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FERTILITY IN WOMEN WITH PHARMACOLOGICAL TREATMENT OF OBESITY DISEASE- REVIEW AND ANALYSIS OF CURRENT CLINICAL DATA

Barbara Reizer *(Corresponding Author, Email: basia.reizer@gmail.com)*
Medical Center in Łańcut, Łańcut, Poland
ORCID ID: 0009-0009-7890-1443

Jagoda Bartman-Białek
Medical Center in Łańcut, Łańcut, Poland
ORCID ID: 0009-0000-8933-2519

Wiktoria Dusiłło
University of Rzeszów, Rzeszów, Poland
ORCID ID: 0009-0006-1764-3100

Jakub Krzysztof Kruk
Medical Center in Łańcut, Łańcut, Poland
ORCID ID: 0009-0002-8027-0520

ABSTRACT

Background: Obesity is one of the key factors negatively affecting female fertility, disrupting hormonal function, ovulation and oocyte quality. In recent years, the development pharmacotherapy for obesity-related disease has opened up new treatment options for patients with excessive body weight, especially in those with polycystic ovary syndrome (PCOS) and insulin resistance. The purpose of this article is to review current clinical data on the effects of pharmacological treatment of obesity on improving reproductive parameters and the safety of drugs in women of reproductive age. Both the therapeutic benefits of weight reduction and the potential risks, including ethical aspects and limitations in the use of drugs during the periconceptional period, are discussed. The need for a multidisciplinary approach involving the cooperation of gynecologists, endocrinologists, nutritionists and psychologists is also pointed out, increasing the effectiveness and safety of treatment
Aim: The purpose of this paper is to present and analyze current clinical data on the impact of pharmacotherapy used in the treatment of obesity on female fertility, with particular emphasis on hormonal mechanisms, the efficacy of individual drugs, the safety of their use during the periconceptional period, and the importance of a multidisciplinary approach in the treatment of overweight women planning a pregnancy.
Materials and methods: The paper is a narrative review. A literature search was conducted in databases to gather current scientific data on the effects of pharmacological treatment of obesity on female fertility: PubMed, Scopus, Google Scholar and the Cochrane Library. Publications were selected with a focus on clinical trials, systematic reviews, guidelines of scientific societies and meta-analyses.
Results: Pharmacotherapy for obesity is a promising tool for treating infertility in overweight women, although it requires further clinical trials and individualization of therapy.

KEYWORDS

Obesity, Pharmacotherapy, Female Fertility, PCOS, Weight Reduction, Hormonal Contraception, Periconceptional Period, Interdisciplinary Approach, Infertility Treatment, Drug Safety

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Introduction

Fertility is one of the primary determinants of a woman's reproductive health and plays a key role at both the individual and societal levels. A woman's fertility not only refers to her ability to conceive a child, but also indicates the overall well-being and efficiency of the reproductive system, itsfunctions and processes. [1] In order to maintain a normal menstrual cycle and the ability to conceive and develop a pregnancy, the proper functioning of the hypothalamic-pituitary-ovarian axis is essential. Any abnormalities resulting from axis dysfunction caused by disease- can lead to reduced fertility or total infertility [2]. Menstrual disorders, lack of ovulation or difficulties in getting pregnant may be due to conditions such as polycystic ovary syndrome (PCOS), endometriosis, hypothyroidism, hyperprolactinemia or obesity.[3] Having a child remains a priority and an important value for many women, and the presence of infertility may be associated with reduced psychological well-being, leading to depression, changes in quality of life, relationship problems with the partner and a decline in the woman's self-esteem. [4] In recent years, there has been an apparent decline in population fertility, which may be partly due to the obesity epidemic increasingly affecting developed countries [5]. For this reason, maintaining and protecting fertility requires a comprehensive approach, including both prevention and treatment of causal disorders, including obesity-related disease.

Obesity is a chronic disease that is one of the greatest health challenges of the 21st century. It is characterised by an excessive accumulation of adipose tissue, thus impairing the normal functioning of the body and leading to the development of other conditions - type 2 diabetes, hypertension, metabolic syndrome, cancer, or fertility disorders [6]. In medicine, obesity is diagnosed on the basis of the body mass index BMI. Values above 30 kg/m² define obesity. Currently, the world is facing an obesity epidemic due to an ever-increasing number of patients. According to WHO data from 2023, more than 1 billion people worldwide are living with obesity - including approximately 650 million adults, 340 million children and adolescents and 39 million children under the age of five.

According to a 2022 report by the National Health Fund (NHF), nearly 58% of Polish adults are overweight or obese, and projections indicate that this number is set to increase further [7, 8]. The increased prevalence of obesity is a result of sedentary lifestyles, reduced physical activity, excessive consumption of highly processed foods, simple sugars, trans fats, as well as the presence of family predisposition, stress, eating disorders, low health awareness, and limited access to healthy food and recreational spaces [9]. With the classification of obesity as a chronic disease, the perception of this condition is changing - it is not just an aesthetic defect, but a serious metabolic disorder requiring appropriate long-term treatment [10]. Pharmacotherapy and reimbursement of treatment has now become possible. The recognition of obesity as a disease is mobilising countries and international organisations to take action to promote the prevention of this condition. The treatment of obesity requires action on many fronts. However, particular attention should be paid to the impact of obesity on women's reproductive health, which is the subject of further analysis in this paper. Numerous clinical and scientific studies show a correlation between excessive body weigh and the presence of endocrine or metabolic disorders, which can cause infertility or limit the chances of natural conception [11]. Women with a higher BMI are significantly more likely to suffer from menstrual cycle disorders, studies show. Excessive body weight is also present in a large proportion of women with polycystic ovary syndrome. PCOS is one of the most common endocrine disorders causing infertility, and obesity further exacerbates the symptoms of the syndrome, such as chronic anovulation, hyperandrogenism, oocyte deterioration and insulin resistance [3]. Weight reduction of up to 5-10% can improve cycle regularity, restore ovulation and increase the chances of pregnancy [12].

