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A Women's Health Perspective on Managing Obesity

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Abstract

While the prevalence of obesity in US men and women is nearly equivalent, obesity management in women requires a different approach that considers age and life stage in development including sexual maturation/reproduction, menopause and post-menopause. In this review, the diagnosis and treatment of obesity using lifestyle modification, pharmacotherapy and metabolic and bariatric surgery are discussed from a women's health perspective, with emphasis on management during pregnancy and post-partum.

Keywords

obesity; women's health; gender/sex; management

Obesity, defined as excess accumulation of body fat, is a highly prevalent, heterogenous, and relapsing medical disease affecting over 650 million adults globally.[1–3] In clinical

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practice, body mass index (BMI) is used to determine disease severity where mild (Class 1 obesity) is characterized by a BMI of 30.0 -34.9 kg/m^2, moderate (Class II obesity) is characterized with BMI 35.0-39.9 kg/m^2 and severe (Class III obesity) is characterized by BMI ≥ 40 kg/m^2.[2] Disease severity correlates to decreased quality of life, increased likelihood of concurrent obesity-related conditions, and cost burden. The United States (US) healthcare system spends nearly $173 billion per year on obesity and obesity co-morbidities. [4]

While the prevalence of obesity amongst US men and women is nearly equivalent at about 43% in adults aged 20 and over, there are significant sex differences in prevalence between race/ethnicity and socioeconomic status that are commonly differentiated using the “obesity transition” framework.[5] In stage 1, there is a higher prevalence of obesity in adult women in compared to adult men and in individuals of higher socioeconomic status, where stage 2 is characterized by a narrowing of difference between sex/gender and socioeconomic status.[5] Stage 3 is characterized by an obesity prevalence that is highest in those from lower socioeconomic status; the US currently in this stage.[5] Within stage 3, there are specific differences in obesity prevalence between men and women based on race/ethnicity and obesity severity. For example, in non-Hispanic Black women, the prevalence of obesity is 56.9%. [6] The overall prevalence of severe obesity is higher in women than men at 11.5% and 6.9%, respectively, regardless of race/ethnicity. [6] Stage 4 is characterized by declining obesity prevalence. There are no countries in this stage of the “obesity transition” framework.[5]

There are over 200 disease states that are associated with obesity. [7] Given the higher prevalence of obesity in specific sub-populations of women, there is an increased likelihood of developing the cardiometabolic disease, including type 2 diabetes, hypertension, and dyslipidemia. In addition, women are at risk for specific medical conditions exclusively pertinent to women’s health, including menstrual cycle irregularities, gynecologic cancer, endometrial and breast cancer, and pelvic floor disorders. From a biological perspective, the treatment of obesity in women is different in contrast to men and varies accordingly to the woman’s age and stage of development. In this review article, we will discuss the management of obesity from a women’s health point of view.

GENDER/SEX GAP

There are minimal data available to fully expound the gender/sex gap regarding obesity prevalence, especially regarding race/ethnicity and disease severity. [5] However, different theories may help to explain this discrepancy.

Development and Biological Mechanisms

Life stages in women, unlike men, are divided into infancy, puberty (adolescence), sexual maturation (reproductive age), menopause, and post-menopause (elderly) years. [8] The timing of the onset of puberty/menarche may have a role in the development of obesity and related comorbidities. [9] Early puberty onset is moderately associated with higher BMI in both men and women. However, this association was stronger for girls when considering

BMI and waist circumference (WC) compared to boys. [9] Of note, these associations were weaker in adulthood after adjusting for childhood BMI. [9]

Sexual maturation marked by pregnancy is when women typically gain weight and have an increased risk for post-partum overweight and obesity. [8] The presence of obesity before pregnancy dictates the amount of weight gain recommended by the care provider. Women with elevated BMI are suggested to gain less weight during pregnancy to reduce neonatal risk, decrease maternal morbidity and lessen the cesarean delivery rate. [8, 10]

