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Impact of male obesity on infertility: a critical review of the current literature

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Objective: To evaluate the current understanding of the effects and potential mechanisms of obesity on male fertility.
Design: Literature review of articles pertaining to obesity and male infertility.
Result(s): Recent population-based studies suggest an elevated risk for subfertility among couples in which the male partner is obese and an increased likelihood of abnormal semen parameters among heavier men. Male factor infertility is associated with a higher incidence of obesity in the male partner. Obese men exhibit reduced androgen and SHBG levels accompanied by elevated estrogen levels. Reduced inhibin B levels correlate with degree of obesity and are not accompanied by compensatory increases in FSH. This complexly altered reproductive hormonal profile suggests that endocrine dysregulation in obese men may explain the increased risk of altered semen parameters and infertility. Additional features of male obesity that may contribute to an increased risk for infertility are altered retention and metabolism of environmental toxins, altered lifestyle factors, and increased risks for sexual dysfunction. Neither reversibility of obesity-associated male infertility with weight loss nor effective therapeutic interventions have been studied yet.
Conclusion(s): The increasing prevalence of obesity calls for greater clinician awareness of its effects on fertility, better understanding of underlying mechanisms, and eventually avenues for mitigation or treatment. (Fertil Steril® 2008;90:897–904. ©2008 by American Society for Reproductive Medicine.)

Key Words: Obesity, male infertility, sperm parameters, oligozoospermia, reproductive hormones, estrogen, testosterone

The word obesity is derived from the Latin *obesus*, which means "one who has become plump through eating." It may have first appeared in the writings of Thomas Venner in 1620 (1). However, the negative effect of obesity on an individual's health has been known for a longer time and can be found in the writings of Hippocrates, Galen, and Avicenna (2). Avicenna was probably among the first who described the relationship between obesity and male infertility in his encyclopedic medical book *The Canon of Medicine*. In a chapter entitled "The health disadvantages of excessive weight," Avicenna wrote, "this human (man) has a cold temperament; this is why he is infertile, unable to impregnate (women) and has low semen" (3). In modern times, the relationship between obesity and male infertility has been largely ignored until recently (4, 5). Interest in the rapid increase in obesity has brought to light the detrimental effects of obesity on health in general and on the reproductive function in particular.

In women, the effects of extremes of body composition on reproductive function are readily evident by altered menstrual function and are well known and extensively studied (6). In men, the negative effects of obesity on reproductive function are less evident and have been less often studied. Numerous recent reports have now been published describing the relationship between obesity and semen characteristics, reproductive endocrine function, sexual function, and male infertility. In the present review, we present a critical analysis of the available literature linking obesity to male infertility. We also discuss the hormonal, toxicologic, and mechanical mechanisms that can explain this relationship.

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OBESITY AND MALE INFERTILITY

Evidence From Epidemiologic Studies

Evidence is accumulating that the observed alterations in semen and sexual function attributable to obesity are manifested as diminished fertility that can be ascertained at the population level. The first report, published in 2006 by Sallmen at al. (7), was a secondary analysis of data extracted from the Agricultural Health Study, which studied 52,395 certified pesticide applicators and 32,347 of their spouses (8). There were 1,329 couples that met the inclusion criteria, including data available regarding body mass index (BMI) for both partners. Infertility was defined as an attempt at conception by the couple that lasted more than 12 months in the last 4 years regardless of whether the couple achieved pregnancy or not. Male BMI was shown to be associated with infertility with an odds ratio (OR) of 1.12 (95% confidence interval [CI] 1.01–1.25) after correction for female BMI, male and female age, smoking status, alcohol use, and exposure to solvents and pesticides. The categorization of BMI into groups showed a dose-effect relationship, with a maximal effect in the BMI 32–43 kg/m^2 group and a plateau of effect beyond this (8). A critical review of this study finds several concerns that limit confidence in its conclusions. The small fraction 2.5% (1329 out of 52,395) of patients included from the population at risk may have distorted or magnified any systematic errors, and there is lack of detail regarding potentially confounding female infertility factors. Moreover, the incidence of infertility in the studied population was very high: 28% (9). This finding was attributed to the elevated age of the population (>30 years old), however, another possible reason might be the exposure to pesticide, a factor that may have affected obese subjects preferentially. Pesticide exposure was shown to be associated with infertility in this population, and modulation of pesticide effects in obese men through altered metabolism or accumulation would have escaped the adjustment for degree of exposure (10, 11). Finally, this analysis assumed that the BMI remained stable over a period of 4 years, an assumption that is not accurate in a young population (majority were <50 years old) (12). Despite these concerns, this study brought to attention the potential relationship between increasing BMI and infertility, perhaps particularly regarding the interaction of environmental toxins, obesity, and male fertility.

