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 American Society for Reproductive Medicine 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 2015 (Fertil Steril 2015;104:1116–26). (Fertil Steril® 2021;116:1266-85. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Infertility, ovulatory dysfunction, treatment, overweight

Over the past four decades, obesity (body mass index [BMI] $>$ 30 kg/m^2 in Western nations) has become a global epidemic affecting an estimated 603.7 million adults, representing 12% of the world's adult population (1). In 1980, 19% of adult American women and 13% of adult American men were obese (2). By 2017–2018, 42% of American women and 43% of American men were obese. Severe obesity (BMI $>$ 40 kg/m^2) now affects 11.5% of adult American women. Ethnic disparities in obesity prevalence exist. Fifty-seven percent of non-Hispanic black, 44% of Hispanic, 40% of non-Hispanic white, and 17% of non-Hispanic Asian American women are obese (3). Fifty-one percent of pregnant American women are overweight or obese at the time of conception (4).

The Global Burden of Disease 2015 Obesity Collaborators estimate that high BMI results in 4,000,000 deaths worldwide annually, or 7.1% of all-cause mortality (1, 5). In the United States, the estimated annual medical cost of illness related to obesity approaches $150 billion, excluding the cost of maternal morbidity and adverse perinatal outcomes (6).

Obesity has adverse effects on reproduction, including on ovulatory and menstrual function, natural fertility and fecundity rates, infertility treatment success rates, infertility treatment safety, and obstetric outcomes. The ability to deliver optimal care to women with obesity can be limited by difficulties in transvaginal ultrasound imaging of the ovaries and safety considerations, such as difficulty in maintaining an airway during oocyte retrieval. Reproductive care specialists are, thus, confronted with the challenge of treating infertility in the increasingly common setting of obesity. Furthermore, previous assumptions that weight loss interventions improve reproductive outcomes are being challenged by the findings of several recent published studies (7–9).

This document outlines the adverse effects of obesity on human reproduction. An assessment of the therapeutic benefits of lifestyle modification, medical management, and bariatric surgery is offered. The issues of safety and BMI treatment thresholds are addressed.

DEFINITION OF OBESITY

Obesity is a disease of excess body fat, and it increases the risk of a number of common conditions, including type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, cholelithiasis, endometrial and postmenopausal breast cancer, stroke, osteoarthritis, and infertility (10–17).

Body fat is difficult to measure directly and is often estimated by the BMI calculation, a formula first described in the 19th century and calculated as body weight in kilograms divided by height in meters squared (18). A number of expert committees have established BMI classifications that aid in screening for individuals at risk of disease related to excess body fat and identifying individuals who may benefit from weight loss interventions. The World Health Organization classification system is commonly used in Western nations and is outlined in Table 1 (19).

A BMI of 30 kg/m^2 is often used to define obesity at a population level because it represents a reasonable cut-off in balancing the sensitivity and specificity for identifying people at risk of disease related to excess body

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TABLE 1

WHO classification of obesity.

Classification	BMI (kg/m^2)	Risk of comorbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	≥25	
Preobese	25–29.9	Increased
Obese	≥30	
Obese class 1	30–34.9	Moderate
Obese class 2	35.0–39.9	Severe
Obese class 3	≥40	Very severe

Note: Adapted from: Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894), 2000 (19). BMI = body mass index; WHO = World Health Organization.

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fat (20). Of note, different BMI cutoffs have been recommended for specific populations on the basis of the local prevalence of adiposity-related disease and population-specific associations between BMI, percentage of body fat, and health risks (21).

Body mass index cutoffs are easily accessible as clinical screening tools, but they do not account for individual differences in frame size and lean body mass. Additionally, they do not help in determining disease risk related to body fat for individuals who are classified as normal BMI, nor do they differentiate by fat distribution pattern (i.e., "apple" vs. "pear" fat distribution), with central obesity associated with greater metabolic risk. Adult weight gain is a readily interpretable number that is more specific to individuals, and it addresses risk tied to excess body fat in individuals with a normal BMI (10–12, 14, 20). This number may be particularly significant for reproductive-aged individuals because most body fat accrues after the age of 19 years in women and after the age of 20 years in men. Adult weight gain is an important risk factor for chronic disease and reduced fecundity (22). Obesity can impair reproduction in both women and men, leading to infertility in couples trying to conceive and subsequent complications in pregnancy (23–25).

OVULATION AND MENSTRUAL CYCLE ABNORMALITIES

Women with increased weight, amenorrhea, and hyperandrogenism were described by the French surgeon/obstetrician Paré as early as 1633 (26). Stein and Leventhal (27) reported obesity in three of the seven amenorrheic–oligomenorrheic patients in their seminal description of the Stein–Leventhal syndrome. Possibly the first systematic study to investigate the relationship between obesity and menstrual disturbances documented a 48% prevalence of obesity in 60 amenorrheic women compared with a 13% prevalence in a eumenorrheic control group (28). Most studies report a prevalence of menstrual cycle irregularities in women with obesity of 30%–36% (29–32); however, ranges of less than 10% (33) to greater than 50% (34, 35) have been reported. In a case-control study of 597 women with anovulatory primary infertility compared with 1,695 primiparous controls, the crude and adjusted (for age and exercise) relative risks of primary anovulatory infertility were 3.1 (95% confidence interval [CI], 2.2–4.4) and 2.4 (95% CI, 1.7–3.3) above a BMI of 27 kg/m^2 (25). The prevalence of amenorrhea or oligomenorrhea increases with increasing degrees of overweight or obesity in adulthood (32, 33) and in adolescence (31). Childhood obesity at the age of 7 years is an independent predictor of menstrual problems by the age of 33 years (36).

Ovulatory dysfunction is more common in women with obesity (27, 28, 37). Much of this ovulatory dysfunction is likely confounded by a diagnosis of polycystic ovary syndrome (PCOS). Data from the Nurses' Health Study illustrate that as BMI rises, the risk anovulatory infertility increases (17). In addition, a greater BMI at the age of 18 years predicted anovulatory infertility, with and without the diagnosis of PCOS (relative risk [RR], 1.0, and BMI, 20.0–21.9; 1.3 and BMI, 24–25.9; 1.7 and BMI, 26–27.9; 2.4 and BMI, 28–29.9; 2.7 and BMI, 30–31.9; and 2.7 and BMI, >32 kg/m^2). Body fat distribution is also important because anovulatory women have a greater waist circumference and more abdominal fat than ovulatory women of similar BMI (38). Another study supported this conclusion by demonstrating that abdominal body fat was more predictive of ovulatory dysfunction than total body fat (39).

Obesity is a common symptom of PCOS, and thus, PCOS is a confounding feature of these associations. Prevalence data delineating the contribution of BMI on the risk of ovulatory dysfunction when the diagnosis of PCOS has been excluded lacks clarity, in part because of the varied diagnostic criteria and phenotypes for PCOS. Whereas the degree of obesity among women with PCOS has increased over time, reflecting the rise observed in the general population (40), it is significant to note that the risk of PCOS is only minimally increased with obesity (40, 41).

