

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.)

Earn online CME credit related to this document at www.asrm.org/elearn

Discuss: You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/asrmpraccom-obesity-reproduction/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

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/m² (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).

Received August 12, 2015; accepted August 12, 2015; published online October 1, 2015.

Reprint requests: Practice Committee, American Society for Reproductive Medicine, 1209 Montgomery Hwy., Birmingham, Alabama 35216 (E-mail: ASRM@asrm.org).

Fertility and Sterility® Vol. 104, No. 5, November 2015 0015-0282/\$36.00

Copyright ©2015 American Society for Reproductive Medicine, Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.fertnstert.2015.08.018>

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/m² 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/m² 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/m² (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/m²) (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/m² increase in women with a BMI >29 kg/m² (hazard ratio: 0.96; 95% CI, 0.91–0.99 versus a BMI 21–29 kg/m²) (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/m²) undergoing IVF have a 10% lower live-birth rate than women of normal weight (BMI, <25 kg/m²) (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/m² (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/m²), 61% (BMI, 35.0–39.9 kg/m²), and 68% (BMI, >40.0 kg/m²) compared with women with a BMI of 18.5–24.9 kg/m² (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/m²) (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/m²) (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/m² 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/m²) (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/m² have a lower live-birth rate (25%) compared with those with a BMI <35 kg/m² (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/m²) (39). In a retrospective analysis of 2,660 couples undergoing IVF, obese women (BMI >30 kg/m²) 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/m²) (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/m²) (68). This finding supports a review of 4,609 women undergoing first-time IVF, which showed women with a BMI >40 kg/m² 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/m²) (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/m²) (53). Similarly, an increased risk for clinical miscarriage before 23 weeks' gestation was observed in obese women (BMI >25 kg/m²) compared with those with a BMI 18.5–24.9 kg/m² 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/m²) were more likely than average-weight women (BMI, 18.5–24.9 kg/m²) 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/m²), 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 ≥ 30 kg/m² or ≥ 27 kg/m² 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 (α -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 α -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 ≥ 35 kg/m², 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/m²) 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 adjunct 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.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Samantha Pfeifer, M.D.; Gregory Fossum, M.D.; Margareta Pisarska, M.D.; Eric Widra, M.D.; Jay Sandlow, M.D.; Mitchell Rosen, M.D.; Michael Vernon, Ph.D.; Daniel Dumesic, M.D.; Clarisa Gracia, M.D., M.S.C.E.; Randall Odem, M.D.; Kim Thornton, M.D.; Samantha Butts, M.D.; Robert Rebar, M.D.; Rebecca Sokol, M.D.; Richard Reindollar, M.D.; Andrew La Barbera, Ph.D.