Research results 1.Obesity

Obesity is a chronic metabolic disease characterized by excessive fat accumulation, which negatively affects the normal functioning of the human body [13]. Diagnosis of obesity is mainly based on anthropometric indices such as BMI, waist circumference, WHR [14].

BMI (Body Mass Index)

The most commonly used index for assessing body weight in relation to height. It is calculated according to the formula:

BMI= body weight (kg)/ height (m2)

WHO BMI classification [15].

Category	BMI value (kg/m²)
Underweight	< 18,5
Normal weight	18,5- 24,9
Overweight	25,0- 29,9
Obesity class I	30,0- 34,9
Obesity class II	35,0- 39,9
Obesity class III	≥40

The BMI index provides a quick and simple calculation and assessment of body weight. It is used in population studies. Unfortunately, using BMI, it is not possible to assess the distribution of body fat, and it is not possible to distinguish between fat and muscle, so people with high muscle content according to the BMI classification may be classified as obese [16].

Waist circumference

Waist circumference measurement is used to assess abdominal (visceral) obesity, which is associated with higher metabolic risk [17].

WHO cut-off points:

Women: > 80 cm - increased risk, > 88 cm - high risk
Men: > 94 cm - increased risk, > 102 cm - high risk

Increased waist circumference predisposes to the development of type 2 diabetes, metabolic syndrome, or cardiovascular disease [18].

WHR (Waist-to-Hip Ratio)

The ratio of waist circumference to hip circumference. This ratio allows assessment of the distribution of body fat in the human body [19].

WHR= waist circumference (cm)/hip circumference (cm) Interpretation (WHO):

Women: WHR > 0.85 - obesity of the android (abdominal) type
Men: WHR > 0.90 - abdominal type obesity

A distinction is made between android, or apple, obesity, where fat accumulates mainly in the abdominal area and indicates a higher risk of metabolic diseases, and gynoid (pear) obesity, where fat accumulates mainly on the hips and thighs and indicates a lower risk of metabolic diseases.

Accurate diagnosis and classification of obesity makes it possible to assess the risk of concomitant diseases, i.e. type 2 diabetes, hypertension, or metabolic syndrome, qualify an obese person for treatment, and monitor the effectiveness of therapy.

1.2 Etiopathogenesis - genetic, environmental, psychological factors

The etiopathogenesis of obesity is complex and multifactorial. It is not solely the result of excessive calorie intake, but also of genetic predisposition, environmental influences, psychological and behavioral factors [20]. The results of studies conducted on related individuals indicate a higher risk of developing obesity in people with a family history of the disease, and the heritability of BMI is as high as 40-70% [21]. In addition, most cases of obesity are polygenic in nature—a tendency toward excessive appetite, slow metabolism, or a tendency to accumulate fat is inherited.

Environmental factors that modify gene expression without changing DNA, such as the mother's diet during pregnancy, stress, or smoking, also influence the later development of obesity in offspring [22]. It is also worth mentioning the changing lifestyle of most of the population. A high- calorie diet rich in highly processed foods, simple sugars, saturated fats, and sweetened beverages leads to an excessive calorie intake and promotes the development of obesity [9]. In addition, a sedentary lifestyle, office work, and reduced spontaneous physical activity significantly reduce total energy expenditure. Irregular meals, lack of sleep, and circadian rhythm disorders (e.g., shift work) increase the risk of obesity by affecting metabolism and appetite. Obesity is also caused by various types of eating disorders, including emotional eating and binge eating disorder, which involves episodes of loss of control over eating, leading to significant weight gain [23]. Mental disorders often coexist with excess weight and can be both a cause and a consequence of mental illness.

Antidepressants and antipsychotics can increase appetite, resulting in obesity [24].

1.3. Health effects of obesity

The endocrine system in obese individuals is significantly burdened, among other things, due to the hormonal activity of adipose tissue. It has aromatase activity, an enzyme that converts androgens into estrogens. The concentration of extra-gonadal estrogens is increased, which can disrupt feedback and inhibit ovulation [25]. Leptin, produced by adipose tissue, affects the hypothalamus and regulates appetite and reproduction. Obese individuals often experience leptin resistance, leading to abnormalities in appetite regulation, and high leptin concentrations disrupt the hypothalamic-pituitary-gonadal axis [26]. Abnormalities in gonadotropin-releasing hormone secretion resulting from obesity lead to disturbances in LH and FSH secretion, resulting in irregular cycles, anovulation, and infertility [27]. Another aspect to consider when analyzing the impact of obesity on the body is the fact that visceral adipose tissue increases the production of pro- inflammatory cytokines (e.g., TNF-α, IL-6), which reduce tissue sensitivity to insulin [28].

Excessive insulin concentration stimulates the ovaries to produce androgens and lowers SHBG (sex hormone-binding globulin) levels, which increases the concentration of free androgens in the serum [29]. Excessive body weight contributes to irregular or absent menstruation and long cycles in women, exacerbates PCOS symptoms, causes infertility, and obese women are more prone to pregnancy complications. Weight reduction, including lifestyle changes, pharmacological and surgical treatment, can significantly improve reproductive function and reduce the risk of complications [30].