With age, both men and women are at risk for weight gain. [5] However, women are particularly vulnerable to weight gain due to decreased ovarian follicle activity leading to reduced estradiol and estrogen, as well as increased androgens, including testosterone. [11, 12] This leads to body composition changes, including skeletal muscle loss or sarcopenia and increased visceral fat in trunk/abdomen, which contribute to decreased energy expenditure and increases risk for cardiovascular disease (CVD) [5, 11–13] Of note, women develop sarcopenia earlier in comparison to men. [11]

During the transition to menopause, weight gain is thought to be driven by two modifiable risk factors: the severity of a woman's menopausal symptoms and lifestyle practices. [13] The symptoms associated with menopause, including hot flashes, emotional volatility, joint pain, and limited mobility, are often associated with decreased sleep and weight gain. [13, 14] On the contrary, hormone replacement therapy (HRT) can promote weight loss. However, HRT use is limited due to concerns of increased risk of stroke, deep vein thrombosis , and other CVD.

Physiological Mechanisms

Neuroimaging studies illustrate specific sex/gender differences underlying one's propensity to develop obesity over time. [5] Women exhibit a greater neural response to highly palatable, energy-dense foods, leading to a higher BMI. [5] Additionally, women with obesity have been shown to exhibit higher resting rate connectivity in areas of the brain that are associated with food reward, including the amygdala and hippocampus leading to excess weight.. [15] More studies are needed to elucidate these findings further. [5]

Behavioral, Sociocultural, and Psychological Mechanisms

Behavioral factors may contribute to differences in food consumption and increase the risk of developing obesity. Gender-targeting food advertisements and depiction of foods as masculine or feminine can shape one's food preference, wherein women demonstrate increased preference for and consumption of foods higher in sugar. [5] Additionally, women are more likely than men to increase the ingestion of calorie-dense food as a coping strategy. [16]

When considering the higher prevalence of obesity among non-Hispanic Black females, there is evidence to support sociocultural etiology. For example, in sub-Saharan Africa, weight gain is associated with wealth and higher socioeconomic status. [5] Thus, in preparation for their wedding, brides are encouraged to discontinue the physical activity

(PA) and eat large amounts of food. [5] This has been shown in other cultures where exercise is limited and multiple pregnancies are encouraged. [5]

From a psychological perspective, excess calorie intake is often used to cope with increased stress in both men and women, though the association is higher in women. [5, 16] Also, one's psychological well-being is often tied to social relationships and interactions, leading to weight gain. In women, marital status and social interactions were correlated with a higher risk of obesity. [5]

DIAGNOSIS

BMI is the most common measure to diagnose obesity. However, BMI fails to differentiate between fat mass, lean muscle mass, and bone density and does not account for race and sex differences, which raises concerns about its efficacy in classifying obesity status. [17] In certain racial and ethnic minority groups, cutoff BMI values that confer increased risk of CVD as consistent with overweight and central adiposity differ from current definitions of obesity based on data from Western, majority-white populations.[18, 19] Validity issues with BMI may also be amplified in post-menopausal women, as menopause induces changes in body composition, mentioned previously, and analogous changes in body weight do not accompany that. [20, 21] Accordingly, Banack and colleagues found that BMI misclassifies a substantial proportion of older women with obesity as not having obesity, highlighting the limitations of using BMI to define obesity for women as they progress into later life stages. [17]

Other indirect measures of adiposity include WC and waist-to-hip ratio. However, both methods are also incapable of distinguishing between body composition components, especially regarding visceral fat. Direct measures of adiposity, such as dual-energy x-ray absorptiometry (DEXA), can more accurately measure body fat percentage (BF%), particularly in older women, but are expensive and impractical for routine clinical application. [22] New therapies like digital anthropometry may prove useful as an accurate, low-cost strategy to evaluate adiposity.[23] There is minimal consensus regarding a meaningful cutoff value for BF%, with a BF% greater than 35% for women most commonly used in the published literature to define obesity. [17, 22]

