



The Impacts of Obesity on Female Infertility

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Absrtact

Obesity is a major health problem throughout the world and defined as a body mass index (BMI) of 30 kg/m² or more. It is strongly associated with reduced fertility in both male and female. Although the effects in men are modest, the increasing rates of obesity in the general population may cause dramatic increases in infertility rates among men in the coming years. The spectrum of reproductive problems associated with obesity encompasses a wide range of disorders including infertility problems, miscarriage and pregnancy complications. Obesity contributes to disorder such as, hirsutism, anovulation, multiple cysts in the ovaries, and insulin resistance characterize a syndrome known as polycystic ovarian syndrome (PCOS). This syndrome is characterized by increased levels of circulating luteinizing Hormone (LH) which is secreted in exaggerated pulses. The increased LH is thought to be responsible for the increased ovarian production of steroids and impaired follicular development. Several studies reported that PCOS patients showed a higher miscarriage rate than non-PCOS patients except for women with a tubal factor similar to what was observed in women with obesity compared to those with normal weight. Miscarriage also known as a spontaneous abortion, refers to the loss of a pregnancy before the 20th week of gestation. It is a relatively common occurrence, with studies reporting that 10-20% of known pregnancies end in miscarriage, though the actual rate could be higher as many early miscarriages occur before a woman even realizes that she's pregnant. Informing Health care, Raising Awareness, Understanding Mechanisms, and Developing interventions are the main goals.

Keywords: BMI, Female Infertility, Miscarriage, Obesity, PCOS

Introduction

Most people agree that obesity is a serious worldwide epidemic with far-reaching effects that go well beyond the health consequences for the individual. The prevalence of obesity has sharply grown in rich nations, and emerging nations are also following suit. One of the main causes of many underlying etiologies linked to infertility is obesity [1]. A body mass index (BMI) of 30 kg/m² or greater is classified as obese, while a BMI of 25 to 29.9 kg/m² is considered overweight [2]. The most widely used measure of abdominal fat is waist circumference (WC), which is a straight forward predictor of central obesity. By dividing the waist by the hip circumference, the waist-to-hip ratio was determined. By dividing the waist circumference by the Height, the waist-to-height ratio (WHtR) was computed and classified as either <0.5 or ≥0.5. WHtR ≥0.5 was used to characterize abdominal obesity which causes infertility [3,4,5]. Obesity contributes to infertility through multiple mechanism, such as Secretion of adipokines consist in leptin, adiponectin, ghrelin, and resistin, from adipose tissue affects gonadal activity. Leptin is by far the best studied of them. One of leptin's reproductive roles is to control the cleavage and growth of early embryos. It has also been discovered that leptin prevents the granulosa cells from producing estradiol in response to luteinizing hormone (LH). These consequences



might help to explain why obese women have poor reproductive results [6]. According to WHO estimates from 2016, 650 million individuals worldwide, or 13% of the total population, are obese, while over 1.9 billion adults, or 39% of the total, are overweight. A woman is considered infertile if she is Unable to conceive or achieve a clinical pregnancy after one year of regular, unprotected sexual activity and therapeutic donor insemination for women under 35 and six months for those over 35 years [7]. Obesity has Different metabolic causes. The fact About Polycystic Ovarian Syndrome that over 50% of PCOS patients are obese and that most of them exhibit the abdominal phenotype of fat distribution which is in and of itself linked to a functional hyperandrogenism state (see the paragraph that follows), insulin resistance and compensatory hyperinsulinemia partially supports this [8]. The growth hormone (GH)–IGF-1 axis, insulin, gonadotropins, and some cytokines especially leptin are the main variables which play Role in infertility [8,9]. Two of the three diagnostic criteria listed below must be present to diagnose PCOS: The presence of polycystic ovarian morphology on ultrasonography Clinical and biochemical indications of hyperandrogenism, Oligo or an ovulation [9]. Regardless of the method of conception, obesity raises the risk of miscarriage. The precise process underlying this is complex and hard to classify [1]. In the first trimester, patients with PCOS have a 30% to 50% increased chance of spontaneous miscarriage [10]. The aims and importance of this review paper are Informing Healthcare Practices Which Provide evidence-based recommendations for healthcare providers regarding the management of obesity in patients seeking fertility treatment and the importance of weight management in improving fertility outcomes. Raising Awareness Increase awareness among healthcare professionals and the public about the relationship between obesity and infertility, promoting education on healthy lifestyle choices that support reproductive health. Understanding Mechanisms Investigate the biological mechanisms through which obesity affects fertility in both men and women. This includes hormonal imbalances, changes in metabolic function, and the impact of excess body fat on reproductive organs. Developing Interventions Explore lifestyle interventions, such as diet and exercise that can help mitigate the effects of obesity on fertility y. This could include weight loss programs and their impact on reproductive health. Identifying Risk Factors: Exploring the various risk factors associated with obesity that may contribute to infertility, such as metabolic syndrome, polycystic ovary syndrome (PCOS), and insulin resistance.

