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

Darcy E. Broughton, M.D. and Kelle H. Moley, M.D.

Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri

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.)

Key Words: Obesity, infertility, lipotoxicity

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14712-23481

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

Received November 30, 2016; revised January 23, 2017; accepted January 25, 2017; published online March 11, 2017.

D.E.B. has nothing to disclose. K.H.M. reports grants from the National Institutes of Health and the American Diabetes Association during the conduct of the study.

Reprint requests: Kelle H. Moley, M.D., Professor and Vice Chair of Obstetrics and Gynecology, Washington University School of Medicine, 425 S. Euclid Ave., Campus Box 8064, St. Louis, MO 63110 (E-mail: moleyk@wustl.edu).

Fertility and Sterility® Vol. 107, No. 4, April 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.01.017

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

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/m^2 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/m^2 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 though 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.

REFERENCES

1. World Health Organization. Obesity and overweight fact sheet 2016. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Last accessed March 6, 2017.
2. National Institute of Diabetes and Digestive and Kidney Diseases. Overweight and obesity statistics 2012. Available at: https://www.niddk.nih.gov/health-information/health-statistics/Pages/overweight-obesity-statistics.aspx. Last accessed March 6, 2017.
3. Vahratian A. Prevalence of overweight and obesity among women of childbearing age: results from the 2002 National Survey of Family Growth. Matern Child Health J 2009;13:268–73.
4. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Extreme obesity in pregnancy in the United Kingdom. Obstet Gynecol 2010;115:989–97.
5. Rachon D, Teede H. Ovarian function and obesity—interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol 2010;316:172–9.
6. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. Am J Obstet Gynecol 2010;203:525–30.
7. Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril 2006;85:1319–40.
8. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab 2015;26:136–43.
9. Escobar-Morreale HF. Surgical management of metabolic dysfunction in PCOS. Steroids 2012;77:312–6.
10. Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 2006;166:2081–6.
11. Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:162–8.
12. Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod 2010;25:253–64.
13. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod 2007;22:1634–7.
14. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod 2007;22:414–20.
15. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod 2008;23:324–8.
16. Marquard KL, Stephens SM, Jungheim ES, Ratts VS, Odem RR, Lanzendorf S, et al. Polycystic ovary syndrome and maternal obesity affect oocyte size in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2011;95:2146–9.e1.
17. Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol 2011;118:63–70.
18. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011;26:245–52.
19. Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril 2009;92:256–61.
20. Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, Petrozza JC, et al. Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. Fertil Steril 2012;98:109–16.
21. Koning AM, Mutsaerts MA, Kuchenbecker WK, Broekmans FJ, Land JA, Mol BW, et al. Complications and outcome of assisted reproduction technologies in overweight and obese women. Hum Reprod 2012;27:457–67.
22. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology 2004;145:1238–47.
23. Tortoriello DV, McMinn JE, Chua SC. Increased expression of hypothalamic leptin receptor and adiponectin accompany resistance to dietary-induced obesity and infertility in female C57BL/6J mice. Int J Obes (Lond) 2007;31:395–402.
24. Brannian JD, Schmidt SM, Kreger DO, Hansen KA. Baseline nonfasting serum leptin concentration to body mass index ratio is predictive of IVF outcomes. Hum Reprod 2001;16:1819–26.
25. Jain A, Polotsky AJ, Rochester D, Berga SL, Loucks T, Zeitlian G, et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab 2007;92:2468–73.
26. Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL, et al. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. J Clin Endocrinol Metab 2009;94:1533–40.
27. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertil Steril 2011;95:1042–7.
28. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 2004;19:2523–8.
29. Pinborg A, Gaarslev C, Hougaard CO, Nyboe Andersen A, Andersen PK, Boivin J, et al. Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. Reprod Biomed Online 2011;23:490–9.
30. Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology 2010;151:4039–46.
31. Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, et al. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. PLoS One 2012;7:e49217.
32. Machtinger R, Combelles CM, Missmer SA, Correia KF, Fox JH, Racowsky C. The association between severe obesity and characteristics of failed fertilized oocytes. Hum Reprod 2012;27:3198–207.
33. Igosheva N, Abramov AY, Poston L, Eckert JJ, Fleming TP, Duchen MR, et al. Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. PLoS One 2010;5:e10074.