ASSESSMENT

The first step in initiating obesity care for women entails a comprehensive assessment. A medical provider begins by taking an obesity-focused history, inquiring about dietary and PA, medications used in the past and currently, and the age of onset of obesity and any concurrent life changes. Pregnancy and menopause are periods of high risk for developing obesity among women. [20, 21, 24, 25] A family history may also provide insight into a patient's predisposing genetic background. Clinicians should inquire about overweight or obesity in childhood or adolescence, given that the early onset of obesity is a predictor of severe obesity as an adult. [26]

Additional lifestyle factors, including sleep patterns, occupational schedules, and situational stressors, should be assessed for their potential influence on a patient's weight gain. It is

crucial to account for a patient's sociocultural and environmental context. For example, access to affordable, healthful food options may be limited for patients in food deserts or swamps. Cultural values regarding body weight and social eating habits similarly influence weight management. [27, 28] A multidisciplinary assessment that encompasses these determinants recognizes that obesity is not merely caused by an individual's choices (i.e., diet, amount of exercise, or willpower), thereby combating weight stigma and centering the treatment discussion from the patient's perspective. [29, 30]

In addition to obtaining initial anthropometrics, including the patient's height, weight, and WC, examinations of the breasts, skin, and lower extremities — areas that may be less easily reached or infrequently examined by the patient — should be inspected. [20] While BMI and WC assist in obesity diagnosis, they are not fully elucidative in determining the severity of weight-related health risks. [31] Therefore, it is imperative that an evaluation for concurrent medical conditions accompanies the physical examination. [32] Psychological health screenings are also important. Mood and anxiety disorders occur at high rates among patients with overweight and obesity. Moreover, disordered eating conditions, such as bulimia, night-eating syndrome, and binge eating disorder, require targeted mental health interventions that should be integrated with a patient's weight management plan. [31, 33] The obesity-focused history and physical examination facilitate the development of treatment recommendations that align with each patient's needs and goals.

TREATMENT

The treatment of obesity in women should take a well-structured and personalized approach. It is important to consider patients' disease severity, age, cultural and food preferences, history and comorbidities, lifestyle, adherence, and insurance coverage when considering treatment modalities, as interventions should be focused on long-term sustained health.

Several medications, including steroids, anti-psychotics, anti-epileptics, antihistamines, some oral hypoglycemics, and anti-retrovirals promote weight gain, with antidepressants, insulin, and beta-blockers associated explicitly with weight gain among postmenopausal women. [34, 35] When treating obesity, clinicians should review patients' medications and consider weight-neutral or adverse alternative medications as first-line agents. If weight-promoting medications are necessary, other adjunctive medications should be considered to reduce dosing requirements and mitigate weight-promoting effects. Patients should be informed of expected weight effects in a shared decision-making process if none are available. [34]

The cornerstone of obesity treatment remains optimizing lifestyle therapies, even if pharmacotherapeutic or surgical interventions are added. Effective nutrition interventions are critical and include macronutrient composition, dietary patterns, or meal timing changes. Improving diet quality with increased micronutrient density and reducing ultra-processed foods is key to producing satiety, weight loss, and maintenance. [36]

Increasing physical activity benefits patients of all ages, as inactivity is related to weight gain and increased risk of cardiovascular disease. However, it is more effective in preventing

weight gain and weight maintenance than treating obesity, as total weight loss is rarely improved by PA.[37] Aerobic and resistance exercise can attenuate muscle mass loss, improve physical functioning, and help maintain total energy expenditure during weight loss. [37, 38]

Sleep quality and duration are thought to have a bi-directional relationship with obesity. Short sleep duration and poor sleep quality are associated with weight gain and obesity-related to sleep-disordered breathing, including obstructive sleep apnea. Moreover, diseases including depression, gastroesophageal reflux disease (GERD), osteoarthritis, and asthma are associated with obesity and sleep disturbances. Therefore, it is essential to intervene in this cycle by improving sleep hygiene and duration and treating sleep disturbances. [39]

Stress also appears to have a bi-directional relationship with obesity, with chronic physical and psychological stress inducing glucocorticoid production that promotes weight gain. Furthermore, weight stigma and obesity-related comorbidities can exacerbate chronic stress. Long-term elevations in cortisol are strongly associated with central adiposity and depression. Mental and physical stress sources should be explored and addressed throughout obesity treatment. [40]

