include increased heart rate, elevated blood pressure, dry mouth, insomnia, and constipation. Despite these side effects, the medication's benefits in the management of obesity often outweigh the potential risks for many patients[31].

Typically, phentermine is prescribed at a dosage of 15-30 mg per day, taken before breakfast or 1-2 hours after breakfast. It's important to note that it is recommended for short-term use, usually over a few weeks, as its efficacy tends to decrease with long-term use, and it can potentially lead to dependence[32].

When compared to other weight loss medications such as sibutramine, rimonabant, fenfluramine, and dexfenfluramine, phentermine has remained on the market, while these others have been withdrawn due to serious side effects. For instance, sibutramine was withdrawn due to an increased risk of cardiovascular events, while rimonabant was associated with psychiatric effects. Fenfluramine and dexfenfluramine were both associated with heart and lung problems[33-35].

Despite the wealth of data on phentermine's role as a weight control aid over several decades and its coverage in numerous studies, there remains a relative scarcity of information regarding its impact on fertility. This lesser-explored area merits further discussion with the objective of shedding light on how phentermine could potentially influence reproductive health, as specific information about its effects on both male and female fertility is still limited.

A retrospective study conducted by Chang, Lathi in an outpatient endocrinology clinic at a tertiary academic medical center examined the use of phentermine in women with obesity and infertility. It was observed that phentermine could induce clinically significant weight loss in obese women during the preconception period. The study found a pregnancy rate of 60% and a live birth rate of 49% following short-term phentermine use, indicating its positive effect on weight control, and therefore, potentially on fertility[36].

Furthermore, Jones et al. in a prospective controlled cohort study found no significant increase in rates of spontaneous pregnancy loss, or major or minor anomalies in the offspring of women who took phentermine/fenfluramine at the recommended daily dose during the first trimester of pregnancy[37].

On the other hand, Bajaj, Jain, and Stanford reported a case of a woman with childhood-onset obesity who temporarily gained 13-15 pounds during each controlled ovarian stimulation (COS) cycle for in vitro fertilization (IVF). This finding raises the need for further research on weight gain resulting from COS and how phentermine might play a role in mitigating this weight increase[38].

In a study conducted by Sarayani et al. prenatal exposure appeared to be significantly lower among phentermine-topiramate users under a Risk Evaluation and Mitigation Strategy (REMS) system, although pregnancy testing and contraceptive use seemed to be inadequate across all groups[39].

Elkind-Hirsch et al. carried out a study comparing phentermine/topiramate with other treatments, and found that dual therapy with EQW/DAPA resulted in the greatest weight and total body fat loss, along with significant improvements in mean blood glucose, insulin sensitivity, and insulin secretion measures, which could have implications for managing infertility in women with Polycystic Ovary Syndrome (PCOS)[40].

A study by Manakova, Kralova, and Hubičková Heringová in which pregnancies exposed to different appetite suppressants, such as sibutramine and phentermine, were prospectively followed, revealed no differences in pregnancy outcomes between the study and comparison groups[41].

In summary, there are no conclusive studies demonstrating that phentermine alone increases the likelihood of conception. However, given the well-documented relationship between weight and fertility, it is likely that women who achieve a healthier BMI with the aid of phentermine may have enhanced fertility. As for male fertility, most studies on phentermine have focused on its effect on weight control and its use in treating obesity, so further research in this area is needed.

2.4 GLP-1 receptor agonists (GLP-1RAs)

GLP-1 receptor agonists (GLP-1RAs), such as liraglutide and semaglutide, have been at the forefront of medical therapeutics since their inception. They are a class of medications that were initially developed to manage hyperglycemia in type 2 diabetes, leveraging the mechanism of glucagon-like peptide-1 (GLP-1), an endogenous hormone that enhances insulin secretion in a glucose-dependent manner[42].

The discovery and development of GLP-1RAs represent a significant milestone in the chronicles of diabetes therapy. Their mode of action involves mimicking the function of the natural incretin hormones, stimulating insulin secretion, and inhibiting glucagon production. This dual action results in improved glycemic control with a lower risk of hypoglycemia[43].

