Obesity in Women
The Clinical Impact on Gastrointestinal and Reproductive Health and Disease Management

Octavia Pickett-Blakely, MD, MHSa,*, Laura Uwakwe, MDb, Farzana Rashid, MDC

INTRODUCTION

Obesity is a well-known, chronic condition that affects individuals in all walks of life (Table 1). Previously considered a disease of privilege, the worldwide obesity epidemic has had significant societal impact, ranging from the social stigma associated with obesity to costly, comorbid diseases. Research efforts have focused on all facets of obesity from the epidemiology to treatment strategies. Thus far, the work done in this area has revealed that, like other chronic diseases, intriguing gender differences exist between women and men. This article focuses on the epidemiologic and pathophysiologic features, clinical manifestations, and management of obesity-related disorders that are unique to women and pertinent to gastroenterologists.

Disclosures: All authors have nothing to disclose.

a Division of Gastroenterology and Hepatology, University of Pennsylvania, 3400 Civic Center Boulevard, 4 South, Philadelphia, PA 19104, USA; b Department of Medicine, Drexel University College of Medicine, 245 North 15th Street, New College Building, Suite 5104, Philadelphia, PA 19102, USA; c Division of Gastroenterology and Hepatology, University of Pennsylvania, 51 North, 39th Street, 218 Wright Building, Philadelphia, PA 19104, USA

* Corresponding author.

E-mail address: octavia.pickett-blakely@uphs.upenn.edu

KEYWORDS

- Overweight
- Obesity
- Women
- Bariatric

KEY POINTS

- Obesity is a multifactorial disease process that affects women differently than men.
- Severe obesity is more common in women.
- Complicated gastroesophageal reflux disease (GERD) is less common in women.
- Obesity adversely affects fertility, conception, and maternal and fetal pregnancy outcomes.
- Obesity-related diet and exercise counseling should take into consideration gender differences in the epidemiology, pathophysiology, and clinical manifestations of obesity.

Gastroenterol Clin N Am 45 (2016) 317–331
http://dx.doi.org/10.1016/j.gtc.2016.02.008
gastro.theclinics.com

0889-8553/16/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
All demographic segments of society, including age, race/ethnicity, and gender, have been impacted by the obesity epidemic. Overall, the prevalence of obesity is similar in women and men, with approximately one-third of adults in the United States being obese. Gender disparities in the prevalence of obesity have been described, however, in certain subpopulations. For example, when different racial groups are examined, obesity is more prevalent in non-Hispanic African American women than men (57% vs 37%, respectively). This gender disparity is not observed, however, in non-Hispanic whites, Hispanics, or Asians. Obesity also seems more prevalent in older women (age >60) than men. Furthermore, more severe forms of obesity affect women more commonly than men. The reasons for the epidemiologic gender disparities in obesity are unclear but may result from the culmination of pathophysiologic and sociologic differences between genders.

PATHOPHYSIOLOGY

Obesity is thought to be the result of a multifactorial process driven primarily by excessive energy/caloric intake and inadequate physical activity. There are a minority of individuals affected by monogenetic disorders where a single gene mutation leads to obesity. Researchers have proposed gender-specific physiologic and biochemical differences, among other factors, to explain differences in excessive body weight in women and men.

Aspects of energy intake, utilization, and storage differ between women and men (Fig. 1). Gender differences in energy metabolism have been reported, with studies showing a higher resting metabolic rate in men compared with women. In terms of
fat storage, the less metabolically active form of fat, subcutaneous fat, is predominant in women. Meanwhile, visceral fat, which is more metabolically active, predominates in men. These factors favor a propensity for fat storage in a distribution that favors obesity in women more so than men. Furthermore, biochemical differences, such as higher circulating levels of leptin and adiponectin, both of which are involved in the regulation of food intake and satiety, have been described in women. Sex hormones may also play a role in the differential expression of obesity in women and men. Later in life, the proandrogen hormonal profile that is characterized by low levels of estrogen and increased levels of androgens has been observed in perimenopausal and postmenopausal women. This hormone shift favors body fat redistribution with increased visceral fat, a phenotype that is seen in men and correlates with the higher prevalence (although not statistically significant) of obesity in women over 60 years of age.