The impact of obesity on female fertility

Hypothalamic-pituitary-ovarian axis disorders

The hypothalamic-pituitary-ovarian (HPO) axis is the primary system regulating female reproductive functions [31]. It enables ovarian follicle maturation, ovulation, regular menstrual cycles, and determines fertility. Inadequate functioning of this axis leads to menstrual disorders, including absence or infrequent menstruation, anovulatory cycles, and, consequently, infertility. Excess leptin resulting from the secretory function of adipose tissue causes the development of leptin resistance. Insulin resistance and hyperinsulinemia increase ovarian androgen production, and chronic inflammation resulting from excessive secretion of pro-inflammatory cytokines disrupts hormonal signaling [32, 33]. All these abnormalities cause HPO axis disorders and directly affect the fertility of obese women.

Polycystic ovary syndrome (PCOS) and obesity

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Its prevalence is estimated at around 5-15% [34]. Obese women are more likely to develop the condition [35]. Obesity can exacerbate the symptoms of PCOS, and PCOS predisposes women to weight gain and metabolic disorders. The Rotterdam criteria are used to diagnose PCOS, and two of the three criteria must be met for a diagnosis [36]:

Irregular or absent ovulation (oligo- or anovulation),

Clinical and/or biochemical signs of hyperandrogenism

Polycystic appearance of the ovaries on ultrasound.

Other causes that may lead to the above-mentioned symptoms, such as hyperprolactinemia, thyroid disease, and adrenal nodules, should also be ruled out. It is estimated that up to 40–80% of women with PCOS are overweight or obese [37]. Abdominal obesity, associated with insulin resistance and inflammation, is most common. Excessive body weight in women with PCOS increases insulin resistance, leading to an increase in insulin concentration, which stimulates the ovaries to overproduce androgens, exacerbating the symptoms associated with hyperandrogenism; hirsutism, acne, male pattern baldness, menstrual cycle abnormalities, and fertility problems [38]. A deterioration in the quality of eggs and endometrium has also been observed, reducing the effectiveness of assisted reproduction procedures [39]. Weight loss is very important in the treatment of PCOS, as it can restore ovulation, reduce androgen levels, improve insulin sensitivity, increase the chances of pregnancy, and reduce the risk of cardiovascular disease and diabetes. That is why it is so important to change your lifestyle, i.e., follow a low-calorie diet and engage in physical activity [12]. Pharmacological treatment of PCOS involves the use of metformin (improvement of insulin sensitivity), hormonal contraception (regulation of cycles, reduction of hyperandrogenism), and drugs that aid weight loss (e.g., GLP-1 agonists). Psychological support should also not be overlooked, as mood disorders are common in women with PCOS and may affect the effectiveness of treatment [40].

The impact of obesity on egg quality, endometrium, and implantation

Obesity negatively affects ovarian follicle maturation because, as mentioned earlier in this article, women who are overweight have hypothalamic-pituitary-ovarian axis disorders. Furthermore, ovarian follicle development is abnormal due to insulin resistance and hyperinsulinemia [41].

Women with a high BMI are more likely to experience abnormal cell division and oocyte immaturity. A higher incidence of aneuploidy is also observed, which reduces the chances of fertilization and the development of a healthy embryo [42]. Due to the disturbed estrogen- progesterone ratio in obese women and suboptimal progesterone levels, endometrial secretory transformation may not occur, reducing the chances of embryo implantation [43]. The lower implantation rate applies to both natural cycles and in vitro procedures, where, despite the transfer of embryos with good morphology, effectiveness may be limited due to the endometrial environment. During in vitro procedures, it is often necessary to increase gonadotropin doses to stimulate ovulation. Stimulation in obese women may be weakened, and the number of mature oocytes obtained may be lower. A higher incidence of early miscarriages, an increased risk of biochemical pregnancy, and ectopic pregnancy have also been observed in women with a BMI >30. In summary, obesity negatively affects every stage of the reproductive process: from oocyte maturation, through endometrial receptivity, to embryo implantation and pregnancy maintenance.

Pharmacotherapy of obesity – an overview of currently used drugs

Drugs approved for the treatment of obesity include orlistat, GLP-1 analogues, and naltrexone/bupropion [44].

Orlistat

An effective drug that aids weight loss in obese women. It does not directly affect fertility, but it can indirectly improve reproductive function by reducing body weight and improving hormonal and metabolic balance. Its mechanism of action involves inhibiting pancreatic and gastric lipase, which inhibits the absorption of undigested fats and causes them to be excreted in the stool [45]. In people with a BMI ≥30 kg/m² (or ≥27 with comorbidities), it causes weight loss of approximately 5–10% within 6–12 months when used in conjunction with a low-calorie diet. Weight loss can lead to improved metabolic parameters: decreased insulin resistance, improved lipid profile, and blood pressure. Weight loss with Orlistat can restore regular menstrual cycles, ovulation, and improve the effectiveness of infertility treatment, e.g., in PCOS [46]. Clinical studies have shown that in women with PCOS, Orlistat improves the metabolic profile and promotes the return of ovulation, and a comparison of metformin, Orlistat, and diet in women with PCOS showed that all methods improved fertility parameters, but the best results were achieved with a combination of diet and pharmacotherapy [47]. Orlistat can therefore be a valuable component of obesity-related infertility treatment, especially when combined with lifestyle changes, a healthy diet, and adequate physical activity.

GLP-1 agonist drugs (e.g., liraglutide, semaglutide)

A modern class of incretin drugs, initially used to treat type 2 diabetes and now also used in obesity therapy. GLP-1 is a natural intestinal hormone that stimulates insulin secretion, inhibits glucagon, delays gastric emptying, and affects the satiety center in the brain [48]. The most commonly used GLP-1 agonists in the treatment of obesity are Liraglutide and Semaglutide. These are effective drugs used to aid weight loss. Liraglutide causes an average weight loss of 8–10% within 6–12 months [49], while semaglutide is even more effective. It allows for weight loss of up to 15–20%, which is close to the effects of bariatric surgery [50].

