Obesity, male infertility, and the sperm epigenome

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Obesity is a growing epidemic and a common problem among reproductive-age men that can both cause and exacerbate male-factor infertility by means of endocrine abnormalities, associated comorbidities, and direct effects on the fidelity and throughput of spermatogenesis. Robust epidemiologic, clinical, genetic, epigenetic, and nonhuman animal data support these findings. Recent works in the burgeoning field of epigenetics has demonstrated that paternal obesity can affect offspring metabolic and reproductive phenotypes by means of epigenetic reprogramming of spermatogonial stem cells. Understanding the impact of this reprogramming is critical to a comprehensive view of the impact of obesity on subsequent generations. Furthermore, and perhaps more importantly, conveying the impact of these lifestyle changes on future progeny can serve as a powerful tool for obese men to modify their behavior. Reproductive urologists and endocrinologists must learn to assimilate these new findings to better counsel men about the importance of paternal preconception health, a topic recently being championed by the Centers for Disease Control and Prevention. (Fertil Steril® 2017;107: 848–59. ©2017 by American Society for Reproductive Medicine.)

Key Words: Obesity, male infertility, sperm epigenetics, transgenerational inheritance

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Obesity, defined as a body mass index (BMI) of >30 kg/m^2, is a disease approaching pandemic proportions, affecting more than 1.9 billion adults over the age of 18 years worldwide (1, 2) (Fig. 1). In the United States alone, the prevalence of obese men who are of reproductive age has tripled since the 1970s and currently affects 33.9% of the population over the age of 20 years (3).

The rise in obesity rates have paralleled reports of rising rates of poor sperm quality and male infertility (4, 5). With the rate of male-related infertility contributing to 45%–50% of infertile couples (6, 7), there is an enlarging body of evidence linking male infertility to obesity. Mechanisms by which obesity may affect spermatogenesis include thermal effects, hyperestrogenism, hypogonadotropic hypogonadism, diabetes mellitus, sexual dysfunction, and sperm epigenetic perturbations. In addition to the immediate effects that obesity has on the father, there is evidence that negative effects may be transmitted to the offspring via genetic and epigenetic alterations of germ cell DNA (8–10). The objective of the present review is to explore the epidemiology and pathophysiology of obesity-induced male infertility with an emphasis on the role of epigenetics.

OBESITY AND MALE INFERTILITY—THE EPIDEMIOLOGIC ASSOCIATION

The negative effects of obesity on semen parameters and androgen profiles have been well established; however, population-based epidemiologic evidence was not available until a decade ago. In 2006, Sallmen et al. (11) described a group of 20,620 families in Iowa and North Carolina. They illustrated a dose-response relationship between BMI and male infertility, with worsening male fertility for every 3-point increase in BMI >25 kg/m^2, with an odds ratio (OR) of 1.12 (95% confidence interval [CI] 1.01–1.25). These findings were confirmed in later studies across the globe, including in Danish (12) and Norwegian (13) cohorts that showed an association between obesity and male infertility with ORs of 1.53 (95% CI 1.32–1.77) and 1.36 (95% CI 1.32–1.77), respectively (12–19). A complete review of these studies is presented in Table 1.

OBESITY AND FERTILITY-RELATED COMORBIDITIES

Obesity-related health deficits include increased risks of diabetes mellitus, cardiovascular disease, epigenetic alterations, and certain malignancies (20–22). Obese men are also at greater risk of developing hypogonadism,