Studies that examine eating behavior with respect to gender show that women exhibit significantly higher cognitive restraint, disinhibition scores, and hunger scores. It has also been reported that a greater proportion of women tend to engage in dieting behavior than men. Studies also show that in women, however, a history of dieting is positively associated with weight gain. It is possible that certain eating behaviors, such as cognitive restraint, are difficult to maintain and may result in increased fat intake and bingeing.

**SOCIOLOGY**

Obesity is associated with a negative social stigma while societal standards of beauty have not evolved in parallel with the obesity epidemic. In general, women tend to be held to a different beauty aesthetic than men, which may influence the aforementioned
behaviors related to food intake. Although obesity is common, studies show that weight-related bias is pervasive in workplaces, health care systems, interpersonal relationships, and the media, although it is unclear if gender differences in weight-related bias exist. The notion that weight is not modifiable contradicts the societal stigma of obesity. There are few data to confirm that society at large believes that weight is not modifiable, although a recent study showed that individuals who believed that weight is unchangeable had poor health practices. Gender was not associated with belief in weight changeability or exercise/dietary behavior. When compared with men, women are more likely to (1) be dissatisfied with their weight, (2) be dissatisfied with their body, and (3) associate body image with self-esteem. Nonetheless, positive body image has been shown an indicator of positive mental and physical health indices in both women and men. From a societal perspective, promoting the concept of self-acceptance and positive body image may ultimately translate into more widespread adoption of healthy lifestyle practices.

**OBESITY-ASSOCIATED GASTROINTESTINAL DISEASE**

**Gastroesophageal Reflux Disease**

Obesity is a known risk factor for GERD. Given the established association between obesity and GERD, it is not surprising that the global obesity epidemic has been accompanied by an increased burden of symptomatic GERD and its complications. Although the existing literature suggests a similar prevalence of symptomatic GERD in women and men, GERD complications, such as erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma, are less common in women.

Of the factors that contribute to GERD, increased abdominal pressure is often present in obesity. Central or abdominal adiposity results in increased abdominal pressure and is a risk factor for GERD complications independent of body mass index (BMI). Central adiposity is less common in women than men and may explain the lower prevalence of such complications in women. The role of sex hormones has been implicated to explain the different manifestations of GERD in women and men. Menon and colleagues showed, however, that increased estradiol levels were associated with physiologic GERD even when controlling for BMI.

Medical management, including behavioral modifications and acid suppressive therapy, is effective in ameliorating GERD symptoms. The association drawn between BMI and GERD has led to an emphasis on weight reduction as an important part of the behavioral modifications for GERD. One systematic review concluded that weight loss resulting from surgical or diet/lifestyle interventions can reduce or eliminate the symptoms of GERD while noting (1) a dose-response relationship between the degree of weight loss and resolution of GERD symptoms and (2) that women have a lower threshold for weight loss to achieve symptom improvement compared with men (5%–10% vs >10% weight reduction).

Obesity is a risk factor for GERD, which is similar in prevalence in women and men. Women are less likely to develop complications of GERD, however, and more likely to derive benefit from smaller amounts of weight loss than men.

**Nonalcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease (NAFLD) is often described as the hepatic manifestation of the metabolic syndrome, which involves insulin resistance, lipid metabolism, and obesity. Studies show strong correlations between NAFLD and obesity in women. In a large cohort study of more than 9300 women in China, 48% of obese
women had NAFLD compared with 12.8% of the general population of women. Although the prevalence of NAFLD is similar in women and men, NAFLD is less common in premenopausal women versus age-matched men, perhaps due to a pathologic process involving the hormonal effects on fat distribution.

Although the pathogenesis of NAFLD remains an area of active research, it is known that the pattern of liver injury involves steatosis and cytotoxic liver injury. In obese individuals, the biochemical effects of increased body weight depress certain molecular anti-inflammatory pathways in the liver, enabling NAFLD to progress. Sex hormones are also linked to obesity and NAFLD. Perimenopausal and postmenopausal women have lower levels of estrogen and increased levels of androgens, a hormonal profile that favors the development of the metabolic syndrome and NAFLD via increased visceral fat deposition. The suggested protective effect of female sex hormones is corroborated by the epidemiologic findings that (1) there is a lower prevalence of NAFLD in premenopausal women compared with men of the same age, (2) women with NAFLD have significantly lower levels of serum estradiol compared with those without NAFLD, and (3) women older than age 50 have a higher prevalence of NAFLD than those younger than 50. It has been suggested that increased concentrations of estrogen inhibit the spontaneous secretion of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor α, and possibly exert an antifibrogenic effect on the liver. Further studies of the pathophysiological link between obesity and gender may provide better insight into therapeutic targets for treating NAFLD.