Obesity

Most people agree that obesity is a serious worldwide epidemic with far-reaching effects that go well beyond the health effects on the individual [1]. A body mass index (BMI) of 30 kg/m² or more is considered obese, whereas a BMI of 25 to 29.9 kg/m² is considered overweight [2] [3]. Because of changes in their pattern of secretion and/or metabolism, changed hormone transport, and/or action at the level of target tissues, obesity is linked to several abnormalities in the endocrine systems, including aberrant circulating blood hormone concentrations [8]. Leptin inhibits IGF-I, which causes steroidogenesis to rise. Leptin has little influence on GC's production of basal estradiol. FSH-stimulated estradiol synthesis is increased by IGF-I. Estradiol's FSH stimulation is unaffected by leptin [11].

Prevalence of obesity

A major public health concern that has sparked alarm throughout the world is obesity. According to the WHO, since 1980, the global obesity rate has more than doubled. In 2014, over 600 million people were fat, and over 1.9 million adults were overweight. Of the adults, 14% were obese and 39% were overweight. Furthermore, 41 million children under the age of five worldwide were overweight or obese in 2014 [6]. Obesity is one of the main causes of co-morbidities, such as diabetes, cancer, cardiovascular illnesses, and other conditions that can cause morbidity and death, according to earlier research. The high overall cost of obesity and overweight places a comparatively heavy financial

strain on the GDP of the majority of nations Obesity is considered a major public health hazard that has caused alarm all over the world. Throughout

Infertility

Obesity negatively affect male reproductive function. Study shown that the mean sperm concentrations [39 million sperm/mL) of overweight and obese men (BMI ≥ 25 kg/m²) were lower than those of normal-weight men (BMI 20–25 kg/m²; 46 million sperm/mL). Overweight and obese men were more likely to present with oligospermia compared with normal weight men (sperm concentration <20 million sperm/mL) (24.4% vs. 21.7%) [8]. As obesity rises, plasma testosterone concentration falls but testicular size remain constant. A decrease in the amount of sex hormone-binding globulin (SHBG) leading to lower in total testosterone. Conversely, the decrease in SHBG seems to be a result of elevated insulin and insulin resistance and SHBG has been utilized as a proxy for elevated risk associated with. Men of normal weight or moderately obese have normal levels of free testosterone relative to total testosterone, but extreme obesity may also result in a drop in free testosterone. Both oestrone and estradiol concentrations increase with male weight. The pituitary gonadotropins stay normal, while testosterone and SHBG fluctuate. Similarly, after receiving an injection of gonadotropin-releasing hormone (GnRH), the pituitary releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH) normally [12,10]. The relationship with obesity is more complex in women than in men due to the cyclical nature and intricacy of the female reproductive system. Table II provides a quick summary of these modifications. Obese women had more atretic follicles and more ovarian hyalinization than obese men, despite the testes being normal in obese males. Compared to females of normal weight, obese girls may experience the onset of menarche earlier. The girls Frisch and Revelle offered one explanation for this phenomenon. It is predicated on the finding that, when growth rates quicken in late infancy, menstruation begins when body weight reaches a "critical mass." [12].

Table I. Testis and obesity

Testis size	N
Serum testosterone (total)	↓
(free)	N
SHBG	↓
Production testosterone	N
FSH-LH (basal)	N
Response to LHRH	N
Clomiphene	N
HCG stimulation	N
Oestrone and oestradiol production	↑

SHBG = sex hormone binding globulin; FSH = follicle stimulating hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone; HCG = human chorionic gonadotrophin.

Table II. Ovary and obesity

Ovary	↑ hyalinization and atretic follicles
SHBG	↓
Oestradiol turnover	↓
Androstenedione → oestrone	↑
DHEA production	↑
Urinary 17-KS	↑
LH + FSH-basal	N
Response to LHRH	N

SHBG = sex hormone binding globulin; DHEA = dihydroepiandrosterone; KS = ketosteroids; LH = luteinizing hormone; FSH = follicle stimulating hormone; LHRH = luteinizing hormone-releasing hormone.

