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Effect of Obesity on Fertility

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ABSTRACT

Prior studies have shown that obesity causes many gynecologic and obstetric disorders, including anovulation, irregular periods, subfertility, abortion, and adverse pregnancy outcomes. Obesity-related infertility or reduced fertility problems were influenced by any step from follicular recruitment to implantation. Adverse effects in reproductive health were not subjected out of entire obese women. Physical activity and nutrition were shown to be the probable determining factors. Assisted reproductive techniques provide obese women with an opportunity to investigate the relationship with pregestational status and reproductive outcomes as well. Although there is a lack of epidemiological data, an association between obesity and abortion is already known in obese women who had spontaneous pregnancy. This study aimed to investigate the effects of obesity among various stages of the reproductive process in recent studies, to summarize multidisciplinary strategies, and to facilitate reproductive outcomes in obese women.

Keywords: Obesity, infertility, body mass index, assisted reproductive technology

Introduction

The term "obesity" comes from the Latin word "obere (obesusu)," which means "over eat," and it is defined as the presence of an extreme amount of fat tissue in the body (1). Body mass index (BMI) is classified considering the ratio of human body weight in kilograms to squared height in meters. According to this classification, a BMI of 18.5–24.9 kg/m^2 is accepted as normal. People with BMI values between 25 and 29.9 kg/m^{2}are overweight, those with BMI values between 30 and 39.9 kg/m^2 are obese, and those with values of 40 kg/m^2 and above are accepted as morbid obese (2). Obesity, which was first encountered in the studies of Thomas Venner in 1620, has become an epidemic concern worldwide, including developing countries as well as developed countries such as the USA (3-6). According to the 2012 Turkish Statistical Institute (TUIK) data (7), 17.2% of the population at the age of 15 years and above is obese. Moreover, according the data of the Turkish Ministry of Health, the rate of obesity among women is 41.0% (http://www.thsk. saglik.gov.tr/obezite-sismanlik, 2010).

Many studies have revealed that obesity is associated with many gynecological and obstetric problems, including anovulation, irregular menstruation, subfertility, miscarriage, and negative pregnancy results (8). It is reported that decreased fertility or infertility related to obesity is resulted from the effects on some different steps in each stage including implantation period beginning from the selection of ovarian follicle, due to imbalance between hypothalamus–pituitary–ovarian axis (9, 10). Understanding the effect of obesity on female reproductive functions is important because it will be carried by children of obese women who are ultimate targets of this effect.

The aim of this study was to review recent studies on the effect of obesity on various stages of reproductive process and to summarize original multidisciplinary strategies that will improve reproductive results in obese women.

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The Effect of Obesity on Target Organs in the Reproductive System

It is clear from the studies on the effects of obesity on fertility functions that obesity affects woman's fertility physiology at different levels. Reproductive goals in obesity include hypothalamus, ovary, follicle, oocyte, embryo, and uterine endometrium (11-18). The negative effect of obesity on fertility can occur at different stages, including the selection of follicle, development and quality of oocyte, fertilization of oocyte, and development and implantation of embryo.

In the study by Tortoriello et al. (11) conducted on murine in 2004, it was revealed that obesity-related oligoamenorrhea and subfertility were of hypogonadotropic origin. They stated that this was due to the fact that hyperleptinemia associated with obesity created GnRh suppression by causing an increase in hypothalamic neuropeptide. Furthermore, in the study by Jain et al. (12) conducted in 2007 on 18 obese women with oligoamenorreic who were not polycytic ovarian syndrome, LH secretion was found to be significantly lower compared with the control group, and this resulted from abnormal GnRH release.

The effect of obesity on the ovary and ovarian follicle is explained by increased ovarian resistance and granulosa cell apoptosis. In this way, a series of abnormal situations including the selection of oocyte, ovulation, and the quality of oocyte occur (16-18). As is known, insulin resistance develops in overweight women. Elevated levels of insulin increase the production of androgen in the ovarian stroma. Moreover, obesity leads to aromatization of androgens to estrogen in peripheral fat tissue and a decrease in the levels of steroid hormone-binding globulin (SHBG). Thus, obesity increases the levels of estradiol and free testosterone. This situation deteriorates hyperinsulinemia and causes the ovarian environment to go round in circles. As a result, increased androgen/estradiol ratio and LH hypersecretion affect ovarian microenvironment, impair folliculogenesis, and cause follicles to undergo atresia (19).