Although studies suggest that hormone replacement therapy (HRT) may be beneficial in treating NAFLD, to date there have been no prospective studies investigating this therapy. Weight loss is typically recommended for obese patients with NAFLD; however, the impact on the natural history of the disease is unclear. Modest weight loss of 5% to 10% or more of body weight can correct abnormal liver chemistries and decrease liver size, fat content, and features of steatohepatitis. Rapid weight loss after gastric bypass surgery, very-low-calorie diets, or prolonged fasting, however, lowers hepatic fat content but can induce hepatic inflammation, thereby worsening steatohepatitis. Because women are more likely than men to diet and undergo bariatric surgery, gastroenterologists should be aware of their risk for this complication and emphasize the importance of slow, gradual as opposed to rapid, weight loss.

NAFLD in women is also linked to diabetes mellitus, the metabolic syndrome, low estrogen levels, and elevated androgen levels. Premenopausal women have a lower prevalence of NAFLD, likely due to the protective effect of estrogen. Effective treatment of NAFLD includes slow, gradual weight loss, which is favored over rapid weight loss that is seen with very-low-calorie diets.

Gallstone Disease

The link between gallstones and both women and obesity is well established. Gallstone disease is approximately 2 to 3 times more common in women than in men. The Nurses’ Health Study showed that elevated BMI is strongly linked to gallstone disease in women. Given the elevated risk for gallstone formation, particularly in obese women, researchers have worked to elucidate the pathways of gallstone formation in this high-risk group.

Cholesterol gallstones form with cholesterol saturation of bile and reduced gallbladder emptying. In obesity, cholesterol saturation of bile may occur as a result of dietary intake. Low-calorie/low-fat diets are linked to an increased likelihood of gallstone formation compared with a low-calorie/high-fat diet with the same weight loss. Although the weight loss process can increase the formation of gallstones, elevated
BMI is an independent risk factor for gallstone disease in women, and the successful reduction of BMI is associated with a lower the risk of future gallstone development. Similar to weight loss rates, hormonal influences have been linked to increased bile cholesterol saturation, which may result in gallstones. It is known that the gravidity of women is a predictor of gallstone formation. The high risk of gallstone formation in women is primarily observed in women of childbearing age. Estrogen is known to increase biliary cholesterol secretion, causing cholesterol supersaturation of the bile. This hormonal link to gallstone formation has also been invoked to explain the increased incidence of gallstones in other states of high estrogen levels, such as in postmenopausal women on hormone replacement therapy as well as in women using oral contraceptives. This relationship may be dose dependent, because women using low-estrogen oral contraceptives do not have an increased incidence of gallstones.

In light of the risk of gallstone formation with obesity and rapid weight loss, women should be encouraged to strive for slow, gradual weight reduction (2.2 kg per week). Primary prevention of gallstones can be achieved with pharmacologic agents, such as ursodeoxycholic acid, and has been used by some during periods of rapid weight loss, like postbariatric surgery. Because women are more likely than men to undergo postbariatric surgery, some investigators advocate the use of ursodeoxycholic acid after bariatric surgery.

Gallstone disease is significantly more prevalent in women than in men and is strongly linked to obesity. Both rapid weight loss and high estrogen levels are associated with the development of gallstones. Gradual weight loss and pharmacotherapy with ursodeoxycholic acid are both effective at preventing gallstone formation in obese women.

**OBESITY IN REPRODUCTIVE HEALTH**

**Conception**

Epidemiologic data suggest that obesity negatively affects reproductive health. One study showed that obesity was more prevalent in a cohort of women seeking medical attention to become pregnant. In addition, the time required to achieve a spontaneous pregnancy is longer and pregnancy rates are lower in obese women, including obese women with regular ovulation. The risk of infertility is 3-fold higher in obese women than in nonobese women in both natural and assisted conception cycles. Although weight loss can improve fertility, the benefits of weight loss are best seen in women under 35 years old.

