Obesity and female infertility: potential mediators of obesity's impact

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The worldwide upward trend in obesity has been dramatic, now affecting more than 20% of American women of reproductive age. Obesity is associated with many adverse maternal and fetal effects prenatally, but it also exerts a negative influence on female fertility. Obese women are more likely to have ovulatory dysfunction due to dysregulation of the hypothalamic-pituitary-ovarian axis. Women with polycystic ovarian syndrome who are also obese demonstrate a more severe metabolic and reproductive phenotype. Obese women have reduced fecundity even when eumenorrheic and demonstrate poorer outcomes with the use of in vitro fertilization. Obesity appears to affect the oocyte and the preimplantation embryo, with disrupted meiotic spindle formation and mitochondrial dynamics. Excess free fatty acids may have a toxic effect in reproductive tissues, leading to cellular damage and a chronic low-grade inflammatory state. Altered levels of adipokines, such as leptin, in the obese state can affect steroidogenesis and directly affect the developing embryo. The endometrium is also susceptible, with evidence of impaired stromal decidualization in obese women. This may explain subfecundity due to impaired receptivity, and may lead to placental abnormalities as manifested by higher rates of miscarriage, stillbirth, and preeclampsia in the obese population. Many interventions have been explored to mitigate the effect of obesity on infertility, including weight loss, physical activity, dietary factors, and bariatric surgery. These data are largely mixed, with few high quality studies to guide us. As we improve our understanding of the pathophysiology of obesity in human reproduction we hope to identify novel treatment strategies. (Fertil Steril® 2017;107:840–7. ©2017 by American Society for Reproductive Medicine.)

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Obesity has become a global epidemic, affecting more than 600 million adults worldwide (1). Rates of obesity in the United States are significantly higher than in other developed nations, with more than one-third of adult Americans affected (2). The number of obese Americans has doubled since 1960 (2). Women of reproductive age have not been spared from this dramatic trend, with 23% of this cohort now obese (3). Certain risks associated with obesity target this cohort, including menstrual irregularity, endometrial pathology, and infertility. Obese women also have higher rates of many complications in pregnancy, including hypertensive disorders, gestational diabetes, preterm birth, and rates of cesarean delivery (4). Although the clinical impact of obesity on female infertility has been well characterized, the mechanistic underpinnings that can lead to effective treatment are still being elucidated.

THE CLINICAL EFFECTS OF OBESITY ON FEMALE INFERTILITY

Obesity has a negative effect on reproductive potential, primarily thought to be due to functional alteration of the hypothalamic-pituitary-ovarian (HPO) axis. Obese women often have higher circulating levels of insulin, which is a known stimulus for increased ovarian androgen production (5). These androgens are aromatized to estrogen at high rates in the periphery owing to excess adipose tissue, leading to negative feedback on the HPO axis and affecting gonadotropin production (6). This manifests as menstrual abnormalities and ovulatory dysfunction. Hyperinsulinemia is highly implicated in the pathogenesis of the polycystic ovarian syndrome (PCOS), characterized by oligomenorrhea and hyperandrogenism. Obesity contributes to insulin resistance and appears to exacerbate the symptoms of PCOS, with obese women often demonstrating a more severe phenotype (7, 8). Elevated androgen levels in PCOS lead to deposition of visceral fat, leading to insulin resistance and hyperinsulinemia, further stimulating ovarian

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and adrenal androgen production in a perpetual cycle (9). The prevalence of PCOS in some obese populations approaches 30%, although a causative role of obesity in the development of PCOS has not been established (10, 11).

Multiple studies have demonstrated that obese women have increased time to pregnancy. Two studies in large cohorts of Danish women planning pregnancies showed a decline in fecundability ratios with increasing body mass index (BMI) (12, 13). Interestingly, obese women remain subfertile even in the absence of ovulatory dysfunction. Examination of a large American cohort of more than 7,000 women by Gesink Law et al. showed reduced fecundity in eumenorrheic obese women, and van der Steeg et al. presented data from a large Dutch cohort of more than 3,000 women with normal cycles, in which the probability of spontaneous conception declined linearly with each BMI point >29 kg/m^2 (14, 15).

Obesity also seems to affect assisted reproductive technology (ART) outcomes, providing more evidence that the pathology extends beyond an ovulatory disorder. Obese women undergoing in vitro fertilization (IVF) have smaller oocytes that are less likely to fertilize normally (16, 17). Multiple studies have demonstrated a negative impact on live birth rates (LBRs), and this appears to correlate with increasing BMI (17–20). A review of ART in overweight and obese women showed a modest impact on LBRs, with a pooled odds ratio of 0.90, but in a large study of women with class III obesity (BMI >40 kg/m^2) there was a 50% decreased probability of live birth (17, 21).

