Obesity and reproduction: an educational bulletin

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

This Educational Bulletin describes the effect of obesity on reproduction and discusses treatment options. (Fertil Steril® 2008;90:S21–9. ©2008 by American Society for Reproductive Medicine.)

Obesity is the most common chronic disease in the United States. In 1998, the National Institutes of Health defined obesity in relation to body mass index (BMI); overweight was defined as a BMI between 25 and 29.9 kg/m^2, obesity as a BMI $\geq$30 kg/m^2, and morbid obesity as a BMI $\geq$40 kg/m^2 (Fig. 1). Using those definitions, data collected between 1999 and 2002 indicated that 31% of non-Hispanic white women, 38% of Hispanic women, and 49% of non-Hispanic black women in the U.S. were overweight or obese (1). Obesity often begins in childhood and becomes increasingly more common during the reproductive years. The purpose of the present document is to describe the effects of obesity on reproductive function and to outline contemporary treatments for obesity.

MENSTRUAL CYCLE DISTURBANCES

Obesity is frequently associated with menstrual cycle disturbances. Data from cross-sectional studies indicate that 30%–47% of overweight and obese women have irregular menses (2, 3). Menstrual irregularity in obese women correlates with increasing BMI (1) and increased truncal obesity (3–5). Obesity in childhood and early adult life increases the risk of irregular menstrual bleeding during the reproductive years (6).

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women. Common clinical features of the disorder include obesity, increased waist-to-hip ratio, and menstrual disturbances. However, not all obese women have PCOS, and not all women with PCOS are obese. The prevalence of PCOS among obese women with menstrual irregularity is unclear, because it varies widely with the diagnostic criteria for PCOS. It is possible that the insulin resistance and hyperinsulinemia associated with obesity may promote the development of the PCOS phenotype in some predisposed women.

INFERTILITY

Most obese women are not infertile. A large study, involving more than 4,000 women, observed no relationship between conception rates and weight or BMI (7). Infertility in obese women relates primarily to ovulatory dysfunction. A large case-control study that compared 2,527 women with anovulatory infertility and 46,718 control subjects, composed largely of married parous nurses having no history of infertility, observed a relationship between BMI at age 18 and the risk of subsequent anovulatory infertility; the relative risk (RR) for anovulatory infertility was 1.3 (95% confidence interval [CI] 1.2–1.6) among women having a BMI between 24 and 31 kg/m^2, and 2.7 (95% CI 2.0–3.7) for those with a BMI $\geq$32 kg/m^2 (8). Conversely, ovulatory function and pregnancy rates frequently improve significantly after weight loss in obese anovulatory women (9). However, infertility among obese women may not relate to ovulatory dysfunction entirely. In a prospective cohort study involving 500 women entering a donor insemination program, an increased waist-to-hip ratio was associated with delay in time to conception, even after adjustment for weight, cycle length, and regularity (10). Other studies also have suggested that fecundity is lower among ovulatory obese women (11–13). A Dutch study found that the probability of natural conception declined by 4% per kg/m^2 in women with a BMI >29 kg/m^2 (hazard ratio 0.96, 95% CI 0.91–0.99) (14). Although the mechanisms responsible for the lower fertility observed in obese women are unclear, attention has focused primarily on the potential adverse effects of elevated insulin levels.

Response to treatment

Studies of the effects of obesity on response to ovarian stimulation and outcomes achieved with assisted reproductive technologies (ART) have yielded conflicting results, but overall, they suggest that obesity has adverse effects. A large retrospective analysis of outcomes in 5,019 cycles of in vitro fertilization (IVF) revealed that obesity was associated with longer durations and increased amounts of gonadotropin stimulation, an increased frequency of cycle cancellation for inadequate response, and lower oocyte yields (15); there was no apparent association between obesity and embryo quality. In another retrospective study in 3,586 women undergoing ART, pregnancy rates were significantly lower in obese (odds ratio [OR] 0.73, 95% CI 0.57–0.95) and very obese (OR 0.5, 95% CI 0.32–0.77) women compared with women who are not obese (16). A third retrospective study of outcomes in 1,293 women under age 38 receiving IVF observed a significantly higher cancellation rate in morbidly obese

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FIGURE 1

Body mass index table

Body Mass Index Table

	Normal						Overweight					Obese										Extreme Obesity														
BMI	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**
Height (inches)	**Body Weight (pounds)**																																			
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

Source: Adapted from *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.* Retrieved from: *http://www.nhlbi.nih.gov/guidelines/obesity/bmi_tbl.pdf.*

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women compared with normal-weight women (25.3% vs. 10.9%, respectively; OR 2.73, 95% CI 1.49–5.0). However, there were no significant relationships observed between BMI and clinical pregnancy or delivery rates (17).