Improved ovulation rates and menstrual regularity have been demonstrated with modest weight loss through lifestyle modification with and without adjunctive weight loss medications in women with PCOS (9, 42–46). Correction of amenorrhea occurs in several women with obesity after bariatric surgery (30). It should be noted, however, that determining the true prevalence or risk of menstrual cycle irregularities in obese women is challenging. A limitation is that most studies of menstrual irregularity rely on retrospective reporting by the study subjects and the validity of retrospective self-reported menstrual cycle length has been challenged, particularly in women with short or long mean menstrual cycle lengths (47).

Reproductive hormone differences exist in women by BMI category, even among those with regular menstrual cycles in each group, suggesting that menstrual cycle dysfunction in obesity falls along a spectrum. Ovulatory menstrual cycles in women with obesity are characterized by lower total cycle luteinizing hormone (LH), decreased early follicular phase LH pulse amplitude, lower total cycle

follicle-stimulating hormone, longer follicular phases, shorter luteal phases, and decreased luteal phase progesterone metabolite compared with normal-weight ovulatory women (48, 49).

Central obesity and visceral fat can result in insulin resistance and hyperinsulinemia. Insulin resistance promulgates hyperandrogenemia through direct actions on the ovary and through decreased hepatic sex hormone-binding globulin production, often suggestive of PCOS. Hyperandrogenemia, increased peripheral aromatization of androgens to estrogens in adipose tissue, storage of sex steroids in adipose tissue, altered levels of leptin and other adipokines, altered insulin-like growth factor binding protein production, and impaired granulosa cell function all contribute to menstrual irregularities through disruption of the hypothalamic–pituitary–gonadal axis (25, 30, 50–52).

ALTERED OVARIAN RESPONSIVENESS AND OOCYTE QUALITY WITH FERTILITY TREATMENTS

In addition to higher rates of ovulatory dysfunction, obesity has been associated with worse outcomes after infertility treatment. Data suggest that altered folliculogenesis and diminished oocyte quality are potential mediators.

Responsiveness to Ovarian Stimulation

In normogonadotropic anovulatory women, increased BMI and abdominal obesity are associated with decreased odds of ovulation in response to clomiphene citrate (increased BMI, odds ratio [OR], 0.92 [0.88–0.96]; increased waist-to-hip ratio, OR, 0.60 [0.40–0.89]) (53). Results from a large randomized trial showed that the live birth rates (LBRs) were greater after letrozole treatment than those after clomiphene citrate, primarily among women with elevated BMI, suggesting altered pathophysiology or underdosing of clomiphene citrate (54). In addition, women with obesity treated with gonadotropins for ovulation induction require higher doses of medication and produce fewer follicles at a given dose (55). Several large retrospective analyses (1,721 to 8,145 women undergoing assisted reproductive technologies [ARTs]) also confirm that obesity impairs ovarian responsiveness to gonadotropin stimulation (i.e., increased duration, amount of gonadotropin administered, increased cycle cancellation; fewer oocytes retrieved) (56–60).

Oocyte Quality

Several studies have investigated the association between obesity and oocyte and resultant embryo quality. Women with obesity undergoing in vitro fertilization (IVF) have an altered follicular environment with higher levels of insulin, markers of inflammation, and elevated levels of free fatty acids, which were correlated with abnormal cumulus-oocyte complexes (61–63). Oocytes from women who are overweight or obese are smaller (63, 64) than those from normal-weight controls. However, fertilization rates have been inconsistently linked to maternal BMI (56, 65–69). Whereas the blastulation rates and metabolics of developing embryos appear to be influenced by obesity (63, 70), the proportion of euploid embryos is not different among BMI categories (71). In 2016, two large retrospective studies using national data from the Centers for Disease Control and Prevention's National ART Surveillance System and from the SART Clinic Outcome Reporting System database analyzed the relationship between BMI and IVF outcomes. Both studies demonstrate a decrease in pregnancy rate and LBR with increasing BMI (72, 73). However, the age-related decline in fertility has a greater impact than BMI on LBR at older ages, suggesting that taking time to lose weight before IVF may be detrimental for older women with overweight or obesity (74) (Fig. 1). In addition, ovulation induction in women with PCOS results in lower LBRs in women as BMI increased (75).

These human studies are supported by diet-induced obese mouse models. In these models, obesity impairs oocyte quality through mitochondrial dysfunction, increases reactive oxygen species, and is associated with abnormal meiotic spindles and chromosomal alignment (76, 77). Interestingly, mouse models have shown that interventions such as weight loss, increased physical activity, and antioxidant therapy are unable to reverse the oocyte quality provoked by the diet-induced obesity (78–80).

In conclusion, increasing BMI is associated with lower ovarian responsiveness to ovulation induction as evidenced by the need for higher doses of oral agents and gonadotropins and the lower number of oocytes retrieved during IVF. In addition, oocyte quality is impaired in both obese animal models and human clinical studies. In a linear manner, higher BMI is correlated with lower implantation and clinical pregnancy rates and LBRs when undergoing IVF/intracytoplasmic sperm injection treatment. This effect is most prominent in younger reproductive-aged women and is significantly attenuated with advancing reproductive age (74).

ENDOMETRIAL FUNCTION

A number of studies have investigated IVF outcomes in obese donor oocyte recipients as a way to independently evaluate obesity's clinical impact on endometrial receptivity and function. Some have demonstrated no effect, whereas others have shown a negative effect with lower implantation rates (72, 81, 82). Regardless, obesity is a well-known risk factor for endometrial hyperplasia and cancer (15). On a molecular level, the endometrium from women with obesity demonstrates increased steroid receptor staining and altered expression of other genes that is more pronounced in the presence of infertility (83, 84).

MISCARRIAGE RATES

Obesity has been associated with an increased risk of pregnancy loss (56, 58, 85–89) in most, but not all, studies (55, 57, 90). Differences in outcomes between studies are likely related to varying levels of comorbidities and the multifactorial mechanisms through which BMI can influence pregnancy outcomes. Both obesity and miscarriage have been associated with thyroid dysfunction (91, 92), insulin resistance (93, 94), leptin resistance (95–97), lipotoxicity and inflammation (25, 98–100), as well as sleep dysfunction (101–103) and mental health (104–106).

FIGURE 1

Age, y	BMI, kg/m²							
	<18.5 Underweight	18.5–24.9 Normal weight	25.0–29.9 Overweight	30.0–34.9 Class I obesity	35.0–39.9 Class II obesity	40.0-44.9 Class III obesity	45.0-49.9 Morbid obesity	≥50 Super obesity
<30	65	64	59	60	50	48	40	25
30	60	63	57	59	54	48	20	20
31	61	59	57	54	46	40	30	.
32	61	58	55	53	43	44	35	22
33	45	56	52	54	44	37	43	.
34	44	51	48	42	44	40	43	.
35	47	50	44	46	42	44	38	17
36	41	43	40	42	43	39	33	.
37	39	39	38	35	38	24	33	30
38	30	32	33	30	25	20	25	21
39	10	25	27	27	28	23	11	.
40	19	20	19	21	17	12	31	.
41	6	13	15	12	19	14	7	.
42	2	11	9	11	9	11	14	.
>42	0	3	4	5	2	5	0	.

