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The impact of obesity on female infertility and treatment methods- summary of current knowledge

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Abstract:
Introduction and Purpose:
Obesity as a disease of civilization has become a new global epidemic. It is affecting a reduced quality of life. As its prevalence increases, the number of women of childbearing age who are overweight and consequently obese is also increasing. As a result, the number of cases with reproductive disorders is increasing. In addition, the topic of a syndrome that combines these two problems, which is polycystic ovary syndrome, is emerging with increasing frequency. This is becoming a challenge for physicians dealing with infertility treatment, pregnancy maintenance, miscarriages and pregnancy complications. This study aims to review current scientific research on the impact of obesity on female fertility and describe currently available treatment options for this group of women.
Brief Description of the State of Knowledge:
Adipose tissue influences gonadal function by secretion of adipokines, such as leptin, adiponectin, ghrelin and resistin. [1] Adipokines are important modulators of glucose metabolism, because they may primarily contribute to adverse fat distribution, altered appetite and satiety, impaired insulin sensitivity or insulin secretion, and to inflammation [2]. Adipokines contribute to metabolic syndrome, insulin resistance, and hyperandrogenism. This predispose patients to PCOS and associated infertility [3].
Summary:
Obesity is an increasingly common challenge in infertility clinical practice. Assessing the impact of this disease on female infertility can provide valuable diagnostic and therapeutic information, potentially improving fertility in women at risk.
Materials and Evidence: A literature review was conducted using the PubMed database.

Keywords: obesity, infertility, adipokines, PCOS, insuline

INTRODUCTION

The lifestyle change that has occurred in society associated with the increased availability of processed food, sweets and fast food has led to a positive energy balance in society. At the same time, there has been an increase in public ownership of motor vehicles, which has led to a decrease in physical activity. As a result, there has been an increase in obesity and thus its complications such as infertility.

Definition of obesity

Obesity is a chronic complex disease defined by excessive fat deposits that can impair health. Obesity it is generally defined using the body mass index (BMI) measurement in the units kg/m2. Based on World Health Organization (WHO) standards, a BMI of

- 18.5–24.9 is considered normal,
- 25–29.9 overweight,
- ≥30 as obese.

Definition of infertility

The definition of infertility is the failure to achieve pregnancy within 12 months of unprotected sexual intercourse or therapeutic donor insemination in women under the age of 35, or within six months in women over the age of 35 [4]. These reproductive sequelae are due to the effects of obesity on a number of different stages of the reproductive process, including ovarian follicle recruitment, oocyte development and quality, oocyte fertilization, and embryo development and implantation [5].

Epidemiology of obesity

In 2022, 1 in 8 people in the world were living with obesity. Worldwide adult obesity has more than doubled since 1990. In 2022, 2.5 billion adults were overweight. Of these, 890 million were living with obesity. In 2022, 43% of adults aged 18 years and over were overweight and 16% were living with obesity [6].

Epidemiology of infertility

Large numbers of people are affected by infertility in their lifetime. Around 17.5% of the adult population - roughly 1 in 6 worldwide – experience infertility. Lifetime prevalence is 17.8% in high-income countries and 16.5% in low- and middle-income countries [7].

Epidemiology of PCOS

PCOS affects an estimated 8-13% of women of reproductive age, and up to 70% of cases are undiagnosed [8].

In clinical studies, unfortunately, it is difficult to determine which stage and which tissue (oocyte, sperm, embryo, placenta, uterine environment) is most affected by obesity. Girls are born with a certain number of oocytes, so the impact of the uterine environment on this cell is particularly significant. In the 16.-20th week of fetal life, the number of primary follicles in both ovaries is the highest, as many as 6-7 million. The primary follicle contains an immature egg cell (oocyte). Starting from the 20th week of pregnancy, the number of oocytes decreases, at birth to about 1 million, and at puberty to about 400,000. During the entire reproductive life,

approximately 400-450 oocytes ovulate from this pool [9]. Negative exposure to environmental factors can affect the developmental competence of the oocyte; defined as the ability of the oocyte to fertilize and support embryo development [10].
Adipose tissue is the site of steroid hormone production, so when there is an excess of steroid hormones, the amount of the hormones in question increases. This leads to an increase in serum insulin and cellular resistance to its action.
Increased insulin leads, also, to a reduced amount of sex hormone binding globulin, or SHBG. This is a protein produced in the liver that binds to testosterone, dihydrotestosterone and estradiol, making it responsible for transporting sex hormones in the blood. As a result, the amount of free androgens and estradiol, which are biologically active in this form, increases. In addition, aromatase contained in fat tissue converts androgens into estrogens. Excess estrogen disrupts the hormonal balance and leads to menstrual disorders, it leading to early menarche in adolescents and potentially early menopause in older women [11]. This which disrupts the hypothalamo-pituitary-gonadal axis during the ovarian cycle. Obesity is associated with chronic inflammation. Adipose tissue is a producer of pro-inflammatory cytokines (TNF-α and IL-6), which cause increased inflammation and oxidative stress. The body can't keep up with antioxidant defenses, which leads to chronic imbalance, exacerbating inflammation of the oxidative stress cycle and metabolic disorder. Such an environment is unsuitable for oocytes, reducing their quality and viability. At the same time, the quality of the endometrial lining decreases , reducing its susceptibility to embryo implantation, thus creating significant challenges to successful conception [12].