Pregnancy loss and adverse pregnancy outcomes

Obesity also has been associated with an increased risk of pregnancy loss. A large retrospective study in women undergoing ART observed a higher 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) in obese women compared with normal-weight women (15). Another retrospective study that examined outcomes in 2,349 pregnancies achieved with ART suggests strongly that the risk of spontaneous abortion increases progressively in overweight (OR 1.29, 95% CI 1.00–1.66), obese (OR 1.71, 95% CI 1.20–2.43), and very obese (OR 2.19, 95% CI 1.27–3.78) women compared with women having a normal BMI (18). Further careful prospective studies are needed to assess the risk of miscarriage in pregnancies conceived without ART among obese women with and without PCOS.

Obesity increases the risk of many complications of pregnancy. The risk of pregnancy complications is greatest among morbidly obese women (Table 1) (19, 20), but still significantly increased for all women with a BMI $\geq$30 kg/m^2. The risks of preeclampsia, gestational diabetes, and cesarean delivery increase with BMI among women who conceived via IVF (17).

Obesity also has been associated with an increased risk of birth defects (Table 2). Possible mechanisms to explain the association include metabolic disturbances, such as undiagnosed diabetes, hyperglycemia, or elevated insulin levels, nutritional deficiencies, and increased requirements for certain nutrients (21). Beyond birth defects, the "fetal origins of adult disease" hypothesis raises concerns about the longer-term impact that maternal obesity may have on subsequent childhood development and adult health (22).

Because pregnancy in women who are overweight, obese, or very obese is associated with increased risks, recommendations for weight loss before pregnancy are prudent for women who are young. Some have urged that a BMI $<$35 should be achieved before conception (23, 24). For women

TABLE 1

Risk of pregnancy-related complications for women with a BMI ≥40 kg/m^2 (19, 20).

	OR	95% CI
Preeclampsia	4.8	4.04–5.74
Gestational diabetes	4.0	3.1–5.2
Large-for-gestational-age infant	3.8	3.5–4.16
Early neonatal death	3.4	2.07–5.63
Hypertension	3.2	2.6–4.0
Shoulder dystocia	3.1	1.86–5.31
Meconium aspiration	2.9	1.6–5.07
Antenatal stillbirth	2.8	1.94–4.02
Cesarean delivery	2.7	2.49–2.90
Fetal distress	2.5	2.12–2.99

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

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TABLE 2

Birth defects associated with maternal obesity (BMI ≥30 kg/m^2) (21).

	OR	95% CI
Ventral wall defects	3.3	1.0–10.3
Neural tube defects	2.7	1.2–6.1
Cardiac defects	2.0	1.2–3.4
Multiple congenital anomalies	2.0	1.0–3.8

Note: Abbreviations as in Table 1.

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in their latter reproductive years, the benefits of postponing pregnancy to achieve weight loss must be balanced against the risk of declining fertility with advancing age.

Pathophysiology

The impact of obesity on reproductive function can be attributed primarily to endocrine mechanisms. Abdominal obesity is associated with an increase in circulating insulin levels, which, in turn, results in increased functional androgen levels via suppression of hepatic SHBG synthesis and increased ovarian androgen production. Circulating estrogen levels are elevated chronically by way of increased aromatization of androgens in peripheral adipose tissue. These effects are most pronounced in women with PCOS, owing to the high prevalence of insulin resistance, independent of obesity (25). In women with PCOS, insulin stimulates ovarian androgen production both directly and indirectly, resulting in hyperandrogenism and menstrual cycle abnormalities (26, 27).

Leptin is a peptide secreted by adipocytes that decreases hunger and food intake and enhances fat metabolism. Leptin also inhibits ovarian follicular development and steroidogenesis and has been associated with reproductive abnormalities in obese women (28, 29). Ghrelin, produced primarily in the stomach, is another peptide involved in the regulation of food intake and energy balance. Ghrelin enhances appetite and reduces fat utilization, but it has no known direct influence on reproductive function.

