Adverse effects of female obesity and interaction with race on reproductive potential

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Across the reproductive spectrum, obesity is associated with greater risks for adverse health outcomes, including higher rates of infertility, subfertility, early pregnancy loss, fetal deaths and stillbirths, congenital anomalies, and pregnancy complications. The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young adults particularly critical in terms of their future reproductive potential. Obese women have a lower chance of pregnancy following in vitro fertilization (IVF), require higher dosages of gonadotropins, and have reduced rates of implantation, clinical intrauterine gestation, and live birth rates and increased rates of pregnancy loss, as well as greater risks for prematurity and preeclampsia even when stratified by plurality. Racial and ethnic differences by overweight and obesity in IVF outcomes have been reported. Compared with normal-weight women, failure to achieve a clinical intrauterine gestation is significantly more likely among obese women overall, normal-weight and obese Asian women, normal-weight Hispanic women, and overweight and obese Black women. Among women who do conceive, compared with normal-weight women, failure to achieve a live birth is significantly more likely among overweight and obese women overall, and among overweight and obese Asian women, overweight and obese Hispanic women, and normal-weight and obese Black women. Although weight loss should theoretically be the first line of therapy for obese women, other lifestyle factors, such as regular physical exercise, elimination of tobacco use and alcohol consumption, and stress management, may be of more immediate benefit in achieving conception. (Fertil Steril® 2017;107:868–77. ©2017 by American Society for Reproductive Medicine.)

Key Words: Obesity, prenatal growth restriction, abnormal glycemic parameters, insulin resistance, metabolic environment

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According to the World Health Organization (1), obesity is a disease defined as the condition of excess body fat to the extent that health is impaired. The most widely accepted measure is the body mass index (BMI; weight (kg)/height $(m)^2$), with cutoff points of 25 kg/m^2 (overweight) and 30 kg/m^2 (obese), as recommended by the National Heart, Lung, and Blood Institute's North American Association for the Study of Obesity expert committee (2). Class I, II, and III obesity are defined as BMI 30.0–34.9, 35.0–39.9, and $\geq$40.0 kg/m^2, respectively. In addition, this expert committee recommends using waist circumference cutoff points of 40 inches (102 cm) for men and 35 inches (88 cm) for women to define central obesity. This measure may be more useful than BMI because of its greater predictive value for future health risks, as well as ease of measurement (2–4). BMI is not the best measure to reflect body fat and does not account for racial and ethnic differences in body build nor higher BMI due to increased muscularity (5). Specifically, the proportion of Asians at high risk for type 2 diabetes and cardiovascular disease is considerable at lower BMI cutoffs for overweight. The World Health Organization Expert Consultation recommended retaining the current BMI cutoffs, but adding additional cutoff points of 23, 27.5, 32.5, and 37.5 kg/m^2 for public health action.

In the United States, two-thirds of adults are overweight or obese (6), with highest rates among Black and Hispanic populations and lowest rates among Asians (Table 1). The prevalence of obesity has more than doubled since the 1970s and is a leading cause of morbidity and mortality, second only to tobacco use (7). Obesity is associated with impaired fertility, primarily owing to disorders of the reproductive hormonal profile. United States national data from 2014 births indicated that 25.6% of women were overweight and 24.8% were obese

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before becoming pregnant (8). The prevalence of overweight and obesity was lowest among women <20 years of age, Asians, and women with a college degree or giving birth for the first time. Women with obesity before pregnancy were more likely to be older (40–54 years of age), be non-Hispanic Black or non-Hispanic American Indian/Alaskan Native, have had three or more previous births, and to be using Medicaid for payment of delivery. An estimated 35% of maternal deaths in the United Kingdom are related to obesity (9).

OBESITY AND REPRODUCTION/PREGNANCY

Obesity is associated with greater risks for adverse health outcomes across the reproductive spectrum (10–13), including higher rates of infertility (14–16), subfertility (increased time to pregnancy) (17–19), early pregnancy loss (20–29), fetal deaths, stillbirths and neonatal deaths (30–33), congenital anomalies (34, 35), pregnancy complications (36–38), greater risk of cesarean delivery and poor wound healing (39), and increased difficulty and shorter duration of breastfeeding (40–42). The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young adults particularly critical in terms of their future reproductive potential. In the United States, between 1988–1994 and 2011–2014, the proportion of adolescents (12–19 years of age) who were obese more than doubled, from 9.7% to 21% (6). Findings from the Study of Women's Health Across the Nation indicate that adolescent obesity is associated with a threefold increased risk of lifetime nulliparity and a fourfold increased risk of lifetime nulligravidity (43). The maternal, fetal, and neonatal complications of obesity have far-reaching adverse health implications for both the mother and her child (44–47).

PRENATAL GROWTH, OBESITY, AND INFERTILITY

Research findings have linked prenatal growth restriction to timing of puberty and subsequent symptoms of polycystic ovary syndrome (48–56). Even after achieving a normal body size by the age of 2 years, singleton children born small for their gestational age tend to become relatively adipose, hyperinsulinemic, hypoadiponectinemic, and with physiologic evidence of low-grade inflammation (54, 55). By 6 years of age, these children are more likely to develop visceral adiposity, even with normal body weight. By 8 years of age, children born small for gestational age with catch-up growth develop high DHEAS and low SHBG levels (56). Precocious puberty (appearance of pubic hair before 8 years of age) has also been demonstrated as part of this sequence, as well as anovulatory and hyperinsulinemic hyperandrogenism in late adolescence and adulthood (51–53). Insulin resistance has been cited as a key mechanism linking prenatal growth restraint to early menarche (48), with insulin-sensitizing therapy improving ovulation rates (49, 50).

TABLE 1

Prevalence (%) of normal weight, overweight, and obesity in the United States, adults aged ≥20 years, 2011–14.

Sex	Racial/ethnic group	BMI Category (kg/m^2)					
		Normal weight, 18.5–24.9	Overweight and obese, ≥25.0	Obese, ≥30.0	Obese (class I), 30.0–34.9	Obese (class II), 35.0–39.9	Obese (class III), ≥40.0
Male	All	26.0	73.0	34.5	22.0	7.6	4.9
	White	25.6	73.7	34.6	19.6	7.8	4.7
	Black	29.0	69.6	37.9	22.0	8.9	7.0
	Asian	50.2	46.9	11.3	9.4	–	–
	Hispanic	19.5	79.6	39.1	27.2	7.3	4.7
Female	All	31.7	66.2	38.1	19.3	9.9	8.9
	White	34.3	63.5	34.0	21.4	9.1	8.2
	Black	16.0	82.0	56.5	24.9	15.1	16.5
	Asian	60.5	34.4	11.9	8.9	2.1	–
	Hispanic	22.3	77.1	45.6	24.1	13.5	8.1

Note: Dashes indicate unreliable estimates owing to low numbers. Adapted from: National Center for Health Statistics. Health, United States, 2015: with special feature on racial and ethnic health disparities. Hyattsville, MD: 2016. BMI = body mass index.

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