65
55
45
35
25
15
5

Cumulative likelihood of live birth (%) on the basis of maternal age and BMI among 51,959 first fresh IVF cycles that started in 2014 + 16,067 frozen embryo cycles between 2014 and 2015, representing data from >90% of IVF cycles in the United States and Puerto Rico. Note that cumulative live birth refers to the live birth rate after both fresh and frozen transfers of embryos derived from the first fresh IVF stimulation and retrieval. BMI = body mass index; IVF = in vitro fertilization. (From Goldman et al. [74]. Reprinted by permission of the publisher.)

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In a 2011 meta-analysis evaluating the association of obesity and miscarriage in unassisted conceptions, women with obesity were 1.3 times more likely to have a pregnancy loss (OR, 1.31; 95% CI, 1.18–1.46) (107). This association was further confirmed in a prospective observational study of more than 18,000 nulliparous Chinese women with unassisted conceptions, in which obesity was associated with an increased risk of miscarriage (adjusted RR, 1.51; 95% CI, 1.13–2.02) (108).

Similarly, women with obesity who conceived with ART also have higher rates of miscarriage. This association was demonstrated in analyses of SART and CDC data (72, 73). In addition, a large 2019 analysis of first frozen embryo transfers with good-quality embryos demonstrated an association between obesity and early pregnancy loss (adjusted OR, 1.46; 95% CI, 1.15–1.87) (65). Finally, a meta-analysis limited to only women with recurrent miscarriage also suggested that obesity is associated with higher miscarriage rates (OR, 1.75; 95% CI, 1.24–2.47) (109).

The mechanism of action underlying the association between obesity and early pregnancy loss has been evaluated using donor oocyte models. A retrospective study of more than 9,000 women was performed, where oocyte donors were of normal weight and oocyte recipients were of varying BMI categories (110). The results demonstrated a decrease in live birth, but no difference in clinical miscarriage rate, with increasing BMI of the recipient. In contrast, a similar analysis of data from the SART database from 2008 to 2010 demonstrated an increase in miscarriage rate when the recipient BMI was >40 kg/m^2 (adjusted OR, 1.67; 95% CI, 1.05–2.63) (111).

Miscarriages in the general population have high rates of aneuploidy, which has well been documented to increase with age. However, an analysis from a well-characterized recurrent pregnancy loss database demonstrated that in pregnancy losses at <10 weeks' gestational age, women with obesity with recurrent pregnancy loss have a 58% chance of having a euploid loss compared with 37% in women without obesity (RR, 1.63; 95% CI, 2.08–2.47) (112). Similarly, an unselected analysis of products of conception from one academic center indicated that women with obesity had a 46% euploid loss compared with 34% in nonobese individuals (OR, 1.56; 95% CI, 1.25–1.95) (113). Interestingly, when blastocyst embryos are biopsied, women with obesity have similar proportion of euploid embryos (71). The observed higher rate of euploid miscarriages in women with obesity suggests that higher BMI is an independent risk factor for miscarriage.

In summary, various studies demonstrate a link between obesity and miscarriage risk regardless of mode of conception. However, the adjusted ORs range between 1.2 and 1.9, suggesting that while a link exists, the association is modest and may be influenced by confounding factors.

MATERNAL–FETAL ENVIRONMENT

Maternal obesity is associated with increased obstetric and neonatal risk (23). In a cohort of 106,552 women in the United States, the relative risks for pregnancy complications attributable to obesity in women without documentation of other

TABLE 2

Obstetric complications of singleton pregnancies among women without prepregnancy diseases by prepregnancy obesity, Consortium on Safe Labor 2002–2008.

	Normal BMI			Overweight			Obese class 1			Obese class 2			Obese class 3		
Outcome	**No. (%)**	**RR**	**AR%**	**No. (%)**	**RR**	**AR%**	**No. (%)**	**RR**	**AR%**	**No. (%)**	**RR**	**AR%**	**No. (%)**	**RR**	**AR%**
Gestational hypertensive disorders	3,351 (5)	–	–	2,096 (8)	1.65 (1.57–1.74)	3	1,274 (11)	2.34 (2.20–2.49)	6	631 (13.2)	2.78 (2.56–3.01)	8.2	536 (17.3)	3.55 (3.26–3.86)	12.3
Gestational diabetes mellitus	1,834 (2.8)	–	–	1,495 (5.7)	1.99 (1.86–2.13)	2.9	959 (8.3)	2.94 (2.73–3.18)	5.5	517 (10.8)	3.97 (3.61–4.36)	8	452 (14.6)	5.47 (4.96–6.04)	11.8
Cesarean delivery	14,872 (22.4)	–	–	7,562 (28.7)	1.26 (1.23–1.29)	6.3	3,936 (33.9)	1.49 (1.45–1.53)	11.5	1,830 (38.3)	1.7 (1.64–1.77)	15.9	1,457 (46.9)	2.01 (1.93–2.10)	23.6
Stillbirth	206 (0.3)	–	–	91 (0.4)	1.07 (0.83–1.37)	0.1	53 (0.5)	1.43 (1.05–1.96)	0.2	15 (0.3)	1.01 (0.59–1.74)	0	14 (0.5)	1.41 (0.82–2.45)	4.7
Large for gestational age	5,272 (7.9)	–	–	3,171 (12)	1.52 (1.45–1.58)	4.1	1,584 (13.7)	1.74 (1.65–1.83)	5.8	712 (14.9)	1.93 (1.79–2.07)	7	538 (17.3)	2.32 (2.14–2.52)	9.4
Congenital anomaly	3923 (5.9)	–	–	1,673 (6.4)	1.08 (1.02–1.14)	0.5	728 (6.8)	1.07 (0.99–1.16)	0.9	317 (6.6)	1.12 (1.00–1.25)	0.7	449 (14.5)	1.2 (1.05–1.36)	1.4
NICU admission	5,880 (8/9)	–	–	2,848 (10.8)	1.16 (1.11–1.21)	1.9	1,335 (11.5)	1.20 (1.13–1.27)	2.6	610 (12.8)	1.3 (1.20–1.41)	3.9		1.38 (1.26–1.51)	5.6

Note: RR adjusted for maternal age, maternal race, insurance type, marital status, parity, smoking and alcohol use. AR% = attributable risk percent, percent of women with complication in the obesity class category minus the percent of women with the complication in the normal-weight category; BMI = body mass index; NICU = neonatal intensive care unit; RR = relative risk.
Adapted from: Kim SS, Zhu Y, Grantz KL, Hinkle SN, Chen Z, Wallace ME, et al. Obstetric and neonatal risks among obese women without chronic disease. Obstet Gynecol 2016;128:104–12.

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chronic diseases (i.e., metabolically healthy but obese) are outlined in Table 2 (114).

While adverse outcomes associated with maternal obesity occur in the absence of other contributing risk factors, comorbidities such as preconception hypertension, obstructive sleep apnea, and diabetes are likely significant in the pathophysiology and incidence of these outcomes (23). Of additional concern for pregnant women with obesity is the limitation excess adiposity places on important assessment tools used during gestation, such as assessment of fetal growth via fundal height and anatomic survey of the fetus with ultrasound (23, 115). Such limitations may also contribute to the incidence of some adverse pregnancy outcomes for women with obesity. Women with obesity who achieve even small weight reductions before pregnancy may have improved pregnancy outcomes (23).