Non-pregnant Patients who are not breast-feeding with a BMI ≥ 30 kg/m^2 or 27-29.9 kg/m^2 with weight-related comorbidity who are unable to lose ≥5% of total body weight with lifestyle therapy over three to six months are candidates for pharmacotherapy. Semaglutide, liraglutide, orlistat, phentermine-topiramate, and bupropion-naltrexone are Food and Drug Administration (FDA)-approved medications for long-term weight management, and sympathomimetic drugs (phentermine, diethylpropion, benzphetamine, and phendimetrazine) are approved as monotherapy for up to 12 weeks. [34] Several other medications with weight-reducing benefits, including metformin, sodium- glucose co-transporter −2 inhibitors, amylin antagonists, zonisamide and monotherapy bupropion, and topiramate, are often used off-label for the treatment of obesity. [41]

Incretin-based therapies, including glucagon-like peptide1 (GLP-) receptor agonists (ie, liraglutide 3.0 mg daily, semaglutide 2.4 mg weekly) and dual gastric inhibitory polypeptide/GLP1-1 receptor agonists (ie tirzepatide) are currently the most effective medications.[42] Semaglutide promotes a 15% average weight loss over the course of the 68-week trial.[43] Tirzepatide, currently FDA approved for diabetes management, promotes about 22% average weight loss over the course of the 72-week trial.[44]These agents are self-administered subcutaneous injections stimulating insulin secretion while inhibiting glucagon release and gastric emptying. However, cost limits are used as many insurers do not cover these medications to manage obesity. [34]

Phentermine is the most commonly prescribed anti-obesity medication and reduces food intake by causing early satiety, leading to a 5-10% weight loss within three months. Phentermine can elevate heart rate and blood pressure and, therefore, is contraindicated in the setting of CVD or high CVD risk. It is also available in combined dosing with topiramate, producing a weight loss of 6-8% over one year, with a similar side effect profile. [34]

Bupropion-naltrexone has shown a 4-5% weight loss efficacy and may be well-suited to patients with co-morbidities treatable with bupropion or naltrexone. However, it can lower the seizure threshold, and its cardiovascular safety profile needs to be well-established.

Orlistat alters fat digestion by inhibiting pancreatic lipases and produces a modest 2-3% weight loss by increasing fecal fat excretion. However, its gastrointestinal side effects of intestinal cramping, incontinence, and oily discharge often make orlistat an untenable option for patients. [34]

Metabolic and bariatric surgery (MBS) is an option for non-pregnant patients with a BMI ≥35 kg/m2 and a BMI ≥30 kg/m^2 with at least one obesity-related comorbidity.[45] The most recent guidelines suggest patients of Asian descent should be offered MBS with a BMI ≥27.5 kg/m^2.[45] Various procedures combine restrictive and metabolic effects to induce weight loss. The most common procedure in the US is vertical sleeve gastrectomy (VSG), where 80% of the stomach is removed. The following restriction and decreased ghrelin production led to an average of 60% excess body weight loss over two years. The VSG carries an increased risk of GERD. [46, 47] The Roux-en-Y gastric bypass is another procedure that produces a small gastric pouch for restriction. It re-routes the small intestine to have malabsorption and alters gut hormones, making an expected weight loss of 70% in two years. Patients are at an increased risk of micronutrient deficiencies and ulcer formation; patients may experience “dumping syndrome” or feel ill after eating certain foods. [46, 48]

Biliopancreatic diversion with a duodenal switch also creates a stomach pouch and produces the highest rate of malabsorption by passing more of the small bowel. It is the most effective MBS for treating type 2 diabetes and obesity, with an expected excess weight loss of 70-80% within two years. It also poses the highest risk of malnutrition and micronutrient deficiencies and can worsen reflux. [46, 48]

