Obesity and reproduction: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

The purpose of this ASRM Practice Committee report is to provide clinicians with principles and strategies for the evaluation and treatment of couples with infertility associated with obesity. This revised document replaces the Practice Committee document titled, "Obesity and reproduction: an educational bulletin," last published in 2008 (Fertil Steril 2008;90:S21–9). (Fertil Steril® 2015;104:1116–26. ©2015 by American Society for Reproductive Medicine.)

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The prevalence of obesity as a worldwide epidemic has increased dramatically over the past two decades. In the United States alone, almost two thirds of women and three fourths of men are overweight or obese, as are nearly 50% of women of reproductive age and 17% of their children ages 2–19 years (1–3). The prevalence of overweight or obese Australian women is 30% and 22%, respectively, with a 2.5% increase in obesity from 1980 to 2000 in women of reproductive age (4). Similarly, in 2010 the proportion of overweight and obese Danish people was about one third among women and one half among men ages 25–44 years, respectively, with the prevalence of obesity increasing in individuals of reproductive age (5).

Obesity increases the risks of hypertension, dyslipidemia, diabetes, cardiovascular disease (CVD), sleep apnea, respiratory problems, osteoarthritis, and cancer, thereby elevating the rate of all-cause mortality (6). In the United States, the estimated annual medical costs of illness related to adult obesity exceed $200 billion (7). This underestimates the economic burden of obesity, since maternal morbidity and adverse perinatal outcomes add additional costs. The problem of obesity is also exacerbated by only one third of obese patients receiving advice from health-care providers regarding weight reduction (7, 8).

This document outlines the adverse effects of obesity on human reproduction, excluding polycystic ovary syndrome (PCOS), and discusses current treatments, including lifestyle modification and medical as well as surgical strategies, to optimize reproductive function and pregnancy outcome.

DEFINITION OF OBESITY

Obesity is a disease of excess body fat that is closely associated with insulin resistance (9–11). Categories of adult obesity are based upon body mass index (BMI) (12) (Table 1). On a population basis, BMI positively correlates with percent body fat, although this relationship varies among individuals by sex, age, and race-ethnicity (13–15). Some Asian populations have a genetically higher percent body fat than Caucasians, resulting in greater risks of developing diabetes and CVD at a lower BMI of 23–25 kg/m^2 (12).

Known associations with metabolic disease and death from CVD include BMI (J-shaped association), increased lean mass (muscle or edema) relative to total body mass (10, 16) (decreased association), and increased abdominal fat mass (increased association) (9,17–20). Specifically, increased abdominal circumference is a component of the metabolic syndrome (MBS), which also includes hypertension, elevated fasting glucose levels, hypertriglyceridemia, and decreased high-density lipoprotein (HDL)-cholesterol levels. Nevertheless, considerable variability in metabolic dysfunction remains among people, even when controlling for BMI and MBS, which likely results from ectopic lipid accumulation in non-adipose cells (i.e., lipotoxicity) (16). With lipotoxicity, when energy intake exceeds the capacity of normal adipose tissue to safely store fat, excess free fatty acids become deposited in abnormal locations, such as muscle and liver. Consequently, oxidative/endoplasmic reticulum stress develops in these tissues and becomes tightly linked with insulin resistance and inflammation (16, 21).

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TABLE 1

Categories of obesity by body mass index.[a]

Category	BMI (kg/m^2)
Underweight	Less than 18.5
Normal	18.5 to 24.9
Overweight	25.0 to 29.9
Obesity, Grade I	30.0 to 34.9
Obesity, Grade II	35.0 to 39.9
Obesity, Grade III	≥40.0

Note: BMI = body mass index.
[a] WHO 2004.

Practice Committee. Obesity and reproduction. Fertil Steril 2015.

Obesity also can impair reproduction in both women and men, leading to infertility in couples trying to conceive, subsequent complications in pregnancy, and adverse effects on their offspring.