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;307:491–7.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* 2012;307:483–90.
3. Vahratian A. Prevalence of overweight and obesity among women of child-bearing age: results from the 2002 National Survey of Family Growth. *Matern Child Health J* 2009;13:268–73.
4. Moran L. Weight management to improve outcomes in infertility. In: Tarlatzis BC, Bulun SE, editors. *Transforming reproductive medicine worldwide*. Birmingham: American Society for Reproductive Medicine; 2013:66–73. Proceedings of the The International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and The 69th Annual Meeting of the American Society for Reproductive Medicine; 2013 Oct 12-17; Boston.
5. Christensen AI, Ekholm O, Davidsen M, Juel K. Sundhed og sygelighed i Danmark 2010 & udviklingen siden 1987. The National Health Interview Survey 2010. Copenhagen: National Institute of Public Health; 2012.
6. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary: expert panel on the identification, evaluation, and treatment of overweight in adults. *Am J Clin Nutr* 1998;68:899–917.
7. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ* 2012;31:219–30.
8. Bleich SN, Bennett WL, Guduzne KA, Cooper LA. Impact of physician BMI on obesity care and beliefs. *Obesity (Silver Spring)* 2012;20:999–1005.
9. Rosenzweig JL, Ferrannini E, Grundy SM, Haffner SM, Heine RJ, Horton ES, et al. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3671–89.
10. Wyatt HR. Update on treatment strategies for obesity. *J Clin Endocrinol Metab* 2013;98:1299–306.
11. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod Update* 2003;9:359–72.
12. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–63.
13. Flegal KM, Shepherd JA, Looker AC, Graubard BI, Borrud LG, Ogden CL, et al. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr* 2009;89:500–8.
14. Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996;143:228–39.
15. Fernández JR, Heo M, Heymsfield SB, Pierson RN Jr, Pi-Sunyer FX, Wang ZM, et al. Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? *Am J Clin Nutr* 2003;77:71–5.
16. Sørensen 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.
17. Folsom AR, Kaye SA, Sellers TA, Hong CP, Cerhan JR, Potter JD, et al. Body fat distribution and 5-year risk of death in older women. *JAMA* 1993;269:483–7.
18. Hartz AJ, Rupley DC, Rimm AA. The association of girth measurements with disease in 32,856 women. *Am J Epidemiol* 1984;119:71–80.
19. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. *N Engl J Med* 1995;333:677–85.
20. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;280:1843–8.
21. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—an allostatic perspective. *Biochim Biophys Acta* 2010;1801:338–49.
22. Douchi T, Kuwahata R, Yamamoto S, Oki T, Yamasaki H, Nagata Y. Relationship of upper body obesity to menstrual disorders. *Acta Obstet Gynecol Scand* 2002;81:147–50.
23. Castillo-Martinez L, López-Alvarenga JC, Villa AR, González-Barranco J. Menstrual cycle length disorders in 18- to 40-year-old obese women. *Nutrition* 2003;19:317–20.
24. Lake JK, Power C, Cole TJ. Women's reproductive health: the role of body mass index in early and adult life. *Int J Obes Relat Metab Disord* 1997;21:432–8.
25. Polotsky AJ, Hailpern SM, Skurnick JH, Lo JC, Sternfeld B, Santoro N. Association of adolescent obesity and lifetime nulliparity—the Study of Women's Health Across the Nation (SWAN). *Fertil Steril* 2010;93:2004–11.
26. McCartney CR, Blank SK, Prendergast KA, Chhabra S, Eagleson CA, Helm KD, et al. Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre- and early pubertal obese girls. *J Clin Endocrinol Metab* 2007;92:430–6.
27. Pasquali R, Casimirri F, Platè L, Capelli M. Characterization of obese women with reduced sex hormone-binding globulin concentrations. *Horm Metab Res* 1990;22:303–6.
28. 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.