OBESITY AND MALE REPRODUCTION

As the prevalence of obesity has increased steadily over more than three decades, a concurrent decline in semen quality has been described (116, 117). The mechanisms by which obesity may result in diminished semen quality and male factor infertility include endocrine alterations, sexual dysfunction, and other medical issues including diabetes mellitus (118), sleep apnea (119), or scrotal hyperthermia due to body habitus (120–122).

Obesity in men is associated with an increased incidence of oligozoospermia and asthenozoospermia in some (123–131), but not all (132–138), studies. One purported and generally accepted mechanism for lower sperm counts is related to aromatization of testosterone to estradiol in peripheral adipose tissue with resultant estradiol-mediated negative feedback and suppression of the hypothalamus–pituitary–testis axis (139, 140). Moreover, increased abdominal adiposity in men of subfertile couples has been associated with reduced sperm count, concentration, and motility (129).

Male obesity may also alter sperm function (141), increase sperm DNA damage (132, 142–146), decrease sperm mitochondrial activity (144, 145), and induce seminal oxidative stress (147). Emerging data suggest that sperm epigenetics is altered in men with obesity (148), with potential implications for future offspring. With respect to ART, male obesity appears to impact blastocyst development (124), with conflicting reports related to clinical pregnancy, miscarriage, and LBRs (111, 124, 126, 132, 141, 149–152). A systematic review found that obese men were more likely to experience infertility (OR, 1.66; 95% CI, 1.53–1.79), their rate of live birth per cycle of ART was reduced (OR, 0.65; 95% CI, 0.44–0.97), and they had a 10% absolute risk increase of pregnancy nonviability (153). A second systematic review and meta-analysis was consistent with this study, finding men with obesity having a decreased LBR after IVF (OR, 0.88; 95% CI, 0.82–0.95) (154).

An inverse relationship between BMI and testosterone is well established (142, 155). Suppression of sex hormone-binding globulin by insulin in men with obesity increases androgen availability for estrogen aromatization, which may lead to reduced gonadotropin secretion (122, 137, 141, 156, 157). Simultaneously, men with obesity have decreased total and bioavailable testosterone levels (134, 137, 139, 141, 147, 157–159) as well as reduced inhibin B concentrations (137, 156, 157, 160), combined with diminished LH pulse amplitude (142). This hormonal profile suggests enhanced estrogen negative-feedback inhibition from increased adipose-derived aromatase activity (161), along with decreased formation of inactive 2-hydroxyestrogens (122, 141, 147, 139, 162–165). Consequently, obesity in men is accompanied by decreased Leydig cell testosterone secretion, with testosterone levels negatively correlated with fasting insulin and leptin levels (159, 164, 166).

In men with obesity, 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 (141, 167, 168). However, proposed treatments aimed at lowering scrotal temperature ("scrotal hypothermia") or reducing the amount of scrotal fat are impractical and unproven (169).

A diagnosis of male infertility may provide a unique opportunity to motivate men with obesity to lose weight. Weight loss results in increased testosterone levels (170, 171) and improvements in sexual function (172, 173). A prospective study assessing shorter- and longer-term impacts of diet-induced weight loss in 118 overweight (N = 32) and obese (N = 86) men tracked testosterone and self-reported sexual function, as reported by the International Index of Erectile Function (IIEF), during a 12-week weight loss period, followed by 40 weeks of maintenance (171). The total testosterone level increased, and the IIEF improved during the acute weight loss period; the total testosterone level continued to increase, and the free testosterone level increased during the maintenance period, whereas the IIEF remained stable.

However, the interplay between weight loss and spermatogenesis is less definitive. There is a dearth of data regarding changes in semen parameters after weight loss in obese men. One study followed 43 men with short-term follow-up at 14 weeks after weight loss achieved via diet and exercise. Men with the largest degree of weight loss demonstrated the most significant increases in sperm count and normal morphology (157). The few published studies exploring bariatric surgery-mediated weight loss and semen parameters provide conflicting results and suffer from small sample sizes and relatively short follow-up intervals (174–177).

MANAGEMENT

Medical Treatment

Weight loss medications may be beneficial when used in conjunction with lifestyle interventions and may increase the likelihood that patients adhere to behavioral and lifestyle interventions, perhaps because of the positive feedback of the rapidity and degree of weight loss. Most result in weight loss through temporary effects on appetite, and thus, patients must reduce energy intake and/or increase energy expenditure in the long term to sustain weight loss achieved with medications. The use of weight loss medications may be considered in patients with a history of unsuccessful weight

loss who meet label indications (178) but should be tailored to the knowledge, experience, and comfort level of the prescribing physician. Alternatively, referral to a weight management provider with more experience in prescribing these medications may also be appropriate.

Medications for treatment of obesity, except for orlistat, typically target appetite to effect weight loss. They work primarily by promoting satiety through stimulation of pro-opiomelanocortin neurons in the arcuate nucleus, often mediated via serotoninergic, dopaminergic, or norepinephrine-releasing agents/reuptake inhibitors (178). Orlistat blocks absorption of fat calories and reabsorption of glucose (178). Some medications are associated with elevation in blood pressure and pulse rate, whereas others may increase the risk of serotonin syndrome in patients using a selective serotonin reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor. Thus, caution is advised in prescribing these medications to patients with cardiovascular disease, hypertension, history of cardiac arrhythmias, seizures, depression, and anxiety and patients using pharmacotherapy for smoking cessation.

Phentermine is approved by the US Food and Drug Administration (FDA) for short-term use and is currently one of the most commonly prescribed weight loss medications, likely because of its low cost. It has been shown to induce over 7% weight loss at 6 months (179). Current recommendations indicate that the dose should only be increased if the patient is not achieving clinically significant weight loss and should be followed every month while undergoing dose escalation, which may extend to at least every 3 months when on a stable dose (178). Current data suggest that the potential for addiction is low (180); however, weight gain is likely to occur on discontinuation of the medication. The combination of phentermine plus topiramate has been approved for chronic management of obesity and has demonstrated a greater weight loss than with either agent alone. It is among the most efficacious of FDA-approved weight loss medications, with an average expected weight loss of 5%–11% over 1 year (181, 182).

In addition to phentermine/topiramate, orlistat, naltrexone/bupropion, and liraglutide are all FDA-approved for the chronic management of obesity. The average expected weight loss with these medications is 2.9–5.8 kg, making them less efficacious in comparison to the phentermine/topiramate combination. It is worth noting that very few of these medications have been studied in the context of infertility, and all are currently considered pregnancy category X (i.e., indicating that studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk on the basis of adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits) when used for the purposes of weight loss. Table 3 shows information regarding indications, side effects, and contraindications for commonly used weight loss medications.

Metformin, although frequently used in patients with PCOS, is not considered a weight loss medication. It is a biguanide that increases peripheral sensitivity to insulin and inhibits hepatic glucose production, resulting in decreased circulating insulin levels. It may promote weight loss when used in combination with lifestyle interventions, although studies suggest that weight loss experienced with metformin is minimal (1.1 kg) (183, 184).