These drugs are recommended for people with a BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities (e.g., PCOS, insulin resistance, hypertension).

By reducing body weight, these drugs have an indirect, positive effect on female fertility. There is an improvement in ovulatory cycles, especially in women with polycystic ovary syndrome (PCOS), as well as a reduction in insulin resistance leading to a decrease in hyperandrogenism. Lipid profile and metabolism also improve, which increases the chances of conception, including in assisted reproduction procedures (IVF). Clinical studies have shown that women with PCOS using liraglutide achieved more frequent ovulation and pregnancy compared to placebo, while in some studies, semaglutide used as a prelude to IVF increased the effectiveness of implantation by improving endometrial function [51]. Additional benefits of using GLP-1 analogues include lower blood pressure, inflammation parameters, and cardiovascular risk. Some studies also indicate an improvement in quality of life and mental well-being in women with obesity and fertility disorders.

Naltrexone/bupropion

These drugs work together to affect the reward center in the brain and the hypothalamus, which controls appetite [52]. They lead to a decrease in appetite and weight loss. Naltrexone is an opioid receptor antagonist, also used in addiction therapy, while bupropion is a dopamine and norepinephrine reuptake inhibitor, also used in the treatment of depression and tobacco addiction therapy. Studies show that the use of naltrexone/bupropion in combination with diet leads to a 5–9% reduction in body weight over 12 months [53]. The drug works mainly by reducing appetite and emotional overeating, and the metabolic benefits include improved lipid parameters, glycemia, and blood pressure. Naltrexone/bupropion has an indirect effect on female fertility, mainly due to weight loss. It may be beneficial in women with PCOS and insulin resistance, factors that often underlie infertility. Naltrexone reduces appetite and compulsive eating, which is common in women with PCOS, while bupropion improves mood and reduces depressive symptoms that co-occur with obesity and fertility disorders [54].

The impact of pharmacological treatment of obesity on fertility

Hormonal changes following drug-induced weight loss

Weight loss is associated with numerous beneficial hormonal changes that can significantly improve the functioning of the body, including female reproductive capacity. Pharmacological treatment of obesity (e.g., liraglutide, semaglutide, orlistat, naltrexone/bupropion) plays a special role in restoring hormonal balance. Weight loss affects the hypothalamic-pituitary-ovarian axis, restoring pulsatile GnRH secretion. LH and FSH levels normalize, which promotes ovulation and restores menstrual cycles. In addition, weight reduction leads to a decrease in insulin levels, improved insulin sensitivity, and a reduction in free and total testosterone levels and symptoms of hyperandrogenism. Leptin sensitivity increases, estrogen levels normalize, improving ovulation quality and ovarian follicle maturation [55]. Clinical trials with liraglutide and semaglutide have shown an increase in ovulation frequency, a decrease in testosterone levels, an improvement in menstrual regularity, and a beneficial effect on the number of pregnancies in women with PCOS.

Data from clinical and observational studies – effects of pharmacological treatment on fertility

Pharmacological treatment of obesity is increasingly used as a method that not only reduces body weight but also improves women's reproductive health. In recent years, many clinical and observational studies have been conducted, indicating the beneficial effects of anti-obesity drugs on ovulation, cycle regularity, pregnancy rates, and egg quality. Women with PCOS are a group that very often suffers from infertility due to elevated BMI, which is why many studies focus on the impact of weight-reducing drugs on fertility in this group.

In the study “Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome” by Jensterle et al., 2015, it was concluded that 1.2 mg of liraglutide per day for 12 weeks in women with PCOS improves insulin sensitivity, causes a decrease in testosterone levels, and restores ovulation in 44% of women. Furthermore, the combination of liraglutide and metformin produces better results than metformin alone [56]. Other studies indicate that semaglutide, although not yet approved directly for women with PCOS, allows for weight reduction by indirectly improving the regularity of menstrual cycles and increasing fertility [57]. In the study “Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study” by Gambineri et al. 2004, it was proven that obese and insulin-resistant women treated with orlistat had a higher chance of spontaneous ovulation than those who only followed a diet [58]. An improvement in the lipid profile and a decrease in leptin levels, which is an important hormone for the hypothalamic-pituitary-ovarian axis, were also observed. There is less clinical data available for naltrexone/bupropion, but observational studies in women with depression and obesity have shown that weight loss led to the normalization of menstrual cycles. In a study of women with PCOS, spontaneous ovulation and pregnancy were achieved in 30–40% of participants resistant to clomiphene who were treated with naltrexone [59].

Safety of medication use in the context of pregnancy planning

Pharmacological treatment of obesity in women of childbearing age often leads to the normalization of hormonal and metabolic disorders resulting from excessive body weight. However, pharmacotherapy requires particular caution in the context of pregnancy planning due to the adverse effects of some drugs on embryo development or the lack of sufficient research to enable their safe use during pregnancy. Therefore, assessing the safety of these pharmaceuticals before and during early pregnancy is crucial [55, 60].

The European Union and the US use different classifications for the safety of drugs during pregnancy. Although the FDA abolished the A–X category in 2015, many sources still refer to it. The general rule is: "Pharmacotherapy for obesity should be discontinued at least several weeks before planned conception, unless there is clear evidence of safety."

Safety assessment of selected anti-obesity drugs:

As mentioned earlier in this article, the main drugs used in the pharmacotherapy of obesity are GLP-1 analogues, orlistat, and naltrexone/bupropion. The safety of these drugs, as well as metformin, during pregnancy is described below.

GLP-1 analogues (liraglutide, semaglutide, dulaglutide) are contraindicated during pregnancy. Data from animal studies have shown harmful effects on embryo development (e.g., reduced fetal weight, developmental defects). Recommendations for the use of GLP-1 analogues indicate the need to discontinue the drug at least 1-2 months before conception. These drugs should not be used during pregnancy or breastfeeding [60].

