

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 $>29 \text{ kg/m}^2$ (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 $>40 \text{ kg/m}^2$) 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. Tortorello 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

CRP, a marker of systemic inflammation (41). Adipose tissue is an endocrine organ that produces many proinflammatory adipokines, including leptin, tumor necrosis factor α , and interleukin (IL) 6 (42). Obese women have lower circulating levels of an important antiinflammatory adipokine called adiponectin. Mice with an adiponectin gene knockout mutation manifest glucose intolerance and hyperlipidemia (43). The tissues of the reproductive tract are not immune to the inflammatory state. Rats with DIO show up-regulation of a range of proinflammatory genes in ovarian tissue (44). In cultured primary human trophoblasts, exposure to IL-6 stimulates fatty acid accumulation and subsequent lipotoxicity (45). As previously mentioned, CRP levels are elevated in the follicular fluid of obese women (26). Inflammatory pathways are critically important in reproductive events such as follicle rupture at the time of ovulation and invasion of the trophoblast into the receptive endometrium. The developing blastocyst produces adiponectin, IL-1, and IL-6 (46). The altered inflammatory milieu in obese women likely exerts an influence on these processes.

Higher serum levels of leptin in obese women correlates with higher levels of leptin in the follicular fluid (47). In vitro studies have shown that leptin affects steroidogenic pathways in granulosa cells, decreasing estrogen and progesterone production in a dose-dependent manner (48–51). This effect of obesity at the level of the oocyte could have downstream effects on endometrial receptivity and embryo implantation.

EFFECTS ON THE EMBRYO

The preimplantation embryo is also affected by an obese environment. Comparison of human IVF cycles with autologous oocytes show that obese women are more likely to create poor quality embryos (52, 53). Mouse embryos created in dams with DIO have lower expression of insulin-like growth factor 1 receptor (IGF-1R), negatively affecting insulin sensitivity and glucose transport at a critical stage in development (30). Leary et al. noted that embryos from women with BMI ≥ 25 kg/m² were less likely to develop after fertilization, and those that did reached the morula stage more quickly. In addition, those that reached the blastocyst stage had fewer cells in the trophectoderm and demonstrated poor glucose uptake and increased levels of triglycerides (54).

Embryos may also be susceptible to lipotoxicity as previously discussed regarding the oocyte. Murine embryos cultured in excess palmitic acid, which is the most common free fatty acid in human serum, have fewer nuclei and altered IGF-1R expression. When these embryos were transferred into dams, the pups had lower birth weights but demonstrated catch-up growth, similarly to the DIO model (55). Similarly, murine trophoblastic stem cells that are exposed to palmitic acid in vitro proliferate less and undergo increased apoptosis in a dose-dependent fashion (55). In women undergoing IVF, elevated levels of a specific omega-3 fatty acid, α -linoleic acid, were associated with decreased pregnancy rates (56). An increased ratio of linoleic acid, an omega-6 fatty acid, to α -linoleic acid correlated with improved pregnancy rates in the same population (57). This suggests that the balance

of certain free fatty acids is important in mediating lipotoxicity in human reproduction.

In addition to acting centrally, elevated leptin levels in obese women may exert a direct negative effect on the developing embryo. In vitro, leptin has a stimulating effect on human trophoblastic stem cell growth, and its inhibition decreases proliferation and dramatically increases apoptosis (58). Tonically elevated levels of leptin in obesity may decrease the sensitivity of the trophoblast to its effects.

EFFECT ON THE ENDOMETRIUM

There are conflicting data as to whether obesity has a significant effect on the endometrium. Some studies examining obese women who receive embryos created from donor oocytes have shown no difference in implantation rates compared with normal control subjects, leading investigators to conclude that obesity does not negatively affect endometrial receptivity (59, 60). However, Desolle et al. published a retrospective review of 450 donor-oocyte frozen embryo transfer cycles and found BMI to be an independent predictor of clinical pregnancy (61).

