Journal of Andrology, Vol. 27, No. 5, September/October 2006

Obesity and Male Reproductive Potential

Minireview

AHMAD O. HAMMOUD,* MARK GIBSON,* C. MATTHEW PETERSON,* BLAKE D. HAMILTON,† AND DOUGLAS T. CARRELL*†‡

*From the *Division of Reproductive Endocrinology & Infertility, Department of Obstetrics & Gynecology; the †Department of Surgery (Urology); and the ‡Department of Physiology, University of Utah School of Medicine, Salt Lake City, Utah.*

Obesity is a well recognized risk factor for female infertility (Pasquali et al, 2003). However, its relation to decreased sperm count was not documented until recently (Jensen et al, 2004; Magnusdottir et al, 2005). It is believed that with the increasing prevalence of sedentary life styles and dietary changes, obesity is emerging as an important cause of adverse health outcomes, including male infertility.

Male factors alone constitute 25%–30% of all cases of infertility, and they contribute to another 30% in combination with female factors. Known etiologies of male infertility include cryptorchidism, testicular torsion or trauma, varicocele, seminal tract infections, antisperm antibodies, hypogonadotropic hypogonadism, gonadal dysgenesis, and obstruction of the reproductive channels (Oehninger, 2000). Obesity was recently proposed for addition to this list (Jensen et al, 2004). Thus, obesity is a chronic disease resulting in compromised physical and psychological well-being, and it may contribute to reduced fecundity as well.

It is known that the incidence of obesity is reaching epidemic levels in the western world. For example, in the United States, the incidence of obesity increased from 12% to 17.9% between 1991 and 1998. In the same period, the incidence of male obesity increased from 11.7% to 17.9% (Mokdad et al, 1999). Recently, the prevalence of male obesity in the US was reported to be 30.6% (Hedley et al, 2004).

Correspondence to: Douglas T. Carrell, Associate Professor of Surgery (Urology), Physiology and OB-GYN, Director of IVF and Andrology Laboratories, University of Utah School of Medicine, 675 Arapeen Dr, Suite 205, Salt Lake City, Utah 84108 (e-mail: douglas.carrell@hsc.utah.edu).

Received for publication April 4, 2006; accepted for publication June 1, 2006.

DOI: 10.2164/jandrol.106.000125

It is possible that the increasing prevalence of overweight and obesity accounts for a portion of the trend, albeit a widely debated one, of decreasing sperm counts over recent decades. Although complicated by varying sample sizes and methodologies for the assembled data, it has been estimated that sperm counts have been decreasing by as much as 1.5% each year in the United States, a finding similar to those for other Western countries and not present in other regions where obesity is less prevalent (Swan et al, 2000). These findings suggest a possible link between life style changes, obesity, semen quality, and possibly male fertility (Jensen et al, 2004).

Obesity and Pubertal Sexual Maturation

Obesity in adolescent girls is associated with increased height and earlier pubertal development (Dunger et al, 2005). There is some evidence that development of sexual characteristics takes place earlier as well (Adair and Gordon-Larsen, 2001). In males, the relationship of body weight with sexual development seems to be reversed. Wang et al studied a sample of 1501 boys and 1520 girls aged 8 to 14 years. They found that the prevalence of obesity was lower in early-maturing boys and higher in early-maturing girls, compared with the group who had average or late sexual maturity (Wang, 2002). This finding was challenged later by Laron, who found no significant difference in the indicators of sexual maturation between obese and nonobese adolescents in both genders; however, the number of patients in this study was small (Laron, 2004).

On the other hand, pubertal development was shown to negatively influence the secretion of adiponectin by adipose tissue. Adiponectin has mainly antidiabetic and antiatherogenic effects. In a multiple regression model adiponectin levels in males were shown to be negatively correlated to the stage of pubertal development ($r^2 = .206$, $P < .001$), body mass index (BMI) ($r^2 = .034$, $P = .021$), and testosterone levels ($r^2 = .039$). This analysis demonstrated that the decrease in adiponectin levels throughout pubertal development stages is more pronounced in obese males than controls (Bottner et al, 2004).