MENSTRUAL CYCLE ABNORMALITIES

In women, excess weight and abdominal fat increase the risk of having menstrual abnormalities (18, 22). Menstrual irregularity occurs more frequently in women above 175% of ideal body weight compared with women below 150% of ideal body weight (54% vs. 19%, respectively) (23). Obese women in the general population have a higher incidence of menstrual irregularity and a lower chance of conception within 1 year of stopping contraception compared with normal-weight women (i.e., 66.4% of obese women conceive within 12 months, compared with 81.4% of those of normal weight) (24). Childhood obesity contributes to the risk of developing these menstrual disturbances (24). In a cross-sectional study, women in the United States who were obese adolescents (i.e., >30 kg/m^2 by self-reporting) had a greater chance of remaining childless than normal-weight women (odds ratio [OR], 2.84; 95% confidence interval [CI], 1.59–5.10), adjusting for adult BMI, nongestational amenorrhea, education, marital status, race, and socioeconomic status (25).

Putative mechanisms for ovulatory dysfunction related to obesity, apart from PCOS, have been proposed. Insulin-induced suppression of hepatic sex hormone-binding globulin (SHBG) reduces gonadotropin secretion due to increased production of estrogen from conversion of androgens by adipose aromatase (11, 26, 27). In addition, increased adipokines produced in adipose tissue can directly inhibit ovarian function (28, 29). Even with normal menstrual cycles, obese women exhibit reduced early follicular luteinizing hormone (LH) pulse amplitude, but not frequency, accompanied by prolonged folliculogenesis and diminished luteal progesterone levels (30–32).

OVULATORY DYSFUNCTION

Obesity is commonly associated with ovulatory dysfunction. Obese women with a BMI >27 kg/m^2 have a relative risk (RR) of anovulatory infertility of 3.1 (95% CI, 2.2–4.4) compared with their lean counterparts with a BMI 20.0–24.9 kg/m^2 (33, 34). Body fat distribution also is important because anovulatory women have a greater waist circumference and more abdominal fat than ovulatory women of similar BMI (35). A case-control study of 2,527 women with anovulatory infertility versus 46,718 control subjects (mostly married parous nurses without infertility) noted a relationship between BMI at 18 years of age and the RR of subsequent anovulatory infertility (1.0, BMI 20.0–21.9; 1.3, BMI 24–25.9; 1.7, BMI 26–27.9; 2.4, BMI 28–29.9; 2.7, BMI 30–31.9; and 2.7, BMI >32 kg/m^2) (33). Conversely, ovulatory function and pregnancy rates frequently improve after weight loss in obese anovulatory women (36, 37).

ALTERED OVARIAN RESPONSIVENESS AND OOCYTE QUALITY

Obesity is associated with higher doses of medications to induce ovulation or stimulate the ovaries for in vitro fertilization (IVF). In normogonadotropic anovulatory women, increased BMI and abdominal obesity are associated with decreased ORs of ovulation in response to clomiphene citrate (increased BMI: OR 0.92 [0.88–0.96]; increased waist-to-hip ratio: OR 0.60 [0.40–0.89]) (38). When gonadotropins are used for ovulation induction, obesity is correlated with an increased total dose of follicle-stimulating hormone (FSH) administered, fewer mature follicles, and a decreased chance of ovulation (39, 40). Several large, retrospective analyses (1,721 to 8,145 women undergoing IVF or intracytoplasmic sperm injection [ICSI]) also confirm that obesity impairs ovarian responsiveness to gonadotropin stimulation (i.e., increased duration, amount of gonadotropin administered, cycle cancellation; decreased oocytes retrieved) (41–45). In this regard, adipose-derived leptin can impair FSH- and/or IGF-I-stimulated granulosa cell steroidogenesis (28, 29).

