

How Obesity Affects Female Fertility

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Abstract

Obesity and excessive weight affect not only overall health but also reproductive health. Many obese women are infertile, and multiple research have demonstrated the link between obesity and infertility. In addition to anovulation and menstrual abnormalities, obesity has been linked to reduced conception rate, as well as a reduced responsiveness to fertility treatment. It also raises the risk of miscarriage and increases the likelihood of neonatal and maternal complications. Treatment of obesity, particularly abdominal obesity treatment, is linked to improved reproductive function thus treating obesity must be the first priority in infertile obese women before considering drugs of ovulation induction or procedures of assisted reproduction.

Keywords: Female, fertility, obesity

INTRODUCTION

Obesity is defined as an abnormal or excessive buildup of body fat which is a common metabolic disturbance.^[1] A body mass index (BMI) of more than 25 kg/m², 30 kg/m², 40 kg/m² are considered as overweight, obese and severely obese respectively according to the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines.^[2] Obesity is linked to a slew of negative consequences. Metabolic problems, cardiovascular events, malignancies, gastrointestinal diseases, and arthritis are just a few of them.^[3] Aside from the cardiometabolic effects of obesity, there is strong confirmation that both female and male obesity increases the chance of subfecundity and infertility. According to previous studies,^[4,5] more than 40% of females with menstruation abnormalities, infertility, and recurrent abortion are obese or overweight. Anovulatory periods, oligoamenorrhea, hirsutism, infertility, and/or sexual disorders are all more common in women with obesity than in normal weight women.^[5]

Obesity interferes with normal endocrine function, resulting in ovulation, endometrial growth, and embryo developmental abnormalities.^[6] So how obesity affects female fertility is the topic of this review.

OBESITY EFFECT ON HYPOTHALAMIC–PITUITARY–OVARIAN AXIS

The HPO axis in women is disturbed by excess body fat via central and peripheral pathways.^[7,8] The clinical investigations show that extreme leanness is linked to delayed of puberty where as overweight or obesity is linked to early puberty. The alterations in the levels of hormone and some substrate cause the HPO axis to deteriorate. Obese females have high luteinizing hormone (LH), androstenedione, estrone, insulin, triglycerides, and very low density lipoprotein levels and lower lipoprotein of high density.^[9] The HPO axis deteriorates as a result of these changes, and various gynecological effects occur. Adipocytokines, notably leptin, have long been studied for their role in the body due to their stimulatory influence on GnRH pulses, leptin has been proven to be a critical gatekeeper of puberty and future fertility in cellular and animal models.^[10,11] The quantity of body fat is directly connected to peripheral leptin levels.^[3] Obese women have

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higher level of leptin, an adipokine that is produced by fatty tissue, than normal-weight.^[10] Women with high leptin levels in their blood and high leptin-to-BMI ratios have a reduced success rate with *in vitro* fertilization (IVF).^[6] In the human ovaries, leptin suppresses the steroidogenesis in both granulosa and thecal cells and disrupts the ovulation process so having a direct effect on fertility.^[3] Finally, an obesity-related central insulin resistance condition could be involved, the infertility mechanisms identified in obesity through the influence on LH secretion pulses' frequency and amplitude.^[12,13]

OBESITY EFFECT ON SEX STEROID AND INSULIN

Obesity is linked to a rise in estrogens (17-estradiol (E2) and estrone (E1)) as well as androgens (testosterone (T), dihydrotestosterone (DHT), androstenedione, and de-hydroepiandrosterone) because of adipose tissue produces androgens directly and converts them to estrogens.^[14] Obesity is also linked to lower levels of circulating sex hormone-binding globulin (SHBG), resulting in greater availability of androgens and estrogens to target tissues.^[15] These connections can be seen as early as adolescence and are more prominent in central obesity; they all contribute to a disorder known as "relative functional hyperandrogenism," which might compromise ovarian function and contribute to obesity-related infertility.^[6,14,15] Obesity notably central obesity is distinguished by resistance to insulin and hyperinsulinemia, which promotes the production of androgens in the ovaries both directly and indirectly by raising the local sensitivity to LH.^[16] Premature follicular atresia, which favors anovulation, may be caused by an excess of intraovarian androgen production.^[17] Furthermore, hyperinsulinemia causes a decrease in hepatic SHBG synthesis, resulting in an increase in the availability of free androgens,^[18] exacerbating peripheral hyperandrogenism, which causes an overproduction of acyclic E1 and, as a result, an excessive production of LH.^[19] Increased LH secretion can cause follicular growth to be arrested earlier, granulosa cell luteinization to be accelerated, and oocyte quality to be compromised.^[20,21] Insulin resistance and compensatory hyperinsulinemia, through all of these mechanisms, may contribute to menstrual, ovulatory, and fertility disturbances.^[3]