29. Greisen S, Ledet T, Møller N, Jørgensen 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.
30. Santoro N, Lasley B, McConnell D, Allsworth J, Crawford S, Gold EB, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. *J Clin Endocrinol Metab* 2004;89:2622–31.
31. 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.
32. Grenman S, Rönnemaa T, Irjala K, Kaihola HL, Grönroos M. Sex steroid, gonadotropin, cortisol, and prolactin levels in healthy, massively obese women: correlation with abdominal fat cell size and effect of weight reduction. *J Clin Endocrinol Metab* 1986;63:1257–61.
33. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol* 1994;171:171–7.
34. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. *Epidemiology* 1994;5:247–50.
35. Kuchenbecker WK, Groen H, Zijlstra TM, Bolster JH, Slart RH, van der Jagt EJ, et al. The subcutaneous abdominal fat and not the intraabdominal fat compartment is associated with anovulation in women with obesity and infertility. *J Clin Endocrinol Metab* 2010;95:2107–12.
36. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998;13:1502–5.
37. Clark AM, Ledger W, Galletley C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995;10:2705–12.
38. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrhic infertility. *Fertil Steril* 2002;77:91–7.
39. Mulders AG, Laven JS, Eijkemans MJ, Hughes EG, Fauser BC. Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis. *Hum Reprod Update* 2003;9:429–49.
40. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulatory/intrauterine insemination cycles. *Fertil Steril* 2011;95:1042–7.
41. Fedorcsák P, Dale PO, Storeng R, Ertzeid G, Bjerkce S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. *Hum Reprod* 2004;19:2523–8.
42. 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.
43. Moragianni VA, Jones SM, Ryley DA. The effect of body mass index on the outcomes of first assisted reproductive technology cycles. *Fertil Steril* 2012;98:102–8.
44. Wang JX, Davies M, Norman RJ. Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. *BMJ* 2000;321:1320–1.
45. 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.
46. Gesink Law DC, Maclehorse RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod* 2007;22:414–20.
47. 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.
48. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ* 1993;306:484–7.
49. Thum MY, El-Sheikhah A, Faris R, Parikh J, Wren M, Ogunyemi T, et al. The influence of body mass index to in-vitro fertilisation treatment outcome, risk of miscarriage and pregnancy outcome. *J Obstet Gynaecol* 2007;27:699–702.
50. Marci R, Lisi F, Soave I, Lo Monte G, Patella A, Caserta D, et al. Ovarian stimulation in women with high and normal body mass index: GnRH agonist versus GnRH antagonist. *Gynecol Endocrinol* 2012;28:792–5.
51. 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.
52. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. *Obstet Gynecol* 2006;108:61–9.
53. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online* 2011;23:421–39.
54. Petersen GL, Schmidt L, Pinborg A, Kamper-Jørgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. *Fertil Steril* 2013;99:1654–62.
55. Depalo R, Garruti G, Totaro I, Panzarino M, Vacca MP, Giogino F, et al. Oocyte morphological abnormalities in overweight women undergoing in vitro fertilization cycles. *Gynecol Endocrinol* 2011;27:880–4.
56. Zhang D, Zhu Y, Gao H, Zhou B, Zhang R, Wang T, et al. Overweight and obesity negatively affect the outcomes of ovarian stimulation and in vitro fertilisation: a cohort study of 2628 Chinese women. *Gynecol Endocrinol* 2010;26:325–32.
57. Orvieto R, Meltzer S, Nahum R, Rabinson J, Anteby EY, Ashkenazi J. The influence of body mass index on in vitro fertilization outcome. *Int J Gynaecol Obstet* 2009;104:53–5.
58. 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.
59. Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. *Hum Reprod* 2015;30:122–32.
60. 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. http://www.ncbi.nlm.nih.gov/pubmed?term=Robker%20RL%5BAuthor%5D&cauthor=true&cauthor_uid=20861227.
61. Minge CE, Bennett BD, Norman RJ, Robker RL. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* 2008;149:2646–56.
62. 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.
63. Jungheim ES, Schoeller EL, Marquard KL, Loudon ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology* 2010;151:4039–46.
64. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. SART writing group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod* 2011;26:245–52.
65. Jungheim ES, Schon SB, Schulte MB, DeUgarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. *Hum Reprod* 2013;28:2720–7.
66. Deugarte D, Deugarte C, Sahakian V. Surrogate obesity negatively impacts pregnancy rates in third-party reproduction. *Fertil Steril* 2010;93:1008–10.
67. Bellver J, Martínez-Conejero JA, Labarta E, Alamá P, Melo MA, Remohí J, et al. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril* 2011;95:2335–41.

68. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. *Obes Res* 2002;10:551–4.
69. Rittenberg V, Sobaleva S, Ahmad A, Oteng-Ntim E, Bolton V, Khalaf Y, et al. Influence of BMI on risk of miscarriage after single blastocyst transfer. *Hum Reprod* 2011;26:2642–50.
70. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. FASTER research consortium. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. *Am J Obstet Gynecol* 2004;190:1091–7.
71. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol* 2004;103:219–24.
72. Rajasingam D, Seed PT, Briley AL, Shennan AH, Poston L. A prospective study of pregnancy outcome and biomarkers of oxidative stress in nulliparous obese women. *Am J Obstet Gynecol* 2009;200:395.e1–9.
73. Dickey RP, Xiong X, Xie Y, Gee RE, Pridjian G. Effect of maternal height and weight on risk for preterm singleton and twin births resulting from IVF in the United States, 2008–2010. *Am J Obstet Gynecol* 2013;209:e1–6.
74. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk of birth defects. *Pediatrics* 2003;111:1152–8.
75. Stothard KJ, Tennant PWG, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;301:636–50.
76. Desai M, Beall M, Ross MG. Developmental origins of obesity: programmed adipogenesis. *Curr Diab Rep* 2013;13:27–33.
77. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115:e290–6.
78. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* 2013;347:f4539.
79. Leese HJ. Effective nutrition from conception to adulthood. *Hum Fertil (Camb)* 2014;17:252–6.
80. Cabler S, Agarwal A, Flint M, du Plessis SS. Obesity: modern man's fertility nemesis. *Asian J Androl* 2010;12:480–9.
81. Sallmén M, Sandler DP, Hoppin JA, Blair A, Baird DD. Reduced fertility among overweight and obese men. *Epidemiology* 2006;17:520–3.
82. Pasquali R. Obesity and androgens: facts and perspectives. *Fertil Steril* 2006;85:1319–40.
83. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sørensen TI, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;22:1634–7.
84. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. *Fertil Steril* 2008;90:2222–5.
85. Bakos HW, Henshaw RC, Mitchell M, Lane M. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. *Fertil Steril* 2011;95:1700–4.
86. Relwani R, Berger D, Santoro N, Hickmon C, Nihsen M, Zapantis A, et al. Semen parameters are unrelated to BMI but vary with SSRI use and prior urological surgery. *Reprod Sci* 2011;18:391–7.
87. Umul M, Köse SA, Bilen E, Altuncu AG, Oksay T, Güney M. Effect of increasing paternal body mass index on pregnancy and live birth rates in couples undergoing intracytoplasmic sperm injection. *Andrologia* 2015;47:360–4.
88. Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* 2013;19:221–31.
89. Braga DP, Halpern G, Figueira Rde C, Setti AS, Iaconelli A Jr, Borges E Jr. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. *Fertil Steril* 2012;97:53–9.
90. Hammiche F, Laven JS, Twigt JM, Boellaard WP, Steegers EA, Steegers-Theunissen RP. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. *Hum Reprod* 2012;27:2365–72.
91. Thomsen L, Humaidan P, Bungum L, Bungum M. The impact of male overweight on semen quality and outcome of assisted reproduction. *Asian J Androl* 2014;16:1–6.
92. Eisenberg ML, Kim S, Chen Z, Sundaram R, Schisterman EF, Buck Louis GM. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. *Hum Reprod* 2014;29:193–200.
