Impact of obesity on women’s health
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Objective: To review the impacts of obesity on women’s reproductive health and fertility.

Design: Literature review.

Setting: Academic medical center.

Patient(s): Forty articles are referenced. The number of patients evaluated in each of the studies varies from 33 to 213,208.

Intervention(s): Articles were identified from an Ovid/Medline search using the search terms obesity, dysfunctional uterine bleeding, contraception, miscarriage, infertility, and weight loss.

Main Outcome Measure(s): The impacts of obesity on reproductive health and fertility.

Result(s): Obesity is associated with early puberty, aberrant menstrual patterns, decreased contraceptive efficacy, ovulatory disorders, an increased miscarriage rate, and worse assisted reproductive technology outcomes. Losing weight can ameliorate many of these problems.

Conclusion(s): Obesity is one of the most significant causes of morbidity and mortality in the U.S. Providers must educate patients about the impacts of obesity on reproductive health and fertility. (Fertil Steril 2009;91:1712–6. ©2009 by American Society for Reproductive Medicine.)

Key Words: Obesity, puberty, dysfunctional uterine bleeding, contraception, anovulation, infertility, miscarriage, ART

Obesity-related illnesses result in approximately 300,000 deaths in the U.S. each year (1). This compares to 42,643 deaths due to motor vehicle accidents (2) and 15,798 deaths due to HIV/AIDS (3). The risk of comorbidities such as diabetes, hypertension, obstructive sleep apnea, many cancers, dyslipidemia, cardiovascular disease, and overall mortality increases with increasing body mass index (BMI) (4). In addition to obesity’s impact on general health, reproductive health is also profoundly affected by BMI (Table 1). The present discussion focuses on the effects of obesity on reproductive health in women and the need for appropriate counseling and intervention.

MATERIALS AND METHODS
This is a review of current data on the reproductive sequelae of obesity. An Ovid/Medline search of articles published after 1996 was performed using key words including obesity, surgery, dysfunctional uterine bleeding, infertility, miscarriage, contraception, and weight loss. Some related data presented at the 2007 annual meeting of the American Society for Reproductive Medicine is also included. Because this is a literature review and does not involve research related to patients’ protected health information, IRB approval was not obtained before writing this manuscript.

RESULTS
Epidemiology
An estimated 97 million adults in the United States are overweight or obese (5). According to the National Health and Nutrition Examination Survey III, about two-thirds of U.S. adults are overweight and one-third of overweight adults are obese. Since 1980, obesity has increased in both children and adults and in all racial, ethnic, and socioeconomic groups (6). The prevalence of obesity is greater in women than in men, and greater in blacks than in whites or Hispanics (4). Asians tend to have higher body fat content at any given BMI and may suffer consequences of obesity at BMIs <25 kg/m² (7). The growing prevalence and impact of obesity make it a major health care issue for women of all ethnic backgrounds.

Obesity’s Impacts on Women’s Health
Puberty and menstrual cycle abnormalities Obesity is associated with early puberty and dysfunctional uterine bleeding (DUB). Obese girls frequently enter puberty at a younger age
TABLE 1

Comorbidities associated with obesity in gynecology, obstetrics, and reproductive health.

<table>
<thead>
<tr>
<th>Gynecology</th>
<th>Contraception and fertility</th>
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<td>Early puberty</td>
<td>Decreased contraceptive efficacy</td>
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<td>Dysfunctional uterine bleeding</td>
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<td>Urinary incontinence</td>
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<td>Postmenopausal breast cancer</td>
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<td>Endometrial cancer</td>
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Obesity continues to have a negative influence on the menstrual cycle throughout life. Postmenarchal overweight women often suffer from dysfunctional uterine bleeding (DUB) resulting from peripheral conversion of androgens to estrogens, and altered estrogen-progesterone ratios. The chronic estrogen-driven proliferation of endometrial tissue leads to endometrial overgrowth and bleeding at irregular intervals.

The ability of weight loss and metformin therapy to improve menstrual cyclicity highlights the role of excess adipose tissue and insulin resistance in causing DUB in obese women. In a randomized, double-blind, placebo-controlled study of 143 obese oligo- or amenorrheic women with polycystic ovary syndrome (PCOS) randomized to receive metformin or placebo, weight loss alone correlated with an improvement in menses (15). Presumably, weight loss restores regular menstrual function by decreasing the aromatization of androgens to estrogens in adipose tissue. Some might argue that weight loss also improves menstrual function by increasing insulin sensitivity.