Surgical Treatment

Bariatric surgery is currently the most effective intervention for significant and sustained weight loss regardless of the type of procedure used (185–187). Patients may lose as much as 70% of excess weight within 12 months after surgery, and on average, 5 years after surgery, patients maintain approximately 50% of their excess weight loss (188, 189). These procedures cause weight loss by restricting the amount of food that the stomach can hold, by causing malabsorption of food, or by a combination of restriction and malabsorption. According to the American Society for Metabolic and Bariatric Surgery (ASMBS), the most commonly performed bariatric procedures are Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion with duodenal switch, with the Roux-en-Y gastric bypass considered the gold standard of weight loss surgery (Fig. 2) (190). This procedure creates a small stomach pouch and attaches it to the jejunum to shorten the length of the intestinal tract. This leads to the restriction of the amount of food the stomach can hold as well as decreased absorption of calories by the small intestine. This often results in significant long-term weight loss; however, it is a more complex procedure, possibly resulting in higher complications rates, and can lead to long-term vitamin and mineral deficiencies requiring lifelong supplementation, particularly vitamin B12, iron, calcium, and folate.

The laparoscopic sleeve gastrectomy is performed by removing approximately 80% of the stomach and works via restricting the volume the stomach can hold, helping reduce the amount of food consumed, and altering gut hormones that affect hunger, satiety, and blood glucose control (191). Rapid and significant weight loss results are comparable to the Roux-en-Y gastric bypass, with a similar risk of long-term vitamin deficiencies. The benefits over Roux-en-Y are that it does not require intestinal anastomosis and typically involves a shorter hospital stay.

The adjustable gastric band procedure involves placement of an inflatable band around the upper portion of the stomach, creating a small stomach pouch above the band leading to weight loss because of food restriction rather than malabsorption. Because there is no malabsorption, there is very low risk of vitamin and mineral deficiencies.

The biliopancreatic diversion with duodenal switch gastric bypass involves creating a tubular stomach pouch by removing part of the stomach and then bypassing a larger portion of the small bowel compared with the Roux-en-Y bypass. This procedure also causes favorable changes in gut hormones to reduce appetite and improve satiety; however, it also has a higher complication rate and risk of mortality compared with the other procedures. Additionally, it requires a longer hospital stay and has greater potential to cause protein, vitamin, and mineral deficiencies.

TABLE 3

Table of weight loss medications (178, 181).

Drug name	FDA approval	DEA schedule	Average weight loss	Mechanism of action	Side effects/warnings	Considerations/ contraindications
Sympathomimetics	Short-term use (≤3 months)		3.6 kg	Release of catecholamines such as dopamine and norepinephrine to suppress appetite	Headache, elevated blood pressure, elevated pulse rate, insomnia, dry mouth, constipation, anxiety, restlessness, tremor	Pregnancy, breastfeeding, anxiety disorders, history of heart disease, uncontrolled hypertension, MAO inhibitors, pregnancy, breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amines
Phentermine		IV				
Diethylpropion		IV				
Benzphetamine		III				
Phendimetrazine		III				
Orlistat	Chronic use	None	2.6 kg	Lipase inhibitor	Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Cyclosporines, chronic malabsorption syndrome, pregnancy, breastfeeding, cholestasis, levothyroxine, warfarin, antiepileptic drugs
Naltrexone SR/bupropion SR	Chronic use	None	5.0 kg	Opioid receptor antagonist, dopamine and norepinephrine reuptake inhibitor	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, increase in blood pressure and heart rate, hepatotoxicity, angle-closure glaucoma	Pregnancy and breastfeeding, uncontrolled hypertension, seizure disorders, anorexia nervosa, bulimia, drug or alcohol withdrawal, MAO inhibitors, chronic opioid use
Liraglutide	Chronic use	None	5.3 kg	GLP-1 receptor agonist	Nausea, vomiting, pancreatitis	Pregnancy, breastfeeding, personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2

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TABLE 3

Continued.

Drug name	FDA approval	DEA schedule	Average weight loss	Mechanism of action	Side effects/warnings	Considerations/ contraindications
Phentermine/ topiramate ER	Chronic use	IV	8.8 kg	GABA receptor modulator, norepinephrine-releasing agent	Increased heart rate, insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia, suicidal behavior and ideation, acute myopia and secondary angle-closure glaucoma, disturbances in attention or memory, metabolic acidosis, elevated creatinine level	Pregnancy, breastfeeding, hyperthyroidism, glaucoma, MAO inhibitors, sympathomimetic amines. Fetal toxicity has been reported and is recommended to obtain a negative pregnancy test before and each month thereafter along with the use of effective contraception

Note: DEA = United States Drug Enforcement Administration; ER = extended release; FDA = Food and Drug Administration; GABA = gamma-aminobutyric acid; GLP-1 = glucagon-like peptide-1; MAO = monoamine oxidase; SR = sustained release.

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A statement issued by the ASMBS in 2017, endorsed by the American College of Obstetricians and Gynecologists and the Obesity Society, noted that "bariatric surgery is effective in achieving significant and sustained weight loss in women with morbid obesity and has been shown in case-control studies to improve fertility… however, the specific impact of bariatric surgery on the responsiveness to subsequent treatments for infertility is not clearly understood at this time" (192, 193).

Unfortunately, there are limited studies evaluating the effect of bariatric surgery on fertility outcome. Two systematic reviews assessing reproductive outcome after bariatric surgery published in 2008 and 2009 found very few studies assessing effect on fertility and LBR, although most demonstrate a decreased risk of some complications during pregnancy such as gestational diabetes, hypertensive disorders of pregnancy, and macrosomia (193, 194). However, other studies have suggested a possibly increased risk of small for gestational age singleton births, preterm births, spontaneous preterm births, and possibly increased neonatal mortality (195–197).

