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REVIEW ARTICLE

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Female infertility: which role for obesity?

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Abstract

Obesity is associated with infertility in women through multiple and complex mechanisms. Briefly, the adipose tissue through the production of many factors, such as leptin, free fatty acids (FFA), and cytokines may affect both ovarian and endometrium functions, with a final alteration in oocyte maturation and endometrial epithelium receptivity. In addition, through the development of peripheral insulin resistance obesity produces a condition of functional hyperandrogenism and hyperestrogenism that contribute to produce anovulation and to reduce endometrial receptivity and, therefore participate to cause infertility. Weight loss is able to restore fertility in most cases, but there are no practical indications to guide the clinician to choice the best method among increased physical activity, diet, drugs, and bariatric surgery.

Introduction

Obesity is associated with a magnitude of complications. These include metabolic complications, cardiovascular events, tumors, gastrointestinal disorders, arthritis, and infertility [1]. The association between obesity and infertility in women is the topic of this review. In particular, the ovarian and extra-ovarian mechanisms at the basis of infertility in obese women are the subject of this review. In addition, the link between obesity and polycystic ovary syndrome (PCOS), the most frequent cause of anovulatory infertility, will be described, as well as the negative impact of obesity on assisted conception and pregnancy outcomes. Finally, the beneficial effect of weight loss in obese infertile women will be summarized.

Obesity and the hypothalamic-pituitary-ovarian axis

Body fat in women impacts the function of the hypothalamus-pituitary-ovarian (HPO) axis through central and peripheral mechanisms [2, 3]. Accordingly, clinical studies demonstrate that excessive leanness is associated with puberty delay, whereas obesity is accompanied by premature puberty [4]. These observations have led several researchers to investigate the metabolic mediators and pathways that directly or indirectly interact with the HPO axis in puberty and fertility. The role of adipocytokines, particulary leptin, has been widely studied. Several pieces of evidence from cellular and animal models have shown leptin to be an essential gate-keeper of puberty and future fertility through its stimulatory action on gonadotropin-releasing hormone (GnRH) pulses [5, 6]. Peripheral levels of leptin are directly related to the amount of body fat. Therefore, conditions of defect of body weight cause a decrease in leptin levels that per se suppresses fertility, whereas conditions of excess of body weight are associated with increased leptin secretion. However, most forms of obesity are characterized by a condition of leptin resistance,

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at least at the central level [7], probably via a down-regulation of leptin receptor expression [8]. Accordingly, Tortoriello et al. observed that mice with higher expression of leptin receptors in the hypothalamus were resistant in developing obesity and infertility [9]. Contrary to the brain, other tissues, such as the ovaries, remain sensitive to leptin, therefore being exposed to the high circulating leptin levels that accompany obesity. Leptin in the human ovary inhibits both granulosa and thecal cell steroidogenesis [10] and interferes with the process of ovulation [11], therefore directly impacting fertility. Finally, a central insulin resistance state that accompanies obesity could be involved in the processes of infertility observed in obesity through the impact on the frequency and amplitude of luteinizing hormone (LH) secretion pulses [12–14].

Obesity and sex steroids

Several alterations of sex steroids follow the increase in body weight. In particular, obesity is associated with an increase in both estrogens (17β-estradiol-E2 and estrone-E1) and androgens (testosterone-T, dihydrotestosterone-DHT, androstenedione, and dehydroepiandrosterone), because adipose tissue directly synthesizes androgens and converts androgens to estrogens [15]. In addition, obesity is associated with a decrease in sex hormone binding globulin (SHBG) circulating levels [16], with a consequent increased availability of androgens and estrogens to target tissues. These relationships are evident already across puberty [17] and are particularly pronounced in central obesity [18, 19]. In addition, adipose tissue is able to store androgens and estrogens leading to an inflated steroid pool in women with obesity [18, 20].