In addition to hyperinsulinemia, systemic changes such as dyslipidemia and inflammatory response, which are related to obesity, have negative effects in follicular microenvironment. In the study by Robker et al. (16), it was demonstrated that inflammatory factors, such as C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and plasminogen activator inhibitor type-1, had a harmful effect on the reproductive circle, and it was emphasized that this situation was associated with abnormal follicle environment. Furthermore, they reported that lipotoxic mechanisms might have influenced the quality of oocyte in the same group of obese women. They emphasized that this situation was similar to the mechanism defined in diabetic heart disease. They concluded that excessive lipid exposure could cause inappropriate storage of lipids in non-adipose tissues; thus, cellular functions might be impaired and might finally lead to cell death (19, 20). In further experimental studies, Yang et al. (17) found that lipid content and endoplasmic reticulum stress increased in rat-cumulus oocytes that were exposed to follicular fluid collected from obese women and accordingly, nuclear maturation was impaired.

Pre-implantation embryos of obese women are associated with abnormal pregnancy results. Jungheim et al. (16) reported in their study that embryos, which developed as a result of decreased insulin-like growth factor-1 expression in oocytes associated with insulin resistance, displayed growth retardation in the middle of gestation. Furthermore, in the study of the same group in 2011, a similar effect was demonstrated in embryos exposed to high amounts of saturated fat (21).

The effect of obesity on uterine receptivity is highly controversial. Gene expression analyses that were performed in the window of implantation of obese women with Polycystic ovary syndrome (PCOS) showed that they had an impaired endometrial genetic profile and suboptimal decidualization compared with normal-weighted women (22). In the study by Bellver et al. (23) on a donation model in 2013, although obese women received oocytes from healthy normal-weighted donors, their conception possibility was found to be lower than that in normal-weighted women. However, in another donation model study conducted by Styne-Gross et al. (24), it was emphasized that BMI did not have an effect on the decreasing rate of implantation. In addition, Luke et al. (25) reported in their study, which was performed in 2011, that conception possibility in obese women using donor oocytes was similar to that in normal-weighted women using donor oocytes, but the possibility of live birth was lower in obese women. This situation supports that the effect of obesity on the quality of oocyte is higher than its effect on endometrial receptive.

Knowledge Acquired From Assisted Reproductive Techniques

Women benefiting from assisted reproductive technology (ART) provide opportunities for investigating the relationship between pre-pregnancy conditions (such as obesity and reproductive functions) and reproductive results. Many studies on women using ART demonstrated that the dose of gonadotropin that was needed for reaching the number of follicles obtained as a result of ovarian stimulation was higer in obese women than in normal-weighted women (26). It is unknown whether this result is associated with decreased drug absorption, ovarian sensitivity, or both. Whatever it is, es-

tradiol level is significantly lower in obese women than in normal-weighted women, although similar number of oocytes are obtained during ovarian stimulation. This shows that there is a difference in the ovarian responses to gonadotropin stimulation in obese women (27, 28). Moreover, fertilization chance of mature oocytes is lower in obese women than in normal-weighted women, which suggests that the quality of oocytes in obese women is lower (27).

According to the results of studies, the rate of clinical conception after in vitro fertilization (IVF) was lower (28), abortion rate after ART was higher (29, 30), and the rate of live birth after IVF was lower (26) in obese women compared with normal-weighted women. These results were attributed to implantation failure due to abnormal endometrial development (18, 23).

In the study by Luke et al. (25) in 2011, decreased possibility of pregnancy and live birth and increased risk for abortion were reported in obese women getting ART support. It should be considered while evaluating these data that researchers conduct studies with limited data. They have a few specific data, except the data on fertility results and conception chance of obese women (25). Prospective studies on reproductive outcomes (neonatal–congenital anomalies, fetal growth abnormalities, and the duration of hospitalization in the neonatal intensive care unit) should also be performed in obese population who spontaneously conceive. The studies on women utilizing ARTs demonstrate that while obesity is an important factor determining reproductive capacities of women in the age <35 years, age is the dominant factor for determining reproductive capacities of women older than 35 years (25, 31). Considering this fact, in women aged >35 years, who have regular menstrual cycles and cannot conceive after unprotected sexual intercourse for at least 6 months, other methods that can provide rapid fertilization are more reasonable than focusing on losing weight. It should be known that conception rate is still good in an obese woman who apply with infertility and who must benefit from ART and age is always the dominant factor for the prediction of conception success.