Obese women with regular menstrual cycles, however, can still experience decreased fecundity (46). A Dutch study of 3,029 ovulatory women (with at least one patent tube and a partner with a normal semen analysis) found a 4% lower spontaneous pregnancy rate per kg/m^2 increase in women with a BMI >29 kg/m^2 (hazard ratio: 0.96; 95% CI, 0.91–0.99 versus a BMI 21–29 kg/m^2) (47). Moreover, in a prospective study of 448 women undergoing donor insemination, presumed to be ovulatory by cervical mucus and basal body temperature assessments, increased abdominal adiposity impaired conception, adjusting for BMI (48). Obese women undergoing IVF also have a reduced chance of clinical pregnancy and live birth as compared with normal-weight women (42–45, 49, 50). A systematic review of 27 IVF studies, 23 of which were retrospective, shows that overweight women (BMI, >25 kg/m^2) undergoing IVF have a 10% lower live-birth rate than women of normal weight (BMI, <25 kg/m^2) (OR 0.90; 95% CI, 0.82–1.0) (51). Although a smaller, retrospective IVF study did not find a relationship between BMI and pregnancy outcome (52), a meta-analysis of 33 IVF studies including 47,967 cycles concludes that overweight or obese women have significantly reduced rates of clinical pregnancy (RR 0.90, $P<.0001$) and live birth (RR 0.84, $P=.0002$) compared with women with a BMI

<25 kg/m^2 (53). In a recent retrospective study of 4,609 women undergoing first IVF or IVF/ICSI cycles, obesity reduced embryo implantation (controlling for embryo quality and day of embryo transfer), reducing the age-adjusted odds of live birth in a BMI-dependent manner by 37% (BMI, 30.0–34.9 kg/m^2), 61% (BMI, 35.0–39.9 kg/m^2), and 68% (BMI, >40.0 kg/m^2) compared with women with a BMI of 18.5–24.9 kg/m^2 (43). More specifically, of 12,566 Danish couples undergoing assisted reproduction, overweight and obese ovulatory women had 12% (95% CI, 0.79–0.99) and 25% (95% CI, 0.63–0.90) reductions in IVF-related live-birth rate, respectively (referent BMI, 18.5–24.9 kg/m^2) (54). In this cohort there was a 2% (95% CI, 0.97–0.99) decrease in live-birth rate for every one-unit increase in BMI (54). In another retrospective analysis of 487 couples undergoing assisted reproduction, obesity had the greatest negative impact on pregnancy outcome in young women (<25 years [OR 0.93; 95% CI, 0.87–0.98]; referent BMI, 18.5–24.9 kg/m^2) (45).

Obesity alters oocyte morphology (55), reduces fertilization in some (56, 57) but not all (41, 55, 58) studies, and impairs embryo quality in women less than 35 years of age (58). Specifically, women with a BMI >25 kg/m^2 have smaller oocytes that are less likely to complete development post-fertilization, with embryos arrested before blastulation containing more triglyceride than those forming blastocysts (59). Moreover, those blastocysts developed from oocytes of high-BMI women are smaller, contain less cells, and have higher triglyceride content, lower glucose consumption, and altered amino acid metabolism compared with embryos from normal-weight women (BMI <24.9 kg/m^2) (59). These human findings mirror those found in rodent studies, whereby obesity induced by diet causes follicle apoptosis, oxidative stress in cumulus-oocyte complexes, meiotic defects in oocytes with impaired fertilization, abnormal embryogenesis with reduced blastocyst survival, and abnormal fetal growth (60–63). The decreased pregnancy rate of obese IVF women using their own oocytes can be overcome with the use of donor oocytes. This suggests that oocyte quality is a primary, but not the only, factor impairing IVF outcomes in obese women using autologous oocytes (64, 65).

ALTERED ENDOMETRIAL FUNCTION

Obesity also appears to alter endometrial receptivity during IVF since third-party surrogate women with a BMI >35 kg/m^2 have a lower live-birth rate (25%) compared with those with a BMI <35 kg/m^2 (49%, $P<.05$) (66). Obese women also have a different pattern of endometrial gene expression during implantation than lean women, which is more pronounced in the presence of infertility (67).