Hormonal Profile in Adult Obese Males

Obese males usually express a characteristic hormonal profile described as "hyperestrogenic hypogonadotropic

Causes of hypoandrogenism and altered spermatogenesis in obese men

Factors that Contribute to Hypoandrogenism in Obese Males	
Schneider et al, 1979; de Boer et al, 2005	Hyperestrogenemia
Tsai et al, 2004; Stellato et al, 2000	Insulin resistance
Luboshitzky et al, 2001; Luboshitzky et al, 2005	Sleep apnea
Potential Etiologies of Altered Spermatogenesis in Obese Males	
Goyal et al, 2003	Increased estrogen levels
Giagulli et al, 1994	Suppression of the hypothalamic-pituitary-testicular axis
Jarow and Zirkin, 2005; Coviello et al, 2004	Decreased androgen levels

hypogonadism.'' In fact, both total and free blood testosterone levels are shown to be decreased in obese men. Total body fat, intra-abdominal fat, and subcutaneous fat have all been associated with low levels of total and free testosterone (Strain et al, 1982; Haffner et al, 1993; Tsai et al, 2004). It appears that central obesity, in particular, is associated with a decrease in circulating androgen levels. The decrease in androgen levels is proportional to the degree of obesity (Giagulli et al, 1994). In obese males, adrenal androgens are diminished as well (Tchernof et al, 1995).

The origin of hypoandrogenism in obese males is multifactorial (Table). It is primarily attributable to an increase in circulating estrogens that appear to result in relative hypogonadotropism, although the diminished levels of sex hormone-binding globulin (SHBG) in obese individuals will by itself result in reduced total testosterone levels, even in the face of unchanged production. In fact, weight correlates negatively with blood testosterone levels and testosterone/estradiol ratio (Fejes et al, 2006). Both estrone and estradiol are increased in obese males compared to controls (Schneider et al, 1979). The aromatization of C19 androgens like testosterone and androstenedione is a key step in estrogen biosynthesis and is catalyzed by the aromatase enzyme, a product of the *CYP*19 gene. It is believed that the increase in estrogens in obese males is due to increased conversion of adrenal and testicular androgens owing to the increase in available aromatase enzyme in the fatty tissue (de Boer et al, 2005). Estrogen production by adipose tissue is dependent on the availability of androgenic precursors in the circulation (Simpson et al, 1999). Estrogens are biologically active at much lower concentrations and production rates than androgens (testosterone production in adult males is several mg per day, whereas estradiol production in women averages 100 μg per day); thus small increases in aromatization of androgens can result in changes in estrogen levels that are substantial in relation to the range of normal circulating levels. Increased circulating estrogen levels resulting from increased peripheral conversion among the obese may therefore inappropriately enhance negative feedback on gonadotropin secretion. Estradiol has significant biologic activity in the hypothalamus and the pituitary. Estrogen receptors (ERα and ERβ) are present in several hypothalamic nuclei and in pituitary gonadotropes, indicating that estrogen modulates the activity of hypothalamus-pituitary axis. Estrogen acts on the hypothalamus to affect gonadotropin-releasing hormone (GnRH) pulses and at the pituitary level to regulate gonadotropin (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) secretion (Akingbemi, 2005). In severe obesity, pituitary gonadotropin secretion appears suppressed with normal or decreased levels of LH in the presence of decreased levels of testosterone (Giagulli et al, 1994). Because aromatization also occurs in the hypothalamus itself, precise dissection of the contribution of increases in circulating estradiol associated with obesity to overall negative steroidal feedback on pituitary gonadotropin secretion is problematic.

The hypothesis that elevated estrogen plays an important role in the androgen abnormalities in obesity is strongly supported by observations of the effect of the aromatase inhibitor letrozole on obese men. Among 10 severely obese men with markedly low testosterone levels and clinical symptoms of hypogonadism, letrozole administration for 6 weeks increased testosterone levels more than 3-fold from a mean baseline of 7.5 $\pm$ 1 nmol/l (mean $\pm$ SE) while diminishing circulating estradiol from 120 $\pm$ 20 to 70 $\pm$ 9 pmol/l (mean $\pm$ SE). Changes in levels in both steroids were highly statistically significant ($P < .001$), and were not accompanied by changes in SHBG. A 3-fold statistically significant increase in both LH and FSH occurred during treatment as well (de Boer et al, 2005). Unfortunately, this study did not include data on measures of semen quality. Raman and Schlegel reported a tripling of the testosterone-estradiol ratio among 16 overweight infertile men treated with the aromatase inhibitor anastrozole but did not report changes in semen parameters for this subgroup of a study cohort that included men with other known causes for male infertility, including varicocele and Klinfelter syndrome (Raman and Schlegel, 2002). The results of this suggest also that aromatase inhibition increases in testosterone levels and decreases

in estradiol in nonobese males, such that the "correction" of hypoandrogenism in obese males during aromatase inhibition is an extension of a general effect of such medications. To the extent that lower circulating testosterone levels reflect decreased testicular testosterone production, lower intratesticular testosterone levels would be expected as well.