Overall, these phenomena lead to a condition of "relative functional hyperandrogenism" that may affect ovarian function therefore contributing to the development of infertility in obesity.

Obesity and insulin

Obesity, especially central obesity, is characterized by a condition of insulin resistance and "compensatory hyperinsulinemia" due to many factors such as free fatty acids (FFA), leptin, cytokines, and androgens [21]. This insulin resistance state interests many tissues, but not all. In particular, muscle, liver, and adipose tissue become resistant to insulin, whereas the ovaries remain sensible to insulin and, therefore, are exposed to the burden effect of hyperinsulinemia. In the ovaries, insulin stimulates theca cells to produce androgens both through a direct effect and by increasing the local sensitivity to LH [22]. The excess of intra-ovarian androgen production may produce premature follicular atresia thus favoring anovulation [22]. In addition, hyperinsulinemia leads to reduced hepatic synthesis of SHBG with a consequent increased availability of free androgens [23], thus aggravating peripheral hyperandrogenism that triggers an overproduction of acyclic E1 which, in turn, determines an excessive production of LH [24]. Increased secretion of LH may arrest follicular growth at earlier stages, may promote early luteinization of granulose cells and may produce a damage of oocyte quality [25–30]. Through all these mechanisms, insulin resistance and compensatory hyperinsulinemia may contribute to menstrual, ovulatory, and fertility disturbances that accompany obesity, particularly central obesity, in women.

Obesity and the somatotropic axis

Obese patients are characterized by a decrease of plasma GH levels due to a reduction of GH secretion and an increased GH clearance rate [31–33]. Many factors participate in reducing plasma GH levels, in particular dysregulation of GH-releasing hormone (GHRH), somatostatin (SS), and ghrelin pathways, as well as hyperinsulinemia and excess of circulating FFA [34]. Data on circulating IGF-1 levels in obesity are contradictory. In fact, several clinical studies showed that in people with obesity total IGF-1 are unaltered, but other studies demonstrated increased levels of IGF-1 [35] and of free IGF-1 for the insulin dependent reduction in IGF Binding Protein (IGFBP)-1 and IGFBP-2 levels [36], which could be responsible for an enhanced feedback inhibition of GH release [35]. These findings provide evidence that obesity is characterized by a condition of hyposomatotropinism [37] that could contribute to affect ovarian and endometrial functions, therefore participating to the fertility alterations that accompany obesity. In fact, GH stimulates growth of small follicles and prevents their atresia, collaborates with gonadotrophins in stimulating later stages of folliculogenesis and luteinization, and facilitates selection and development of dominant follicle. In addition, GH increases the ovarian production of oestrogens and progesterone and stimulates endometrium and myometrium in the uterus, all mechanisms that are a prerequisite for successful reproduction [38].

Obesity and the ovary

Sex steroids, insulin, and the somatotropic axis act at the level of the ovary [38]. Therefore, the dysfunctions that affect these systems when body weight increases may be involved in producing functional alterations in the ovary. However, there is emerging evidence that obesity may

directly impact the oocyte, impairing its quality. Animal studies have, in fact, demonstrated that oocytes from obese mice are smaller, show delayed meiotic maturation and increased follicular apoptosis and have significant spindle or chromosome misalignment defects [39, 40]. These defects are likely to generate embryos with massive aneuploidy, therefore cause of spontaneous miscarriages. Similar results were obtained in human studies where the comparison of failed fertilized oocytes from patients with severe obesity or who were normal-weight demonstrated that women with obesity have a significantly higher prevalence of "disarrayed meiotic spindles with non-aligned chromosomes" [41]. One proposed mechanism at the basis of the altered oocyte quality in women with obesity includes altered mitochondrial activity. In fact, mitochondria perform numerous regulatory functions during oocyte maturation, fertilization, preimplantation, and normal embryo development [42–44]. Furthermore, mitochondria from obese female mice present an aberrant distribution within the oocyte [45] and are more oxidized with a rate of Reactive Oxygen Species (ROS) production 2.1-fold higher with respect to lean controls and with depleted levels of glutathione [45]. Accordingly, the mitochondrial DNA copy number is significantly higher in oocytes from obese mice with respect to lean controls [45], probably as compensatory mechanism in response to oxidative-stress-induced mitochondrial damage [40].