MISCARRIAGE

Obesity is linked with increased pregnancy loss in many (39, 41, 43, 68, 69), but not all (40, 56), studies. During gonadotropin therapy for anovulatory infertility, obesity is associated with an increased miscarriage rate (OR 3.05; 95% CI, 1.45–6.44; referent BMI, 25–30 kg/m^2) (39). In a retrospective analysis of 2,660 couples undergoing IVF, obese women (BMI >30 kg/m^2) experienced a higher early pregnancy loss rate (OR 1.69; 95% CI, 1.13–2.51) and a lower live-birth rate (OR 0.75; 95% CI, 0.57–0.98) than normal-weight women (BMI, 18.5–24.9 kg/m^2) (41). In a similar analysis of 2,349 pregnancies conceived through ART, maternal BMI positively correlated with the risk of spontaneous abortion (overweight: OR 1.29; 95% CI, 1.00–1.66; obese: OR 1.71; 95% CI, 1.20–2.43; very obese: OR 2.19; 95% CI, 1.27–3.78; referent BMI, 18.5–24.9 kg/m^2) (68). This finding supports a review of 4,609 women undergoing first-time IVF, which showed women with a BMI >40 kg/m^2 to have an increased risk of biochemical and spontaneous pregnancy loss (OR 1.92; 95% CI, 1.14–3.22) compared with lean women (BMI, 18.5–24.9 kg/m^2) (43). A meta-analysis of 33 IVF studies including 47,967 cycles concluded that overweight or obese women have a higher rate of miscarriage (RR 1.31, $P<.0001$) compared with normal-weight women (BMI <25 kg/m^2) (53). Similarly, an increased risk for clinical miscarriage before 23 weeks' gestation was observed in obese women (BMI >25 kg/m^2) compared with those with a BMI 18.5–24.9 kg/m^2 who underwent a single blastocyst transfer in fresh (adjusted OR 2.7; 95% CI, 1.5–4.9) and cryothawed IVF cycles (adjusted OR 6.8; 95% CI, 1.5–31.1) (69).

MATERNAL-FETAL ENVIRONMENT

Maternal and perinatal morbid obesity are strongly associated with pregnancy and perinatal complications, including gestational diabetes and hypertension, preeclampsia, preterm delivery, stillbirth, cesarean or instrumental delivery, shoulder dystocia, fetal distress, early neonatal death, and small- as well as large-for-gestational age infants (70–72). Obese women who conceive by IVF also are at increased risk of preeclampsia, gestational diabetes, preterm delivery, and cesarean delivery (52, 73). In a population-based, case-control study of major birth defects in Atlanta during 1993–1997 (40,000 births annually), obese women (BMI >30 kg/m^2) were more likely than average-weight women (BMI, 18.5–24.9 kg/m^2) to have infants with heart defects (N = 32; OR 2.0; 95% CI, 1.2–3.4), ventral wall defects (N = 5; OR 3.3; 95% CI, 1.0–10.3), neural tube defects (N = 10; OR 2.7; 95% CI, 1.2–6.1), and multiple anomalies (N = 16; OR 2.0; 95% CI, 1.0–3.8) (74), although the absolute risk for all of them remains low. A meta-analysis of 18 observational studies confirms the associations between maternal obesity and obese mothers were at increased odds of pregnancies affected by neural tube defects (OR, 1.87; 95% [CI], 1.62–2.15), spina bifida (OR, 2.24; 95% CI, 1.86–2.69), cardiovascular anomalies (OR, 1.30; 95% CI, 1.12–1.51), cardiac septal anomalies (OR, 1.20; 95% CI, 1.09–1.31), cleft palate (OR, 1.23; 95% CI, 1.03–1.47), cleft lip and palate (OR, 1.20; 95% CI, 1.03–1.40), anorectal atresia (OR, 1.48; 95% CI, 1.12–1.97), hydrocephaly (OR, 1.68; 95% CI, 1.19–2.36), and limb reduction anomalies (OR, 1.34; 95% CI, 1.03–1.73) (75). These fetal abnormalities are linked with maternal metabolic dysfunction (62), which also promotes in the offspring an increased risk for obesity in later life, thereby perpetuating obesity in subsequent generations (76–78). As a result, maternal obesity is also associated with an increased risk of premature death in adult offspring; this strongly suggests

that maternal metabolic dysfunction negatively impacts the health of the offspring in later life (78, 79).