The newest surgery available is the single anastomosis duodeo-Ileal bypass with sleeve gastrectomy. A sleeve gastrectomy is performed, and the stomach is directly attached to the distal duodenum. This reduces micronutrient malabsorption, can be performed on patients with previous sleeve gastrectomy, and is highly effective, with an average excess weight loss of 85% in two years. There is less long-term data available, and the procedure may worsen reflux and cause loose stools. [46, 49]

SPECIAL CONSIDERATIONS FOR WOMEN

There are special considerations for weight management through sexual maturation (reproduction), menopausal and post-menopausal life stages in women. Women who have overweight or obesity pre-conception are encouraged to lose weight, as optimizing weight status may reduce maternal and fetal risk. [50, 51] In anovulatory women with overweight or obesity, including those with polycystic ovarian syndrome , weight loss can decrease use of assisted reproductive technologies . [51]. A BMI greater than 25 kg/m^2 increases the risk of pregnancy complications and the future risk of chronic disease affecting the mother and child. [52–54] Encouraging weight loss before pregnancy is of particular importance since weight loss is not recommended during pregnancy, and the use of pharmacotherapy

for weight management is not approved in the setting of pregnancy. The current standard of care for managing obesity before pregnancy is lifestyle modification. Metabolic and bariatric surgery-induced weight loss reduces maternal adverse pregnancy outcomes but may increase adverse infant outcomes. [55]

The goal of weight loss before pregnancy should be to optimize any pre-existing weight-related conditions, including type 2 diabetes, metabolic syndrome, hypertension, hyperlipidemia, obstructive sleep apnea, and nonalcoholic fatty liver disease. [56] A randomized controlled trial by LeBlanc and colleagues found that participants of a pre-pregnancy weight loss intervention lost more weight than the control group before conception. However, the intervention group experienced more significant weight gain in the 2^{nd} and 3^{rd} trimesters. [57] This indicates that to limit excess weight gain throughout pregnancy and improve maternal and child outcomes, pre-pregnancy weight loss interventions must be combined with intensive weight management that continues following delivery. [57]

For patients who have undergone MBS, the American College of Obstetricians and Gynecologists recommends waiting 12 to 24 months before conceiving so that the fetus is not affected by rapid maternal weight loss and so that the patient can achieve maximum weight loss postoperatively. [58] Contraception and preconception counseling should be provided for all women of reproductive age who undergo MBS. The use of contraceptives in adolescents is essential because pregnancy rates in the post-bariatric surgery adolescent population are twice that of the general adolescent population (12.8% vs. 6.4%). [58] In addition, the risk of oral contraceptive failure is increased after bariatric surgery, so it is imperative only to consider non-oral forms of contraception. [59]

Risks for chronic diseases, including obesity and diabetes, are further increased if the mother gains excessive weight during her pregnancy. [60, 61] Excessive gestational weight gain (EGWG) is defined by the Institute of Medicine according to pre-pregnancy BMI. Weight gain above 16.0 kg, 11.5 kg, and 9.0 kg is considered excessive for women of normal weight, overweight, and obesity BMI categories, respectively. [62] About half of the women exceed gestational weight gain guidelines during pregnancy, with a higher prevalence seen in those with an elevated pre-pregnancy BMI. [63] Research suggests that pregnant women with a BMI ≥ 25.0 kg/m^2 can prevent EGWG by engaging in a lifestyle intervention during pregnancy that includes both nutrition and PA. [64, 65]

Pregnant women with obesity are more likely to have an early pregnancy loss. They have an increased risk of congenital fetal malformations, delivery of large for gestational age infants, shoulder dystocia, spontaneous and medically indicated premature birth, and stillbirth. Late pregnancy complications include gestational diabetes and pre-eclampsia, associated with long-term morbidities post-partum. [66] Diagnosis and treatment of gestational diabetes may improve maternal weight management, but this benefit is limited to late pregnancy. [67]