Also the lipotoxicity may directly alter the oocyte quality, thus contributing to infertility in obese women [46–48]. In particular, both animal and human studies demonstrate that the accumulation of FFA within the ovary is associated with endoplasmic reticulum (ER) stress, mitochondrial dysfunction of the oocytes, and finally apoptosis of the cumulus–oocyte complexes [49, 50]. These data provide new informations about the mechanisms that may lead to impaired ovulation, reduced oocyte and embryo quality, and therefore to infertility in women with obesity.

Obesity and the endometrium

The endometrium is another target of obesity. Studies of mice with diet-induced obesity demonstrated that endometrial decidualization is impaired [51]. These results were confirmed in in vitro and in vivo human studies, where a decreased stromal decidualization was observed in women with obesity [52]. The pathogenesis of this phenomenon may lie on proinflammatory cytokines and ROS inducing endothelial dysfunction [53] and on haptoglobulin, an inflammatory marker whose endometrial levels of expression have been found to be increased in women with obesity who had recurrent miscarriages [54]. In addition, in a recent study, the ERK signal transduction, which belongs to MAPK/ERK pathways, necessary for invasion of trophoblasts into the endometrium, was found to be downregulated during implantation in women with obesity [55]. All these phenomena represent possible mechanisms of decreased implantation and high miscarriage rates in women with obesity. It has also been suggested a condition of reduced endometrial receptivity in obesity due to many factors, in particular the relative hyperestrogenemia, the reduction of glycodelin and of IGFBP1 that follow insulin resistance and hyperinsulinemia, and the dysregulation of leptin pathways [56–58]. Leptin, other than modulating endometrial receptivity, exerts a regulatory role in remodeling the endometrial epithelium and in stimulating proliferation and apoptotic cell pathways [58]. All these data support the notion that infertility in obesity in sustained by an unfavorable intrauterine milieu and impaired endometrial receptivity, other than by an altered oocyte quality.

Obesity and assisted conception

Several clinical studies have focused on the impact of female obesity on the outcome of assisted reproduction technology (ART). Up to date, although some studies have not reported adverse effect of obesity on ART outcomes [59–63], most studies have linked obesity with negative ART outcomes. In particular, obesity is associated with the need for higher doses of gonadotropins, fewer oocytes collected, higher number of cycles canceled for poor or high oocytes retrieved (overstimulation), higher miscarriage rates and reduced pregnancy and live-birth rates [64–66]. Moreover, a specific meta-analysis made by Rittenberg et al. that included 33 studies for a total of 47,967 IVF/ICSI cycles interestingly demonstrated that the poorer outcome of IVF treatment was not limited to women with obesity, but included also women with overweight [67].

The elevated doses of gonadotropins used to compensate for the relative gonadotropin resistance induced by obesity may be deleterious for fertility, leading to impairment of uterine receptivity and of embryonic development and implantation [68–70].

In summary, it is widely accepted that overweight and obesity negatively impact the ART outcomes in women. Accordingly, it has been observed that a reduction in body weight is able to improve IVF treatment success in term of number of oocytes retrieved, number of mature oocytes developed and pregnancy rate [71, 72].

Obesity and pregnancy outcome

Maternal obesity increases the risk of complications in pregnancy, labor, and birth for both the mother and the

neonate. In fact, maternal obesity in associated with increased rates of pregnancy complications, mainly in the third trimester [73, 74], as well as increased rates of fetal malformations [75, 76] and increased risk of intrauterine fetal death and of death of the neonate in the first year of life [73, 77]. In addition, neonates of mothers with obesity have increased rates of neonatal complications such as head trauma, shoulder dystocia, brachial plexus lesions, fractures of the clavicle, meconium aspiration, and respiratory distress [73, 77].