EFFECT ON THE HPO AXIS

We have evidence from human studies as well as animal models that obesity affects regulation of the HPO axis. Tortoriello et al. showed that mice with diet-induced obesity (DIO) had a 60% decline in natural pregnancy rates, but that this defect could be overcome with exogenous gonadotropins, indicating a central mechanism (22). That group also engineered a mouse model with genetic mutations leading to an obese and infertile phenotype independently from diet. They found that mice that were resistant to developing this phenotype had higher levels of leptin receptors in the hypothalamus (23). Obese women have higher circulating levels of leptin, a cell-signaling protein produced in adipose tissue and termed an adipokine, than normal-weight control subjects, which may lead to chronic down-regulation of this receptor in the brain. Women with high serum concentrations of leptin and elevated leptin-BMI ratios have lower rates of pregnancy with IVF (24). Jain et al. studied eumenorrheic obese women and found that the amplitude of LH pulsatility was significantly decreased, again pointing to a central defect that may be unique to this disease (25).

EFFECTS ON THE OOCYTE

There is abundant literature supporting an effect of obesity on the oocyte. Obese women undergoing IVF have an altered follicular environment, with higher levels of insulin, triglycerides, and markers of inflammation, such as lactate and C-reactive protein (CRP), in follicular fluid (26). Obesity affects the ovarian response to gonadotropin stimulation, with higher doses and longer treatment courses needed for follicular development (27, 28). The oocyte yield is lower in obese women, and they have a higher rate of cycle cancellation (28, 29). In DIO mouse models, the ovaries demonstrate more apoptotic follicles and oocytes are smaller and less likely to be mature (30). Closer examination of these abnormal oocytes in DIO mice reveals high rates of meiotic aneuploidy with fragmented disorganized meiotic spindles and chromosomes not properly aligned on the metaphase plate (31). Machtinger et al. examined the oocytes that failed to fertilize in IVF cycles of morbidly obese women and similarly described disarrayed meiotic spindles with misaligned metaphase chromosomes (32). Independently from aneuploidy, obesity also appears to alter mitochondrial function in the oocyte. Mitochondria in DIO mice have disrupted architecture with fewer cristae, more vacuoles, and evidence of swelling (31). There is also a change in mitochondrial distribution, with clumping throughout the ooplasm compared with uniform perinuclear localization in control subjects (33). These abnormal mitochondria show evidence of metabolic stress, with lower levels of citrate, a tricarboxylic acid cycle end-product. This stress may lead to a compensatory increase in production of mitochondria, supported by elevated mitochondrial DNA copy number in oocytes of obese mice (31, 33, 34). In addition to mitochondria, there is evidence of endoplasmic reticulum (ER) stress in the obese state. The cumulus-oocyte complexes of mice fed a high-fat diet demonstrate increased expression of ER stress markers ATF4 and GRP78 and have increased granulosa cell apoptosis (35). This correlates with increased activating transcription factor levels in the follicular fluid of obese women undergoing IVF (35). There is evidence that women with PCOS also exhibit impaired oocyte competence, with lower rates of conception with ovulation induction and altered follicular fluid biomarkers. However, those studies are often confounded by high rates of obesity and metabolic disturbances in women with PCOS (36).

One potential mechanism for oocyte organelle damage in obesity is lipotoxicity. Excess fatty acids obtained from the diet can be stored as triglycerides in adipocytes, and they do not appear to cause cellular damage in this storage compartment. However, when this capacity is overwhelmed with continued dietary excess, fatty acids accumulate in other tissues and exert toxic effects, which is termed lipotoxicity (37). Obese women have higher levels of circulating free fatty acids, which damage nonadipose cells by increasing reactive oxygen species (ROS) that induce mitochondrial and ER stress leading to apoptosis (38). In obese women undergoing IVF, elevated levels of free fatty acids in the follicular fluid correlated with abnormal morphology of cumulus-oocyte complexes (39). The oocytes of obese mice have twofold increased production of ROS and depleted levels of glutathione, an important intracellular defense against ROS damage (33). Lipotoxicity plays a role in the development of insulin resistance and a heightened inflammatory state in obese women (40).

Obesity is considered to be a chronic low-grade inflammatory state. Obese women have higher circulating levels of