In DIO mouse studies, it has been shown that endometrial decidualization, the necessary step for uterine receptivity to occur, is impaired in the obese mice (62). Those mice also experience decreased implantation sites and decreased response to hormonal stimulation in the endometrial stromal cells. Similar findings were found in an immortalized human endometrial stromal cell line triggered to undergo decidualization (47, 62). In the same study, the authors examined decidualization in primary cells from obese versus control women and found a decrease in obese women. Finally, both the nonhuman and the human studies demonstrated a relationship between decidualization and the process of autophagy, a “self-eating” that is normally triggered by starvation. Although many factors contribute to poor reproductive outcomes in obese women, our study suggests the importance of decidualization defects. Such defects may contribute to compromised endometrial receptivity and poor implantation. Decidualization and implantation defects may negatively affect the placentation process. Many of the pregnancy complications seen in obese women are linked to placental dysfunction, including stillbirth and pregnancy-induced hypertension. Similar trends are seen in the PCOS population, and the pathogenesis may be similar, with proinflammatory cytokines and ROS inducing endothelial dysfunction and abnormal placentation (63). As discussed above, obesity also affects the preimplantation embryo, and cross-talk between the endometrium and the embryo is critical for normal implantation to occur. Effects of obesity on the endometrium and the embryo may have an additive negative impact on pregnancy outcomes.

The role of obesity in first-trimester miscarriage is also debated. An Italian study of 700 women undergoing donor-oocyte cycles found significantly higher spontaneous abortion rates in obese women: 38.1% compared with 13.3% in normal-weight control women (64). A follow-up study from the same investigators with a larger cohort of donor-oocyte cycles, more than 2,600, showed no significant differences

in implantation, pregnancy, and miscarriage rates between BMI groups. There were trends toward a negative impact of obesity on these parameters, so a composite measure of ongoing pregnancy per cycle was calculated and shown to be significantly lower in the obese cohort (65). A meta-analysis in 2008 of both spontaneous and assisted reproductive conception showed that women with a BMI ≥ 25 kg/m² had a significantly higher risk of miscarriage at <20 weeks of gestation, with an odds ratio of 1.67. Subgroup analysis confirmed this finding in donor-oocyte cycles but not in the general cohort undergoing IVF with the use of intracytoplasmic sperm injection (ICSI) (66). A large nested case-control study showed an increased risk of recurrent miscarriage in the obese group, with an odds ratio of 3.5 (67). In women with a history of recurrent pregnancy loss (RPL), obesity is a known risk factor for miscarriage in a subsequent pregnancy (68). A chromosomal analysis of 117 miscarriage specimens from patients with RPL demonstrated that obese women had a much higher rate of euploid miscarriage, again suggesting a potential independent effect of obesity on the endometrium (69).

Leptin appears to affect the endometrium as well. Human endometrial endothelial cells in culture express the leptin receptor (70). Leptin appears to have a regulatory role in remodeling of the human endometrial epithelium, stimulating proliferation and apoptotic cell pathways in vitro (71). It may also modulate endometrial receptivity, as evidenced by up-regulation of markers of receptivity with leptin exposure in both epithelial and stromal cells (70). Chronic dysregulation of leptin pathways in obesity may negatively affect implantation.

TRANSGENERATIONAL EFFECTS

There is a mounting and concerning body of evidence suggesting that maternal obesity may confer a risk of metabolic dysfunction through multiple generations. We know that obesity affects intergenerational risk, meaning risk to offspring of developing disease later in life. Children of obese mothers are more likely to develop obesity, type II diabetes, and cardiovascular disease as adults (72). This may be due to epigenetic modifications in utero. In the DIO mouse model, pups are smaller at birth but then demonstrate catch-up overgrowth and development of metabolic syndrome (30). Gene expression in the placentas of dams with DIO demonstrates alterations in imprinted genes and genes regulating lipid metabolism (73). Nomura et al. examined the placentas of obese mothers and found increased levels of global methylation (74). Finally, a recent study in a DIO mouse model showed that metabolic dysfunction mediated through impaired mitochondrial dynamics can be passed through the maternal germline to second- and third-generation offspring (75). The authors demonstrated that maternal diet-induced metabolic syndrome in an inbred mouse model results in transgenerational inheritance of aberrant mitochondria. Abnormal expression of mitochondrial electron transport chain complex and dynamic proteins were seen in 1st through 3rd generation offspring (F1-F3), despite the fact that they were eating a regular diet immediately after

weaning. The transmission appeared to be germline and through aberrant oocytes. In humans, with the diets of children closely paralleling those of their parents, the effects of maternal metabolic syndrome may be greater than in this mouse model.

POTENTIAL MEDIATORS OF OBESITY'S IMPACT

Given the pervasive reproductive targets of obesity outlined above, there is intensive exploration of potential interventions that could provide benefit.