Metformin is also an effective therapy for dysfunctional uterine bleeding. In addition to altered androgen levels and estrogen-progesterone ratios, obese women frequently display some degree of insulin resistance, a feature characteristic of PCOS. A number of studies support the ability of metformin to restore normal menses in women with DUB (16, 17). In a prospective, randomized, double-blind placebo controlled study of 45 oligo- or anovulatory women with PCOS randomized to receive metformin or placebo, only the women with insulin resistance who were treated with metformin demonstrated an improvement in menstrual cyclicity (80% in the metformin group vs. 18% in the placebo group) (17). In that study, improvements in menstrual cyclicity occurred independently of weight and hormonal changes. Those findings suggest that insulin resistance may be an independent contributor to DUB in obese women, separate from the effects of excess adipose tissue.

Given the deleterious effects of obesity on reproductive function in both girls and women, physicians should encourage their patients from a young age to maintain a normal weight and counsel obese patients that weight loss may ameliorate their menstrual dysfunction. Obese women with insulin resistance may also benefit from metformin therapy.

Contraception Paradoxically, obesity hinders contraception while also contributing to infertility. Several methods of steroid contraception, including oral contraceptive pills, progestin-only pills, transdermal contraceptive patches, and the vaginal ring, have been shown to be less effective in obese women (18). A multicenter study of 1,672 healthy ovulatory sexually active women randomized to receive the Ortho-Evra patch for 6 or 13 cycles found a higher rate of failure (pregnancy) in women weighing greater than 90 kg (19). Likewise, a study of 1,005 women using the Levonorgestrel vaginal ring revealed higher pregnancy rates with higher body weights. In that study population, the pregnancy rate at 1 year was 1.7% for a 40 kg woman, whereas it was 9.8% for an 80 kg woman (20). Even tubal ligation appears to be adversely affected by weight. In a multicenter study of female sterilization using tubal rings, obesity was a risk factor for technical failure (18). The intrauterine device (IUD) is one of the few reliable contraceptive methods whose efficacy does not appear to be affected by BMI.

Variations in steroid distribution and metabolism may explain the lower efficacy of steroid contraceptives in obese individuals. Increased storage of steroid hormones in adipose
tissue lowers blood levels of steroid contraceptives, thereby reducing their ability to prevent pregnancy. In contrast, IUDs, which effect contraception via local changes in the endometrium, are less likely to be affected by steroid hormone distribution and metabolism.

Although many contraceptive devices are less efficacious in obese patients, overweight patients require a reliable form of birth control. No difference in efficacy between BMI groups has been demonstrated for IUDs. Therefore, IUDs may be an appropriate choice in obese patients that want to delay pregnancy for several years. Although overweight women are more likely than their average-weight peers to become pregnant on oral contraceptive pills, patches, and rings, the failure rate of steroid contraceptives is still quite low, and hormonal treatments remain an important form of contraception in women regardless of weight. Moreover, hormonal contraceptives have a number of other beneficial effects, including regulation of menses and a small reduction in endometrial and ovarian cancer risk (21). Nonetheless, obese females have a baseline increased risk of thrombosis that can be increased as much as tenfold by taking oral contraceptive pills (22). Obese patients should know of their risk of thrombosis and should be counseled on the added risk of taking steroid contraceptives. In the World Health Organization medical eligibility criteria, BMI >30 kg/m² is a category 2 condition for all combined hormonal methods, meaning that the methods can generally be used but more careful follow-up may be required (18).

**Fertility** Obesity contributes to anovulation and subfecundity and may increase the risk of miscarriage. The endocrinopathy associated with obesity is characterized by excess estrogen and low progesterone. Many obese women are hyperinsulinemic and therefore have endocrine profiles characteristic of PCOS. Insulin and LH are elevated, the FSH-LH ratio is abnormal, and midluteal progesterone is low. This hormonal profile reflects anovulation. The endocrine changes seen after Roux-en-Y gastric bypass provide evidence that weight loss helps to correct the abnormal hormonal milieu that leads to anovulation (23). The ability of metformin to restore ovulation further emphasizes the role of insulin resistance in preventing regular oocyte development and release in obese individuals. A Cochrane Database meta-analysis of 13 randomized controlled trials investigating insulin-sensitizing drugs reported that metformin was effective at achieving ovulation in women with PCOS with an odds ratio of 3.88 compared with placebo (24).