34. Grindler NM, Moley KH. Maternal obesity, infertility and mitochondrial dysfunction: potential mechanisms emerging from mouse model systems. Mol Hum Reprod 2013;19:486–94.
35. Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ, et al. High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. Endocrinology 2010;151:5438–45.
36. Palomba S, Daolio J, la Sala GB. Oocyte competence in women with polycystic ovary syndrome. Trends Endocrinol Metab 2016 [Epub ahead of print].
37. Sorensen TI, Virtue S, Vidal-Puig A. Obesity as a clinical and public health problem: is there a need for a new definition based on lipotoxicity effects? Biochim Biophys Acta 2010;1801:400–4.
38. Broughton DE, Jungheim ES. A focused look at obesity and the preimplantation trophoblast. Semin Reprod Med 2016;34:5–10.
39. Jungheim ES, Macones GA, Odem RR, Patterson BW, Lanzendorf SE, Ratts VS, et al. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. Fertil Steril 2011;95:1970–4.
40. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective. Biochim Biophys Acta 2010;1801:338–49.
41. Salazar J, Martinez MS, Chavez M, Toledo A, Anez R, Torres Y, et al. C-Reactive protein: clinical and epidemiological perspectives. Cardiol Res Pract 2014;2014:605810.
42. McGown C, Birerdinc A, Younossi ZM. Adipose tissue as an endocrine organ. Clin Liver Dis 2014;18:41–58.
43. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. Am J Clin Nutr 2010;91:258S–61S.
44. Ruebel M, Shankar K, Gaddy D, Lindsey F, Badger T, Andres A. Maternal obesity is associated with ovarian inflammation and upregulation of early growth response factor 1. Am J Physiol Endocrinol Metab 2016;311:E269–77.
45. Lager S, Jansson N, Olsson AL, Wennergren M, Jansson T, Powell TL. Effect of IL-6 and TNF-alpha on fatty acid uptake in cultured human primary trophoblast cells. Placenta 2011;32:121–7.
46. Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400–8.
47. Hill MJ, Uyehara CF, Hashiro GM, Frattarelli JL. The utility of serum leptin and follicular fluid leptin, estradiol, and progesterone levels during an in vitro fertilization cycle. J Assist Reprod Genet 2007;24:183–8.
48. Lin Q, Poon SL, Chen J, Cheng L, HoYuen B, Leung PC. Leptin interferes with 3′,5′-cyclic adenosine monophosphate (cAMP) signaling to inhibit steroidogenesis in human granulosa cells. Reprod Biol Endocrinol 2009;7:115.
49. Brannian JD, Zhao Y, McElroy M. Leptin inhibits gonadotrophin-stimulated granulosa cell progesterone production by antagonizing insulin action. Hum Reprod 1999;14:1445–8.
50. Greisen S, Ledet T, Moller N, Jorgensen JO, Christiansen JS, Petersen K, et al. Effects of leptin on basal and FSH stimulated steroidogenesis in human granulosa luteal cells. Acta Obstet Gynecol Scand 2000;79:931–5.
51. Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-I augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab 1999;84:1072–6.
52. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular hCG concentrations, embryo quality and IVF outcome. Reprod Biomed Online 2001;3:109–11.
53. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online 2007;15:532–8.
54. Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Hum Reprod 2015;30:122–32.
55. Jungheim ES, Louden ED, Chi MM, Frolova AI, Riley JK, Moley KH. Preimplantation exposure of mouse embryos to palmitic acid results in fetal growth restriction followed by catch-up growth in the offspring. Biol Reprod 2011;85:678–83.
56. Jungheim ES, Macones GA, Odem RR, Patterson BW, Moley KH. Elevated serum alpha-linolenic acid levels are associated with decreased chance of pregnancy after in vitro fertilization. Fertil Steril 2011;96:880–3.
57. Jungheim ES, Frolova AI, Jiang H, Riley JK. Relationship between serum polyunsaturated fatty acids and pregnancy in women undergoing in vitro fertilization. J Clin Endocrinol Metab 2013;98:E1364–8.
58. Magarinos MP, Sanchez-Margalet V, Kotler M, Calvo JC, Varone CL. Leptin promotes cell proliferation and survival of trophoblastic cells. Biol Reprod 2007;76:203–10.
59. Styne-Gross A, Elkind-Hirsch K, Scott RT Jr. Obesity does not impact implantation rates or pregnancy outcome in women attempting conception through oocyte donation. Fertil Steril 2005;83:1629–34.
60. Wattanakumtornkul S, Damario MA, Stevens Hall SA, Thornhill AR, Tummon IS. Body mass index and uterine receptivity in the oocyte donation model. Fertil Steril 2003;80:336–40.
61. Dessolle L, Darai E, Cornet D, Rouzier R, Coutant C, Mandelbaum J, et al. Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. Hum Reprod 2009;24:3082–9.
62. Rhee JS, Saben JL, Mayer AL, Schulte MB, Asghar Z, Stephens C, et al. Diet-induced obesity impairs endometrial stromal cell decidualization: a potential role for impaired autophagy. Hum Reprod 2016;31:1315–26.
63. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update 2015;21:575–92.
64. Bellver J, Rossal LP, Bosch E, Zuniga A, Corona JT, Melendez F, et al. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril 2003;79:1136–40.
65. Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. Fertil Steril 2007;88:446–51.
66. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril 2008;90:714–26.
67. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod 2004;19:1644–6.
68. Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertil Steril 2010;94:290–5.
69. Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertil Steril 2014;102:455–9.
70. Gonzalez RR, Leavis P. Leptin upregulates beta3-integrin expression and interleukin-1beta, upregulates leptin and leptin receptor expression in human endometrial epithelial cell cultures. Endocrine 2001;16:21–8.
71. Tanaka T, Umesaki N. Leptin regulates the proliferation and apoptosis of human endometrial epithelial cells. Int J Mol Med 2008;22:683–9.
72. van Dijk SJ, Molloy PL, Varinli H, Morrison JL, Muhlhausler BS. Members of Epi S. Epigenetics and human obesity. Int J Obes (Lond) 2015;39:85–97.
73. Sasson IE, Vitins AP, Mainigi MA, Moley KH, Simmons RA. Pre-gestational vs. gestational exposure to maternal obesity differentially programs the offspring in mice. Diabetologia 2015;58:615–24.
74. Nomura Y, Lambertini L, Rialdi A, Lee M, Mystal EY, Grabie M, et al. Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. Reprod Sci 2014;21:131–7.
75. Saben JL, Boudoures AL, Asghar Z, Thompson A, Drury A, Zhang W, et al. Maternal metabolic syndrome programs mitochondrial dysfunction via germline changes across three generations. Cell Rep 2016;16:1–8.
76. Kort JD, Winget C, Kim SH, Lathi RB. A retrospective cohort study to evaluate the impact of meaningful weight loss on fertility outcomes in an overweight population with infertility. Fertil Steril 2014;101:1400–3.
77. Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. Clin Obes 2014;4:61–8.
78. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, et al. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:4048–58.