Fertility after weight loss

Many interventions have been studied to reduce the effect of obesity on infertility, including weight loss, dietary factors, physical activity and bariatric surgery but, to date, there are still no precise indications on how to solve the problem in the most effective way. Clark and colleagues [78] showed that weight loss in obese infertile women is extremely effective for the resumption of ovulation, improvement of spontaneous pregnancy rate, and reduction of miscarriage rate. The amount of weight loss required for the resumption of fertility is however unclear. Sim and colleagues recently demonstrated that a loss of only 6.9% of initial body weight is sufficient to enhance pregnancy rates [79]. In women with massive obesity, bariatric surgery has been shown to improve fertility, but to date there is no consensus on the role of bariatric surgery in the management of infertility-associated obesity within the medical community. Musella and coworkers described a 78.5% of pregnancies in obese infertile women after weight loss induced by Bioenterics Intragastric Balloon (BIB) treatment [80]. The beneficial effect of bariatric surgery on anovulatory infertility was demostrated in a survey study of 195 anovulatory obese women who regained ovulation in 71% of cases after surgery [81]. However, a recently performed pilot study demonstrated that a brief intensive weight loss intervention in subfertile women with severe obesity resulted in improvement in ovulation similarly to bariatric surgery [82]. More studies are warranted to corroborate these interesting results.

Obesity and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility in women. Obesity, that affects approximately half of PCOS women [83], aggravates infertility through the negative impact on menses, ovulation, as well as pregnancy and live birth rates [84, 85]. Moreover, a blunted responsiveness to pharmacological treatments to induce ovulation, as well as higher gonadotropin requirements during ART stimulation with, however, fewer oocytes recruited, have been described in obese with respect to non-obese PCOS [86, 87]. Pathophysiological mechanisms by which obesity negatively impacts fertility in PCOS are complex and not completely understood. Undoubtedly, obesity aggravates hyperandrogenism and insulin resistance, and is associated with hyposomatotropinism in PCOS, particularly in abdominal obesity [19, 88, 89]. The important impact of obesity in aggravating infertility in PCOS is supported by the studies that demonstrate that lifestyle interventions, including dietary advice and standardized physical activity programs, have a significant positive impact on ovulation, menses abnormalities and infertility [90, 91], and these beneficial effects have been observed even after modest weight loss of 5–10% [92–94]. Studies on the effects of bariatric surgery in women with severe obesity and PCOS reported interesting data on the benefits of sustained weight loss on fertility. In particular, a recent meta-analysis [95] demonstrated that after 1 year from bariatric surgery in women with severe obesity and PCOS, the prevalence of menstrual irregularities decreased from 56.2 to 7.7% and the prevalence of infertility declined from 18.2 to 4.3%.

Conclusion

In conclusion, obesity is associated with infertility in women through multiple and complex mechanisms that are summarized in Fig. 1. Briefly, obesity is associated with high serum leptin levels due to leptin produced by the adipose tissue. Leptin acts at the level of the ovary and of the endometrium where it inhibits both human granulosa and thecal cell steroidogenesis, which interferes with the development of the dominant follicle and oocyte maturation, and alters endometrial epithelium receptivity. High leptin levels may also contribute to the development of peripheral insulin resistance. On the other hand, the condition of selective leptin resistance at central level that accompanies obesity reduces stimulation of GnRH. Obesity, particularly the abdominal phenotype, is also associated with an increase in E2, E1 and in some androgens, such as T, DHT, androstenedione, and dehydroepiandrosterone for an increased synthesis and storage at the level of the adipose tissue, and with a parallel decrease in SHBG circulating levels, with a consequent increased delivery of androgens and estrogens to target tissues. The exposure of the ovary at high androgen levels produces premature follicular atresia, thus contributing to anovulation. On the other hand, hyperestrogenemia may have a detrimental effect upon endometrial receptivity, thus contributing to infertility. Hyperandrogenemia, hyperleptinemia, but also high FFA and cytokines such as Interleukin-6 (IL6) and Tumor Necrosis Factor-α (TNFα) contribute to induce a state of insulin resistance, that interestingly affects classic target tissues of insulin action (i.e., muscle, liver and adipose