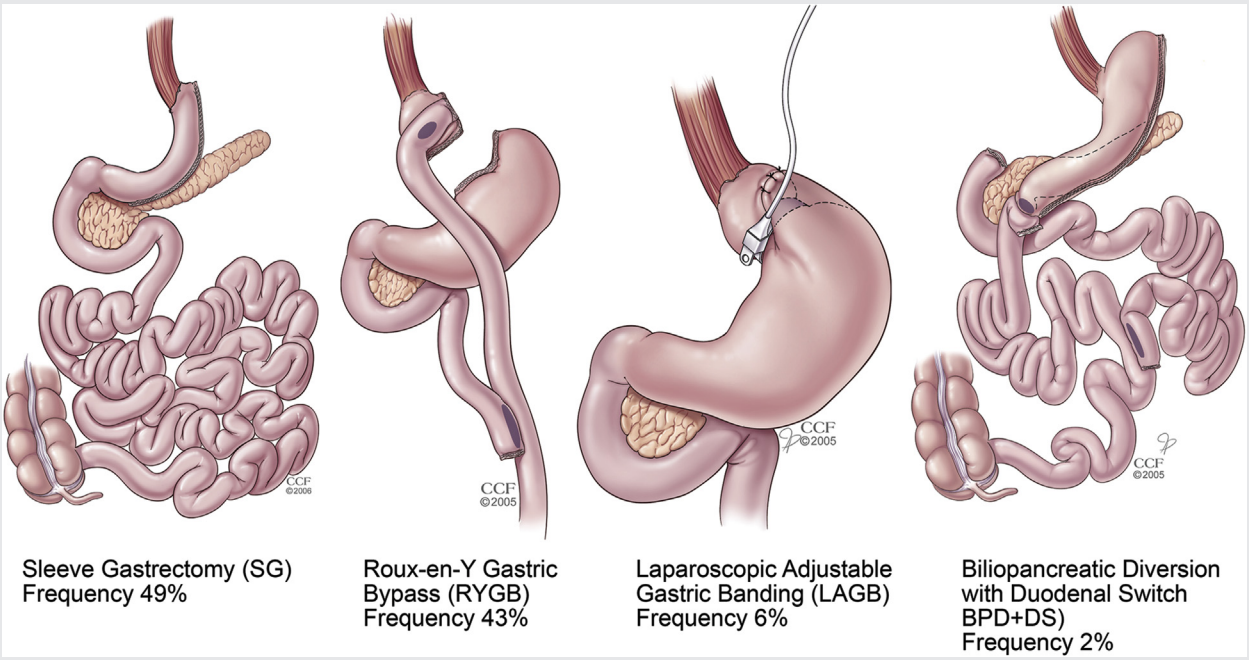
A meta-analysis published in 2016 found that the incidence of diagnostic features associated with PCOS significantly decreased after bariatric surgery (46% preoperatively vs. 7% postoperatively, $P<.001$) as did the incidence of infertility (18% preoperatively vs. 4% postoperatively, $P=.0009$) (198). Two studies assessing the effect of bariatric surgery on IVF in patients who had previously failed IVF found conflicting outcomes. The first study published in 2014 included seven patients who underwent IVF before and after bariatric surgery and found a decrease in the amount of gonadotropin units required for stimulation but no difference in peak estradiol level, number of follicles and oocytes, fertilization rate, or number of top-quality embryos (199). The second larger study published in 2017 included 40 patients and, similar to the previous study, noted a decrease in required gonadotropin units but found an increased number of mature follicles, retrieved oocytes, mature oocytes, fertilization rate, and top-quality embryos. The pregnancy rate after bariatric surgery was found to be 37.5%, and the LBR was 35%. Given that all patients had previously failed IVF, the changes in pregnancy rate and LBR were found to be significant ($P<.001$) (200).

Because of concerns regarding malabsorption, prepregnancy assessment of a patient's nutritional status and micronutrient supplementation after bariatric surgery is imperative (193, 194, 201). Delaying pregnancy until 1–2 years after bariatric surgery has been recommended to avoid fetal exposure to nutritional deficiencies from rapid maternal weight loss (193, 202), and the ASMBS recommends waiting 12–18 months (203). 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.

WEIGHT LOSS INTERVENTION TRIALS AND FERTILITY OUTCOMES

Three multisite randomized controlled trials (RCTs) have been recently published assessing the effects of weight loss

FIGURE 2



Common metabolic procedures and their frequency of use. Reprinted with permission from Cleveland Clinic Foundation.

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interventions on fertility outcomes. The OWL PCOS study was a two-site RCT that randomized 149 women with PCOS (BMI range, 27–42 kg/m^2; median, approximately 35) to one of three arms: oral contraceptive pills (OCPs); lifestyle modification; and combined OCP and lifestyle modification before infertility treatment (9). The lifestyle modification intervention consisted of caloric restriction, behavioral modification, increased physical activity, and weight loss medications (sibutramine or orlistat if the BMI was at least 30 kg/m^2). Caloric restriction consisted of prescribed diets centered on meal replacements. In addition, participants consumed two servings of fruit and skim milk per day and three servings of vegetables per day. The diet was designed to create a caloric deficit on the basis of initial weight with at least 15% calories from protein, less than 30% calories from fat, and the remaining calories from carbohydrate. Physical activity included brisk walking or similar aerobic activity 5 days a week with the initial goal of 10 minutes per day, gradually increasing over 4 months to 30–35 minutes per day, for a total activity goal of 150 minutes per week. Women in the lifestyle intervention arms also underwent behavioral modification sessions delivered by trained study coordinators.

These investigators found that women in the lifestyle and combined groups achieved significantly more weight loss compared with those in the OCP group (−6.2 and −6.1 vs. −1.1 kg, respectively; $P<.001$), although there was a 12%–14% dropout rate for the lifestyle intervention arms. Metabolic parameters improved as did the likelihood of ovulation in the lifestyle and combined groups compared with the OCP group (60% and 67% vs. 46%, respectively; $P<.05$). However, there were no significant differences in pregnancy or pregnancy loss rates or LBRs (26%, 24%, and 12%, respectively; $P=.13$) between the groups (9). In a post hoc analysis, when patients from both the lifestyle modification group (group 2) and combined group (group 3) were combined and compared with the OCP group (group 1), the probability of live birth bordered statistical significance ($P=.05$) (9).

The Dutch LIFEstyle study randomized 577 infertile women with a BMI of ≥29 kg/m^2 (median BMI, 36 kg/m^2) to 6 months of lifestyle intervention before 18 months of infertility treatment vs. prompt 24 months of infertility treatment (7). The lifestyle intervention consisted of a 6-month structured program including six outpatient visits and four telephone consultations during a 24-week period, with the goal of 5%–10% body weight loss. Women were advised to decrease energy intake by 600 kcal daily while maintaining at least 1,200 kcal per day and were encouraged to engage in moderate-intensity physical activity (target of 10,000 steps per day) with at least 30 minutes of moderate-intensity exercise two or three times per week. They were also provided motivational counseling and developed individualized goals with the assistance of weight management coaches. Similar to the OWL PCOS study, they found significantly greater weight loss in the intervention arm (−4.4 vs. −1.1 kg,

$P<.001$), although there was no difference noted between the groups at 5-year follow-up (204).

The LIFEstyle study reported a 22% dropout rate. However, of those who completed the intervention, 43% achieved weight loss of at least 5% of the initial body weight. The study found that women in the intervention group were significantly less likely to experience a live birth within 24 months after randomization (27% vs. 35%; rate ratio, 0.77; 95% CI, 0.60–0.99). However, when accounting for pregnancies conceived during the 24 months in addition to those delivered within that time frame, there were no significant between-group differences in the LBR. It is notable that the women in the intervention group were significantly more likely to have an unassisted conception compared with those in the control group (26% vs. 16%; rate ratio, 1.61; 95% CI, 1.16–2.24), ultimately requiring fewer fertility treatments. Also worth noting is that participants in the intervention group who achieved the most weight loss had a lower risk of pregnancy complications such as hypertension and preterm birth. A cost-effective analysis of this study demonstrated that lifestyle intervention preceding infertility treatment is less costly but not more effective than prompt infertility treatments regarding LBR (205).

A subsequent Swedish multicenter trial randomized 317 women with BMIs of ≥ 30 and <35 kg/m^2 (median BMI, approximately 33 kg/m^2) to either 16 weeks of weight reduction followed by IVF or immediate IVF treatment (8). The weight reduction intervention aimed to reach a BMI as close to normal as possible and began with 12 weeks of a strict low-calorie liquid formula diet with a daily energy intake of 880 kcal followed by individual visits with a dietician for the reintroduction of solid foods and weight control stabilization. They found that weight reduction in the intervention group was significantly higher than in the control group (-9.44 vs. $+1.19$ kg, $P<.0001$). Interestingly, as opposed to findings in the previously mentioned studies, the dropout rate for the intervention group was only 4%. This study also did not find a statistically significant difference in overall LBR (29.6% vs. 27.5%, weight loss group vs. control, respectively; $P=.77$). However, similar to the Dutch study, they found a significantly higher rate of spontaneous pregnancy in the weight loss group (11% vs. 3%, $P=.009$) although it is unclear how many women in the immediate IVF group had the opportunity for pregnancy before beginning IVF treatments (8). Two subgroup analyses were performed comparing women with PCOS in the two randomized groups and women who achieved a BMI of ≤ 25 kg/m^2 in the weight reduction group and similarly found no differences in LBRs.