79. Legro RS, Dodson WC, Kunselman AR, Stetter CM, Kris-Etherton PM, Williams NI, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. J Clin Endocrinol Metab 2016;101:2658–66.
80. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, et al. Randomized trial of a lifestyle program in obese infertile women. N Engl J Med 2016;374:1942–53.
81. American College of Obstetricians and Gynecologists. Practice bulletin no. 156: Obesity in pregnancy. Obstet Gynecol 2015;126:e112–26.
82. Palomba S, Falbo A, Valli B, Morini D, Villani MT, Nicoli A, et al. Physical activity before IVF and ICSI cycles in infertile obese women: an observational cohort study. Reprod Biomed Online 2014;29:72–9.
83. Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis AH, Hatch EE. A prospective cohort study of physical activity and time to pregnancy. Fertil Steril 2012;97:1136–42.e1-4.
84. Farinha JB, Steckling FM, Stefanello ST, Cardoso MS, Nunes LS, Barcelos RP, et al. Response of oxidative stress and inflammatory biomarkers to a 12-week aerobic exercise training in women with metabolic syndrome. Sports Med Open 2015;1:3.
85. Carmina E, Legro RS, Stamets K, Lowell J, Lobo RA. Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. Hum Reprod 2003;18:2289–93.
86. Carmina E. Metabolic syndrome in polycystic ovary syndrome. Minerva Ginecol 2006;58:109–14.
87. Esposito K, Marfella R, Ciotola M, di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292:1440–6.
88. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EA, et al. The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril 2010;94:2096–101.
89. Toledo E, Lopez–del Burgo C, Ruiz-Zambrana A, Donazar M, Navarro-Blasco I, Martinez-Gonzalez MA, et al. Dietary patterns and difficulty conceiving: a nested case-control study. Fertil Steril 2011;96:1149–53.
90. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Dietary fatty acid intakes and the risk of ovulatory infertility. Am J Clin Nutr 2007;85:231–7.
91. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Protein intake and ovulatory infertility. Am J Obstet Gynecol 2008;198:210.e1-7.
92. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Use of multivitamins, intake of B vitamins, and risk of ovulatory infertility. Fertil Steril 2008;89:668–76.
93. Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. Hum Reprod 2007;22:1340–7.
94. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstet Gynecol 2007;110:1050–8.
95. Bentov Y, Casper RF. The aging oocyte—can mitochondrial function be improved? Fertil Steril 2013;99:18–22.
96. Bentov Y, Hannam T, Jurisicova A, Esfandiari N, Casper RF. Coenzyme Q10 supplementation and oocyte aneuploidy in women undergoing IVF-ICSI treatment. Clin Med Insights Reprod Health 2014;8:31–6.
97. Boots CE, Boudoures A, Zhang W, Drury A, Moley KH. Obesity-induced oocyte mitochondrial defects are partially prevented and rescued by supplementation with co-enzyme Q10 in a mouse model. Hum Reprod 2016;31:2090–7.
98. el Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. Reprod Biomed Online 2014;29:119–24.
99. Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med 2015;372:814–24.
100. Teitelman M, Grotegut CA, Williams NN, Lewis JD. The impact of bariatric surgery on menstrual patterns. Obes Surg 2006;16:1457–63.
101. Legro RS, Dodson WC, Gnatuk CL, Estes SJ, Kunselman AR, Meadows JW, et al. Effects of gastric bypass surgery on female reproductive function. J Clin Endocrinol Metab 2012;97:4540–8.
102. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2005;90:6364–9.