Orlistat is a potentially safe drug, but it is not recommended for use during pregnancy due to the risk of deficiencies in fat-soluble vitamins (A, D, E, K), which are essential for fetal development. There is no clear data on its harmfulness, but there is also no confirmed safety.

Naltrexone/bupropion are contraindicated during pregnancy. Bupropion is sometimes used in pregnant women with depression, but its combination with naltrexone has not been well studied. The risk of teratogenic or toxic effects on the fetal CNS cannot be ruled out. Treatment should be discontinued before planned pregnancy and the drug should not be used during lactation.

Metformin can be used off-label in the treatment of obesity, especially in women with PCOS. It supports fertility and increases the rate of ovulation and pregnancy. Its use can be continued during pregnancy in patients with PCOS and insulin resistance [61].

In order to reduce the risk of weight regain and hormonal disorders resulting from discontinuation of pharmacotherapy in women planning pregnancy, it is recommended to first stabilize body weight and complete pharmacological treatment of obesity after achieving the expected results.

Preconception consultation with a gynecologist or endocrinologist is also necessary.

4.4 Comparison of pharmacotherapy for obesity with other treatment methods (diet, bariatric surgery)

The three main therapeutic strategies used to treat obesity are: lifestyle changes (diet, physical activity), pharmacotherapy, and bariatric surgery. Each of these methods differs in terms of effectiveness, risk of complications, duration of action, and impact on fertility.

The advantages of diet and lifestyle modification are low cost and no side effects. A moderate weight loss of approximately 5-10% is observed within 6-12 months. In addition, this method is characterized by a reduction in insulin resistance and a beneficial effect on menstrual cycles and ovulation. On the other hand, there may be difficulties in maintaining the effects in the long term, and in cases of severe obesity (BMI >35), diet and lifestyle changes are not very effective. In addition, in women with PCOS, this method is often insufficient to restore fertility [62].

Pharmacotherapy for obesity is mainly based on the use of liraglutide, semaglutide, orlistat, and naltrexone/bupropion. The benefits of this method include an 8-15% reduction in body weight within 6-12 months and a visible improvement in ovulation, sex hormones, and menstrual cycles. It is also important to note the disadvantages of using weight loss drugs, namely their temporary effect, meaning that once the drugs are discontinued, their effect ceases. There may also be potential side effects, most commonly gastrointestinal, associated with pharmacotherapy, such as nausea and vomiting. It is important to remember that treatment must be discontinued before planning a pregnancy [55, 57].

Bariatric surgery is another treatment option for people with obesity. The most common procedures performed in this field are sleeve gastrectomy and gastric bypass. This is the most effective form of obesity treatment, leading to a 20-35% reduction in body weight. There is a steady improvement in metabolic

parameters and a significant improvement in fertility, with normalization of ovulation, a decrease in androgens, and an increase in the number of pregnancies. On the other hand, bariatric surgery is an invasive procedure associated with the risk of surgical complications and may lead to deficiencies in micronutrients important for normal fetal development: iron, folic acid, and vitamin B12 [58,59,60]. It should also be noted that it is necessary to refrain from planning a pregnancy for approximately 12-18 months after the procedure [63].

In summary, for women with mild to moderate obesity, pharmacotherapy combined with diet and lifestyle modification can effectively improve fertility without the need for surgery, but in patients with severe obesity (BMI >40) or in cases of resistance to conservative treatment, bariatric surgery offers the best long-term results. Regardless of the method, pregnancy planning requires individualized treatment and hormonal and nutritional monitoring.

Problems and controversies

Pharmacological treatment of obesity in women of childbearing age poses numerous ethical and clinical challenges, resulting from the need to balance the therapeutic benefits for the woman with the potential risk to the health of the fetus [64]. Therapeutic decisions in this context require individualization and interdisciplinary cooperation. The benefits of pharmacotherapy before pregnancy include, above all, weight reduction, which improves ovulation and hormonal profil and, among other things, reduces insulin resistance. Treatment can increase the chances of natural conception, especially in women with PCOS, and also reduces the risk of pregnancy complications such as gestational diabetes and hypertension [65]. On the other hand, the use of pharmacotherapy in women of reproductive age is associated with risks resulting from the lack of long-term data on the use of certain drugs during the periconceptional period. Most obesity drugs are contraindicated during pregnancy, but there is also a risk of vitamin deficiencies that can affect fetal development. The potential impact of pharmacotherapy on the effectiveness of contraception is also important.

From an ethical point of view, it is very important to respect the autonomy of the patient, who has the right to make an informed decision about treatment, as well as to be provided with reliable information by the doctor about the benefits, possible risks, and possible alternatives. The goal of many women of reproductive age with a high BMI is to optimize their health by reducing their body weight through pharmacotherapy before pregnancy, rather than at the expense of endangering their future child. Therefore, drugs with unknown teratogenic effects should not be used during pregnancy, as this could be contrary to the principle of "primum non nocere" [66]. Another ethical issue is unequal access to treatment due to high prices and lack of reimbursement, which may limit access to safe and effective therapies for women with low socioeconomic status. Attention should be paid to the presence of ethical dilemmas, also in the context of clinical trials. Women planning pregnancy are often excluded from clinical trials, and there are no clear protocols for monitoring fertility and possible exposure to drugs, which limits the availability of data and the ability to make fully informed decisions [67].

Conclusions

Increased body weight has a negative impact on ovulation, egg quality, endometrial receptivity, and the chances of embryo implantation. In women with PCOS, obesity exacerbates symptoms, increases insulin resistance, and causes hormonal disorders. Referring to the scientific literature, it can be concluded that pharmacotherapy improves fertility by reducing body weight, which is associated with improved cycle regularity, ovulation, hormonal profile, and metabolic parameters.