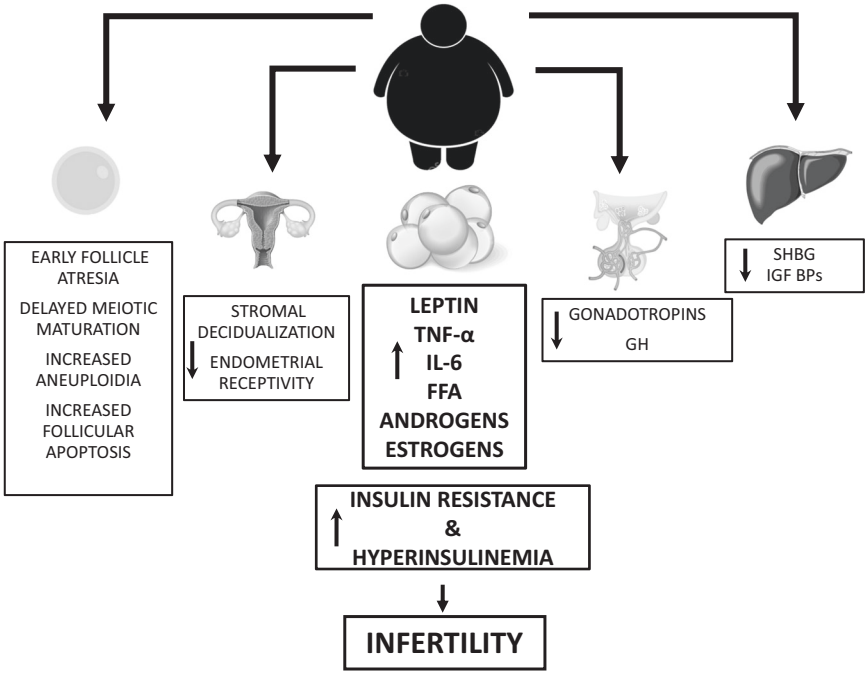

Fig. 1 Mechanisms linking obesity with infertility. TNF-α tumor necrosis factor-α, IL-6 interleukin-6, FFA free fatty acid, GH growth hormone, SHBG sex hormone binding globulin, IGFBPs insulin-like growth factor-binding proteins

tissue), but not the ovaries. The ovary, under the effect of hyperinsulinemia that compensates insulin resistance, synthetizes more androgens, particularly A and T that cause premature follicular atresia. Hyperinsulinemia and excess of circulating FFA, in association with a dysregulation of GHRH, SS, and ghrelin pathways contribute to determine the low GH status that accompanies obesity and that could contribute to affect ovarian and endometrial functions. Accumulation of FFA within the ovary is also associated with ER stress, mitochondrial dysfunction of the oocytes, and apoptosis of the cumulus–oocyte complexes, with a consequent delayed meiotic maturation, increased aneuploidia and follicular apoptosis. In addition, high FFA and cytokines and a reduction of glycodelin and of IGFBP1 that follow insulin resistance and hyperinsulinemia interfere with endometrial decidualization, the necessary step for uterine receptivity.

Weight loss is able to restore fertility in most cases. However, nowadays, there are no convincing studies to guide the choice of the best method to be used to induce weight loss among physical activity, diet and bariatric surgery and to tailoring therapy.

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Compliance with ethical standards

Conflict of interest AG is a consultant for Bayer. The remaining authors declare that they have no conflict of interest.

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