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The effects of obesity on the menstrual cycle

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A B S T R A C T

The prevalence of childhood and adolescent obesity has significantly increased in the United States and worldwide since the 1970s, a trend that has been accelerated by the COVID-19 pandemic. The complications of obesity range from negative effects on the cardiovascular, endocrine, hepatobiliary, and musculoskeletal systems to higher rates of mental health conditions such as depression and eating disorders among affected individuals. Among adolescent girls, childhood obesity has been associated with the earlier onset of puberty and menarche, which can result in negative psychosocial consequences, as well as adverse effects on physical health in adulthood. The hormones leptin, kisspeptin and insulin, and their actions on the hypothalamic-pituitary-ovarian axis, have been implicated in the relationship between childhood obesity and the earlier onset of puberty. Obesity in adolescence is also associated with greater menstrual cycle irregularity and the polycystic ovary syndrome (PCOS), which can result in infrequent or absent menstrual periods, and heavy menstrual bleeding. Hyperandrogenism, higher testosterone and fasting insulin levels, and lower levels of sex hormone-binding globulin, similar to the laboratory findings seen in patients with PCOS, are also seen in individuals with obesity, and help to explain the overlap in phenotype between patients with obesity and those with PCOS. Finally, obesity has been associated with higher rates of premenstrual disorders, including premenstrual syndrome and premenstrual dysphoric disorder, and dysmenorrhea, although the data on dysmenorrhea appears to be mixed. Discussing healthy lifestyle changes and identifying and managing menstrual abnormalities in adolescents with obesity are key to reducing the obstetric and gynecologic complications of obesity in adulthood, including infertility, pregnancy complications, and endometrial cancer.

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Introduction

Obesity in childhood and adolescence has been linked to a myriad of adverse health consequences, including insulin resistance and type 2 diabetes mellitus, hypertension, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), gallbladder disease, pseudotumor cerebri, slipped capital femoral epiphysis (SCFE) and Blount disease, depression, and disordered eating. Among adolescent females, the neuroendocrine effects of obesity manifest as earlier onset of puberty and menarche, hyperandrogenism leading to irregular or absent menses, abnormal uterine bleeding, polycystic ovary syndrome (PCOS), and higher rates of dysmenorrhea and premenstrual disorders. This chapter will provide an overview of the effects of obesity on adolescent menstrual cycles, with a review of the literature, pathophysiology, and implications for gynecologic and mental health.

Background

In the United States, childhood and adolescent obesity is defined as a body mass index (BMI) at or above the 95th percentile on Centers for Disease Control and Prevention (CDC) growth charts, while severe obesity is defined as a BMI at or above 120 percent of the 95th percentile[1]. Similarly, the World Health Organization (WHO) defines obesity as a BMI-for-age greater than 2 standard deviations above the WHO Growth Reference median for children ages 5 to 19 years[2]. Data from the United States National Health and Nutrition Examination Surveys (NHANES) has demonstrated increases in the prevalence of obesity among children and adolescents ages 2 to 19 years in recent decades, from 5.2 percent in the 1971-1974 survey period to 19.3 percent, or almost one in five children, in the 2017-2018 survey period[1]. Similarly, the prevalence of severe obesity in this age group increased from 1.0 percent in the 1971-

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1974 survey period to 6.1 percent in the 2017-2018 survey period[1]. Importantly, the presence of racial and ethnic disparities in the prevalence of obesity in American youth results in African American and Hispanic youth being disproportionately affected compared to Caucasian and Asian youth[3]. Data from the 2013-2016 NHANES demonstrated significantly higher obesity prevalence in non-Hispanic black youth (20.4 percent) and Hispanic youth (23.6 percent) compared to non-Hispanic white youth (14.7 percent) and non-Hispanic Asian youth (9.8 percent)[4]. The COVID-19 pandemic has further exacerbated these healthcare disparities[5]. In one study, almost 25 percent of Hispanic, non-Hispanic Black, publicly insured, or lowest income quartile patients seen during the pandemic were obese, compared to 11.3 percent of non-Hispanic white patients, 12 percent of patients with commercial insurance, and 9.1 percent of highest income quartile patients[5].