OBESITY AND MALE REPRODUCTION

Not all obese men have infertility, but those who do can have reduced semen quality, impaired erectile function, and other physical problems, including sleep apnea and increased scrotal temperatures (80–83). Obesity in men is associated with an increased incidence of oligozoospermia and asthenozoospermia in some (84–90), but not all (91–97), studies. Moreover, increased abdominal adiposity in men of subfertile couples has been associated with reduced sperm count, concentration, and motility (90). Evidence, however, varies as to whether male obesity alters sperm function (98), increases sperm DNA damage (91, 99–103), decreases sperm mitochondrial activity (101, 102), induces seminal oxidative stress (104), impairs blastocyst development (85), reduces pregnancy outcome, or increases miscarriage following assisted reproduction (85, 87, 91, 98, 105–108). These discrepancies likely represent differences in data acquisition, study populations, patient lifestyles, and comorbidities (98).

Despite conflicting reports regarding obesity and sperm parameters, suppression of SHBG by insulin in obese men increases androgen availability for estrogen production by adipose aromatase, which may lead to reduced gonadotropin secretion (82, 96, 98, 109, 110). Simultaneously, obese men have decreased total and bioavailable testosterone (T) levels (93, 96, 98, 104, 110–113) as well as reduced inhibin B concentrations (96, 109, 110, 114), combined with diminished LH pulse amplitude (113). This hormonal profile suggests enhanced estrogen negative-feedback inhibition from increased adipose-derived aromatase activity (115), along with decreased formation of inactive 2-hydroxyestrogens (82, 98, 104, 113,116–119). Consequently, obesity in men is accompanied by decreased Leydig cell T secretion, with T levels negatively correlated with fasting insulin and leptin levels (112, 118, 120).

In obese men, the scrotum remains in closer contact with surrounding tissue than in normal-weight men, predisposing to increased scrotal temperature that may adversely affect semen parameters (98, 121). Unfortunately, treatments aimed at lowering scrotal temperature (“scrotal hypothermia”) or reducing the amount of scrotal fat are impractical (122).

MANAGEMENT

Lifestyle Modification

Because of pregnancy complications related to obesity, obese women wishing to conceive should consider a weight management program that focuses on preconception weight loss (to a BMI <35 kg/m^2), prevention of excess weight gain in pregnancy, and long-term weight reduction (4, 123). Preconception weight loss in obese women is also important to reduce morbidity from anesthesia-related surgical procedures, such as oocyte retrieval (124). To date, however, there is no strong evidence that preconception weight loss in women improves IVF-related pregnancy outcome (125), and the data are less clear in men. Nevertheless, weight loss is assumed to benefit fertility as it does for diabetes and CVD. Weight management in all individuals is best achieved through a lifestyle modification program that combines dietary modification, physical activity, and behavioral interventions, including psychological, behavioral, and stress management strategies (4). The benefits of postponing pregnancy in women to achieve preconceptional weight loss must be balanced against the risk of declining fertility with advancing age, although optimizing weight gain during pregnancy can lower the incidence of gestational diabetes (126, 127).

Weight reduction in obese women with anovulatory infertility improves the rate of pregnancy (36, 37). Specifically, of 67 obese anovulatory infertile women who lost an average of 10 kg through a 6-month weight loss program, ovulatory function returned in 60 subjects (90%), of whom 52 (78%) conceived with a miscarriage rate of 18% (36). Modest short-term weight loss (approximately 3.1 kg decrease over 140 days) preceding IVF is associated with a higher number and percentage of metaphase II (MII) oocytes unrelated to pregnancy outcome (128). Weight reduction in obese men can improve total sperm count and morphology as well as increase SHBG and total T (110).

Current recommendations for lifestyle modification for obesity in all individuals include a weight loss of 7% of body weight and increased physical activity to at least 150 minutes weekly of moderate activity such as walking (10, 129). A 500–1,000 kcal/day decrease from usual dietary intake should lead to a 1–2-pound weight loss per week, with a low-calorie diet of 1,000–1,200 kcal/day, achieving an average 10% decrease in total body weight over 6 months (130). Calorie restriction is a fundamental principle of successful weight loss, with dietary composition being less important (10,131–133). Unfortunately, behavioral weight loss of at least 10% for more than 1 year occurs in only about 20% of individuals (134). Weight gain recurs when lifestyle modifications are not sustained, so that 60%–86% of lost weight is regained after 3 years and 75%–121% after 5 years (135). Women participating in lifestyle modification programs may be more successful than those who attempt weight loss on their own (136), although dropout remains a serious problem in any program for overweight infertile women (137).