Weight Loss

The body of literature on the effect of weight loss in obese women desiring conception is mixed. In a cohort of 170 women undergoing IVF, short-term weight loss was associated with a higher yield of metaphase II oocytes in obese women, but clinical pregnancy rates and LBRs were not affected (20). In another retrospective cohort study, Kort et al. presented data from 52 overweight or obese women with infertility who were referred to weight loss counseling with a goal of 10% weight loss. A total of 32% of patients achieved the weight loss goal, and those patients had significantly higher conception rates and LBRs (76). In a small randomized controlled trial (RCT) of 49 obese women undergoing fertility treatment, those randomized to an intensive 12-week lifestyle intervention had an average 6.6 kg weight loss and a significantly higher LBR than the control group (44% vs. 14%), and required fewer treatment cycles (two vs. four) (77).

Other studies examined the effect of weight loss in obese women with PCOS, which may represent a different pathophysiology than obesity alone. A recent trial randomized overweight and obese women with PCOS to 16 weeks of treatment with the use of oral contraceptive pills (OCPs), lifestyle intervention with weight loss medication, or combined treatment with the use of OCPs and lifestyle intervention. After the intervention, the women underwent ovulation induction (OI) with timed intercourse for four cycles. Both the lifestyle and the combined cohorts had >6% weight loss and demonstrated higher rates of ovulation compared with the OCP cohort. The study was underpowered to detect a difference in LBRs, but there was a trend toward benefit with the use of the lifestyle intervention (78). A post hoc analysis of two multicenter clinical trials in overweight and obese infertile women with PCOS compared immediate treatment with the use of OI versus delayed treatment after a lifestyle intervention and weight loss, demonstrating improved ovulation and LBRs in the delayed group (79).

A recent large RCT conducted by Mutsaerts et al. in the Netherlands randomized more than 600 obese infertile women to a 6-month lifestyle intervention before 18 months of infertility treatment, or prompt infertility treatment for 24 months. There was substantial discontinuation rate in the intervention group (21.8%), which is a common issue in weight loss studies. The average weight loss in the intervention group was 4.4 kg, and only 43% reached the target of 5% weight loss. The primary outcome was term vaginal birth rate within 24 months, which was significantly higher in the

immediate treatment group (35.2% vs. 27.1%). When carried out to 24 months of treatment for both groups, there was no difference in LBRs, and the spontaneous conception rate was higher in the intervention group (80). Many would argue that these results suggest that we should not be delaying infertility treatment for attempts at weight loss. This study had a clinically realistic design but was unable to answer the mechanistic question as to whether weight loss improves fertility outcomes. We must also keep in mind that weight loss before conception in the obese population can ameliorate risks in pregnancy (81).

Physical Activity

Attempts have been made to examine the effect of physical activity in the obese infertile population, independently from weight loss. In a retrospective cohort of obese infertile women undergoing 216 cycles of IVF/ICSI, the outcomes of patients that engaged in regular physical activity were compared with those who were sedentary, as assessed by the validated Global Physical Activity Questionnaire. There were significantly higher pregnancy rates and LBRs in the active group (41 cycles), with a 3.71 relative risk of live birth (82). Wise et al. explored the effect of exercise on time to pregnancy in a large Danish cohort ($n = 3,628$). They observed an inverse relationship between fecundity and vigorous physical activity when comparing women who completed >5 hours per week to those who did none. However, this relationship did not exist for overweight or obese women who performed vigorous physical activity. Moderate physical activity was associated with a small increase in fecundity across the cohort (83). Physical activity has been shown to decrease systemic inflammatory mediators, which may contribute to the improvement in fertility suggested by the sum of evidence (84).

Dietary Factors

It is highly likely that fertility is not affected solely by excess caloric intake, but by the distribution of those calories across food groups. In a study comparing dietary factors in women with PCOS in the United States and Italy, it was noted that the American women had higher average body mass and more cardiovascular risks (impaired glucose tolerance, elevated low-density lipoprotein cholesterol). Interestingly, the caloric intake was similar for both cohorts, but American women ingested more saturated fats (85). A follow-up study sought to determine the prevalence of metabolic syndrome in the Italian PCOS cohort, which approaches 50% in American women with PCOS. It is much lower in Italian women, ranging from 8% to 16% depending on the diagnostic criteria used (86). These and similar observational studies of disease prevalence, including obesity and type II diabetes, across populations led to interest in the potential therapeutic benefit of the “Mediterranean” diet, characterized by higher intake of unsaturated fats, lower intake of animal fats, and lower ratios of omega-6 to omega-3 fatty acids (87). Adherence to a Mediterranean diet for 2 years in patients with metabolic syndrome significantly decreased insulin resistance and serum concentrations of inflammatory markers, including CRP and