Polycystic ovary syndrome (PCOS)

The current reality is that there is a set of symptoms that combines the problems of infertility and obesity. It is, an endocrine disorder that mainly affects women of childbearing age. Polycystic ovary syndrome (PCOS) leads to infertility, insulin resistance, obesity, and cardiovascular problems, including a litany of other health issues. PCOS is a polygenic, polyfactorial, systemic, inflammatory, dysregulated steroid state, autoimmune disease, manifesting largely due to lifestyle errors [13]. Its cause is an imbalance between female hormones, resulting in a lack of ovulation and a disruption of the menstrual cycle. This disease leads to cysts in the ovarian antral follicles. A cyst is a water-filled sac containing the egg, that should have been normally discharged for possible fertilization. The conversion of the egg into a cyst, termed as ‘functional cyst’, prevents ovulation. As ovulation is blocked, it results in the disruption of the menstrual cycle, causing ‘amenorrhea’. When multiple cysts are formed in the ovarian follicles due to the hormonal imbalance, it is characterized as PCOS. [14] The cysts can vary in size, up to 10mm, resulting in an increase in the size of the ovary. Ovarian cells also proliferate under the influence of insulin, causing ovarian hyperthyroidism.
The essence of the disorder in PCOS is an alteration in the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. It stimulates the pituitary gland to secrete folliculotropic hormone (FSH), which is responsible for the growth of the ovarian follicle, and luteinizing hormone (LH), which is responsible for stimulating ovulation. Increased

gonadotropin-releasing hormone (GnRH) pulse frequency in PCOS promotes synthesis of luteinizing hormone (LH) over follicle-stimulating hormone (FSH), leading to elevated circulating LH to FSH ratios in women with PCOS.
Increased LH levels stimulate androgen synthesis from ovarian theca cells, and FSH deficiency, relative to increased LH, disrupts follicular development, resulting in anovulation and accumulation of small antral follicles. Increased LH levels stimulate androgen synthesis from ovarian theca cells, and FSH deficiency, relative to increased LH, disrupts follicular development, resulting in anovulation and accumulation of small antral follicles [15].
The rest of the components (hyperinsulinaemia, insulin resistance and hyperandrogenaemia) of this syndrome also contribute to infertility.
Insulin stimulates androgen production by ovarian theca cells. In addition, hyperinsulinemia inhibits the production of insulin-like growth factor 1 (IGF1) binding protein in the liver, leading to elevated levels of circulating IGF1, which increases androgen production by the ovaries. Excess insulin also inhibits hepatic production of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen levels [16].
Hyperinsulinemia induces expression of LH receptors on granulosa cells of small antral follicles in the early phase of the folliculogenesis and leads to premature differentiation of these cells. This premature differentiation results in follicular growth arrest and, consequently, accumulation of immature follicles and anovulation [17].

Weight loss methods

Weight loss through a balanced diet, adequate caloric intake and increased exercise reduces obesity and, consequently, its complications. In women, weight loss from diet and exercise is associated with improved chances of becoming pregnant, with a trend toward improved live birth rate [18].
In 2007 created a pattern of “fertility diet,” consisting of a lower intake of animal protein with a higher supply of vegetable protein, a high iron content, an increased supply of monounsaturated fatty acids with a simultaneous lower consumption of trans-fatty acids, consumption of high-fat dairy products, and the presence of carbohydrate products with a low glycemic index. The study was conducted in women and showed that participating in this nutritional pattern was associated with a lower risk of fertility impairment due to other factors [19]. Protein obtained from red meat and poultry has been shown to significantly increase the risk of infertility due to anovulation. Moreover, it has been shown that consuming 5% of energy from plant protein instead of animal protein reduces the risk of anovulatory infertility by over 50%. The difference may be due to the different influence of plant and animal proteins on insulin and insulin-like growth-factor I (IGF-I) secretion. The potentially beneficial effect of plant protein on fertility may arise from the fact that the insulin response is weaker with the consumption of plant protein than with animal protein. [20] Diet with a high glycemic index and low dietary-fiber content are also strongly correlated with inflammation, which negatively affects the fertility. [21] A low-protein diet has been also identified as a potential risk factor for