Medical Treatment

Until recently, the only medication approved for long-term management of obesity has been orlistat (138, 139). As a lipase inhibitor, orlistat interferes with hydrolysis of dietary fat into absorbable free fatty acids, thereby decreasing fat absorption from the gut by approximately 30% (139, 140). Orlistat (120 mg orally with meals) also decreases absorption of fat-soluble vitamins, primarily vitamin D, so that supplementation with a multivitamin containing vitamin D, administered at least 2 hours before or after orlistat ingestion, is recommended. Gastrointestinal side effects are common. Contraindications for the use of orlistat include chronic malabsorption syndromes and cholestasis.

In 2011, the US Food and Drug Administration (FDA) approved a new formulation of phentermine, a central

norepinephrine-releasing drug with anorectic properties originally approved in 1959 for short-term monotherapy of obesity (138, 141). The recommended dosage is 15–30 mg orally daily. To minimize sleep disturbances from central nervous system stimulation, phentermine can be taken in the early morning. Side effects include hypertension, insomnia, dry mouth, constipation, and palpitations. After prolonged use, abrupt cessation of phentermine may cause extreme fatigue and depression. Phentermine is contraindicated for individuals with cardiovascular disease, uncontrolled hypertension, hyperthyroidism, glaucoma, and agitated states. Phentermine is a pregnancy category C drug and should not be used by pregnant women.

The FDA recently has approved additional drugs as adjuncts to lifestyle modification for adult women and men with a BMI of $\geq$30 kg/m^2 or $\geq$27 kg/m^2 and at least one weight-related coexisting condition (138). None of these drugs have been studied in women or men trying to lose weight before conception, and their effects on menstrual cycles, ovulation, and fecundity in women are unknown.

One drug combines phentermine with an extended-release form of topiramate, an anticonvulsant with weight loss properties that modulates sodium and gamma-aminobutyric acid (GABA)-activated chloride channels, and inhibits carbonic anhydrase (10). The combination of phentermine and topiramate (Phen/TPM: 3.75–15.0 mg/23–92 mg orally daily) has resulted in greater weight reduction than either agent alone. In three randomized, placebo-controlled, phase 3 trials, the average expected weight loss over 1 year was 5%–11% with Phen/TPM versus 1%–2% with placebo (10). Potential safety issues are increased heart rate, depression, anxiety, insomnia, paresthesia, altered taste, dry mouth, glaucoma, metabolic acidosis, and teratogenicity (138). Specifically, women who receive topiramate during pregnancy are more likely to have infants born with orofacial cleft defects and therefore need to use effective contraception (142).

The FDA has also approved lorcaserin (10 mg orally twice daily) for weight loss. It is a selective serotonin 2C receptor agonist that acts centrally to increase satiety, while avoiding the serotonin 2B receptor in heart valves (141). Specifically, lorcaserin stimulates pro-opiomelanocortin (POMC) neurons in the arcuate nucleus to release alpha-melanocortin-stimulating hormone (a-MSH), which acts in the paraventricular nucleus to suppress appetite. In two randomized, placebo-controlled, phase 3 trials, weight loss over 1 year was 5%–6% (slightly less than that of Phen/TPM) (10). Routine cardiac echocardiography is not recommended since the RR of cardiac valvulopathy from lorcaserin versus placebo is 1.16 (95% CI, 0.81–1.67) (141). Although well tolerated, common adverse effects of lorcaserin are headache, nausea, dizziness, fatigue, dry mouth, and constipation. Lorcaserin should not be used with selective serotonin reuptake inhibitors (SSRIs) or with monoamine oxidase inhibitors (MAOIs), because of the risk of serotonin syndrome (confusion, fever, seizures, irregular heart rate and high blood pressure, dilated pupils) (141).