Insulin resistance, a predisposition of obesity, has also been reported to be associated with low testosterone levels. Age-adjusted fasting insulin and C-peptide were shown to be inversely correlated to total and free testosterone in men (Tsai et al, 2004). This association is confounded by the independent relation between SHBG and insulin resistance (Stellato et al, 2000). However, after adjusting for SHBG levels, low testosterone levels remain correlated with insulin resistance (Tsai et al, 2004). The direction of this association is not clear. In a recent review, men with type 2 diabetes had a mean decrease of testosterone levels of (−71.5 ng/dl, 95% CI: −116.4 to −26.8 ng/dl) compared to controls. Moreover, the analysis of prospective studies showed that the risk of developing type 2 diabetes was 42% (RR = 0.58, 95% CI: 0.39 to 0.87) lower in men with high testosterone levels (range, 449.6–605.2 ng/dl) than men with low testosterone levels (range 213.2–446.7 ng/dl) (Ding et al, 2006). Whether the association between glucose intolerance and low androgen levels is an independent relation remains a matter of debate, as any association between hyperinsulism and hypoandrogenism is confounded by the association of obesity with hyperinsulism and insulin resistance.

The third suggested cause of hypoandrogenism in obese males is sleep apnea. Patients with sleep apnea often have fragmented sleep course due to repetitive episodes of upper airway obstructions and hypoxia followed by arousal (Young et al, 2004). It has been demonstrated that patients with fragmented sleep have a blunted nocturnal rise of testosterone (Luboshitzky et al, 2001). Patients with obstructive sleep apnea have lower mean testosterone and LH values compared to both young and middle-aged controls. Morning testosterone levels were also found to be lower in patients with obstructive sleep apnea (Luboshitzky et al, 2005). Finally, in patients with obstructive sleep apnea, weight loss increases testosterone levels (Semple et al, 1984). These alterations in testosterone levels are likely to contribute to hypogonadism in a number of obese males. This observation is confounded by obesity, such that an independent effect on testosterone levels of sleep apnea separate from obesity requires further confirmation.

It is mandatory to mention leptin in the context of obesity and infertility. The role of leptin in reproduction was discovered in ob^{-}/ob^{-} mice. The lack of obesity (ob) gene encoding for leptin caused obesity and infertility in both male and female mice. Leptin administration in leptin deficient ob^{-}/ob^{-} mice restored fertility (Chehab et al, 1996). Obesity is associated with increased levels of circulating leptin, since white adipose tissue is the main site of leptin synthesis (Margetic et al, 2002). The effect of excess leptin on male reproduction is unknown. In hypogonadal men, testosterone substitution normalized elevated serum leptin levels (Jockenhovel et al, 1997). Leptin effects on reproduction are largely thought to be central, altering the hypothalamic pituitary axis (Margetic et al, 2002). Recent discovery of leptin in semen suggests a peripheral function as well (Aquila et al, 2005).

Obesity and Spermatogenesis

Body mass index is associated with alterations in sperm parameters in several reports. In a recent study investigating factors associated with semen quality among couples who visited an assisted reproduction clinic, the prevalence of obesity among men with infertility (defined as at least 2 findings among density less than 10 million, total count less than 20 million, motility less than 30%) was 3 times greater than among male partners of couples with idiopathic or female factor infertility. Groups were small in this study, and specific etiologies for lower sperm parameters among obese subjects were not described. Among the 47 men in this study with normal semen parameters at enrollment, but not among men with male infertility, sperm density and total count showed a statistically significant negative association with increasing BMI (Magnusdottir et al, 2005). Among a sample of 1558 Danish military recruits, several semen parameters were correlated with body mass index, with less favorable values reflecting spermatogenesis observed in individuals with either above or below the BMI range of 20–25 kg/m^2 (Jensen et al, 2004). After correction for multiple factors, including exposures, illnesses, and abstinence period prior to sample collection, sperm concentration and total count per ejaculate among men with BMI > 25 kg/m^2 were reduced by 26.1% and 23.9%, respectively, when compared to the reference group with BMI between 20 and 25 kg/m^2. The frequency of sperm density less than 20 million/ml was 29% among the overweight men compared to 21.7% in the normal weight reference group. Reductions in these measures were similar among the subjects with BMI less than 20 kg/m^2, such that total sperm count and sperm concentration exhibited an inverted U-shaped distribution relative to BMI. The endocrine findings in the heavy and thin men trended in opposite directions relative to the reference BMI group in several instances,