Effect of obesity on the male reproductive system

Whereas most studies of the effects of obesity on reproduction have focused on the female partner, a growing body of evidence suggests that obesity also has independent adverse effects on male reproductive function (30–32). The incidence of oligozoospermia and asthenospermia increase with BMI, from 5.3% and 4.5% in normal-weight men to 9.5% and 8.9% in overweight men and to 15.6% and 13.3% among obese men (33). Obesity may adversely affect male fertility by endocrinologic, thermal, and genetic mechanisms. In obese men, more androgen is converted to estrogen via aromatization in peripheral fat (34). Consequently, serum total testosterone levels are reduced (35). Gonadotropin concentrations also may be suppressed by increased negative feedback of estrogens (36). These endocrine abnormalities are apparent in all obese men and are more pronounced in infertile obese men. However, whether they cause infertility or reflect testicular dysfunction in obese men is not clear.

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 (37). Historically, treatments aimed at lowering scrotal temperature ("scrotal hypothermia") have proven to be impractical (38).

Specific genetic abnormalities associated with obesity also may cause infertility. Leptin administration has no effect on male fertility in animals with defects in the leptin receptor, but it increases sperm production and restores normal fertility in rodent models with defective leptin protein (39).

In summary, obesity may affect male fertility adversely though a variety of mechanisms that have not yet been elucidated completely, and the threshold weight above which such adverse effects may become manifest is not yet defined.

MEDICAL CONSEQUENCES OF OBESITY

Obesity causes or contributes to a large number of health problems, including type II diabetes, hypertension, coronary heart disease, dyslipidemia, respiratory dysfunction, sleep apnea, nonalcoholic steatohepatitis, reflux esophagitis, osteoarthritis, urinary incontinence, and increases in breast, endometrial, ovarian, and colon cancers. The medical consequences of obesity correlate with BMI and with increased waist circumference (≥80 cm) and increased waist-to-hip ratio (>0.85) in women, all of which reflect the metabolic impact of abdominal obesity.

The risk of death from cardiovascular disease increases with BMI and waist-to-hip ratio (40, 41). A longitudinal study of nonsmoking women aged 30–55 years who were followed for 16 years observed that the RR of death from cardiovascular disease was increased four-fold (RR 4.1, 95% CI 2.1–7.7) for those having a BMI >32.0 kg/m^2 (40). The cardiovascular consequences of obesity can be attributed to the increased prevalence of hypertension, diabetes, hypercholesterolemia, and hyperinsulinemia among the obese.

Obesity correlates strongly with an increased risk of diabetes that rises progressively with BMI. Compared with those of normal weight, the RR of diabetes is higher for overweight (RR 7.6, 95% CI 6.3–9.2) and significantly increased for obese (RR 20.1, 95% CI 16.6–24.4) and very obese (RR 38.8 95% CI 31.9–47.2) individuals (42). The risk of diabetes is also increased for women with PCOS, with an estimated incidence between 7% and 10% (43, 44), likely because the disorder is associated with both insulin resistance and obesity.

Large prospective studies have demonstrated a causal relationship between obesity and cancers of the colon, breast, endometrium, kidney (renal cell), and esophagus (adenocarcinoma) (45). Among obese individuals, the incidence and death rate for cancers of the cervix, pancreas, gall bladder, liver, and hematopoietic system also are increased, although no causal relationship has been established (45).

Risk of idiopathic intracranial hypertension is increased for reproductive-age women having a BMI >20% above normal (46). Body mass index also correlates with risk of depression after controlling for chronic disease, familial depression, and demographic risk factors (47, 48). However, by itself, obesity is not associated with an increased risk of psychopathology.

MANAGEMENT

Dietary and Lifestyle Changes

In a study of over 28,000 overweight women, intentional weight loss of ≥20 pounds was associated with a 25% reduction in all-cause, cardiovascular, and cancer mortality (49). Weight loss also has been shown to improve menstrual cyclicity (predominantly in women with PCOS) and reproductive outcomes (9, 50–52). Ovulatory function returns in a majority of obese anovulatory women with PCOS after a 5%–10% decrease in body weight (52). Weight loss also improves insulin resistance in obese women, and in women with PCOS, androgen levels decrease and SHBG concentrations increase after weight loss (53).