There is also a limited amount of clinical data available. Most studies focus on women with PCOS, who are often also affected by obesity, but further well-designed studies involving women planning pregnancy are needed. It is important to mention certain concerns regarding the safety of pharmacotherapy during the periconceptional period. Most weight loss medications should not be taken during pregnancy or immediately before conception. It is recommended to discontinue most medications at least 1–2 months before planned pregnancy, while the use of contraception during treatment is standard practice. It should also be remembered that obesity treatment should be individualized, and women must be consciously informed about the potential benefits and risks.

Obesity is recognized as a significant factor leading to infertility in women. It causes disturbances in the hypothalamic-pituitary-ovarian axis, irregular ovulation, insulin resistance, and chronic inflammation. Pharmacotherapy for obesity is becoming a promising component of integrated infertility treatment, especially in women who do not respond to lifestyle modifications. It can increase the chances of natural pregnancy and improve the effectiveness of assisted reproductive technology treatments. However, its use requires caution, planning, and interdisciplinary supervision, especially with regard to pregnancy safety. Evidence from clinical

trials indicates the potential for improved fertility resulting from pharmacological treatment of obesity. The main effect of medication is weight loss, which in itself increases the chances of pregnancy by improving metabolic and hormonal parameters. Pharmacological treatment of obesity should be considered in women with a BMI ≥30 kg/m² who have irregular cycles or lack of ovulation, do not respond to diet and physical activity alone, have coexisting metabolic disorders such as insulin resistance, hyperandrogenism, or PCOS, and are eligible for infertility treatment (e.g., IUI, IVF) as a preparatory therapy. Pharmacotherapy should be considered a supplement to, not a substitute for, dietary and hormonal treatment and requires the cooperation of a gynecologist, endocrinologist, or dietitian.

Obesity is a complex chronic disease that affects many body systems, including reproductive functions. The treatment of infertility in overweight women requires an integrated medical approach that addresses hormonal, metabolic, dietary, and psychological aspects. In this context, interdisciplinary collaboration between a gynecologist, endocrinologist, dietitian, and psychologist is crucial. Comprehensive care contributes to a higher number of ovulations, pregnancies, and births, thus increasing the effectiveness of treatment, minimizing the risk of side effects through appropriate supervision of pharmacotherapy and metabolic status, and increasing patient engagement and long-term maintenance of treatment effects. An individualized approach is also possible, meaning that each woman can receive care tailored to her hormonal profile, mental health, and lifestyle. Interdisciplinary collaboration is therefore very beneficial for the patient and increases the chances of achieving the treatment goal.

Authors Contributions:

Conceptualization: Jagoda Bartman- Białek Methodology: Jakub Krzysztof Kruk, Wiktoria Dusiłło Software: Barbara Reizer

Check: Jakub Krzysztof Kruk, Wiktoria Dusiłło

Formal analysis: Jagoda Bartman- Białek, Barbara Reizer Investigation: Jagoda Bartman- Białek, Barbara Reizer,