Similar trends towards increasing obesity prevalence have been seen across the world, with the WHO estimating that worldwide obesity has almost tripled since 1975, with over 340 million children and adolescents ages 5 to 19 years meeting criteria for overweight or obesity in 2016[2].

Gynecologic consequences of obesity

The gynecologic complications of obesity can be seen across a woman's reproductive lifespan. Beginning with the earlier onset of puberty and menarche, which can result in adverse mental health and psychosocial consequences for girls, to higher rates of irregular menses, amenorrhea, abnormal uterine bleeding, PCOS, dysmenorrhea, and premenstrual disorders in adolescence and adulthood, and greater risks of infertility, pregnancy complications, breast and endometrial cancers, obesity can have a multitude of deleterious effects on women's health [6-8]. This chapter will focus on the effects of obesity on the timing of puberty and menarche, menstrual cycle regularity and the relationship with PCOS, and associations with dysmenorrhea, premenstrual disorders, and heavy menstrual bleeding.

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Impact of obesity on the timing of puberty and menarche

The onset of puberty and menarche in girls is determined by a combination of genetic and environmental factors. Since the 19th century, improvements in health and nutritional status, among other socio-economic and geographic factors, have resulted in secular trends towards earlier onset of puberty and earlier age at menarche in girls[9,10]. However, since the 1970s, the increasing prevalence of obesity has correlated with an even earlier onset of puberty and menarche in girls across the world, and it has been hypothesized that obesity and increased adiposity have directly contributed to this phenomeon[11-15]. A recent systematic review and meta-analysis found that age at thelarche, the first clinical sign of puberty in females, has decreased by a mean of almost 3 months per decade from 1977 to 2013[16]. The study additionally found that the median age of thelarche varied by geographic location, with girls in the United States experiencing thelarche at the youngest ages (8.8 to 10.3 years) and girls in Africa experiencing thelarche at the oldest ages (10.1 to 13.2 years)[16]. Similarly, recent data from the 2013-2017 National Survey of Family Growth

(NSFG) found that the median age at menarche in the United States had decreased to 11.9 years, with more girls experiencing menarche at younger ages, compared to previous decades[17].

Studies examining the relationship between higher BMI and adiposity in childhood and the earlier onset of puberty and menarche in girls have found a positive association between higher weight status in childhood and earlier timing of puberty. One study of 354 girls in the United States found that higher BMI z score at 3 years of age and a higher rate of change of BMI between 3 years of age and grade 1 were associated with earlier onset of puberty[18]. Similarly, a study following 183 girls from ages 5 to 9 years found that girls with a higher percent body fat at age 5 years, and girls with higher percent body fat, higher BMI percentile, or larger waist circumference at age 7 years, were more likely to have pubertal development by age 9 years[19]. The researchers also found that larger increases in percent body fat between ages 5 to 9 years, and larger increases in waist circumference between ages 7 to 9 years, were associated with pubertal development at age 9 years[19]. Finally, an analysis of NHANES survey data evaluating the attainment of puberty and menarche in girls with normal and excessive BMI (defined as >84th percentile) found that girls with excessive BMI were more likely to experience thelarche by age 8 to 9.6 years, pubarche by age 8 to 10.2 years, and menarche by age 10.6 to 12.9 years compared to normal weight girls[20].

Studies examining the relationship between nutritional status/obesity and age at menarche have similarly demonstrated an inverse relationship between BMI and age at menarche

Studies examining the relationship between nutritional status/obesity and age at menarche have similarly demonstrated an inverse relationship between BMI and age at menarche [21-24]. One longitudinal study of almost 1000 girls in the United States found that girls with an overweight or obese BMI at baseline achieved menarche 0.3 years earlier compared to normal weight girls, while girls who were underweight at baseline achieved menarche 0.5 years later than normal weight girls[21]. Additional studies have demonstrated an association between higher BMI and earlier age at menarche (< 12 years old) in girls[21,24].