such that total testosterone, FSH, inhibin B, and SHBG were lower and estradiol higher in the overweight group relative to the reference group, while the reverse of these observations obtained for the leaner men. Thus, putative endocrine mechanisms underlying the apparent reduction in spermatogenesis, if any, among the lean and overweight subgroups can be inferred to be quite different. In a study of normozoospermic partners in an infertile population, sperm concentration was reduced among men with BMI greater than 30 compared to leaner members of the study group (Koloszar et al, 2005). Kort et al described the relation between sperm parameters and BMI in a generally overweight selection of subjects. An index of semen quality appeared to exhibit a decline with increasing BMI, as did the number of normal sperm per ejaculate. In his study, the total number of normal spermatozoa correlated negatively with body mass index in 520 semen analyses. The total number of normal motile spermatozoa differed statistically according to weight group (BMI < 25 kg/m^2 $= 18.6 \times 10^6$; BMI ≥ 25 kg/m^2 and < 30 kg/m^2 $= 3.6 \times 10^6$; and BMI $\geq 30 = 0.7 \times 10^6$, $P < .05$, ANOVA) (Kort et al, 2005). The relationship between BMI and sperm parameters was not preserved when obesity was expressed as waist/hip ratio. An absence of correlation with semen parameters with waist/hip ratio has been reported elsewhere (Fejes et al, 2005). A recent report showed that bariatric surgery may result in male infertility. Six severely obese men with at least 1 previous child were found to be azoospermic after Roux-en-Y gastric bypass operation (di Frega et al, 2004).

To the extent that obesity is causal of diminished sperm count and sperm density, such findings may relate to endocrine abnormalities of obese males. Where lower total and free levels of testosterone are found, it can be inferred (though it has not been shown) that these levels reflect decreased testicular testosterone production, and therefore lower intratesticular testosterone levels would be expected as well. Intratesticular testosterone levels (normally 100-fold greater than circulating concentrations) are correlated with spermatogenesis (Coviello et al, 2004; Coviello et al, 2005; Jarow and Zirkin, 2005; Matthiesson et al, 2005). It is not known whether the modest reductions in testosterone levels associated with obesity are accompanied by a reduction in intratesticular testosterone concentrations sufficient to explain the reductions in sperm count that have been observed in obese subjects. Although the observations of Raman and Schlegel that effecting an increase in low testosterone-estradiol ratios with aromatase inhibition is accompanied by improvement in semen parameters during aromatase inhibition hints that this may be so, it is clear that this issue requires further investigation (Raman and Schlegel, 2002). Moreover, it is important to note evidence that diminished intratesticular testosterone concentrations alone, absent concomitant suppression of FSH, may be insufficient for effective suppression of spermatogenesis (Narula et al, 2002).

The consensus observation that obesity and overweight are associated with a reduction in semen quality must be qualified by the observation that the studies cited here demonstrate only trends, and many overweight and obese subjects have consistently been shown to exhibit normal semen quality. Moreover, it is important to consider the possibility that nutritional or lifestyle factors associated with overweight and obesity, rather than a direct effect of obesity per se, account for these frequently observed associations. In addition, it is notable that decreased sperm quality (morphology) has not been found in men with higher BMIs (Jensen et al, 2004; Magnusdottir et al, 2005). However, there is consistent enthusiasm in the literature, with considerable circumstantial support, for the hypothesis that alterations of sperm parameters associated with obesity can be attributed to inappropriate suppression of the hypothalamic-pituitary-gonadal axis by elevated estrogens derived from peripheral aromatization, and resulting decreased testosterone production reflected in low levels of circulating testosterone and intratesticular testosterone (Table).