Resources: Barbara Reizer

Data curation: Jakub Krzysztof Kruk, Jagoda Bartman- Białek,

Writing -rough preparation: Jagoda Bartman-Białek

Writing - review and editing: Jakub Krzysztof Kruk,

Visualization: Barbara Reizer

Supervision: Wiktoria Dusiłło

Project administration: Jagoda Bartman-Białek

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REFERENCES

1. Vigil, P., Blackwell, L. F., & Cortés, M. E. (2012). The importance of fertility awareness in the assessment of a woman's health: A review. *The Linacre Quarterly, 79*(4), 426–450.
2. Tsatsoulis, A., & Paschou, S. A. (2020). Female reproductive dysfunction in obesity and the role of the hypothalamic–pituitary–ovarian axis. *Hormones, 19*(2), 123–131.
3. Escobar-Morreale, H. F. (2021). Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. *Nature Reviews Endocrinology, 17*(9), 548–561.
4. Luk, B., & Loke, A. Y. (2015). The impact of infertility on the psychological well-being, marital relationships, sexual relationships, and quality of life of couples: A systematic review. *Journal of Sex & Marital Therapy, 41*(6), 610–625.
5. Silvestris, E., de Pergola, G., Rosania, R., & Loverro, G. (2018). Obesity as disruptor of the female fertility. *Reproductive Biology and Endocrinology, 16*(1), Article 22.
6. Cleveland Clinic. (2023). *Obesity: What it is, types, causes & treatment*.
7. World Health Organization. (2023). *Obesity and overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
8. Narodowy Fundusz Zdrowia. (2022). *Otyłość i jej konsekwencje*.
9. Verywell Health. (2023). *Split opinions on obesity as a disease*.
10. Jungheim, E. S., & Moley, K. H. (2010). Obesity and reproductive function: A review of the evidence. *Fertility and Sterility, 94*(7), 2181–2187.
11. Moran, L. J., Hutchison, S. K., Norman, R. J., & Teede, H. J. (2011). Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*, 2011(7), Article CD007506. https://doi.org/10.1002/14651858.CD007506.pub3
12. Bray, G. A., Kim, K. K., & Wilding, J. P. H. (2017). Obesity: A chronic relapsing progressive disease process. *Endocrine Reviews, 38*(1), 1–30. https://doi.org/10.1210/er.2016-1030
13. World Health Organization. (2022). *Obesity and overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
14. World Health Organization. (2008). *Waist circumference and waist–hip ratio: Report of a WHO expert consultation*. WHO.
15. Frühbeck, G., Toplak, H., Woodward, E., Yumuk, V., Maislos, M., & Oppert, J. M. (2013). Obesity: The gateway to ill health—An EASO position statement. *Obesity Facts, 6*(2), 117–120.
16. Després, J. P. (2012). Body fat distribution and risk of cardiovascular disease: An update. *Circulation, 126*(10), 1301–1313. https://doi.org/10.1161/CIRCULATIONAHA.111.067264
17. Björntorp, P. (1988). Abdominal obesity and the development of non-insulin-dependent diabetes mellitus. *Diabetes/Metabolism Reviews, 4*(6), 615–622. https://doi.org/10.1002/dmr.5610040605
18. Lemieux, S., Prud'homme, D., Bouchard, C., Tremblay, A., & Després, J. P. (1996). A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *The American Journal of Clinical Nutrition, 64*(5), 685–693. https://doi.org/10.1093/ajcn/64.5.685
19. Blüher, M. (2019). Obesity: Global epidemiology and pathogenesis. *Nature Reviews Endocrinology, 15*(5), 288–298. https://doi.org/10.1038/s41574-019-0176-8
20. Loos, R. J. F., & Yeo, G. S. H. (2022). The genetics of obesity: From discovery to biology. *Nature Reviews Genetics, 23*(2), 120–133. https://doi.org/10.1038/s41576-021-00414-z
21. Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., & Friedman, J. M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature, 372*(6505), 425–432. https://doi.org/10.1038/372425a0
22. Dallman, M. F., Pecoraro, N. C., & la Fleur, S. E. (2005). Chronic stress and comfort foods: Self-medication and abdominal obesity. *Brain, Behavior, and Immunity, 19*(4), 275–280. https://doi.org/10.1016/j.bbi.2004.11.004
23. Serretti, A., & Mandelli, L. (2010). Antidepressants and body weight: A comprehensive review and meta-analysis. *Journal of Clinical Psychiatry, 71*(10), 1259–1272. https://doi.org/10.4088/JCP.09r05346blu
24. Ouchi, N., Parker, J. L., Lugus, J. J., & Walsh, K. (2011). Adipokines in inflammation and metabolic disease. *Nature Reviews Immunology, 11*(2), 85–97. https://doi.org/10.1038/nri2921
25. Ahima, R. S., & Flier, J. S. (2000). Leptin. *Annual Review of Physiology, 62*(1), 413–437. https://doi.org/10.1146/annurev.physiol.62.1.413
26. Tena-Sempere, M. (2007). Feeding the reproductive axis: Environmental and metabolic signals. *Human Reproduction Update, 13*(6), 575–587.
27. Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature, 444*(7121), 860–867. https://doi.org/10.1038/nature05485
28. Diamanti-Kandarakis, E., & Papavassiliou, A. G. (2006). Molecular mechanisms of insulin resistance in polycystic ovary syndrome. *Trends in Molecular Medicine, 12*(7), 324–332. https://doi.org/10.1016/j.molmed.2006.05.006

29. Moran, L. J., Pasquali, R., Teede, H. J., Hoeger, K. M., & Norman, R. J. (2009). Treatment of obesity in polycystic ovary syndrome: A position statement of the Androgen Excess and PCOS Society. *Fertility and Sterility, 92*(6), 1966–1982.
30. Goldsammler, M., Merhi, Z., & Buyuk, E. (2018). Role of hormonal and inflammatory alterations in obesity-related reproductive dysfunction at the level of the hypothalamic-pituitary-ovarian axis. *Reproductive Biology and Endocrinology, 16*, Article 45. https://doi.org/10.1186/s12958-018-0366-6
31. Pan, H., Guo, J., & Su, Z. (2014). Advances in understanding the interrelations between leptin resistance and obesity. *Physiology & Behavior, 130*, 157–169. https://doi.org/10.1016/j.physbeh.2014.03.010
32. Esser, N., Paquot, N., & Scheen, A. J. (2015). Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. *Diabetes & Metabolism, 41*(6), 397–405. https://doi.org/10.1016/j.diabet.2015.02.006
33. Azziz, R., Carmina, E., Chen, Z., et al. (2016). Polycystic ovary syndrome. *Nature Reviews Disease Primers, 2*, Article 16057. https://doi.org/10.1038/nrdp.2016.57
34. Barber, T. M., Hanson, P., Weickert, M. O., & Franks, S. (2019). Obesity and polycystic ovary syndrome: Implications for pathogenesis and novel management strategies. *Clinical Medicine Insights: Reproductive Health, 13*, 1179558119874042. https://doi.org/10.1177/1179558119874042
35. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility, 81*(1), 19–25. https://doi.org/10.1016/j.fertnstert.2003.10.004
36. Lim, S. S., Norman, R. J., Davies, M. J., & Moran, L. J. (2013). The effect of obesity on polycystic ovary syndrome: A systematic review and meta-analysis. *Obesity Reviews, 14*(2), 95–109. https://doi.org/10.1111/j.1467-789X.2012.01053.x
37. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., et al. (2015). Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. *Endocrine Reviews, 36*(5), 487–525. https://doi.org/10.1210/er.2015-1018
38. Vitek, W. S., & Hoeger, K. M. (2020). Obesity and reproductive dysfunction: A review of the evidence. *Current Opinion in Obstetrics and Gynecology, 32*(3), 173–179.
39. Teede, H. J., Misso, M. L., Costello, M. F., et al. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction, 33*(9), 1602–1618. https://doi.org/10.1093/humrep/dey256
40. Pasquali, R., Gambineri, A., & Pagotto, U. (2006). The impact of obesity on reproduction in women with polycystic ovary syndrome. *BJOG, 113*(10), 1148–1159. https://doi.org/10.1111/j.1471-0528.2006.01090.x
41. Luzzo, K. M., Wang, Q., Purcell, S. H., et al. (2012). High fat diet induced developmental defects in the mouse: Oocyte meiotic aneuploidy and fetal growth retardation. *Biology of Reproduction, 87*(4), Article 73.
42. Jungheim, E. S., Schon, S. B., Schulte, M. B., et al. (2013). IVF outcomes in obese donors: Reduced oocyte quality, endometrial receptivity, and embryo quality. *Fertility and Sterility, 100*(6), 1570–1575.
43. Apovian, C. M., Aronne, L. J., Bessesen, D. H., McDonnell, M. E., Murad, M. H., Pagotto, U., et al. (2015). Pharmacological management of obesity: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism, 100*(2), 342–362. https://doi.org/10.1210/jc.2014-3415
44. Hutton, B., Fergusson, D., Wu, P., Yazdi, F., Bassler, D., Kazemi, M., et al. (2016). Orlistat for weight loss in adults. *Cochrane Database of Systematic Reviews*, 2016(3), Article CD003641. https://doi.org/10.1002/14651858.CD003641.pub4
45. Yanovski, S. Z., & Yanovski, J. A. (2014). Long-term drug treatment for obesity: A systematic and clinical review. *JAMA, 311*(1), 74–86. https://doi.org/10.1001/jama.2013.281361
46. Jayagopal, V., Kilpatrick, E. S., Holding, S., Jennings, P. E., & Atkin, S. L. (2005). Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *Journal of Clinical Endocrinology & Metabolism, 90*(2), 729–733. https://doi.org/10.1210/jc.2004-0176
47. Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., et al. (2015). A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *New England Journal of Medicine, 373*(1), 11–22. https://doi.org/10.1056/NEJMoa1411892
48. Davies, M. J., Bergenstal, R., Bode, B., Kushner, R. F., Lewin, A., Skjøth, T. V., et al. (2015). Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE Diabetes randomized clinical trial. *JAMA, 314*(7), 687–699. https://doi.org/10.1001/jama.2015.9676
49. Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., et al. (2021). Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine, 384*(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183
50. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: A comprehensive review. *Endocrine Reviews, 30*(1), 1–50. https://doi.org/10.1210/er.2008-0030