The production of leptin increases with the size of the body fat mass. The reproductive system of the obese (ob/ob) mice remain prepubescent when this protein is faulty. When the body has enough food reserves to sustain the fetus until term, leptin signal the Hypothalamus that the body has enough energy reserves to support Reproduction. On average, women with ovulatory periods and Hirsutism weigh 14 kg more than women without irregular menstruation. The proportion of women with ovulatory cycles rose in tandem with the degree of excess weight. Compared to 8.4% of women who were

over 74% overweight, just 2.6% of women who were under 20% overweight experienced an ovulatory cycle [12][10]. The metabolism of steroids in other organs, which results in the creation of physiologically active steroidal compounds, complicates the reproductive system's function in women. The stromal cells of adipose tissue can transform the adrenal glands A4-androstenedione into oestrone. Oestrone can also be converted to estradiol by muscles. The increased conversion of A4-androstenedione to oestrone in obese women does not raise circulating estrogen concentrations because premenopausal women have significant ovarian synthesis of estradiol. On the other hand, the levels of estrogen seem to rise in the postmenopausal woman. A4-androstenedione and free testosterone levels were higher in obese women than in non-obese women after castrated obese women received estradiol implants. Research on the metabolism of estradiol reveals that obese women had lower hydroxylation at the C2 position and increased oxidation at the 17-oc position. Hydroxylation of the 16-oc position, however, was not significantly influenced by obesity [13].

PCOS (Polycystic Ovarian Syndrome)

Polycystic ovarian syndrome (PCOS) a condition of uncertain etiology is characterized by obesity, hirsutism, anovulation, numerous ovarian cysts, and insulin resistance. Furthermore, the significant prevalence of increased fat tissue in these women points to the connection between nutrition and reproduction [12]. Exaggerated pulses and elevated amounts of circulating LH are the hallmarks of this condition. It is believed that elevated ovarian steroid production and compromised follicular development are caused by the elevated LH. Androgen production decreases when LH secretion is suppressed with long-acting GnRH agonists, demonstrating the significance of LH stimulation of the ovary in the hyperandrogenization linked to this condition. As opposed to the increased levels of LH, FSH concentrations are generally reduced [10].

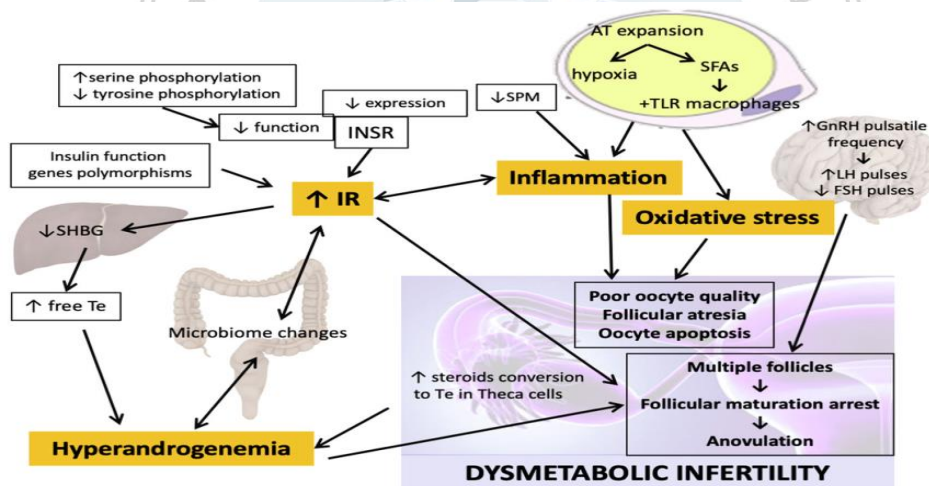


FIGURE 1 Mechanisms underlying dysmetabolic infertility. The main culprits of dysmetabolic infertility are depicted in orange: Insulin resistance, inflammation, oxidative stress and hyperandrogenemia. These are finely interconnected and no single one is causing the other, but they altogether contribute in causing polycystic ovary syndrome and, more generally, infertility. AT, adipose tissue; FSH, Follicle stimulating hormone; GnRH, Gonadotropin releasing hormone; INSR, insulin receptor; IR, insulin resistance; LH, Luteinizing Hormone; SFAs, saturated fatty acids; SHBG, Sex Hormone, Binding Globulin; SPM, proresolving lipid mediators; Te, Testosterone; TLR, Toll like receptor.

Miscarriage

Regardless of the method of conception, obesity raises the risk of miscarriage. The precise process underlying this is complex and challenging to classify. The well-established connection between obesity and polycystic ovarian syndrome (PCOS) is covered in more detail below [1]. In the first trimester, patients with PCOS have 30% to 50% increased chance of spontaneous miscarriage [10]. It is widely established that obesity and Hyperinsulinism, two metabolic comorbidities frequently present in PCOS patients, that reduce implantation rates and are linked to early and recurrent pregnancy loss [10]. According to several studies, women with



PCOS had a greater miscarriage rate than those without PCOS, except for those who had a tubal factor comparable to that of obese women compared to those of normal weight [14]. When a pregnancy ends before the twentieth week of gestation, it is referred to as a miscarriage or spontaneous abortion. It is a quite common event; research suggests that 10–20% of known pregnancies terminate in miscarriage. However, as many early miscarriages happen before a woman even knows she is pregnant, the true rate may be greater [15].