The role of estrogen in male reproductive health was highlighted with the growing public concerns that exposures to environmental chemicals with estrogenic activity may impact human reproductive health (Oliva et al, 2001). Obese men have been shown to exhibit higher levels of circulating estradiol and/or elevated estradiol/testosterone ratios in multiple studies (Schneider et al, 1979; Jensen, 2004; Fejes, 2006). Estrogens may affect spermatogenesis directly within the testis as well as by alterations in gonadotropin secretion by the pituitary. Excess estrogen has a direct deleterious effect on spermatogenesis in animal models (Goyal et al, 2003). However, elevated circulating estradiol owing to increased peripheral aromatization in obesity may not importantly affect intratesticular estrogen concentrations. It is true, also, that elevated circulating estrogen levels, as seen among obese men, have not specifically been linked to infertility. If there is an obesity-estrogen link, it may lie in the observation that obesity increases the accumulation and levels of estrogenic and endocrine disrupting environmental toxins that can affect fertility (Magnusdottir et al, 2005). The evidence cited thus far leads to the conclusion that obesity negatively influences sperm production (concentrations and total count), though further studies will be required to settle whether this effect is convincingly a cause for infertility attributable to obesity by itself.

To the extent that reduced total sperm counts and sperm concentration result from obesity, it is certainly true also that fertility does correlate with total count and sperm density. It has been shown that altered spermatogenesis and abnormal sperm parameters are correlated to subfertiltiy and infertility of a couple. Slama et al demonstrated that the ratio of conception for subjects $<20\times10^6$/ml sperm compared to those $>20\times10^6$/ml was 0.68 (95% CI: 0.52–0.91). This study also demonstrated that factors in addition to sperm density, such as morphology, may be important to fertility, and in this regard evidence that obesity adversely affects sperm morphology is lacking (Slama et al, 2002). In couples trying to conceive for the first time, the probability of succeeding increases with sperm count up to 40 million/mL (Bonde et al 1998). Most of the previously discussed alterations in the physiology of obese males can affect their reproductive potential and lead to subfertility or infertility.

Obesity and Erectile Dysfunction

The association between obesity and erectile dysfunction can frequently be shown to comprise another mechanism by which obesity may contribute to infertility. Erectile dysfunction is defined as the persistent or recurrent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. In men reporting symptoms of erectile dysfunction, 79% of the subjects are found to be overweight or obese (Feldman et al, 2000). The relation between obesity and erectile dysfunction can be explained in part by the elevated levels of several proinflammatory cytokines in obese individuals. These markers of inflammation are positively associated with endothelial dysfunction that is linked directly to male erectile dysfunction through the nitric oxide pathway (Sullivan et al, 1999). It is not clear if the association is due to an independent effect or due to cardiovascular risk factors that are commonly associated with obesity (Chung et al, 1999). In fact, well-recognized risk factors for cardiovascular diseases, such as smoking, diabetes, hypertension, and dyslipidemia, have strong epidemiological links with erectile dysfunction (Feldman et al, 2000). Hypoandrogenism contributes to the sexual dysfunction found in obese males (Seftel, 2005). Whether obesity is coupled with erectile dysfunction independently or through cardiovascular risk factors or hypoandrogenism, it is evident that obese men have a higher incidence of erectile dysfunction that affects their sexual life and fertility. In a randomized study, obese men who received detailed advice about how to achieve a loss of 10% or more in their total body weight by reducing caloric intake and increasing their level of physical activity had a higher rate of weight loss and improvement in erectile dysfunction than controls (Esposito et al, 2004).