Additionally, GLP-1RAs have the unique property of delaying gastric emptying and promoting satiety, resulting in weight loss - an attribute that has expanded their therapeutic potential beyond diabetes to include obesity management. Notably, trials have consistently shown significant weight reduction, ranging from moderate to substantial, with doses of liraglutide (1.8-3.0mg/day) and semaglutide (0.5-1.0mg/week)[44].

GLP-1RAs, however, are not without side effects. Gastrointestinal disturbances, including nausea,

vomiting, and diarrhea, are the most common, but these usually subside with continued use. More serious concerns have been raised in recent years due to reports of suicide attempts, warranting careful patient monitoring and continued pharmacovigilance[45].

On the economic front, while the cost of these medications can be significant, it must be weighed against their broad-ranging therapeutic effects. Indeed, the marvel of these drugs extends beyond glycemic control and weight management to potential benefits on other organ systems, offering cardiovascular and renal protection[47].

However, as these drugs have only been in the market for a few years, long-term safety data and certain aspects of their effects, like their impact on fertility, are limited. The focus of the next section will be to explore the emerging data on the influence of GLP-1RAs on fertility, a topic that has been relatively unexplored due to their relatively recent introduction into the market.

The centrality of weight management in ameliorating fertility and pregnancy outcomes is a common theme across many studies. Cena, H., Chiovato, L., & Nappi, R.E illuminated a potential pathophysiological link between obesity, alterations in glucagon-like peptide-1 (GLP-1) kinetics, and the development of polycystic ovary syndrome (PCOS). Their research highlighted the promising outcomes of using GLP-1 receptor agonists (GLP-1 RAs), especially liraglutide, that included significant weight loss and testosterone reduction[48].

Insulin resistance is another crucial factor in the pathogenesis of PCOS as emphasized by Bednarz, K. et al. They posited that GLP-1 RAs could potentially counter insulin resistance and improve fertility through various mechanisms including modulation of glucose transporters in insulin-dependent tissues, reduction of inflammation and oxidative stress, and alteration of lipid metabolism[49].

Highlighting the broader metabolic impacts of GLP-1 RAs, Papaetis, G.S. & Kyriacou, A. discussed their beneficial effects in reducing weight, abdominal fat, and insulin resistance markers. They further underscored the ongoing research on the potential influence of these agonists on the hypothalamic-pituitary-gonadal axis[50].

In a 2019 study, Jensterle, M. et al. suggested that GLP-1 could be a pivotal modulator connecting the reproductive and metabolic systems. Their work provided preliminary evidence of improved menstrual regularity and increased fertility rates in overweight and/or obese women with PCOS treated with GLP-1 Ras[51].

Advancing this narrative, Violette, C.J. et al. explored the potential use of GLP-1 receptor agonists in fertility-sparing treatment for obese patients with malignant endometrial pathology. Their proposition entailed the potential enhancement of subsequent pregnancy chances through reductions in weight, inflammation, and insulin resistance by these agonists[52].

Corroborating the effectiveness of GLP-1 analogues, Reiser, E. et al. provided evidence that they, alongside metformin, were successful in regulating menstrual cycles in adolescents diagnosed with PCOS. Elkind-Hirsch, K.E. et al. further demonstrated that GLP-1 receptor agonists resulted in significant improvements in glucose regulation and insulin sensitivity, even in cases where equivalent BMI reductions were achieved with other treatments[53,54].

While GLP-1 receptor agonists show promise in improving fertility outcomes in the context of obesity, insulin resistance, and PCOS, further comprehensive studies are necessary to better assess their potential benefits and impacts.

Turning to male fertility, it appears that GLP-1 RAs also have a role to play. Rago et al. found that human sperm cells express GLP-1 receptors, impacting sperm function and metabolism. They suggested that these receptors could serve as new targets for GLP-1 incretin, thereby enhancing our understanding of male reproduction[55].

Gill and Mackey discussed the role of GLP-1 RAs, particularly liraglutide, as a treatment for obesity in women. This could have implications for male fertility, given that obesity is a known factor affecting reproductive health[56].

On a note of caution, Fontoura et al. reported an adverse effect of liraglutide on male reproductive function, raising concerns about its use in men, particularly those desiring fatherhood[57].