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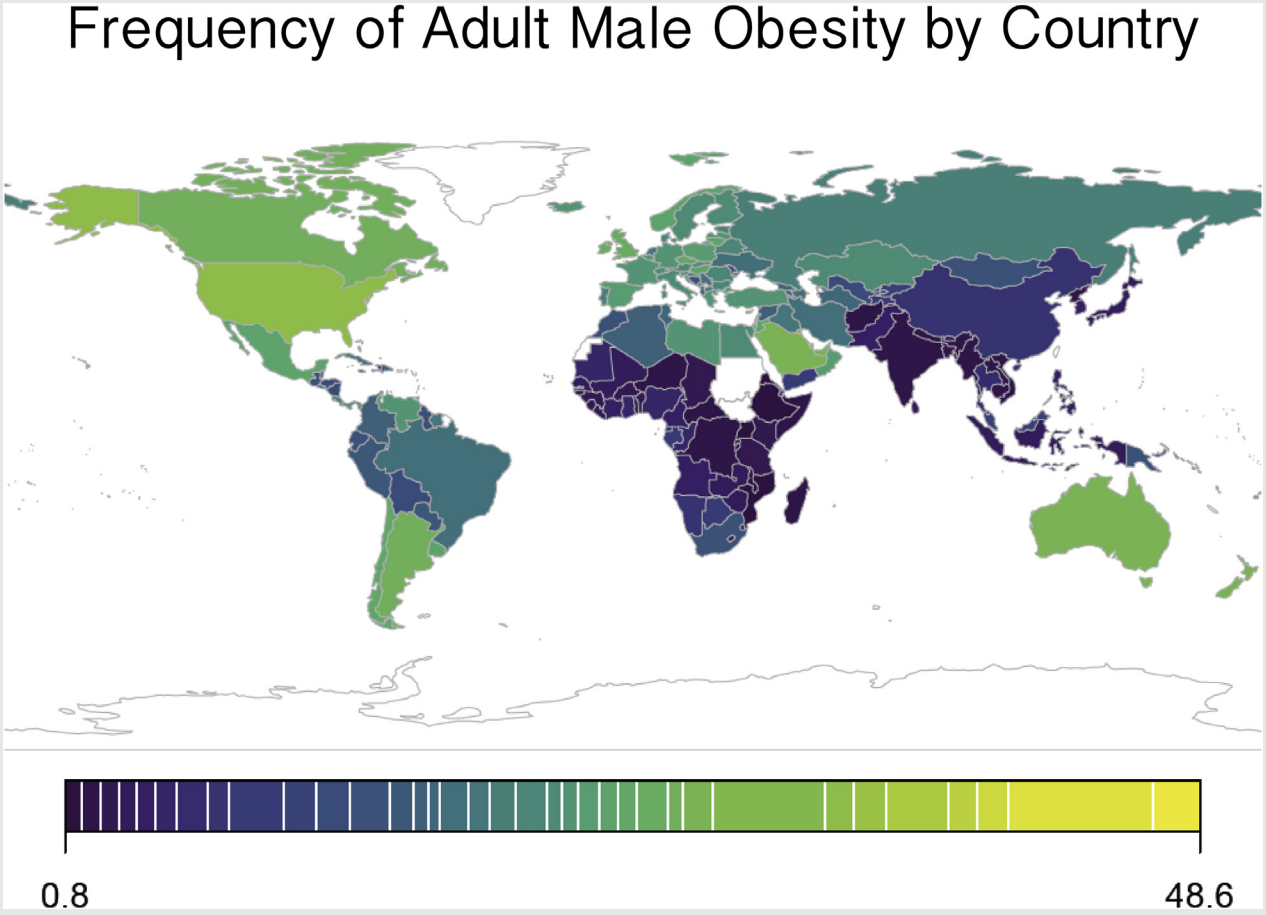
FIGURE 1



Worldwide obesity incidence.

Craig. Obesity and sperm epigenetics. Fertil Steril 2017.

impaired spermatogenesis, and erectile dysfunction (23–26). All of these factors are potential contributors to increased rates of male infertility in these patients.

Obesity-Induced Endocrine Axis Derangements

Normal intratesticular testosterone levels are a prerequisite for normal spermatogenesis (27). Currently, our understanding of the hypothalamic-pituitary-gonadal (HPG) axis constitutes the core of our understanding of male reproduction. However, recent evidence has indicated that a number of "neohormones," which include leptin (28, 29) and kisspeptin (30), may also impact this axis. Furthermore, many of the comorbidities of obesity, such as diabetes (24) and sleep apnea (31–34), exacerbate these endocrine derangements. Below, we discuss in more detail the HPG axis, the effect of obesity on the HPG axis, and how these neohormones effect these pathways.

Testosterone levels measured within the testicle are found to be 25–125-fold greater than levels in serum (35–39). The physiologic need for elevated intratesticular levels is not completely understood; however, levels >70 nmol/L have been shown to be required for normal spermatogenesis (40). Thus, even a small decrease of the systemic testosterone levels can reflect a major reduction of the intratesticular levels. GnRH is produced by the hypothalamus in a pulsatile manner and stimulates LH and FSH. Normally, LH is produced by the pituitary gland and acts to induce steroidogenesis of testosterone by the Leydig cells. Once testosterone diffuses out of the Leydig cells, it is bound by proteins in circulation, mainly SHBG, and is then metabolized to estrogen by aromatase (41). FSH, while not strictly required for spermatogenesis in humans, does augment Sertoli cell function, making it a core component of optimal testicular function (42).

Hypogonadism in obesity can be mediated by both reduced pulse amplitude of the cyclical secretion of LH from the pituitary as well as decreased response to LH by the testis (25). Reductions in SHBG, FSH, and inhibin B and elevated E_2, via increased aromatization of testosterone to E_2 peripherally, are also commonly seen (17, 43–45). All of these changes result in reductions in the throughput and fidelity of human spermatogenic function and, possibly, alter the sperm epigenome (46).