The earlier onset of puberty and menarche can have multiple physical and psychosocial implications for adolescent girls. Early puberty and younger age at menarche have been associated with a higher risk of obesity, type 2 diabetes mellitus, and cardiovascular disease in adulthood, as well as shorter adult height, increased postmenopausal breast cancer risk, and higher all-cause mortality[25-31]. Additionally, girls who experience early puberty and menarche are more likely to have behavioral issues during adolescence, have earlier sexual experiences, and abuse substances, and they are more likely to report depressive symptoms, self-harm behaviors, and disordered eating[32-38].

Pathophysiology

The onset of puberty is marked by the pulsatile release of gonadotropin-releasing hormone (GnRH) from neurons in the hypothalamus, the result of a complex neuroendocrine network with numerous internal and external signals[39]. GnRH stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary, which act on ovarian theca and granulosa cells, respectively, resulting in ovarian production of androgens and estradiol. Feedback loops in the hypothalamic-pituitary-ovarian (HPO) axis result in the onset and maintenance of menstrual cycles.

The mechanism behind the initiation of the pulsatile release of GnRH has yet to be elucidated, although it has been hypothesized that kisspeptin neurons within the arcuate nucleus use the neuropeptides neurokinin B and dynorphin to signal to GnRH neurons, resulting in the pulsatile secretion of gonadotropins[39]. Thus, the role of kisspeptins, peptides encoded by the *Kiss1* gene, appears to be vital to the onset and normal progression of puberty[40].

Nutritional status remains an important indicator for the onset of puberty and menarche. It has been hypothesized that a "critical body weight" is necessary to trigger the onset of puberty[41]. The effects of leptin, a hormone secreted by adipocytes, on both puberty and reproduction have been widely studied. Leptin provides information on an organism's nutritional

status to the GnRH neuronal system, acting indirectly on GnRH neurons via stimulation of *Kiss1* neurons, and appearing to act as a permissive factor in the initiation and progression of puberty rather than the primary signal for the onset of puberty[25,40,42,43]. Levels of leptin in children with obesity have been found to be elevated, correlating with adiposity and BMI, suggesting a possible neuroendocrine mechanism for the earlier onset of puberty and menarche seen in these children[44]. A study of 343 girls evaluating body composition, serum leptin levels, and timing of menarche confirmed an inverse relationship between leptin levels and age at menarche[45]. The researchers additionally found a strong association between leptin levels and body fat and BMI[45]. Similarly, a cross-sectional study of 22 prepubertal obese girls found significantly higher kisspeptin and leptin serum levels in the obese girls compared to healthy weight controls, further demonstrating the relationship between adiposity, leptin, and kisspeptin[46].

Additional endocrine mechanisms for the earlier onset of puberty and menarche seen in obese girls include increased aromatization of androgens to estrogen in adipose tissue, resulting in earlier thelarche, and the effects of hyperinsulinemia on sex steroid bioavailability[6]. Specifically, insulin resistance in obesity leads to compensatory hyperinsulinemia, which increases the bioavailability of sex steroids by stimulating the production of androgens by the ovaries and adrenal glands, reducing hepatic synthesis of sex hormone-binding globulin (SHBG), and increasing aromatase activity in adipocytes[25]. The association between obesity and hyperandrogenism in adolescent girls will be further discussed in the next section.