The pathophysiologic impact of obesity on reproduction is a complex, multifactorial process and ranges from menstrual dysfunction to infertility. Specifically, obesity is associated with (1) oligo-ovulation/anovulation, (2) abnormal oocyte recruitment/ovulation and poor oocyte quality, (3) poor embryo quality and development, and (4) decreased uterine receptivity and embryo implantation. Several biochemical alterations in obese women may explain the physical manifestations. First, white adipose tissue regulates energy homeostasis and metabolism by secreting adipokines, leading to insulin resistance. The resulting hyperinsulinemia stimulates ovarian androgen production and increases peripheral aromatization of sex hormones. Conversion of excess androgens to estrogens in adipose tissue leads to increased free estrogen, which impairs the hypothalamic-pituitary-gonadal axis. The hypothalamic-pituitary-gonadal axis is further impaired by decreased luteinizing hormone, androstenedione, estrone, insulin, triglycerides, and very low-density lipoprotein. These factors may alter gonadotropin-releasing hormone secretion (via negative feedback), altering follicular development and leading to irregular or anovulatory cycles.
Pregnancy

As seen in the general population, the prevalence of obesity in pregnant women has dramatically increased since the early 1990s, and now 28% of pregnant women are obese. Obesity affects both maternal and fetal pregnancy outcomes (Table 2).

Pregnancy outcome is influenced by obesity and is associated with an increased risk of first-trimester and recurrent miscarriage. Specifically, a meta-analysis showed that a BMI over 25 kg/m² carries a higher risk of miscarriage independent of mode of conception. The exact pathophysiology for the link between obesity and miscarriage is unclear but may involve poor oocyte quality, deranged ovarian function, and/or endometrial function. A strong link has also been seen between obesity and stillbirth. Late, unexplained stillbirth is associated with increasing BMI in obese women compared with normal weight women. Although the data vary, a recent meta-analysis reported a 20% increased risk of stillbirth in obese women that increased with greater degree of obesity. The risk of fetal and neonatal death is also increased in obese women. Obesity is associated with prolonged and post-term pregnancy (beyond 41 weeks’ gestation and at or beyond 42 weeks’ gestation, respectively), which may be explained by inaccurate estimation of gestational dating in obese women. Another possibility is that elevated estrogen levels in obese women compared with nonobese women may hinder the onset of spontaneous labor.

Hypertensive disorders of pregnancy are more common with increased maternal weight. Observational studies demonstrate a 2.5-fold to a 3.2-fold increased risk of hypertensive disorders in obese women. In particular, obesity is linked to pre-eclampsia with elevated prepregnancy BMI a dose-dependent, independent risk factor for preeclampsia. Although unclear, the pathogenesis of preeclampsia

| Table 2 |
| Maternal and fetal complications of pregnancy in overweight and obese women |
| Preconceptual period | • Subfertility/infertility |
| | • Menstrual disorder |
| Antenatal period | • Miscarriage (including recurrent) |
| | • Stillbirth |
| | • Fetal anomalies |
| | • Difficulty with ultrasound assessment of fetus |
| | • GDM |
| | • Preeclampsia |
| Intrapartum | • Prolonged pregnancy |
| | • Need for induction of labor |
| | • Stillbirth (unexplained) |
| | • Caesarean section |
| | • Anesthesia difficulties |
| | • Postpartum hemorrhage |
| | • Difficulty with fetal monitoring |
| | • Fetal macrosomia |
| | • Shoulder dystocia |
| | • Fetal distress |
| | • Perinatal morbidity and mortality |
| | • Birth injury |
| Postpartum | • Thromboembolism |
| | • Wound infection |
| | • Difficulty with breastfeeding |
| Long term | Risk for long-term diabetes mellitus, hypertension, cardiovascular disease |
may involve insulin resistance, endothelial cell activation, dyslipidemia, and elevated cytokines, such as tumor necrosis factor.