Smaller RCTs and observational studies have reported conflicting evidence for the benefit of lifestyle interventions on fertility outcomes, with most studies either being underpowered to detect a difference or demonstrating no effect on LBR (42, 206–209). Although a post hoc analysis of the LIFEstyle study demonstrated decreased risks of hypertensive pregnancy complications and preterm birth, there were no significant differences in excessive gestational weight gain, gestational diabetes, induction of labor, spontaneous vaginal delivery, or cesarean section (210). A systematic review of interventions for improving fertility in overweight and obese patients published in 2017 included 40 studies and assessed outcome by intervention and study type (46). In the analysis of the RCTs assessing the effect of diet and exercise, there was an improvement noted in the ovulation rate (RR, 4.00; 95% CI, 1.25–12.84) and pregnancy rate (RR, 1.59; 95% CI, 1.01–2.50), but there was no benefit found for unassisted conceptions (RR, 2.20; 95% CI, 0.98–4.93), IVF conceptions (RR, 1.06; 95% CI, 0.53–2.13), or LBR (RR, 1.54; 95% CI, 0.93–2.56). The investigators performed a subanalysis excluding the LIFEstyle study, citing its significant contribution to heterogeneity, and found that diet and exercise offered a statistical advantage for LBR (RR, 1.86; 95% CI, 1.25–2.77). A second meta-analysis published in 2020 included eight RCTs and found that lifestyle programs had no impact on LBR and were possibly associated with an increased risk of miscarriage (RR, 1.50; 95% CI, 1.04–2.16) (211).

Taken together, these data suggest that lifestyle interventions, weight loss medications, and bariatric surgery lead to significant weight loss and may improve chances of unassisted conception; however, their effects on birth outcomes are still unclear. Whereas weight loss intervention trials have not typically demonstrated an improvement in LBR among patients pursuing fertility treatments, some studies have demonstrated reduced pregnancy morbidities, possibly suggesting an increased likelihood of a *healthy* pregnancy and live birth. In anovulatory women with obesity, studies support implementation of a weight loss intervention for those seeking to improve their chances of unassisted conception and improve the ovulation rate in response to ovulation induction. In obese ovulatory women and in those needing IVF, the intervention trials do not support the implementation of a weight loss intervention for the purpose of improvement in LBR. However, weight loss before IVF may lead to a lower IVF procedural complication rate, and weight loss before pregnancy may decrease the risk of some pregnancy complications. Additional research is needed to further our understanding of maternal and fetal risks and benefits associated with prepregnancy weight loss interventions, particularly because they relate to hypertensive disorders of pregnancy and miscarriage risk.

BMI THRESHOLDS AND INFERTILITY TREATMENT

Arbitrary BMI thresholds, below which fertility treatment is permitted and above which fertility treatment is denied until the patient loses weight, have been enacted or contemplated by some programs as well as some national health systems. Proponents of BMI thresholds cite anesthetic and procedural safety during oocyte retrieval and obstetric risk as primary concerns (212–214). They may assume that weight loss is an achievable goal that will lead to improved infertility treatment and obstetric outcomes (215, 216). Challenges in adequately performing retrievals, embryo transfers, inseminations, and ultrasound monitoring can occur in women with obesity (213, 214). Obesity during pregnancy increases a broad spectrum of maternal, fetal, and neonatal risks (23, 114), leading to ethical concerns about causing harm to women with obesity and their offspring (213).

Concern about violating the ethical principle of justice by allocating limited resources to at-risk patients with poorer outcomes has been expressed (217, 218).

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists has recommended a BMI threshold of 35 kg/m^2 (219), and New Zealand limits access to publicly funded IVF to women with a BMI of <32 kg/m^2 (220). In the United Kingdom, the Clinical Commissioning Groups typically set BMI thresholds in the 30–35 kg/m^2 range, above which women cannot access publicly funded fertility care (218). In North America, there are no recommended national BMI thresholds. A survey of Canadian IVF centers found that 50% of programs had a declared BMI threshold, which ranged from 35 to 45 kg/m^2. The most frequent reason given for having a cutoff was concern about obstetric risk (212).

In the United States, 65% of SART member programs responding to a survey had a declared BMI threshold. Excepting one center with a threshold BMI exceeding 50 kg/m^2, the BMI range was 35–45 kg/m^2. The most frequent reason given for having a cutoff was anesthetic concern. All large programs (1,000 or more cycles annually) had a formal policy, and a higher percentage of programs in mandated states had a BMI threshold policy compared with nonmandated states. Some programs have additional criteria such as actual weight, neck/abdomen/waist circumference, waste–hip ratio, percentage of body fat, presence of other comorbidities, and inadequate trial transfer (213). Most maternal-fetal medicine and reproductive endocriniology and infertility subspecialists queried in a recent survey favor the establishment of an upper BMI threshold, and over 99% believe that "an official statement to guide clinicians" should be issued by a national professional organization (221).

Opponents of BMI thresholds refer to the American College of Obstetricians and Gynecologists' stance that "it is unethical for obstetrician-gynecologists to refuse to accept a patient or decline to continue care that is within their scope of safe practice solely based on an arbitrary BMI cutoff or because the patient has obesity" (222). They cite recent data that challenge assumptions about the risks of oocyte retrieval in women with obesity and that triage to lifestyle modification to achieve weight loss before infertility treatment can achieve that goal and improve fertility treatment success rates. They also note that weight loss after bariatric surgery is associated with some improved obstetric outcomes but also an increased risk of certain adverse obstetric outcomes (7, 196, 214, 216). Concern about violating the ethical principles of patient autonomy, beneficence/nonmaleficence, and justice is prominent among opponents to BMI thresholds (3, 217–219, 222).

Regarding safety concerns, a recent series from a hospital-based IVF program evaluating 256 retrievals in 144 women with a BMI of >40 kg/m^2, including 32 retrievals for women with a BMI of >50 kg/m^2, suggests that retrievals can be performed safely in women with class 3 and 4 obesity managed in the appropriate clinical setting. The need for abdominal retrieval, conversion from simple mask to laryngeal mask airway oxygenation, or need for an oral or nasal airway was required in less than 7% of retrievals. The use of continuous positive airway pressure therapy to manage oxygen desaturation was required in 18% of women with a BMI of >40 kg/m^2. Compared with retrievals with a BMI of <40 kg/m^2, higher doses of anesthetic medications were required, and the duration of the retrieval was approximately 20% longer in the highest BMI categories (214). Findings from this series are encouraging; however, they require validation from additional studies. Table 4 shows the factors favoring and not favoring the adoption of BMI thresholds.