In a broader context, Ammar et al. suggested that GLP-1 RAs might offer new strategies for managing weight and infertility in obese men, a premise supported by Zhang et al.'s study that demonstrated the attenuating effects of a GLP-1 RA, exenatide, on reduced sperm quality and increased testicular inflammation in obese mice[58,59].

Overall, GLP-1 RAs could significantly impact both male and female reproductive health. However, a more in-depth understanding of these effects is needed to develop optimal treatment strategies.

2.5 Dual agonists of GLP-1 and GIP

Dual agonists of GLP-1 and GIP, like tirzepatide, represent the next wave of innovation in the realm of

diabetes management and weight loss therapy. Exploiting the synergistic actions of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), these novel therapeutics promise to reshape the landscape of metabolic disease treatment[60].

Both GLP-1 and GIP are incretin hormones secreted by the gut in response to nutrient intake. While GLP-1's role in enhancing glucose-dependent insulin secretion and inducing satiety is well-established, GIP was initially known for its insulinotropic effect. However, recent evidence points to its role in lipid metabolism and energy homeostasis, which has been leveraged in the development of dual GLP-1/GIP agonists[61].

The action of these dual agonists, therefore, combines the benefits of both incretin pathways: improved glucose control, weight loss, and potential benefits in lipid metabolism. Notably, early-phase trials with tirzepatide have shown substantial weight reduction and significant improvement in glycemic control[62].

As a relatively new development, data on the side effects of dual GLP-1/GIP agonists are limited but are anticipated to align with those of GLP-1 agonists, including gastrointestinal disturbances such as nausea, vomiting, and diarrhea. However, close patient monitoring remains a priority due to the novel nature of this medication class[63].

As tirzepatide is yet to hit the market, the cost implications are uncertain. However, the potential broad-spectrum benefits extending beyond glycemic control and weight loss, to potentially improving other metabolic parameters, are promising. Comparatively, dual GLP-1/GIP agonists like tirzepatide appear to offer more robust weight loss compared to GLP-1 monoagonists, suggesting a potential edge in obesity management[64].

However, as with any novel therapy, there is a significant knowledge gap regarding the long-term safety and certain aspects of its effects, such as fertility. In the following section, we will explore what is known about the impact of dual GLP-1/GIP agonists on fertility, a topic that has been relatively untouched given the novelty of these agents.

Research data so far has shown both promise and potential concerns for the use of tirzepatide in relation to fertility and reproductive health.

The official prescribing information for tirzepatide, marketed as Mounjaro, provides key information on the potential effects on fertility. According to the FDA-approved label, in studies conducted in rats, tirzepatide did not show any effects on sperm morphology, mating, fertility, or conception in males. In female rats, however, there were changes in reproductive parameters including prolonged diestrus and decreased numbers of corpora lutea, implantation sites, and viable embryos. These changes were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight. The same prescribing information also highlighted a significant interaction between tirzepatide and oral hormonal contraceptives. In the presence of a single dose of tirzepatide 5 mg, the maximum concentration (Cmax) of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, respectively. The total amount of drug absorbed, represented by the area under the curve (AUC), was reduced by 20%, 21%, and 23%, respectively. Therefore, patients using oral hormonal contraceptives are advised to switch to non-oral contraceptive methods for 4 weeks after initiation and 4 weeks after each dose escalation with tirzepatide[65].

Anala et al. proposed tirzepatide as a potential treatment for PCOS. Although weight loss facilitated by glucagon-like peptide-1 receptor (GLP-1R) agonists has been found to improve the metabolic features of PCOS, side effects including gastrointestinal discomfort can hinder patient compliance. Tirzepatide may benefit obese patients with PCOS who have metabolic syndrome. However, its effectiveness in PCOS patients of normal weight is uncertain[66].

Tirzepatide shows potential as a treatment in specific aspects of reproductive health, particularly in relation to metabolic issues associated with PCOS. However, the drug's interactions with oral hormonal contraceptives and potential effects on fertility underscore the need for careful consideration and additional research.

Conclusion

The intersection of obesity, metabolic disease, and reproductive health continues to be a significant focus of research. In this review, we have explored the current evidence for the impact of five key classes of anti-obesity medications on reproductive parameters: metformin, orlistat, phentermine, GLP-1 receptor agonists, and dual GLP-1 and GIP agonists.