Likewise, gestational diabetes mellitus (GDM) is more common in obese women and the risk of GDM increases in a dose-dependent fashion as well.\textsuperscript{53,54} GDM and suboptimal glycemic control can lead to fetal macrosomia and an increased risk of caesarean delivery and birth trauma (eg, perineal tears, shoulder dystocia, and asphyxia).\textsuperscript{59} Furthermore, GDM increases maternal risk for developing diabetes mellitus later in life and is a predictor of developing the metabolic syndrome by 10 years postpartum.\textsuperscript{39} Lastly, obese women are at increased risk for venous thromboembolism during pregnancy. Obesity compounds the pregnancy-related hypercoagulable state through its effect on clotting factors, impeding venous return through adipose tissue deposition and immobility, and endothelial cell damage.\textsuperscript{54}

The preconception, pregnancy, and postpartum periods can influence the mother and the infant. Gestational weight gain (GWG) usually persists postpartum in women and increases with increasing parity. Persistent GWG can result in central adiposity, dyslipidemia, and glucose intolerance, leading to obesity, type 2 diabetes mellitus, the metabolic syndrome, and potentially cardiovascular disease (Fig. 2).\textsuperscript{39} In addition, excessive maternal gain between the first and second pregnancies is associated with increased risks of preeclampsia, large-for-gestational-age birth, caesarean delivery, and future GDM.\textsuperscript{60}

---

**Fig. 2.** Metabolic consequences of excess GWG and postpartum weight retention in reproductive age women. (Adapted from Gilmore LA. Pregnancy as a window to future health: excessive gestational weight gain and obesity. Semin Perinatol 2015;39:301; with permission.)
Maternal obesity is associated with an increased risk of fetal anomalies, including neural tube defects, spina bifida, congenital heart defects, orofacial clefts, anorectal atresia, hydrocephaly, limb reduction defects, diaphragmatic hernia, and omphalocele.\textsuperscript{53,54} Congenital anomalies are perhaps more likely in gestational obesity due to undiagnosed diabetes mellitus, reduced dietary folate intake, and/or the technical limitations of visualizing defects by prenatal ultrasound.\textsuperscript{61}

Obesity is also a risk factor for fetal macrosomia (even in the absence of diabetes mellitus) and intrauterine fetal growth restriction.\textsuperscript{53,54} Furthermore, greater degrees of maternal weight gain during pregnancy are associated with increased infant birth weight.\textsuperscript{62}

In the intrapartum period, monitoring contractions and assessing the progression of labor can be challenging in obese women. Manual palpation and/or external tocodynamometry are difficult, and fetal scalp electrode monitoring is frequently needed. To this end, maternal obesity is linked to longer labor inductions, longer or dysfunctional labor, failure of regional anesthesia, and increased risk of emergent and complicated cesarean delivery.\textsuperscript{53}

In the postpartum period and beyond, initiation and duration of breastfeeding reduced gestational obesity.\textsuperscript{63,64} Difficulty obtaining correct positioning and impaired prolactin response to suckling have been proposed mechanisms for this phenomenon.\textsuperscript{65} Long term, there is a growing body of literature suggesting that the in utero environment can predict future neonatal, child, and adult health.\textsuperscript{66} Infants born to obese mothers are at increased risk of developing childhood obesity and type 2 diabetes mellitus.\textsuperscript{67} In a large cohort of more than 8400 children, Whitaker\textsuperscript{68} showed that children of obese mothers were twice as likely to be obese by age 2.

**Menopause**

Menopause refers to the last physiologic menstrual period in a woman’s life, during which time the loss of ovarian estrogen causes vasomotor symptoms of hot flushes, night sweats, insomnia, depression, vaginal dryness, and dyspareunia. The age at menopause and body mass are not clearly associated.\textsuperscript{69} Some studies report later age of natural menopause with increased BMI and upper body fat distribution,\textsuperscript{70,71} whereas others refute this association.\textsuperscript{72,73}

Women with more abdominal adiposity are more likely to report vasomotor symptoms during the transition to menopause.\textsuperscript{74} One possible explanation is that adipose tissue functions as an insulator, thereby affecting normal thermoregulatory mechanisms of heat dissipation.\textsuperscript{69} Another explanation is that adipose tissue may have an endocrine function that influences vasomotor symptoms.\textsuperscript{75} Vulvovaginal atrophy is another common symptom of menopause that is related to estrogen deficiency that more commonly causes vaginal dryness, dyspareunia, itching, and irritation in obese women.\textsuperscript{76}

Weight gain and changes in the distribution of adipose tissue after menopause may be, in part, due to the dramatic fall in serum estrogen levels and relative hyperandrogenism. Weight gain and obesity in midlife women, however, seem related more to age and a more sedentary lifestyle rather than to menopause.\textsuperscript{51,69} Results from human studies show that postmenopausal women had significantly greater reductions in their physical activity compared with their premenopausal controls.