male infertility as it can lead to a significant reduction in the weight of the testicles, epididymis, and seminal vesicles, as well as a decrease in serum testosterone. [22]
The right amount and quality of fatty acids consumed is of great importance in the context of the prevention of fertility problems. Both excessive and insufficient dietary fat contribute to fertility disorders. Most of the evidence supports the negative effects of diets high in trans-fatty acids and low in PUFAs (polyunsaturated fats) on reproductive performance in healthy women. [23] In the case of ovulation disorders, the most important thing is the quality, not the quantity of fat [24]. Trans-fatty acids (TFAs) appear to have the most negative impact on fertility. TFAs have been found to negatively affect ovulation function in women, promoting insulin resistance, and their increased consumption leads to an increase in inflammatory markers. [25]
Food items such as margarine, crackers, bakery products, cookies, and deep-fried foods contains with industrial trans fatty acids. Unfortunately trans fatty acids cannot be completely removed from human diets due to their presence in the meat and dairy products of ruminants. [26] In contrast, the main sources of saturated fatty acids in the food supply are animal products, such as butter, cows' milk, meat, salmon, and egg yolks, and some plant products such as chocolate and cocoa butter, coconut, and palm kernel oils. [27] PUFA supplementation has a positive effect on female fertility by influencing the concentration of LH and FSH, dominant-follicle maturation, oocyte quality, and the induction of ovulation [28]
The mediterranean nutritional pattern is characterized by high consumption of plant-derived food (vegetables, legumes, fruit, nuts, cereals, and seeds), fatty saltwater fish, low-fat dairy and poultry, and whole-grain cereal products with a low consumption of simple sugars (sweets) and red meat. Olive oil is the main source of fat. The traditional Mediterranean diet is one of the healthiest dietary patterns and has been linked to many beneficial health effects: decreased risk of all-cause mortality, cardiovascular disease, cancer, and other chronic diseases. [29] Additionally, the Mediterranean diet appears to reduce the risk of weight gain and insulin resistance in women of childbearing age, which may increase the likelihood of getting pregnant. [30]
Avocados are not a staple of the Mediterranean diet, but they fall into the category of fruits rich in antioxidants and fiber, and their fatty acid profile is naturally high in monounsaturated fats (MUFAs), which are linked to better pregnancy outcomes. In addition, it contains significantly higher amounts of the important nutrients folic acid and potassium, which are usually supplied in insufficient amounts in the mother's diet. [31]
Lifestyle changes have become a key therapeutic strategy for treating infertility in obese women.

Pharmaceutical drugs as a method of weight loss

An important issue in weight reduction in women has, also pharmaceutical drugs. One of them is metformin (1,1 dimethylbiguanide hydrochloride). It is a biguanide antidiabetic drug. It inhibits gluconeogenesis in liver, reduces glucose content, promotes the utilization of peripheral glucose and increases insulin sensitivity to decrease blood glucose levels [32]. Metformin also shows a slight beneficial effect on serum lipid levels, reducing triglycerides, total cholesterol, LDL and VLDL. Its most common side effects include gastrointestinal disorders, mainly

diarrhea, vomiting, nausea, abdominal pain and lack of appetite. There are also several contraindications to keep in mind before including this drug in a patient, such as [33]:

- acute complications of diabetes, such as diabetic ketoacidosis
- severe renal failure (eGFR <30 ml/min/1.73 m2) or risk of impaired renal function (e.g., dehydration, severe infection, shock, need for iodine-containing contrast agents),
- conditions associated with tissue hypoxia (including heart failure , shock, respiratory failure),
- liver failure,
- acute alcohol intoxication or alcoholism,
- pregnancy and lactation.

Currently, medications approved by the FDA/EMA for treatment of obesity include [34]:

- short-term phentermine - enhances the release of norepinephrine, dopamine and serotonin thereby centrally regulating appetite suppression,
- orlistat- is an active gastric and pancreatic lipase inhibitor, suppressing the hydrolysis of triglyceride in the gut lumen resulting in reduced fat absorption,
- naltrexone- is an opioid antagonist that enhances POMC secretion by attaching the μ-opioid receptor and blocking the autoinhibitory loop mediated by β-endorphin,
- Bupropion stimulates POMC via the arcuate hypothalamic nucleus that releases α-melanocyte-stimulating hormone leading to increased satiety and energy expenditure,
- Liraglutide and semaglutide are Glucagon-like peptide-1 receptor (GLP-1R) agonists and they have anti-obesity and anti-hyperglycaemic effects,
- Tirzepatide is a dual GIPR/GLP-1R agonist.