93. Al-Ali BM, Gutschi T, Pummer K, Zigeuner R, Brookman-May S, Wieland WF, et al. Body mass index has no impact on sperm quality but on reproductive hormones levels. *Andrologia* 2014;46:106–11.
94. Duits FH, van Wely M, van der Veen F, Gianotten J. Healthy overweight male partners of subfertile couples should not worry about their semen quality. *Fertil Steril* 2010;94:1356–9.
95. Lotti F, Corona G, Colpi GM, Filimberti E, Degli Innocenti S, Mancini M, et al. Elevated body mass index correlates with higher seminal plasma interleukin 8 levels and ultrasonographic abnormalities of the prostate in men attending an andrology clinic for infertility. *J Endocrinol Invest* 2011;34:e336–42.
96. MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Hum Reprod Update* 2010;16:293–311.
97. Povey AC, Clyma JA, McNamee R, Moore HD, Baillie H, Pacey AA, et al. Modifiable and non-modifiable risk factors for poor semen quality: a case-referent study. *Hum Reprod* 2012;27:2799–806.
98. Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function and molecular composition. *Spermatogenesis* 2012;2:253–63.
99. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril* 2010;93:2222–31.
100. Dupont C, Faure C, Sermondade N, Boubaya M, Eustache F, Clément P, et al. Obesity leads to higher risk of sperm DNA damage in infertile patients. *Asian J Androl* 2013;15:622–5.
101. Fariello RM, Pariz JR, Spaine DM, Cedenho AP, Bertolla RP, Fraietta R. Association between obesity and alteration of sperm DNA integrity and mitochondrial activity. *BJU Int* 2012;110:863–7.
102. La Vignera S, Condorelli RA, Vicari E, Calogero AE. Negative effect of increased body weight on sperm conventional and nonconventional flow cytometric sperm parameters. *J Androl* 2012;33:53–8.
103. Rybar R, Kopecka V, Prinosilova P, Markova P, Rubes J. Male obesity and age in relationship to semen parameters and sperm chromatin integrity. *Andrologia* 2011;43:286–91.
104. Tunc O, Bakos HW, Tremellen K. Impact of body mass index on seminal oxidative stress. *Andrologia* 2011;43:121–8.
105. Keltz J, Zapantis A, Jindal SK, Lieman HJ, Santoro N, Polotsky AJ. Overweight men: clinical pregnancy after ART is decreased in IVF but not in ICSI cycles. *J Assist Reprod Genet* 2010;27:539–44.
106. Colaci DS, Afeiche M, Gaskins AJ, Wright DL, Toth TL, Tanrikut C, et al. Men's body mass index in relation to embryo quality and clinical outcomes in couples undergoing in vitro fertilization. *Fertil Steril* 2012;98:1193–9.e1.
107. Merhi ZO, Keltz J, Zapantis A, Younger J, Berger D, Lieman HJ, et al. Male adiposity impairs clinical pregnancy rate by in vitro fertilization without affecting day 3 embryo quality. *Obesity (Silver Spring)* 2013;21:1608–12.
108. Ramasamy R, Bryson C, Reifsnnyder JE, Neri Q, Palermo GD, Schlegel PN. Overweight men with nonobstructive azoospermia have worse pregnancy outcomes after microdissection testicular sperm extraction. *Fertil Steril* 2013;99:372–6.
109. Teerds KJ, de Rooij DG, Keijzer J. Functional relationship between obesity and male reproduction: from humans to animal models. *Hum Reprod Update* 2011;17:667–83.
110. Håkonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY, et al. Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. *Reprod Health* 2011;8:24.

111. Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, et al. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. *J Clin Endocrinol Metab* 1990;71:929–31.
112. Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, et al. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab* 2005;90:2636–41.
113. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab* 1993;76:1140–6.
114. Stewart TM, Liu DY, Garrett C, Jørgensen N, Brown EH, Baker HW. Associations between andrological measures, hormones and semen quality in fertile Australian men: inverse relationship between obesity and sperm output. *Hum Reprod* 2009;24:1561–8.
115. Jarow JP, Kirkland J, Koritnik DR, Cefalu WT. Effect of obesity and fertility status on sex steroid levels in men. *Urology* 1993;42:171–4.
116. Baker HW. Reproductive effects of nontesticular illness. *Endocrinol Metab Clin North Am* 1998;27:831–50.
117. Schneider J, Bradlow HL, Strain G, Levin J, Anderson K, Fishman J. Effects of obesity on estradiol metabolism: decreased formation of nonuterotropic metabolites. *J Clin Endocrinol Metab* 1983;56:973–8.
118. Isidori AM, Caprio M, Strollo F, Moretti C, Fratese G, Isidori A, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab* 1999;84:3673–80.
119. Wake DJ, Strand M, Rask E, Westerbacka J, Livingstone DE, Soderberg S, et al. Intra-adipose sex steroid metabolism and body fat distribution in idiopathic human obesity. *Clin Endocrinol* 2007;66:440–6.
120. Hofny ER, Ali ME, Abdel-Hafez HZ, Eel-D Kamal, Mohamed EE, Abd El-Azeem HG, et al. Semen parameters and hormonal profile in obese fertile and infertile males. *Fertil Steril* 2010;94:581–4.
121. Jung A, Schill WB. Male infertility. Current lifestyle could be responsible for infertility. *MMW Fortschr Med* 2000;142:31–3.
122. Mulcahy JJ. Scrotal hypothermia and the infertile man. *J Urol* 1984;132:469–70.
123. Nelson SM, Fleming R. Obesity and reproduction: impact and interventions. *Curr Opin Obstet Gynecol* 2007;19:384–9.
124. Sankar A, Johnson SR, Beattie WS, Tait G, Wijeyesundera DN. Reliability of the American Society of Anesthesiologists physical status scale in clinical practice. *Br J Anaesth* 2014;113:424–32.
125. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev* 2014;15:839–50.
126. Quinlivan JA, Lam LT, Fisher J. A randomised trial of a four-step multidisciplinary approach to the antenatal care of obese pregnant women. *Aust N Z J Obstet Gynaecol* 2011;51:141–6.
127. Phelan S, Phipps MG, Abrams B, Darroch F, Schaffner A, Wing RR. Randomized trial of a behavioral intervention to prevent excessive gestational weight gain: The Fit for Delivery Study. *Am J Clin Nutr* 2011;93:772–9.
128. 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.
129. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care* 2013;36:S11–66.
130. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. *Obes Res* 1998;6:515–2095.
131. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082–90.
132. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, weight watchers, and zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005;293:43–53.
133. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–73.
134. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr* 2001;21:323–41.
135. Bray GA. Uses and misuses of the new pharmacotherapy of obesity. *Ann Med* 1999;31:1–3.
136. Wadden TA, Foster GD. Behavioral treatment of obesity. *Med Clin North Am* 2000;84:441–61.
137. Mutsaerts MA, Kuchenbecker WK, Mol BW, Land JA, Hoek A. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review. *Hum Reprod* 2013;28:979–86.
138. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. *N Engl J Med* 2012;367:1577–9.
139. Hussain SS, Bloom SR. The pharmacological treatment and management of obesity. *Postgrad Med* 2011;123:34–44.
140. Keating GM, Jarvis B. Orlistat: in the prevention and treatment of type 2 diabetes mellitus. *Drugs* 2001;61:2107–19.
141. Ryan DH, Bray GA. Pharmacologic treatment options for obesity: what is old is new again. *Curr Hypertens Rep* 2013;15:182–9.
142. Margulis AV, Mitchell AA, Gilboa SM, Werler MM, Mittleman MA, Glynn RJ, et al. National birth defects prevention study. Use of topiramate in pregnancy and risk of oral clefts. *Am J Obstet Gynecol* 2012;207:e1–7.
143. Pucci A, Finer N. New medications for treatment of obesity: metabolic and cardiovascular effects. *Can J Cardiol* 2015;31:142–52.
144. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:342–62.
145. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000;85:2767–74.
146. Crave JC, Fimbel S, Lejeune H, Cugnardey N, Dechaud H, Pugeat M. Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. *J Clin Endocrinol Metab* 1995;80:2057–62.
147. Asnani S, Richard BC, Desouza C, Fonseca V. Is weight loss possible in patients treated with thiazolidinediones? Experience with a low-calorie diet. *Curr Med Res Opin* 2003;19:609–13.
148. Samenuk D, Link MS, Homoud MK, Contreras R, Theoharides TC, Wang PJ, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002;77:12–6.
149. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. *Obes Surg* 2013;23:427–36.
150. Devlieger R. Reproductive outcomes after bariatric surgery. In: Tarlatzis BC, Bulun SE, editors. Transforming reproductive medicine worldwide. Birmingham: American Society for Reproductive Medicine; 2013:59–65. Proceedings of the The International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and The 69th Annual Meeting of the American Society for Reproductive Medicine; 2013 Oct 12-17; Boston.
151. Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet* 2012;379:2300–11.
152. Vetter ML, Cardillo S, Rickels MR, Iqbal N. Narrative review: effect of bariatric surgery on type 2 diabetes mellitus. *Ann Intern Med* 2009;150:94–103.
153. Nguyen NT, Nguyen B, Gebhart A, Hohmann S. Changes in the makeup of bariatric surgery: a national increase in use of laparoscopic sleeve gastrectomy. *J Am Coll Surg* 2013;216:252–7.
154. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;307:56–65.
155. Zitsman JL, Digiorgi MF, Marr JR, Witt MA, Bessler M. Comparative outcomes of laparoscopic adjustable gastric banding in adolescents and adults. *Surg Obes Relat Dis* 2011;7:720–6.