**TREATMENT/MANAGEMENT OF OBESITY**

Despite the widely recognized obesity epidemic and its societal impact, obesity tends to be underdiagnosed by health care providers, with only one-third of obese patients receiving a diagnosis.\textsuperscript{77} Female gender, however, is a positive predictor of being
diagnosed as obese. Diet, behavioral modifications, and exercise are the mainstays of treatment of obesity, undoubtedly because of the known positive impact of modifiable health behaviors on overall morbidity and mortality. Although an obesity diagnosis is a positive predictor of receipt of diet/nutrition, exercise, and weight reduction counseling from a health care provider, such counseling is provided to only a minority (20%–30%) of obesity individuals and there seems a difference between women in men in receipt of counseling. One study did, however, show that diet/nutrition and exercise counseling is more likely to occur in male gender concordant patient provider pairs compared with female gender concordant pairs, a finding perhaps explained by the perception by health care providers that women are more sensitive about weight and less amenable to weight-related discussions.

Diet/Exercise/Behavioral Modifications

Some literature suggests that women are more likely to engage in positive health behaviors, like eating a healthy diet. Likewise, the concept of dieting is more common in women and is not surprising because women are more likely to be dissatisfied with their body and weight. It is unclear from the existing literature that exercise practices are different between genders, but limited data suggest that the effect of exercise may differ with respect to gender and exercise type. For example, aerobic exercise has been shown to lead to greater weight loss in men. In a randomized control trial, Sanal and colleagues recently showed that aerobic-resistance exercise was effective in reducing the fat free mass in the upper/whole body and trunk in men, whereas fat free mass was only reduced in the lower body of women. Such data can be used as a guide for prescribing gender-specific, tailored exercise regimens.

Bariatric Surgery

Bariatric surgery is a well-established means of weight loss that is both effective and durable. Although obesity is equally prevalent in women and men, and men have greater obesity-related comorbidities, women comprise the majority of the bariatric surgery population. One study noted that women who underwent bariatric surgery had a lower baseline BMI and mean age. In terms of outcomes, there is no reported difference in weight loss between genders during the first 3-year after bariatric surgery. In 1 study, however, male patients who underwent laparoscopic adjustable gastric banding had greater BMI reduction than female patients (−8.2 ± 4.3 kg/m² vs −3.9 ± 1.9 kg/m²; P = .02). Furthermore, complications of bariatric surgery are also reportedly higher in men compared with women but it is unclear that this finding influences the selection of bariatric surgery candidates.

SUMMARY

Although on the surface obesity affects women and men in similar proportions, there are stark differences in how obesity develops and manifests itself in the 2 genders. More severe forms of obesity affect women at a higher rate, which underscores the need for health care providers, and gastroenterologists in particular, to identify and recommend treatment of obese women.

Comorbid gastrointestinal diseases like GERD and NAFLD affect women differentially, whereas gallstone disease is highly prevalent in women. Obesity similarly has adverse effects on the reproductive health of women as well ranging from impaired fertility and conception to pregnancy complications, such as preeclampsia, GDM, fetal anomalies, and macrosomia.
Lastly, given the impact of obesity, efforts should focus not only on understanding the pathophysiologic mechanisms but also on effective, gender-specific treatment strategies that begin with accurate diagnosis of obesity and, thereafter, offering weight-related counseling and referrals for bariatric surgery when appropriate. Given the female predominance of the bariatric surgery population, gastroenterologists must be well versed in the care of patients after bariatric surgery. In light of the known gender-specific biochemical differences in dietary intake, metabolism, and storage of energy, gastroenterologists are uniquely positioned to influence the management of obese patients.

REFERENCES


40. Vahratian A, Smith YR. Should access to fertility-related services be conditional on body mass index? Hum Reprod 2009;24:1532–7.