OBESITY EFFECT ON OOCYTE AND EMBRYO

Obesity has been shown to affect the oocyte in a number of studies. Changes in numerous hormones, particularly those that trigger oocyte maturation, may impact oocyte competence and maturation in obese people.^[22] Because adipose tissue is a key site for production of steroid hormones and metabolism, its overproduction in obesity can change steroid hormone levels.^[23] Increased BMI in women was linked with lower SHBG and higher insulin, glucose, lactate, triglycerides, and C-reactive

protein, an inflammatory marker in follicular fluid.^[22,23] Insulin provokes steroidogenesis in ovaries and increases expression of LH receptor in the theca and granulosa cells. Obesity disrupts the ovulation and maturation of oocytes in women due to LH hyper-secretion and alteration of LH: follicular stimulating hormone (FSH) ratio.^[13] In addition, greater levels of free fatty acids (FFAs) in circulation lead to an increase in reactive oxygen species (ROS) which causes apoptosis and damage of mitochondria and endoplasmic reticulum.^[24] Furthermore, obese women have greater levels of leptin in their serum and follicular fluid, and as a result of *in vitro* investigations, leptin reduces estrogen and progesterone synthesis in granulosa cells in a dose-dependent manner.^[6] The effects of obesity on the oocytes might have ramifications for receptivity of endometrium and implantation of embryo. Moreover, obese infertile women who are treated with assisted reproductive technology confront some challenges. Several studies have found that obese women undergoing IVF have a poor ovarian response to regulated ovarian stimulation, reduced oocyte number and quality, bad embryo quality, decrease the number of transferred embryos, decreased intra-follicular human chorionic gonadotrophins and estrogen levels.^[25]

Obesity also affects the preimplantation embryo; obese women are expected to produce low-quality embryos in IVF cycles using autologous oocytes.^[26] Increased leptin levels in obese women may have a direct detrimental effect on the developing embryo in addition to acting centrally.^[27] Leptin stimulates the formation of human trophoblastic stem cells *in vitro*, whereas inhibiting it reduces proliferation and drastically increases apoptosis.^[28] In obesity, tonically increased levels of leptin may reduce the trophoblast's susceptibility to its effects.^[6]

OBESITY EFFECT ON ENDOMETRIUM

Obesity's impact on uterine receptivity is a hotly debated topic. Obese women with polycystic ovary syndrome (PCOS) have an inferior endometrial genetic profile and unsatisfactory decidualization when compared to normal-weighted women, according to gene expression investigations performed during the implantation window.^[29] Endometrial decidualization is hindered in mice with diet-induced obesity; these findings were validated in human investigations conducted *in vitro* and *in vivo*, where stromal decidualization was found to be reduced in obese women.^[30] The pathogenesis of this phenomenon could be traced back to proinflammatory cytokines and ROS that cause endothelial dysfunction,^[31] as well as obese women with recurrent miscarriages had greater endometrial levels of expression of haptoglobin, an inflammatory marker.^[32] Furthermore, the ERK signaling pathway, which is part of the MAPK/ER and is required for invasion of trophoblast into endometrial lining of uterus was demonstrated to be downregulated in obese women

during implantation period.^[33] It has also been proposed that obesity reduce endometrial receptivity due to a variety of reasons including; relative hyperestrogenemia, low level of glycodelin and insulin growth factor binding protein 1 (IGFBP1) that occurs as a result of insulin resistance and hyper-insulinemia, and dysregulation of leptin level.^[34,35] Leptin has a regulatory role in modifying the uterine epithelium and activating proliferative and apoptotic cell pathways, in addition to influencing endometrial receptivity.^[36] Furthermore, leukemia inhibitory factor (LIF) has been linked to the regulation of implantation, with a strong negative relationship found between endometrial LIF and BMI.^[37] Obesity, as previously stated, is an inflammatory condition, and women with high BMI have been proven to demonstrate elevated pro-inflammatory cytokines interleukin 6 (IL 6) and tumor necrosis factor (TNF) levels, which are likely to have a deleterious impact on implantation.^[38] All of these phenomena could be contributing factors to low implantation and increased miscarriage rates in obese women.

CONCLUSION

There is an increase in obesity worldwide, and its detrimental influence on reproductive function, fertility state, and pregnancy rate is severe for both men and women. Obesity was also reported to influence the quality and number of oocyte and embryo, receptivity of endometrium and implantation process in both natural and assisted conception. The need of losing weight before pregnancy should be highlighted to overweight and obese patients, who should be encouraged to lose weight prior to any therapy intervention to avoid the negative consequences of obesity.

Ethical consideration

Not applicable.

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Conflicts of interest

There are no conflicts of interest.

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