Impact of obesity on menstrual cycles and risk of PCOS

In addition to the earlier onset of puberty and menarche, obesity is also associated with irregular and infrequent menstrual cycles, amenorrhea, anovulation, PCOS, and heavy menstrual bleeding in both adolescence and adulthood [6,8,47]. A large study of 1516 adult participants from the Australian Childhood Determinants of Adult Health Study (CDAH) and 1247 adult participants from the United States Bogalusa Heart Study (BBS) found that childhood obesity was associated with an increased risk of menstrual irregularities in adulthood[47]. Additionally, an association between childhood obesity and PCOS in adulthood was demonstrated in the CDAH study, while in the BBS study, the association between childhood obesity and PCOS in adulthood was demonstrated for white, but not black, participants[47]. Similarly, obesity in adulthood is associated with irregular menstrual cycles[48,49]. One study of 726 Australian women aged 26-36 years found that women with higher BMIs ($\geq$25 kg/m^2), higher waist circumferences (greater than 80 cm), and higher waist-to-hip ratios (indicative of central adiposity) were more likely to have irregular menstrual cycles[48]. Specifically, women with obesity (BMI $\geq$30 kg/m^2) were twice as likely as normal weight women to have an irregular menstrual cycle. Furthermore, women with higher waist circumferences and waist-to-hip ratios were more likely to have long cycles (greater than 35 days). Importantly, the study found that BMI, waist circumference, and waist-to-hip ratio were positively associated with fasting insulin and testosterone levels and the free androgen index, and negatively associated with SHBG levels. Higher levels of testosterone, and the free androgen index, and lower levels of SHBG, were, in turn, associated with higher likelihood of long and irregular menstrual cycles.

Obesity in childhood and adolescence also results in greater menstrual cycle irregularity for adolescent girls. While anovulatory cycles are initially common in adolescents following menarche, the majority of adolescent menstrual cycles will be 21 to 45 days in length, even in the first gynecologic year[50]. One study of 835 adolescent girls found that those with higher BMI and percentage body fat were more likely to experience irregular menstrual cycles and have higher ovarian volumes compared to girls with lower BMI and lower percentage body fat, suggesting a possible link to the development of PCOS[51]. Similarly, a study of 25 adolescent girls with obesity undergoing bariatric surgery found a high prevalence of menstrual disorders in that cohort[52]. Specifically, the researchers found that 36 percent of the girls had

In addition to the earlier onset of puberty and menarche, obesity is also associated with irregular and infrequent menstrual cycles, amenorrhea, anovulation, PCOS, and heavy menstrual bleeding in both adolescence and adulthood

PCOS, 32 percent had oligomenorrhea, and 28 percent had menorrhagia, all higher rates than those in the general population.

Pathophysiology

The metabolic and neuroendocrine mechanisms behind the menstrual irregularities observed in obese adolescent girls and adult women share several common features with PCOS. PCOS, the most common endocrinopathy in young adult women and the most common cause of anovulatory infertility, is a heterogeneous syndrome characterized by hyperandrogenism and ovulatory dysfunction[53-55]. Symptoms of PCOS often begin in adolescence, with ovulatory dysfunction manifesting as amenorrhea, oligomenorrhea, or abnormal uterine bleeding. Forty to 80 percent of patients with PCOS are overweight or obese, and up to 80 percent of patients have clinical (acne, hirsutism) or biochemical (elevated free and total testosterone and androstenedione levels) evidence of androgen excess[53]. PCOS is characterized by aberrations in the HPO axis and hyperinsulinemia, resulting in elevated circulating levels of androgens in affected patients[55]. Specifically, rapid GnRH pulse frequency favors LH secretion from the anterior pituitary while limiting FSH secretion, resulting in relative FSH deficiency. Increased LH pulse frequency and amplitude results in excess production of LH, which stimulates the production of androgens by ovarian theca cells. Hyperinsulinemia in PCOS, exacerbated by obesity, further stimulates ovarian androgen production, increases adrenal androgen production, and inhibits the hepatic synthesis of SHBG, thereby contributing to hyperandrogenemia[55]. Relative FSH deficiency leads to follicular growth arrest, manifesting as the presence of multiple small follicles, but no dominant follicle, and anovulation. Laboratory findings in patients with PCOS typically demonstrate elevated free and total testosterone levels, an elevated androstenedione level, a low SHBG level, mildly elevated dehydroepiandrosterone sulfate (DHEAS), and occasionally an elevated LH to FSH ratio[53]. Ovarian ultrasound, which may reveal an increased ovarian volume with multiple small follicles in adult women, is not recommended for the diagnosis of PCOS in adolescents[53].