Lifestyle alterations, including diet modification and regular exercise, are the first-line treatment of obesity. Regular physical exercise is essential for weight loss and long-term weight management; a minimum of 30 min of moderately intense exercise at least 3 days/week is recommended (54). Women participating in structured weight loss programs that include a behavioral modification component are more successful than those who attempt weight loss on their own (55). In a study of a group of anovulatory infertile women, 67 of 87 subjects completed a 6-month structured weight loss program and lost an average of 15 pounds; ovulatory function returned in 60 of 67 subjects (90%), 52 of 67 (78%) conceived (18 without intervention), and the miscarriage rate was 18% (compared with 75% of previous pregnancies in the same women) (56).

Dietary interventions should focus on restricting calories and increasing energy expenditure. A low-calorie diet, generally consisting of 1,000–1,200 kcal/day, should be expected to achieve an average 10% decrease in total body weight over 6 months (57). A 500–1,000 kcal/day decrease from usual intake should result in a 1–2-pound weight loss per week.

Calorie restriction is the most important element of any weight loss program; dietary composition is less important. After 6 months, a low-carbohydrate diet results in greater weight loss than a low-fat diet, but the two diets achieve similar results after 12 months (58). The Atkins, Ornish, Weight Watchers, and Zone diets result in similar weight reduction over 1 year (59). Greater weight loss was achieved by those who best adhered to a diet. Decreases in insulin, total cholesterol, and C-reactive protein were associated with weight loss and did not differ between diets. In obese women with PCOS, low-carbohydrate and low-fat diets achieve similar decreases in weight and abdominal fat and improved insulin sensitivity (50).

The challenge is to find a diet that the individual can maintain in making a change in lifestyle. Weight is inevitably regained when lifestyle changes are not sustained. Unfortunately, diet and behavioral therapies often ultimately fail. Sixty to 86% of lost weight is regained after 3 years, and 75% to 121% after 5 years (60).

Medical Treatment

After six months of efforts at lifestyle modification, adjunctive pharmacotherapy is appropriate for women with a BMI ≥30 mg/kg^2 and for those with a BMI ≥27 mg/kg^2 in association with obesity-related risk factors or diseases (61, 62). A meta-analysis of clinical trials involving medical treatment for obesity observed that the average weight loss achieved with single-agent therapy ranged between 2 and 4 kg after subtracting the weight loss associated with placebo treatment; the average duration of treatment ranged from 7 to 48 weeks (63). Longer durations of treatment were associated with greater weight loss. Combining medical treatment with counseling on lifestyle modification achieves greater weight loss than medical treatment alone (64). There are several different classes of drugs that may be used to induce weight loss; none has proven to be clearly superior. Although the absolute weight loss achieved with medical treatment may be relatively small, treatment merits consideration for those in whom lifestyle modifications prove to be unsuccessful.

TABLE 3

Comparative cost analysis (68).

Medication and dosage	Weight loss in excess of placebo, kg (%)	Cost per month, $
Phentermine resin, 30 mg/day	8.1 (7.9)	60
Sibutramine hydrochloride, 15 mg/day	5.0 (4.3)	116
Orlistat, 120 mg (with meals)	3.4 (3.4)	119

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In one study, combined treatment with two or more drugs produced placebo-subtracted weight loss of 1.0–9.6 kg (61); best results were achieved with a combination of fenfluramine and phentermine (fen-phen). However, the combination has been associated with the development of valvular heart disease and primary pulmonary hypertension. Consequently, fenfluramine and dexfenfluramine (but not phentermine) were removed from the market in 1997 (65, 66).

Anti-absorptive drugs Orlistat, a saturated derivative of lipostatin (a potent natural inhibitor of pancreatic lipases isolated from the bacterium *Streptomyces toxytricini*), interferes with hydrolysis of dietary fat into absorbable free fatty acids and decreases fat absorption from the gut by approximately 30% (67). Orlistat treatment (120 mg, administered with meals) also decreases absorption of fat-soluble vitamins, primarily vitamin D. Supplementation with a multivitamin containing Vitamin D, administered at least 2 h before or after orlistat treatment, is therefore recommended. Contraindications for the use of orlistat include chronic malabsorption syndromes and cholestasis. Gastrointestinal side effects are common.