Other Factors Affecting Fertility in Obese Women

In general, existing epidemiological, clinical, and laboratory studies demonstrate that obesity affects reproductive functions. However, it is not necessary that reproductive health of all obese women is negatively influenced. Therefore, identifying factors affecting reproductive functions of these women apart from obesity is important. Two possible factors are nutrition and physical activity. It can be difficult to reveal the contributions of each of these factors to reproductive functions in obese women. In the study by Chavarro et al. (32), the authors analyzed women with ovulatory infertility in terms of age, body size, parity, smoking, physical activity, total energy intake, and oral contraceptive usage. They reported that glycemic index (a measurement on how a specific food raises blood glucose) was directly related to ovulatory infertility and the risk for ovarian infertility was higher in women whose daily diet mostly included carbohydrates than in women who restricted the intake of carbohydrates. Moreover, they found that increased intake of saturated fat was associated with ovarian infertility risk and vegetable oils posed a lower risk than fats of animal origin. In the same study, it was also specified that multivitamin and iron support decreased ovarian infertility risk.

In addition to nutrition, physical activity is also important for fertility for the general energy balance. In an internet-based study conducted on Danish women who were planning to be pregnant, Wise et al. (33) found a direct relationship between severe physical activity and prolonged period of conception, but not in obese and overweight women. On the other hand, they revealed the benefit of moderate physical activity for women who wanted to become pregnant.

Effects of Obesity on Abortion and Late Pregnancy

There is no enough epidemiological data on the relationship between obesity and abortion in obese women conceiving spontaneously. This is not surprising because many obese women are anovulatory and need medical intervention for getting pregnant. Moreover, some obese women having irregular menstruation might not have reported abortion or might have confused bleeding due to abortion with irregular menstrual bleeding. In order to eliminate the lack of knowledge on this issue, Boots et al. (34) published a systematic review and meta-analysis investigating obesity and abortion risk in 2011. In this meta-analysis, 16 studies on obesity were examined and abortion risk was found to be higher in women with a BMI of ≥25 kg/m^2 than in normal-weighted women who became pregnant spontaneously (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.18–1.46).

It is well known that there is a complicated relationship among obesity, infertility, and PCOS, and the incidence of coexistence of these three findings is presently increasing. However, obesity is an independent risk factor for both spontaneous abortion and pregnancy complications regardless of the presence of PCOS (35). In a review conducted by Metwally et al. (36) in 2008, it was revealed that the rate of abortion significantly increased in women with a BMI of ≥25 kg/m^2 (OR, 1.67; 95% CI, 1.25–2.25). Similarly, in a study in which pregnancies following oocyte donation were investigated, the rate of abortion was detected to be higher in overweight and obese women (37).

It is well known that obese mothers are at risk in terms of antenatal, intrapartum, and postpartum complications

during pregnancy and labor. In addition to recurrent abortions before delivery, the most common problems include congenital anomalies, preeclampsia, gestational diabetes mellitus (GDM), and venous thromboembolism. Furthermore, the rate of cesarean sections increases due to fetal distress and prolonged labor in obese women. Although increased risk for cephalopelvic disproportion (CPD) due to obesity was reported in some studies (38, 39), Athukorola et al. (40) emphasized that CPD rate did not increase in obese parturients. In addition, the babies of obese women are mostly macrosomic, and the duration of hospitalization can be extended (41).

Conclusion

The prevalence of infertility and amenorrhea is high among obese women, and there is an increase in the risk for abortion after infertility treatment (42). However, there are many other factors that affect fertility treatment in obese women and contribute to infertility. Age is still the most important factor in infertility treatment in obese women as in normal-weighted women. As mentioned before, according to the studies on women benefiting from ART, the effect of obesity on fertility has mostly been observed in women younger than 35 years (25, 41). After the age of 35 years, age is a more important factor than obesity for conception.

On the other hand, although there are limited data classified according to age of obese women for pregnancy outcomes, it will be beneficial to lose weight at any age in obese women. The most important informative knowledge that supports the idea that losing weight will provide benefit in pregnancy has been obtained from women who become pregnant after undergoing obesity surgery and their next pregnancies (43). These data suggest that losing weight decreases the complications during pregnancy, but this study is narrow-scoped for demonstrating differences in pregnancy or neonatal results.

Similarly, the conducted studies show that nutrition and exercise are also important for improving fertility in obese women. The recommendations of Chavarro et al. (32) about improving ovulation and fertility (to remove trans fats from diet, to prefer unsaturated fats in food, to prefer vegetable proteins rather than animal proteins, to prefer brown bread instead of simple and processed carbohydrates, to take daily multivitamin and iron supplement) will be useful for many clinicians to manage the cases of obese women.

In conclusion, during infertility treatment, a clinician must also encourage obese women that want to become pregnant to lose weight and to follow an appropriate diet program for obtaining better fertility results. Moreover, obese women must be warned about pregnancy complications that can occur due to obesity. However, it must be kept in mind that age is always the most dominant factor in the prediction of conception success.

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