IL-6 (87). Vujkovic et al. examined the dietary patterns of 161 couples undergoing IVF/ICSI and compared two categories, a “health conscious, low processed” diet versus a Mediterranean diet. Increasing adherence to a Mediterranean diet correlated with an increased chance of pregnancy (88). A Spanish nested case-control study compared the dietary patterns of fertile and infertile women categorized as “Western” or “Mediterranean.” A lower risk of infertility was observed in women in the highest quartile of adherence to the Mediterranean diet (89). Chavarro et al. have published extensively on the “fertility diet,” a pattern of dietary intake that has been associated with lower risk of ovulatory infertility and characterized by less consumption of trans fats and animal protein and more consumption of low-glycemic carbohydrates, high-fat dairy, and multivitamins (90–93). That group followed a cohort of more than 17,000 women in the Nurses’ Health Study for 8 years as they attempted pregnancy. They were assigned dietary scores based on their adherence to the aforementioned “fertility diet.” Women in the highest quartile of adherence had an adjusted relative risk of 0.34 for ovulatory infertility, suggesting a significant impact of diet (94).

Better understanding of the mechanisms underlying obesity’s impact on fertility has led to investigation of targeted dietary supplementation. Given that ROS have been implicated in oocyte mitochondrial dysfunction, antioxidants may moderate obesity’s impact on the ovary. A key antioxidant in the electron transport chain is coenzyme Q-10, which has been shown to decline with aging (95). In an aged murine model, mice supplemented with CoQ-10 had higher rates of ovulation and larger litter size. This correlated with lower mitochondrial DNA copy number, indicating less mitochondrial stress (95). A small randomized trial in older women undergoing IVF showed potential benefit with lower rates of aneuploidy and higher pregnancy rates (96). Results of CoQ-10 supplementation in the DIO mouse model have had varying results. CoQ-10 did not decrease the level of ROS in obese mice, but it did appear to improve oocyte mitochondrial distribution and spindle and chromosome alignment (97). CoQ-10 has been studied in the PCOS population: An RCT of 100 patients undergoing OI that had previously been resistant to clomiphene showed that CoQ-10 supplementation improved ovulation and pregnancy rates (98). These studies have yet to be undertaken in the obese infertile population.

Bariatric Surgery

Literature on the effect of bariatric surgery on reproductive health outcomes is limited. A retrospective cohort study examining pregnancy outcomes after bariatric surgery demonstrated lower risk of gestational diabetes and large-for-gestational-age infants. However, it also showed a concerning increased risk of small-for-gestational-age infants and a trend toward higher risks of stillbirth and neonatal death with no improvement in preterm birth (99). In a survey study of 195 female patients with a history of bariatric surgery, 71% of women who were anovulatory before surgery had regained normal menses, and this correlated with a higher degree of weight loss (100). Surprisingly, in a prospective cohort of 29

morbidly obese women undergoing Roux-en-Y bypass, 90% were ovulatory before surgery. The only significant change noted after surgery was a shortening of the follicular phase, but the impact of this is unclear in the absence of fertility outcomes (101). Bariatric surgery does appear to improve the PCOS phenotype. In a small study of 17 women with PCOS who underwent biliopancreatic diversion or laparoscopic bypass, 16 did not sustain the diagnosis owing to lowering of androgen levels and return of regular menses. Metabolic parameters, including insulin sensitivity and blood pressure, were also improved (102). This again demonstrates that obesity has a significant impact on the pathophysiology of PCOS. Clearly, more studies are needed regarding the effect of bariatric surgery on obesity-related infertility.

CONCLUSION

Clinical studies definitively demonstrate an impact of obesity on the risk of subfertility. This extends beyond reduced fecundity to suboptimal responses to ART. Work in the laboratory has implicated a diverse range of mechanisms affecting the oocyte, endometrium, and preimplantation embryo. Interventions including weight loss, physical activity, dietary modification, and bariatric surgery hold some promise for obese patients wishing to conceive. However, more translational work will be necessary to better understand the interplay between obesity and reproduction, with the goal of building healthy families.

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