Appetite suppressants Phentermine is a sympathomimetic amine that enhances the concentration of norepinephrine in the periventricular and perifornical regions of the hypothalamus, resulting in satiety. Phentermine has been available commercially since 1960; the recommended dosage is 15 mg or 30 mg daily. To minimize the likelihood of sleep disturbances that may result from central nervous system stimulation, phentermine should 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 those with cardiovascular disease, uncontrolled hypertension, hyperthyroidism, glaucoma, and agitated states. To date, treatment with phentermine alone has not been associated with primary pulmonary hypertension, left-sided cardiac valvular lesions, or renal or hepatic toxicity.

Sibutramine is a centrally acting serotonin-norepinephrine reuptake inhibitor. The recommended oral dosage is 10–15 mg once daily, administered in the early morning. Side effects include hypertension, palpations, dry mouth, headache, insomnia, and constipation. Contraindications for the use of sibutramine include hypertension, renal impairment, hepatic dysfunction, glaucoma, cardiovascular disease, and agitated states.

The effects of appetite suppressants on menstrual cyclicity, ovulation, and fecundity are unknown. Both phentermine and sibutramine are pregnancy category C drugs and generally should not be used in pregnancy. The comparative effectiveness and costs of treatment with the two appetite suppressants and with orlistat are summarized in Table 3 (68).

Insulin-sensitizing agents Metformin is a biguanide that inhibits hepatic glucose production and increases peripheral tissue sensitivity to insulin. In obese anovulatory women with PCOS, metformin has been used successfully to treat ovulatory dysfunction (69). As an ovulation-inducing drug, metformin is less effective in obese women than in women of normal weight (70), and it is no more effective than weight loss in obese women (71).

Metformin-induced decreases in circulating insulin and androgen levels also may be associated with decreases in body weight and visceral fat (72). Although metformin treatment may result in modest weight loss, it does not reliably achieve that goal in obese women with PCOS (49, 51, 52). When metformin is combined with a restricted-calorie diet, significant weight loss and decrease in visceral fat have been observed (72,73). In prediabetics, metformin treatment can decrease the risk of progression to diabetes by 31% (74). However, lifestyle changes (involving 7% weight loss and at least 150 min of exercise per week) yield a 58% reduction in risk and should therefore be emphasized (74). Thiazolienediones, another class of insulin-sensitizing drugs, are not associated with weight loss (75, 76).

The optimal dosage of metformin is 1,500–2,000 mg/day. Side effects are primarily gastrointestinal and may be severe enough to discourage or prevent its use; lactic acidosis is a rare complication. Hepatic and renal function should be assessed before treatment begins and monitored at least annually during continued treatment. Metformin is a pregnancy category B drug and currently is not approved by the FDA for the treatment of obesity (77).

Herbal supplements Although safety and effectiveness have not been demonstrated, many obese women self-medicate with herbal supplements. Ephedra-containing supplements have potentially life-threatening cardiovascular side effects and have been banned by the FDA (78).

Cannabinoid receptor antagonists The recently discovered endocannabinoid system is overactivated in genetic animal models of obesity and has been implicated in the modulation of food intake and energy homeostasis (79). Rimonabant selectively blocks the cannabinoid-1 receptor and suppresses tonic endogenous activation of the endocannabinoid system, both centrally (resulting in decreased food intake) and

TABLE 4

Bariatric surgery options.

Restrictive procedures	Largely restrictive, mildly malabsorptive	Largely malabsorptive, mildly restrictive
Vertical banded gastroplasty Adjustable gastric banding Intragastric balloon	Roux-en-Y gastric bypass: • short-limb • long-limb	Biliopancreatic diversion Duodenal switch

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peripherally (resulting in altered adipocyte function) (79). Accumulated clinical evidence indicates that numerous cardiovascular and metabolic risk factors improve during rimonabant treatment, including body weight, waist circumference, high-density lipoprotein cholesterol, triglycerides, and glucose metabolism (79–82). The effects appear to be mediated by both the central and the peripheral actions of the drug, because they are greater than the improvements that would be expected from weight loss alone. Some concern has been raised regarding the potential for adverse neurologic and psychiatric effects, including depression and increased suicide risk (83). The effectiveness of rimonabant has not been compared directly with that of other weight control medications.