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The presence of insulin resistance and the metabolic syndrome in individuals with obesity and excess adiposity helps to explain the overlap in phenotype between obese girls with irregular menses and women with PCOS[56,57]. The metabolic syndrome, characterized by hyperglycemia, dyslipidemia, central adiposity, and hypertension, is seen in both patients with obesity and PCOS, with the common finding of insulin resistance leading to compensatory hyperinsulinemia[56]. Multiple studies have demonstrated that obesity and central adiposity are associated with similar hormonal abnormalities as those seen in PCOS, namely elevated insulin and testosterone levels, and low SHBG levels[58-60]. A study evaluating sex steroid concentrations in 74 peripubertal girls with obesity (BMI $\geq 95^{th}$ percentile) compared to 30 normal weight girls found significant hyperandrogenism throughout puberty in the obese girls, particularly during Tanner stages 1, 2, and 3[61]. In prepubertal (Tanner 1) obese girls, the mean total testosterone was 4.5-fold higher compared to normal weight girls, and in Tanner 2 and 3 girls, it was 1.6- and 3.3-fold higher, respectively. Furthermore, mean SHBG levels were 59 to 69 percent lower in obese Tanner 1, 2, and 3 girls, resulting in higher levels of mean free testosterone in those study participants. Additionally, the researchers found elevated mean fasting insulin levels in obese girls across puberty, but particularly during Tanner stages 1, 2, and 3, during which the obese girls' mean insulin levels were 2.8- to 7-fold higher compared to normal weight girls. Additional studies have demonstrated that girls with higher total body fat have higher levels of serum androgens, including free and total testosterone and androstenedione, compared to girls with lower total body fat[62]. Similarly, a study of 91 Korean girls aged 6 to 17 years found significantly higher levels of free testosterone and DHEAS in the obese pubertal girls compared to normal weight girls, with free testosterone levels approximately twice as high in obese girls compared to normal weight girls[63].

Further evidence for the overlap in pathophysiology between obesity and PCOS comes from studies evaluating LH in obese adolescent girls[64,65]. One study

comparing the LH pulse frequency of nine postmenarchal obese girls with oligomenorrhea, but without clinical or biochemical hyperandrogenism, to girls with PCOS and controls with regular menstrual cycles found striking similarities between the obese girls without PCOS and the girls with PCOS[64]. Specifically, the mean number of LH pulses per 24 hours and the patterns of LH secretion were comparable between the two groups, with greater LH pulse frequency seen in the obese girls with oligomenorrhea and the girls with PCOS compared to the control group. Similarly, a study examining the relationship between insulin, LH, and free testosterone concentrations in 92 obese adolescent girls found that both morning LH levels and fasting insulin levels were independent predictors of free testosterone levels in the study participants[65].

Finally, the pathophysiological link between obesity and PCOS is further strengthened by data demonstrating that weight loss results in improved ovulatory function and PCOS phenotype in affected individuals. In one study of 24 obese women with PCOS, weight loss of at least 5 percent through caloric restriction resulted in a reduction of fasting insulin levels, an increase in SHBG concentrations, and a reduction in free testosterone levels[66]. Additionally, nine women in the weight loss group demonstrated an improvement in reproductive function, as evidenced by conception or a more regular menstrual pattern. Similarly, a randomized controlled trial of 60 adolescent girls and young adult women with PCOS and a BMI greater than 30 kg/m^2 found that participants assigned to a dietary weight loss group had improvements in hirsutism scores and menstrual function, as demonstrated by greater number of menstrual episodes, compared to the control (no weight loss) group[67].

Importantly, both obesity and PCOS can result in negative psychological, physical, and reproductive consequences for affected individuals, including an increased risk of endometrial hyperplasia and cancer due to prolonged endometrial exposure to unopposed estrogen in the setting of chronic anovulation and inadequate progesterone exposure, reduced fertility, dyslipidemia, impaired glucose tolerance and type 2 diabetes mellitus, hypertension, cardiovascular disease, anxiety, depression, and poor self-esteem[53-55].