Glucagon-like peptide-1 analogs (GLP-1RAs) mimic incretin secreted by the distal small intestine, bind to insulin receptors on beta cells, stimulate insulin secretion, reduce glucagon secretion, inhibit hunger centers and delay gastric emptying. They also exhibit anti-inflammatory properties. As a result, GLP-1RA therapy has excellent therapeutic effects in improving hyperandrogenemia, increasing menstrual frequency, and reducing symptoms of metabolic disorders. The combination of GLP-1RAs and metformin appears to be superior to any single agent in reducing weight, hyperandrogenemia and ovulatory disorders in women with PCOS. Unfortunately, most GLP-1RAs are administered subcutaneously, and as a result, their improper administration can result in a large number of side effects [35].
Most drugs cause weight loss through temporary effects on appetite, so patients need to reduce energy intake and/or increase energy expenditure in the long term to maintain the weight loss achieved by the drugs [36].

Surgical operations as a method of weight loss

Surgical interventions are another aspect widely developing in obesity treatment methods. In particular, bariatric surgery, whose main goal is to induce significant weight loss, has a positive impact on fertility outcomes. According to the American Society for Metabolic and Bariatric

Surgery (ASMBS), the most commonly performed bariatric procedures are Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion with duodenal switch, with the Roux-en-Y gastric bypass considered the gold standard of weight loss surgery. Delaying pregnancy until 1–2 years after bariatric surgery has been recommended to avoid fetal exposure to nutritional deficiencies from rapid maternal weight loss, and the ASMBS recommends waiting 12–18 months [37]. Bariatric surgery has proven to be the most effective long-term treatment for weight loss and management along with improving reproductive function [38].

Infertility treatment methods

As for infertility treatment itself, there are three options at this point. They are gonadotropin therapy, clomiphene citrate and assisted reproductive technology (ART).

The first involves folitropin alfa, which is a recombinant preparation of FSH/LH in a fixed 2:1 ratio, administered in combination with human chorionic gonadotropin (hCG), important in the development of ovarian follicles [39]. Clomiphene citrate acts as an estrogen receptor modulator and is another option for restoring folliculogenesis by inhibiting the negative feedback mediated by estrogen on the hypothalamus and pituitary, thereby increasing FSH secretion [40]. ARTs include intrauterine insemination, in vitro fertilization, in vitro maturation and sperm injection into the cytoplasm [41].

Complications in children born to obese women

Because of the epidemic of obesity in the world today, complications in children born to obese women is a topic of great interest to researchers. It is known that pregnancy itself in obese mothers is associated with an increased risk of complications, including gestational diabetes, hypertensive disorders, preterm labor and cesarean section. [42]

Maternal obesity propagates a vicious cycle of metabolic disorders passed down from mother to fetus in utero, with long-lasting impact on child and adult health. Children born to obese mothers have a two-fold increased risk for childhood obesity [43]. In addition, children born to obese mothers are at increased risk for metabolic, cardiovascular and neurological disorders later in life [44].

Maternal adipokines, i.e., interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), leptin and adiponectin link maternal nutritional status and adipose tissue metabolism to placental function. Adipokines and metabolic hormones have direct impact on placental function by modulating placental nutrient transport. In addition, obese pregnant women are at risk for hypertension and preeclampsia with reduced placental vascularity and blood flow, which would restrict placental nutrient delivery to the developing fetus. [45] Also newborns born to obese mothers had a higher incidence of bacterial and viral infections and required admission to neonatal intensive care units, indicating maternal obesity impacts the fetal immune system [46].

Obesity reduces fertility, with a 2.7-fold increased risk of infertility in women with a BMI of >30 kg/m2 and a 25-37% increased risk of miscarriage in pregnant women compared with

normal-weight counterparts. Also Obese women also respond less well to infertility treatments and have a higher risk of early miscarriage after in vitro fertilization, with the live-birth rate reduced by 20%. [47]

Summary:
The global nature of obesity and its impact on women's reproductive health has become a key concern for doctors of the day. The complications associated with this disease are quite a challenge for those trying to manage them. A number of options for dealing with the situation have emerged. Both lifestyle modification, pharmacological interventions and bariatric surgery offer promising solutions. Women struggling with PCOS face complex symptoms that negatively affect their overall quality of life and well-being on physical, mental and social dimensions. They should undertake lifestyle change interventions and pharmaceutical therapy, as these can be effective strategies for improving insulin sensitivity while increasing ovulation and lowering androgen levels. It is also worth noting that the victims of the complications of obesity are not only obese women, but also the children born by them.
Society should pay attention to this global problem, which with its complications affects people at every stage of life.

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As a review paper, our work does not present new data or analyses. Therefore, there arenospecific databases or data availability to report. The information and findings presentedinthisreview are based on previously published studies, which can be accessed throughtheirresective sourses as cited in the reference section.

Conflicts of Interest Statement

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