Obesity is also associated with infertility. A cohort study of 53,910 couples enrolled in the Danish National Birth Cohort found a dose-response relationship between increasing BMI category and subfecundity (time to pregnancy >12 months). The odds ratio for this trend was 1.32 in women and 1.19 in men (25).

Both anovulation and altered leptin concentrations are likely to contribute to the association between obesity and infertility. Zhang et al. showed that ob/ob female mice (which lack functional leptin) are typically obese and sterile (26). Exogenous leptin administration, but not food restriction, can restore fertility in ob/ob mice (27, 28). These findings suggest that leptin deficiency may be an independent cause of infertility in obese women.

There is also evidence that obesity increases spontaneous abortions. A nested case-control study of 1,644 obese and 3,288 age-matched normal-weight women found an increased risk of miscarriage and recurrent early miscarriage in women with a BMI >30 kg/m² (OR 1.2 and 3.5, respectively) (29).

There are numerous theories to explain the increased miscarriage rate observed in obese women. Impaired progesterone release resulting from insulin resistance may inhibit normal corpus luteum function (30). Low leptin levels may be detrimental to early embryo development and impair trophoblast invasion (31, 32). Obesity may also damage endometrial receptivity to embryo implantation and growth (33). In a retrospective study of 712 ovum donation cycles, Bellver et al. showed the rate of spontaneous abortion to be 13.3% in normal-weight patients (BMI 20–24.9 kg/m²), 15.5% in overweight patients (BMI 25–29.9 kg/m²), and 38.1% in obese patients (BMI ≥30 kg/m²) (34). By accounting for the confounding effects of obesity on oocyte development and ovulation using oocyte donation, this model suggests that poor endometrial receptivity contributes to the increased miscarriage rate observed in obese women. In a large retrospective study, spontaneous abortion rates were higher in obese women undergoing hormonally substituted frozen embryo transfer cycles but not in fresh IVF/ICSI cycles or frozen cycles after spontaneous ovulation (35). That study suggests that follicle development contributes to (or at least is reflective of) an environment conducive to early embryo development.

**Assisted reproductive technology** In addition to impairing spontaneous conception, high BMI may impair the probability of achieving pregnancy with ART. In one study, Dokras et al. found that whereas normal-weight women have a 10.9% IVF cycle cancellation rate, morbidly obese women have a 25% IVF cycle cancellation rate (36). That study found no difference in delivery rates between BMI groups. In a retrospective study of 5,019 IVF or intracytoplasmic sperm injection (ICSI) treatments in 2,660 couples, Fedorcak et al. found a positive correlation between BMI and gonadotropin requirement during stimulation and a negative correlation between BMI and the number of oocytes collected (37). That study showed a lower live birth rate (41.4% vs 50.3%) in obese compared with normal-weight women. The weak response to ovarian stimulation reported in both of these studies is consistent with Imani et al.’s earlier analysis of the impact of BMI on threshold FSH levels required to recruit follicles (38). Selection of follicles during ovarian stimulation with exogenous FSH requires the serum FSH concentration to exceed a certain threshold. This threshold increases in relation to increasing BMI (38). An elevated FSH threshold may explain, in part, the relative resistance of obese women’s ovaries to gonadotropin stimulation, and, therefore, their impaired success rate with ART.
Although it is not advisable to lose weight during pregnancy, physicians should encourage their patients to lose weight before conception. Obese women seeking fertility treatment are particularly good candidates for weight-loss counseling, because weight loss is likely to both help them conceive and improve the safety of their future pregnancy. In their review article, Norman et al. suggest that even modest weight loss, about 5 kg, can improve menstrual function and fertility (33). In their analysis of recurrent miscarriage, Jauniaux et al. also advise that weight loss should be a first-line treatment for overweight women with recurrent miscarriages (40).

**CONCLUSION**

Given the growing epidemic of obesity in America, it is important that Reproductive Endocrinologists educate patients about the impact of obesity on menstrual function, contraception, and infertility.

**REFERENCES**