Obesity has additionally been associated with higher rates of dysmenorrhea, premenstrual disorders, and heavy menstrual bleeding

Effects of obesity on dysmenorrhea, premenstrual disorders, and heavy menstrual bleeding

Obesity has additionally been associated with higher rates of dysmenorrhea, premenstrual disorders, and heavy menstrual bleeding . As with irregular menstrual cycles, the relationship between BMI and dysmenorrhea appears to be a U-shaped curve, with women at both the lower and higher ends of the BMI spectrum experiencing higher rates of dysmenorrhea compared to normal weight girls, although the data with respect to obesity is conflicting[68]. In one study of 25 adolescent girls with obesity undergoing bariatric surgery, dysmenorrhea was the most commonly reported menstrual concern, affecting 40 percent of participants[52]. Similarly, a prospective cohort study of 9671 Australian young women followed for 13 years found that obesity was more common among women with persistent dysmenorrhea[69], and a cross-sectional study of 217 Iranian women demonstrated a significant association between BMI, waist circumference, waist-to-hip ratio, and skinfold thickness and dysmenorrhea[70]. On the other hand, a cross-sectional study of 370 young adult women found a higher prevalence of moderate and severe dysmenorrhea in underweight compared to obese participants[71]. A second cross-sectional study of 857 young women also found that the risk of dysmenorrhea was 1.5-times higher in underweight women compared to overweight or obese women[72], and a third cross-sectional study of 2282 Japanese college women found that women with an underweight BMI were more likely to experience dysmenorrhea than the overweight group when compared to normal weight controls[73]. Finally, a cross-sectional study of 1383 female adolescents in Africa found no association between BMI or waist circumference and dysmenorrhea[74].

Higher BMI has also been associated with increased risk for premenstrual disorders (PMDs). A prospective cohort study of 6524 adult females found that higher childhood BMI was associated with a higher risk of development of PMDs, including premenstrual dysphoric disorder (PMDD), and a higher burden of premenstrual symptoms in young adulthood[75]. Similarly, a cross-sectional study of 874 adult women found that

women with obesity (BMI ≥30) were almost three times as likely to suffer from premenstrual syndrome (PMS) when compared to underweight women, with the prevalence of PMS positively correlating with BMI[76]. Finally, a prospective study that included 1057 adult women who developed PMS over 10 years of follow-up found a strong positive correlation between BMI and risk of PMS[77]. Specifically, the researchers found that for every 1 kg/m^2 increase in BMI, the risk of PMS increased by 3 percent, with risk of PMS significantly higher for women with a BMI ≥ 27.5 kg/m^2 compared to women with a BMI < 20.0 kg/m^2.

Finally, obesity may be associated with heavy menstrual bleeding. A recent study of 121 adult women found a weak positive association between BMI and menstrual blood loss, as represented by the pictorial-based assessment chart (PBAC) score[78]. The researchers then used a mouse model to evaluate the role of increased body weight on endometrial repair and prolonged menstrual bleeding. They found that mice fed a high fat diet that resulted in weight gain had significantly delayed endometrial repair compared to mice fed a normal diet. The mice in the high fat diet group also had higher levels of local inflammatory mediators in their uterine tissue following a progesterone withdrawal. The researchers concluded that increased body weight can alter endometrial function and result in increased menstrual blood loss. While the link between obesity and the development of endometrial cancer has been well-established, less is known about the prevalence of heavy menstrual bleeding in obese adolescents and adult women[79,80]. It is plausible that the same mechanisms that result in endometrial hyperplasia may contribute to heavy menstrual bleeding. These include: 1) increased aromatization of androgens to estrogens in adipose tissue, resulting in a hyperestrogenic state that stimulates endometrial growth, and 2) the production of adipokines by adipose tissue contributing to a proinflammatory state.

Conclusion

Obesity in childhood and adolescence is associated with earlier onset of puberty and menarche, hyperandrogenism leading to menstrual irregularities, and can increase the risk of premenstrual disorders, dysmenorrhea, and heavy menstrual bleeding in adolescent girls and young adult women. Maintaining a healthy weight can reduce the risk of menstrual disorders and protect against the gynecologic complications of obesity in adulthood.

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