Bariatric Surgery

Increasingly, bariatric surgery is being used in the treatment of morbid obesity. Between 1990 and 2000, the national annual rate of bariatric surgical procedures increased six-fold, from 2.4 to 14.1 per 100,000 adults (P=.001) (84). The bariatric surgical procedures currently in use generally are classified as restrictive procedures or as combined restrictive/malabsorptive procedures (Table 4). Restrictive procedures involve the creation of a small gastric pouch which fills rapidly, leading to early satiety. Malabsorptive procedures bypass a large section of the small bowel, thereby reducing the surface area for absorption. High-osmolar material in the jejunum induces a dumping syndrome and avoidance of food.

Worldwide survey data from 2002 and 2003 reveal that gastric bypass procedures (Roux-en-Y) are the most commonly performed type of bariatric surgery (65.1%); more than one-half are performed via laparoscopy. Laparoscopic adjustable gastric banding (24%), vertical banded gastroplasties (5%), and biliopancreatic diversion procedures (5%) are performed less frequently (85). Endoscopic placement of intragastric balloons has less associated morbidity and has been proposed as a short-term treatment for morbid obesity in conjunction with an appropriate diet (86).

The 1991 National Institutes of Health Consensus Development Panel recommended that surgical treatment be considered for patients with a BMI $\geq$40 kg/m^2 or with a BMI $\geq$35 kg/m^2 and serious coexisting medical problems aggravated by obesity (87). Additional selection criteria for bariatric surgery include failed dietary therapy, psychologic stability, high motivation, knowledge of the operation and its sequelae, and likelihood of surviving surgery.

The primary goal of bariatric surgery is to ameliorate medical problems related to obesity. Data from two large meta-analyses indicate that patients with a preoperative BMI $\geq$ 40 kg/m^2 can be expected to lose 20–40 kg over 2 years and to maintain their reduced weight for up to 10 years (88, 89). Gastric bypass procedures achieve a greater mean weight loss than gastric banding procedures, but the incidence of postoperative nutritional and electrolyte abnormalities also is greater (17% vs. 2.5%) (89). Overall mortality from all bariatric surgical procedures is less than 1% (88, 89). Beyond weight loss, bariatric surgery offers significant improvements in diabetes, hypertension, dyslipidemia, and sleep apnea (88, 89). Bariatric surgery can also improve menstrual regularity and fertility in women (90), but it may adversely affect fertility in men. One report has described six previously fertile men who lost 60–80 kg after a Roux-en-Y gastric bypass but developed secondary infertility and complete azoospermia ultimately attributed to complete spermatogenic arrest (91).

Pregnancy is not recommended during the first year after bariatric surgery, during which the majority of weight loss occurs. A number of studies have observed that previous bariatric surgery is not associated with an increased risk of adverse perinatal outcomes (92–94). Although weight loss after bariatric surgery decreases the risk of pregnancy complications compared with obese pregnant women, the incidence of anemia due to iron, folate, vitamin B12, and nutritional deficiencies may be increased. One case report has described a maternal and fetal death during pregnancy after gastric bypass surgery, related to herniation of a segment of bowel through a mesenteric defect that ultimately resulted in necrosis and acidosis (95). Such herniations have been reported in approximately 2% of patients after bariatric surgery, but whether pregnancy may predispose to or increase the risk of the complication is unknown.

SUMMARY

- Obesity is associated with menstrual dysfunction, decreased fertility, and increased risk of miscarriages.

- Obesity decreases fecundity, even in ovulatory women.
- Obesity increases the risks of obstetric and neonatal complications.
- Obesity is associated with abnormal semen parameters and may adversely affect male fertility.
- Preconceptual counseling for obese women should address the medical, obstetric, and neonatal consequences of obesity and its longer-term implications for offspring.
- Lifestyle changes involving a diet and exercise program are the first-line treatment for obesity.
- Adjunctive medical therapy for obesity is indicated when lifestyle changes prove to be inadequate or fail.
- When combined with a low-calorie diet, metformin may result in weight loss, restore ovulation, and improve fecundity in women with PCOS.
- Bariatric surgery is more effective than other treatments for weight loss and improves comorbidities related to obesity in patients with a BMI ≥ 40 kg/m^2.

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