Causes of Miscarriage

Miscarriages can be caused by a variety of factors, and often, the exact cause is unknown. Some common reasons include Chromosomal abnormalities: Most miscarriages are due to random genetic issues in the embryo, which prevents it from developing normally.

Maternal health conditions: Conditions like diabetes, thyroid disorders, lupus, or infections can increase the risk.

Hormonal imbalances: Problems with hormone levels such as insufficient progesterone can affect pregnancy maintenance.

Structural issues: Conditions like uterine abnormalities (e.g., fibroids or septum) or cervical insufficiency can lead to miscarriage.

Age: Women over 35 are at a higher risk of miscarriage due to age-related declines in egg quality and increased chromosomal abnormalities.

Lifestyle factors: Smoking, heavy drinking, excessive caffeine consumption, and drug use can contribute to miscarriage risk.

Symptoms of Miscarriage: Vaginal Bleeding (which may or may not be accompanied by pain).

Abdominal cramps, loss of pregnancy symptoms such as Nausea or Breast Tenderness, Passage of Tissues which occur in late stage of pregnancy.

Types of Miscarriage

Threatened Miscarriage: When there is bleeding but the cervix is closed and the pregnancy may continue

Complete Miscarriage: When the pregnancy and all its tissues are passed from the body.

Incomplete miscarriage: When some but not all of the pregnancy tissue is expelled.

Missed miscarriage: When the embryo has died but hasn't been expelled yet, and there are no obvious symptoms briefly, in most cases, a miscarriage does not lead to infertility. However, if you experience multiple miscarriages it could indicate an underlying fertility problem that requires investigation and treatment. Seeking medical advice and exploring potential causes can help improve the chances of a successful pregnancy in the future [12,16].

BMI (Body mass index) The prevalence of overweight and obesity is commonly assessed by using body mass index (BMI), defined as *the weight in kilograms divided by the square of the height in meters (kg/m²)*. The BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness across different populations due in part to different body proportions. Therefore, ideally additional tools such as waist circumference and waist-hip ratio should also be used to assess obesity [9]. Dybiosis refers to disturbances in the interdependent relationship between intestinal lumen cells and gut microbes [17,18]. Changes in the relative abundance of specific microbial populations in the gut are correlated with increased intestinal and systemic inflammation [19,22].



WHO Classification of Overweight in Adults according to BMI

Classification	BMI (kg/m ²)	Risk of Associated Illness
Normal Range	18.5-24.9	Normal range
Underweight	<18.5	low but risk of other disease
Over weight	> 25.0	Average
Pre obese	25.0-29.9	increased
Obese Class 1	30.0-34.9	Moderate
Obese Class 2	35.0-39.9	Sever
Obese Class 3	>40.0	very sever [15,31].

Conclusion

Obesity affects female reproduction by disturbing general body metabolism, hormone metabolism, and follicular environment. In both sexes, obesity may impair fertility. This adverse effect appears to be mainly related to disorders of sex hormone secretion and/or metabolism, leading in turn to a condition of relative hyperandrogenism in obese women and hypotestosteronemia in obese men. These hormonal alterations may also play an important role in the pathophysiology of different obesity phenotypes and associated metabolic and cardiovascular comorbidities. The promotion of physical activity and an adequate nutritional plan is essential to promote ovulation and fertilization.

Suggestions

1- Hormonal Imbalance: While it's well-established that obesity can lead to hormonal imbalances (e.g., increased levels of estrogen, insulin resistance, and alterations in gonadotropin levels), the exact mechanisms by which these changes impact both male and female fertility require further investigation. Understanding how these hormonal disruptions affect oocyte quality, sperm function, and implantation is essential.

2- Inflammation and Immune Response: Obesity is associated with chronic low-grade inflammation, which could affect reproductive outcomes. More research is needed to explore how inflammatory cytokines and immune responses influence the reproductive system, particularly in women with polycystic ovary syndrome (PCOS), which is commonly associated with obesity.

3-Female vs. Male Infertility: While obesity's effects on female fertility have been extensively studied, less attention has been given to its impact on male fertility. Future research should examine the effects of obesity on sperm quality, semen parameters, and testicular function, as well as how these effects might influence fertility outcomes.



4-Social Stigma and Fertility Treatment Access: The social stigma associated with obesity may influence the willingness of individuals to seek fertility treatment, or it may affect the quality of care they receive. Future studies could explore how societal attitudes toward obesity impact fertility treatment access, compliance, and outcomes.

5-Preventative Measures and Public Health Campaigns: Although obesity is a preventable risk factor for infertility, public health campaigns and education on the link between obesity and infertility remain underdeveloped. Further research into how to design effective interventions that target obesity prevention and promote fertility health is essential.

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