A randomized controlled trial by Price and colleagues demonstrated substantial weight loss among mothers on a very low-energy diet. Although the weight loss did not alter fasting glucose at 26 to 28 weeks gestation, it did vary postprandial glucose control and reduce

a composite of adverse pregnancy outcomes (including gestational diabetes, gestational hypertension/preeclampsia, pre-term delivery, shoulder dystocia/birth injury, and neonatal special care nursery/intensive care unit admission) in both mothers and children. [68] While interpregnancy weight loss is associated with a lower risk of developing hypertensive disorders during pregnancy, optimizing weight status before conception and limiting excess weight gain during pregnancy is of greater importance. [69]

After delivery, the retention of pregnancy weight contributes to long-term overweight, obesity, and associated obesity-related medical conditions, such as CVD, type 2 diabetes, and various cancer types. Therefore, postpartum weight normalization is highly recommended. [70] However, 75% of women do not return to their pre-pregnancy weight in the year following delivery. Studies show a mean postpartum weight retention of four to five kilograms one year after delivery. [71, 72]

An important risk factor for postpartum weight retention is EGWG, which occurs in approximately 35% to 50% of pregnancies. [72] Other risk factors identified by Bijlholt and colleagues include pre-pregnancy BMI, excessive gestational weight gain, male sex of the infant, lack of exclusive breastfeeding, and no history of depressive feelings. Several previous pregnancies, sedentary behavior, emotional eating, energy intake, and uncontrolled eating behaviors are not significantly associated with postpartum weight retention. [70] There are minimal studies that target pregnancy and postpartum life stages in women with obesity, and results are inconsistent. [73] Dietary quality should be emphasized for postpartum women to optimize their health and nutrient status and the infant's health for breastfeeding women.

Data from Burton and colleagues demonstrated that PA in the postpartum period improved mental well-being and assisted with weight loss. Lack of time and childcare were the most common barriers to PA, and social support was a common enabler.[74] Relatedly, psychosocial, cultural, and economic factors also play a role in postpartum weight loss programs. Interventions for racial and ethnic minority women and women of low income with postpartum obesity should address the psychological effects of childbearing, affordability, and body image perceptions and incorporate family-centered approaches with social support and weight loss maintenance strategies. [75, 76]

FDA-approved anti-obesity medications are not approved in the setting of pregnancy or breastfeeding, although Metformin, used off-label for obesity treatment, can be used during this time. Data shows that despite passage across the placenta and transfer of limited amounts to breastmilk, there is no significant risk of teratogenesis, and the risk of neonatal hypoglycemia is negligible. [77, 78] MBS can be considered postpartum as long as a subsequent pregnancy is not anticipated for at least 1-2 years post-surgery. Surgery appears to positively affect fertility and reduce the risk of gestational diabetes and preeclampsia. In addition, there appears to be a reduced incidence of fetal macrosomia post-bariatric surgery. However, there remains uncertainty about the increased rates of infants who are small-for-gestational-age or have intrauterine growth restriction, as well as premature rupture of membranes in women post-bariatric surgery. Case reports demonstrate that pregnancy after

bariatric surgery is not without complications. An interdisciplinary team should manage these high-risk patients. [79]

CONCLUSION

Despite the equivalent prevalence of obesity among US men and women, many etiologies ranging from biological to sociocultural, environmental, and psychological factors increase a woman's risk of excess weight leading to obesity and obesity-related conditions. All women, regardless of weight status, are at higher risk of cardiovascular disease due to increased age and decreased estrogen production in the setting of menopause. Women with obesity have higher cardiovascular risk in the setting of excess adipose tissue and underlying inflammation. There is a need to increase awareness of obesity management from a women's health perspective while considering the various changes that occur in a woman's body over her lifetime. Future research is needed to address disparities in obesity prevalence and treatment, especially in sub-populations of US women disproportionally affected by the disease.

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Abbreviations

BMI	body mass index
CVD	cardiovascular disease
EGWG	excessive gestational weight gain
GERD	gastroesophageal reflux disease
FDA	Food and Drug Administration
GLP-1	glucagon-like peptide 1
MBS	metabolic and bariatric surgery
PA	physical activity
US	United States
VSG	vertical sleeve gastrectomy
WC	waist circumference

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