In another report, Ramlau-Hansen et al. (13) analyzed data extracted form the Danish National Birth Cohort (14). The original study included 100,000 pregnant women that were interviewed about several topics, including time to achieve pregnancy and male partner BMI. Time to pregnancy and BMI data were available for 53,910 women. Of those, 47,835 were used for final analysis after exclusion of women with possible female factor infertility. Subfecundity was defined as waiting time of more than 12 months to achieve a pregnancy that resulted in a live birth, and the analysis corrected for female BMI and the age of both partners. Couples with overweight (BMI 25–29 .99 kg/m^2) and obese (BMI $\geq$30 kg/m^2) male partners were more likely to have subfecundity, with ORs of 1.15 (95% CI 1.09–1.22) and 1.49 (95% CI 1.34–1.64), respectively, after correction for female BMI and male and female age (14). Some limitations in this study include the fact that BMI data were obtained more than 2 years after the attempt at pregnancy and that subfecundity was defined in relation to live birth. Patients who had miscarriages might have been misclassified as subfertile. Finally, this study included only couples with eventual success at conception, so that an effect of male obesity on failure to conceive altogether would not have have been ascertained. The major advantage of this study is the large number of subjects available for final analysis, which showed a clear relationship between increasing male BMI and subfecundity with a dose-response effect.

The most recent report came from a secondary analysis of a Norwegian database, the Norwegian Mother and Child cohort study, which considered women in their second trimester of pregnancy. Infertility was defined as time to pregnancy of more than 12 months. The weight and height of the male partner were reported by the female participant. The final analysis was performed on 26,303 women out of 45,132 at risk and was corrected for coital frequency, female BMI, male and female age, smoking status, and various risk factors for female infertility. In this study, couples with overweight men (BMI 25–29.9 kg/m^2) had an OR for infertility of 1.19 (95% CI 1.03–1.62), and those with obese men had an OR for infertility of 1.36 (95% CI 1.12–1.62). When BMI was divided into categories, the effect of BMI on infertility showed a dose-response relation with a plateau of the effect at the high BMI levels ($\geq$35 kg/m^2) (15). This plateau at high BMI levels was also seen in the study by Sallmen et al. (7). The use of BMI derived from partner reports is a concern addressed by the authors, who showed a good correlation of this data with self-reported height and weight for the men in this cohort. Another, more important, concern is limitation of the study population to couples who had successfully conceived, so that couples with more severe degrees of infertility could not be considered in the analysis. Such a selection bias can potentially dilute the effect of male obesity on infertility. The advantages of the study are the large number of patients analyzed and the accounting for coital frequency in the analysis. By accounting for coital frequency, it demonstrated that the relationship between male obesity and infertility can be mediated by factors other than sexual dysfunction.

Evidence From Studies of Couples Seeking Fertility Treatment

Evidence of the relationship between obesity and male factor infertility among infertile couples generally supports the thesis that obesity is associated with compromised male fertility. In this context, Magnusdottir et al. (16) studied male partners among 72 couples with infertility classified into three groups: male factor subfertility (abnormal sperm concentration and motility), idiopathic subfertility, and female factor subfertility. The incidence of obesity (BMI $\geq$30 kg/m^2) was three