Metformin, a pharmaceutical stalwart in managing type 2 diabetes mellitus, has displayed extensive implications for reproductive health. Notably, it has been beneficial in managing Polycystic Ovary Syndrome (PCOS), a common disorder affecting a significant percentage of women of reproductive age. However, its efficacy compared to other treatments such as oral contraceptive pills (OCPs) may vary based on the patient's body mass index. Interestingly, studies suggest the combination of metformin and myo-inositol could improve fertility outcomes in infertile women with

PCOS. In men, metformin has shown promising improvements in sperm quality, especially in obese individuals. Yet, it is vital to individually weigh the potential risks and benefits, particularly given the ongoing controversy regarding metformin's safety during pregnancy.

Orlistat, an inhibitor of pancreatic and gastric lipases, reduces total caloric intake by preventing the absorption of dietary fat. The drug can effectively promote weight loss and maintain it, but it may also lead to deficiencies in fat-soluble vitamins. Research into its effects on fertility is sparse, but emerging evidence suggests potential benefits for obese women undergoing fertility treatments and men. However, the consistency of findings across studies is yet to be established, calling for further research to definitively elucidate Orlistat's impact on fertility.

Phentermine, a stimulant used for short-term obesity treatment, promotes weight loss by suppressing appetite through neurotransmitter release. Although well-documented for its weight control effectiveness, little is known about its direct influence on fertility. The drug, often combined with a low-calorie diet and exercise, is usually prescribed for a short term due to its potential for dependency. Side effects are typically mild and temporary. Unlike some weight loss drugs, phentermine remains available due to its effectiveness and safety. In comparison to other weight loss medications, phentermine has remained on the market due to its efficacy and safety profile, while others have been withdrawn due to serious side effects. However, despite the extensive data supporting phentermine's role in weight control, specific research on its direct impact on both male and female fertility is limited. The indirect influence on reproductive health through significant weight loss and improvement in metabolic parameters is plausible, though the exact impact remains under-explored and warrants further investigation.

GLP-1 receptor agonists (GLP-1RAs) like liraglutide and semaglutide demonstrate significant weight reduction and improved metabolic aspects of Polycystic Ovary Syndrome (PCOS), indicating potential reproductive benefits. Originating as type 2 diabetes treatments, their dual action improves glycemic control and aids in weight loss, broadening their utility to obesity management, despite potential side effects including gastrointestinal disturbances and serious mental health concerns. While effective for hyperglycemia management and weight loss, data on their fertility impacts are sparse. Nevertheless, they've shown promise in addressing weight management and insulin resistance, key to PCOS, and some evidence suggests improved menstrual regularity and fertility rates in overweight or obese women with PCOS. They have also been proposed for fertility-sparing treatments in obese patients with endometrial pathology. Regarding male fertility, early studies suggest a potential role for GLP-1RAs, although concerns exist about potential negative impacts on reproductive function. In summary, GLP-1RAs, potentially influencing both male and female reproductive health by addressing metabolic factors, obesity, and insulin resistance, warrant further investigation to ascertain their fertility effects.

Finally, Dual GLP-1 and GIP agonists, such as tirzepatide, are emerging innovations in the treatment of diabetes and weight loss, offering significant improvements in glucose control and weight reduction. However, there are unknowns regarding side effects, long-term safety, and impacts on fertility. Tirzepatide shows potential for treating Polycystic Ovary Syndrome (PCOS) by facilitating weight loss, a key factor in managing PCOS. But its interactions with oral contraceptives and unclear effects on fertility demand more research. While tirzepatide appears to provide stronger weight loss outcomes than GLP-1 monoagonists, comprehensive studies are necessary to fully understand its safety, efficacy, and broader implications on reproductive health.

Pharmaceutical interventions like Orlistat, Metformin, Phentermine, GLP-1 agonists, and dual GLP-1/GIP agonists show promising potential in managing metabolic disorders and obesity, with possible positive impacts on reproductive health. However, current knowledge about their direct effects on fertility is limited and often ambiguous. It's vital that future research is directed towards closing this information gap, to better understand their full impact and safely broaden their therapeutic applications in reproductive health.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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