51. Greenway, F. L., Whitehouse, M. J., Guttadauria, M., Anderson, J. W., Atkinson, R. L., Fujioka, K., et al. (2009). Rational design of a combination medication for the treatment of obesity. *Obesity, 17*(1), 30–39. https://doi.org/10.1038/oby.2008.448
52. Wadden, T. A., Foreyt, J. P., Foster, G. D., Hill, J. O., Klein, S., O'Neil, P. M., et al. (2011). Weight loss with naltrexone-bupropion combination therapy as an adjunct to behavior modification: The COR-BMOD trial. *Obesity, 19*(1), 110–120. https://doi.org/10.1038/oby.2010.147
53. Grilo, C. M., Lydecker, J. A., Fineberg, S. K., Moreno, J. O., Ivezaj, V., & Gueorguieva, R. (2022). Naltrexone plus bupropion combination medication and behavior therapy, alone and combined, for binge-eating disorder: Randomized double-blind placebo-controlled trial. *American Journal of Psychiatry, 179*(12), 927–937. https://doi.org/10.1176/appi.ajp.20220267
54. Grundy, S. M. (2004). Obesity, metabolic syndrome, and cardiovascular disease. *Journal of Clinical Endocrinology & Metabolism, 89*(6), 2595–2600.
55. Jensterle, M., Kocjan, T., Kravos, N. A., Pfeifer, M., & Janez, A. (2015). Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocrine Research, 40*(3), 133–138. https://doi.org/10.3109/07435800.2014.966385
56. Kristensen, S. L., Rørth, R., Jhund, P. S., Docherty, K. F., Sattar, N., Preiss, D., et al. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomized trials. *The Lancet Diabetes & Endocrinology, 7*(10), 776–785.
57. Gambineri, A., Patton, L., Altieri, P., et al. (2004). Polycystic ovary syndrome is a risk factor for type 2 diabetes: Results from a long-term prospective study. *Diabetes, 53*(3), 785–791.
58. Brownley, K. A., Berkman, N. D., Sedway, J. A., Lohr, K. N., & Bulik, C. M. (2007). Binge eating disorder treatment: A systematic review of randomized controlled trials. *International Journal of Eating Disorders, 40*(4), 337–348.
59. U.S. Food and Drug Administration. (2023). *Drug safety communication: FDA warns about risks of use of GLP-1 receptor agonists in pregnancy*.
60. Glueck, C. J., & Wang, P. (2002). Metformin during pregnancy and lactation in women with the polycystic ovary syndrome: Medical therapy without fetal or neonatal toxicity. *Journal of Laboratory and Clinical Medicine, 140*(3), 169–176.
61. Thom, G., & Lean, M. E. J. (2017). Is there an optimal diet for weight management and metabolic health? *Gastroenterology, 152*(7), 1739–1751.
62. Compher, C. W., & Badell, M. L. (2016). Pregnancy after bariatric surgery. *Clinical Obstetrics and Gynecology, 59*(1), 136–145.
63. DeMarco, L. M., & Berry, D. C. (2013). Ethical issues in the treatment of obesity in women of childbearing age. *Journal of Midwifery & Women's Health, 58*(5), 489–495.
64. Legro, R. S., Dodson, W. C., Kunselman, A. R., et al. (2016). Benefit of delayed fertility treatment with preconception weight loss in obese women with PCOS. *Journal of Clinical Endocrinology & Metabolism, 101*(7), 2658–2666.
65. Beauchamp, T. L., & Childress, J. F. (2013). *Principles of biomedical ethics* (7th ed.). Oxford University Press.
66. Lyerly, A. D., Little, M. O., & Faden, R. R. (2008). The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics, 1*(2), 5–22.