156. Teitelman M, Grotegut CA, Williams NN, Lewis JD. The impact of bariatric surgery on menstrual patterns. *Obes Surg* 2006;16:1457–63.
157. Tan O, Carr BR. The impact of bariatric surgery on obesity-related infertility and in vitro fertilization outcomes. *Semin Reprod Med* 2012;30:517–28.
158. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, et al. Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA* 2008;300:2286–96.
159. 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.
160. Marceau P, Kaufman D, Biron S, Hould FS, Lebel S, Marceau S, et al. Outcome of pregnancies after biliopancreatic diversion. *Obes Surg* 2004;14:318–24.
161. Musella M, Milone M, Bellini M, Sosa Fernandez LM, Leongito M, Milone F. Effect of bariatric surgery on obesity-related infertility. *Surg Obes Relat Dis* 2012;8:445–9.
162. Rochester D, Jain A, Polotsky AJ, Polotsky H, Gibbs K, Isaac B, et al. Partial recovery of luteal function after bariatric surgery in obese women. *Fertil Steril* 2009;92:1410–5.
163. Reis LO, Zani EL, Saad RD, Chaim EA, de Oliveira LC, Fregonesi A. Bariatric surgery does not interfere with sperm quality—a preliminary long-term study. *Reprod Sci* 2012;19:1057–62.
164. Sermondade N, Massin N, Boitrelle F, Pfeffer J, Eustache F, Sifer C, et al. Sperm parameters and male fertility after bariatric surgery: three case series. *Reprod Biomed Online* 2012;24:206–10.
165. di Frega AS, Dale B, Di Matteo L, Wilding M. Secondary male factor infertility after Roux-en-Y gastric bypass for morbid obesity: case report. *Hum Reprod* 2005;20:997–8.
166. Lazaros L, Hatzl E, Markoula S, Takenaka A, Sofikitis N, Zikopoulos K, et al. Dramatic reduction in sperm parameters following bariatric surgery: report of two cases. *Andrologia* 2012;44:428–32.
167. Legro RS, Kunselman AR, Meadows JW, Kesner JS, Krieg EF, Rogers AM, et al. Time-related increase in urinary testosterone levels and stable semen analysis parameters after bariatric surgery in men. *Reprod Biomed Online* 2015;30:150–6.
168. Reis LO, Dias FG. Male fertility, obesity, and bariatric surgery. *Reprod Sci* 2012;19:778–85.
169. Doblado MA, Lewkowksi BM, Odem RR, Jungheim ES. In vitro fertilization after bariatric surgery. *Fertil Steril* 2010;94:2812–4.
170. Hirshfeld-Cytron J, Kim HH. Empty follicle syndrome in the setting of dramatic weight loss after bariatric surgery: case report and review of available literature. *Fertil Steril* 2008;90:1199.e21–3.
171. Dumesic DA, Lesnick TG, Abbott DH. Increased adiposity enhances intrafollicular estradiol levels in normoandrogenic ovulatory women receiving gonadotropin-releasing hormone analog/recombinant human follicle-stimulating hormone therapy for in vitro fertilization. *J Clin Endocrinol Metab* 2007;92:1438–41.
172. Moore KA, Ouyang DW, Whang EE. Maternal and fetal deaths after gastric bypass surgery for morbid obesity. *N Engl J Med* 2004;351:721–2.
173. Guelinckx I, Devlieger R, Vansant G. Reproductive outcome after bariatric surgery: a critical review. *Hum Reprod Update* 2009;15:189–201.
174. Hezelgrave NL, Oteng-Ntim E. Pregnancy after bariatric surgery: a review. *J Obes* 2011;2011:501939.
175. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. *Obstet Gynecol* 2009;113:1405–13.
176. Lesko J, Peaceman A. Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. *Obstet Gynecol* 2012;119:547–54.
177. Dixon JB, Dixon ME, O'Brien PE. Birth outcomes in obese women after laparoscopic adjustable gastric banding. *Obstet Gynecol* 2005;106:965–72.
178. Roos N, Neovius M, Cnattingius S, Lagerros YT, Sääf M, Granath F, et al. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. *BMJ* 2013;347:f6460.
179. Sheiner E, Levy A, Silverberg D, Menes TS, Levy I, Katz M, et al. Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. *Am J Obstet Gynecol* 2004;190:1335–40.
180. Apovian CM, Baker C, Ludwig DS, Hoppin AG, Hsu G, Lenders C, et al. Best practice guidelines in pediatric/adolescent weight loss surgery. *Obes Res* 2005;13:274–82.
181. Beard JH, Bell RL, Duffy AJ. Reproductive considerations and pregnancy after bariatric surgery: current evidence and recommendations. *Obes Surg* 2008;18:1023–7.
182. Sheiner E, Edri A, Balaban E, Levi I, Aricha-Tamir B. Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery. *Am J Obstet Gynecol* 2011;204:50.e1–6.
183. Patel JA, Patel NA, Thomas RL, Nelms JK, Colella JJ. Pregnancy outcomes after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2008;4:39–45.
184. Paulen ME, Zapata LB, Cansino C, Curtis KM, Jamieson DJ. Contraceptive use among women with a history of bariatric surgery: a systematic review. *Contraception* 2010;82:86–94.