The combination of bupropion, a dopamine/norepinephrine reuptake inhibitor, with naltrexone, an opioid receptor antagonist, also is used for the treatment of obesity. The anorectic effect of bupropion (32 mg orally) combined with naltrexone (360 mg orally) results from activation of POMC neurons in the arcuate nucleus, releasing a-MSH as a potent anorectic neuropeptide. Average expected weight loss is about 5% so that bupropion/naltrexone rank below Phen/TPM, but above lorcaserin and orlistat, in weight loss efficacy (143). Adverse side effects include nausea, headache, insomnia, constipation, and tremor (10).

Liraglutide has recently been FDA approved as a long-acting glucagon-like peptide-1 receptor (GLP-1R) agonist that resists rapid metabolism by dipeptidyl peptidase-IV (143). Liraglutide (3 mg subcutaneous daily) is accompanied by an approximate 6% weight loss over 1 year (143). Adverse side effects include nausea, vomiting, and the risk of pancreatitis (144). Contraindications for the use of liraglutide include pregnancy or a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (144).

Metformin has been proposed as a weight loss medication. Metformin is a biguanide that inhibits hepatic glucose production and increases peripheral tissue sensitivity to insulin, resulting in reduced circulating insulin and androgen levels accompanied by decreased body weight and visceral fat (145, 146). Metformin alone is not associated with weight loss; however, when metformin is combined with a low-calorie diet, weight loss has been demonstrated (145). The thiazolidinediones, as another class of insulin-sensitizing drugs, are not associated with weight loss (147).

Many obese women and men also self-medicate with herbal supplements, although their safety and effectiveness have not been demonstrated. Ephedra-containing supplements have potentially life-threatening cardiovascular side effects and have been banned by the FDA (148).

Several weight-loss medications are no longer available due to concerns regarding their adverse effects. Aminorex, an amphetamine-like agent, was associated with pulmonary hypertension. Fenfluramine and dexfenfluramine, serotonin 2B receptor agonists, were linked with cardiac valvulopathy. Phenylpropanolamine, a norepinephrine-releasing agent, was associated with stroke. Rimonabant, a cannabinoid 1 receptor blocker, was accompanied by suicidal ideation and behavioral changes. Sibutramine, a serotonin-norepinephrine reuptake inhibitor, was linked to myocardial infarction and stroke (138).

Bariatric Surgery

In 2011, over 340,000 bariatric surgical procedures were performed worldwide, with the United States/Canada performing the largest number of operations (over 100,000 cases) (149). Common bariatric surgical procedures are either restrictive (i.e., sleeve gastrectomy [SG], laparoscopic adjustable gastric band [LAGB], or combined restrictive/malabsorptive [Roux-en-Y gastric bypass, RYGB]). Restrictive procedures create a small gastric pouch with staples or a band that fills rapidly to induce early satiety. The RYGB creates a small stomach pouch and attaches it to a loop of jejunum to shorten the length of the intestinal tract, restricting food intake and

causing malabsorption (150). Besides limiting energy intake and/or absorption, bariatric surgery also can alter food preference, insulin secretion, gut hormones, gut microbiome, and bile acid release (151, 152). In 2011, the most commonly performed bariatric procedures worldwide were RYGB (47%), SG (28%), and LAGB (18%) (150). More recently, laparoscopic SG has gained popularity over LAGB (153).

The percentage of excess body weight lost at 2 years or more after bariatric surgery is 63%–49%, with obese individuals showing postoperative decreases in total body weight after 2, 10, 15, and 20 years of 23%, 17%, 16%, and 18%, respectively (154). Bariatric surgery in women can restore menstrual regularity (155, 156), correct ovulation (157, 158), shorten folliculogenesis with ovulation, reduce serum T levels, diminish percent body fat, and improve both sexual function (159) and chance of pregnancy (160, 161), with weight loss predicting conception (161). In eumenorrheic women with a BMI $\geq$35 kg/m^2, however, surgically induced weight loss only partially improves deficient luteal progesterone production with a rise in LH secretion, suggesting persistent corpus luteum dysfunction (162).