On the basis of available evidence, there is no medical or ethical directive for adopting a society-wide BMI threshold; rather, there is considerable evidence arguing against such a policy. However, there are significant safety concerns that must be acknowledged with increasing BMI, particularly in the case of IVF. In the United States, most oocyte retrievals and other fertility enhancing procedures are conducted in outpatient facilities where endotracheal intubation is not readily available and where the ability to manage procedural complications may be limited. Women with morbid obesity have reduced functional residual capacity and increased oxygen use and desaturate rapidly if they become apneic. Face mask ventilation to maintain adequate oxygenation can be challenging (225), and patients may require oral/nasal airway or continuous positive airway pressure therapy, which may not be available at several clinics.

The outcome data for ambulatory surgery for patients with a BMI between 40 and 50 kg/m^2 are limited, and therefore, it is suggested that other factors such as difficult airway, cardiovascular disease (e.g., hypertension), obstructive sleep apnea, and endocrine dysfunction are taken into consideration. Ideally, patients with these comorbidities should be evaluated before the day of surgery (226). Equipment such as operating room tables may not be adequate to support patients with a high BMI. Imaging of the ovaries and cervix in obese patients is often challenging, leading to concerns about being able to safely perform retrievals, embryo transfers, and inseminations. Given these limitations, individual programs may need to adopt program-specific BMI thresholds that should be based solely on the safety and ability to perform oocyte retrievals and other procedures within their clinical environment. Consultation with their supporting anesthesia team is an essential aspect of developing thresholds. Concurrently, consideration of the medical evidence, acknowledgment of potential bias, and respect for the ethical principles of patient autonomy, beneficence, nonmaleficence, and justice should be incorporated into clinic-specific policies.

SUMMARY

- Although obesity increases the risk of infertility, most women and men with obesity are fertile.
- Obesity in women is associated with ovulatory dysfunction, reduced ovarian responsiveness to agents that induce ovulation, altered oocyte as well as endometrial function, and lower birth rates after IVF.
- Women with obesity are at increased risk of developing maternal and fetal complications during pregnancy.
- Men with obesity may exhibit impaired reproductive function.

TABLE 4

BMI threshold pros and cons.

Favoring BMI thresholds	Not favoring BMI thresholds
Anesthetic and procedural safety and technical concerns (213, 214).	Preliminary data, requiring validation by additional studies, demonstrate that oocyte retrieval in class 3 and 4 obesity can be safely managed in the proper setting (214).
Decreased IVF pregnancy and live birth rates with increasing BMI (72, 223).	Access to IVF is permitted in the presence of other factors with decreased pregnancy and live birth rates, such as advanced reproductive age or diminished ovarian reserve (217–219).
Increased maternal, fetal, and neonatal risks related to pregnancy in women with obesity (23, 114).	Access to IVF is permitted in the presence of conditions such as hypertension, diabetes, cancer, and maternal use of medications that confer maternal, fetal, and neonatal risks (224).
Assumption that weight loss is achievable and will lead to improved infertility treatment and obstetric outcomes (215, 216).	Weight loss goals are often not achieved, time to achieve pregnancy is prolonged, and the live birth rates are either equivalent or lower in women undergoing pretreatment lifestyle weight loss intervention vs. immediate infertility treatment. Weight loss after bariatric surgery decreases the risk of gestational diabetes and macrosomia but increases the risk of small for gestational age and preterm delivery (7, 8, 196, 216).
Concern about violating the ethical principle of beneficence/nonmaleficence by causing harm to women with obesity and their offspring as a result of fertility treatment and pregnancy (213).	Concern about violating the ethical principle of beneficence/nonmaleficence by exacerbating underlying psychological suffering due to low self-esteem, anxiety, and depression if treatment is denied (217, 219).
Concern about violating the ethical principle of justice by allocating limited resources to at-risk patients with poorer outcomes (217, 218).	Concern about violating the ethical principle of justice by denying choice to procreate to the minority of women with obesity who are infertile, discriminating against ethnic groups with higher obesity prevalence, and being influenced by societal and individual biases toward women with obesity (3, 217–219, 222).
Evidence that weight loss improves the likelihood of spontaneous unassisted conception (7, 8).	Concern about violating the ethical principle of autonomy by denying obese infertile women the choice to procreate (217).

Note: BMI = body mass index; IVF = in vitro fertilization.

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- Lifestyle modification and medical therapy have demonstrated effectiveness in promoting weight loss.
- Bariatric surgery in women and men is a significant adjuvant to lifestyle modification and medical therapy for weight loss, but pregnancy in women should be deferred for 1 year postoperatively.
- In anovulatory women with obesity, weight loss interventions improve the chance of unassisted conception.
- In anovulatory women with obesity, weight loss interventions improve the ovulation rate in response to ovulation induction. However, they have not been shown to improve the LBR.
- In ovulatory women with obesity, prepregnancy weight loss interventions have not been shown to improve the outcome of live birth after both non-ART therapy and IVF.
- The effect of prepregnancy weight loss interventions on maternal and fetal complications is unclear.
- On the basis of available evidence, there is no medical or ethical directive for adopting a society-wide BMI threshold for offering infertility treatment; rather, there is considerable evidence arguing against such a policy.
- Before an IVF cycle, women with obesity should be carefully evaluated with a multidisciplinary team to determine the safety of oocyte retrieval under anesthesia, considering factors such as BMI and comorbidities.

CONCLUSION

- Obesity should not be the sole criteria for denying a patient or couple access to infertility treatment.
- Individual programs should be empowered to adopt program-specific BMI thresholds solely on the basis of the ability to safely perform oocyte retrievals and other procedures within their clinical environment.
- When obesity increases medical risks, a process of shared decision-making should be undertaken, balancing patient autonomy with nonmaleficence.
- Additional research is needed to determine best practices, validate safety data, and optimize access to oocyte retrievals in the setting of class 3 and 4 obesity.
- Women with obesity are at increased risk of infertility and of developing maternal and fetal complications during pregnancy.
- Prepregnancy counseling for couples with obesity should address the reproductive and maternal–fetal consequences of obesity.
- Weight loss intervention trials in women with obesity and infertility have not shown an improvement in the outcome of live birth after treatment. However, weight loss may improve the chance of unassisted conception.
- Weight loss intervention trials in women with obesity and infertility often demonstrated a high dropout rate, and

thus, consideration should be given to patient desire and readiness to lose weight as well as the potential effect on the overall chances of success with delayed fertility treatment when recommending deferring conception for the purposes of weight loss.
- Additional research is needed to further our understanding of the relationship between obesity in men and reproductive function.
- Additional research is needed to further our understanding of maternal and fetal risks and benefits associated with prepregnancy weight loss interventions, particularly because they relate to hypertensive disorders of pregnancy and miscarriage risk.

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Obesidad y Reproducción: una opinión de comité.

El propósito de este reporte del Comité de Práctica Médica de la Sociedad Americana de Medicina Reproductiva es proveer a prestadores de servicios médicos, principios y estrategias para la evaluación y tratamiento de parejas con infertilidad asociada con la obesidad. Este documento revisado reemplaza el documento del Comité de Práctica Médica titulado "Obesidad y Reproducción: Un boletín educacional" publicado por última vez en 2015 (Fertil Steril 2015;104:1116– 26).