Surgically induced weight loss in men can improve sexual function; increase gonadotropin, SHBG, total and free T levels; decrease estradiol concentration; but not necessarily alter sperm quality (163). Of more concern, case reports of obese men undergoing bariatric surgery have shown a worsening of their semen parameters, perhaps from postoperative nutritional deficiencies, causing secondary infertility from spermatogenic arrest (164, 165) and impaired IVF pregnancy outcome (166). In another case series, however, semen parameters of three obese men remained stable up to 1 year following bariatric surgery (167). Without larger studies to confirm the impact of bariatric surgery on sperm quality, individualized management with cryopreservation of semen samples should be considered in selected circumstances (168).

Available evidence, although limited, suggests that IVF after bariatric surgery can be safe provided that special nutritional requirements after surgery are met. Of five women (BMI, 23–39 kg/m^2) undergoing IVF following bariatric surgery 1–5 years earlier, four women had term deliveries without complications related to previous surgery (169). One IVF patient remained obese after previous bariatric surgery; however, she experienced empty follicle syndrome at oocyte retrieval, perhaps from reduced intrafollicular human chorionic gonadotropin (hCG) bioavailability (170, 171).

Rare surgical complications (i.e., bowel obstructions, internal hernia, gastric ulcer, band events, and staple-line stricture) can occur in pregnancy due to increased intra-abdominal pressure, intra-abdominal organ displacement by the gravid uterus, and vomiting (158,172–174). Surgically induced weight loss data suggest that 1) maternal risks of gestational diabetes, preeclampsia, hypertensive disorders, and macrosomia are reduced (158,172–175); 2) the chance of fetal growth restriction is increased in some (176), but not all (177), reports; and 3) the incidences of preterm birth, preterm premature rupture of the membranes, miscarriage, neonatal death, and malformation are unclear (158,172–176). Of concern, however, in a matched cohort study from the Swedish National Health Service, the chances of preterm and small-for-gestational age (SGA) singleton births were greater in women with a history of bariatric surgery (preterm birth 9.7%; SGA birth 5.2%) than in women without such surgery (preterm birth 6.1%; SGA birth 3.0%), controlling for maternal age, parity, early pregnancy, BMI, and environmental factors (ORs: preterm birth 1.7 [1.4–2.0]; SGA birth 2.0 [1.5–2.5]) (178). Although some studies suggest that overall adverse perinatal outcomes do not appear elevated after bariatric surgery (160, 174, 179), post-surgical nutritional deficiencies of protein, iron, vitamins B12 and D, folate, and calcium occur more frequently after malabsorptive versus restrictive procedures and have been associated with fetal malformations (150).

Therefore, preconceptional assessment of a patient's nutritional status and micronutrient supplementation after bariatric surgery are imperative (150, 157, 158, 173). Delaying pregnancy until 1–2 years after bariatric surgery has been recommended to avoid fetal exposure to nutritional deficiencies from rapid maternal weight loss (173, 180, 181), although limited data suggest that pregnancy within the first year after bariatric surgery may not necessarily increase the risk for adverse maternal or perinatal outcomes (177, 182, 183). Particularly in late reproductive years, the benefits of postponing pregnancy to achieve weight loss must be balanced against the risk of declining fertility with advancing age. In women who are sexually active, non-oral hormonal contraception should be considered after bariatric surgery rather than oral contraceptives, which increase the risk of postoperative thromboembolism and may exhibit decreased efficacy from gastrointestinal malabsorption, prolonged diarrhea, and vomiting following surgery (150, 184).

SUMMARY

- Many obese women and men are fertile.
- Obesity in women is associated with ovulatory dysfunction, reduced ovarian responsiveness to agents that induce ovulation, altered oocyte as well as endometrial functions, and lower birth rates.
- Obese women are at increased risk of developing maternal and fetal complications during pregnancy.
- Obesity in men may be associated with impaired reproductive function.
- Lifestyle modification in women and men is the first-line treatment for obesity, followed by adjunctive medical therapy.
- Bariatric surgery in women and men is an important adjuvant to lifestyle modification and medical therapy for weight loss, but pregnancy in women should be deferred for 1 year postoperatively.

CONCLUSIONS

- Preconceptional counseling for obese couples should address the reproductive and maternal-fetal consequences of obesity.

- The health benefits of postponing pregnancy to achieve weight loss must be balanced against the risk of declining fertility with advancing age of the couple.

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