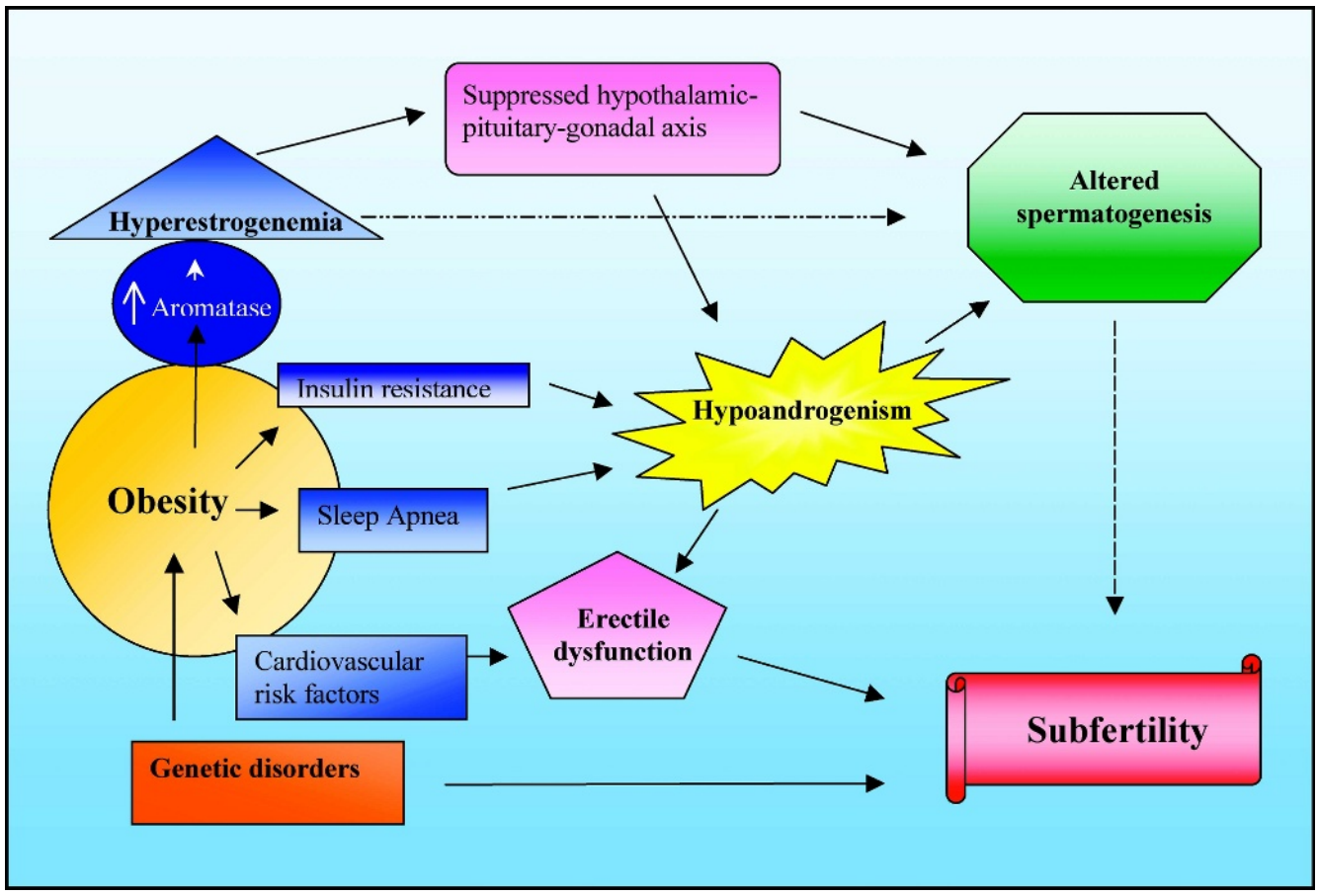
It is known that erectile dysfunction is associated with infertility. In a recent study where participants answered the Sexual Health Inventory for Men questionnaire, 27% of infertile men reported an abnormal score (erectile dysfunction) compared to 11% of the control fertile group (O'Brien et al, 2005). In a survey of health professionals, obesity was associated with a 1.3 relative risk for erectile dysfunction (Bacon et al, 2003).

Genetic Causes of Obesity and Male Infertility

Recognition of the possibility that infertility found in an obese subject may relate to underlying undiagnosed genetic or developmental abnormalities that adversely affect spermatogenesis independently of obesity is important both to researchers and clinicians.

Genetic factors that contribute to obesity are often complex and rely on the interaction of several genes in association with environmental factors such as nutrition and activity levels (Boutin and Froguel, 2001). This multifactorial mechanism explains the majority of cases of common obesity. However, there are conditions where obesity and infertility can result from a defined chromosomal or genetic defect. These defined genetic causes are rare and invoke measures and mechanisms beyond the primary effects of obesity itself on male infertility. Detection of such aberrations allows couples to be informed about the potential to transmit genetic abnormalities to their offspring. Klinfelter syndrome is the most common chromosomal disease causing infertility in men. This syndrome results from a numerical aberration in sex chromosome. The typical karyotype is 47,XXY. The diagnosis is confirmed by a karyotype analysis of blood lymphocytes (Kamischke, 2003). The numerical chromosome aberrations in this syndrome are due to nondisjunction predominantly during meiotic divisions occurring in germ-cell development or less frequently in early embryonic mitotic cell divisions. Phenotypically, patients can be obese with feminine pattern of fat distribution and gynecomastia; however, obesity is not a consistent feature. They have tall stature, small testis, hypogonadism, and severe alteration in spermatogenesis resulting in severe oligozoospermia or azoospermia (Diemer and Desjardins, 1999). In adult patients, about 70% complain of decreased libido and impotence. It is not known if the defect in the testis arises from an intrinsic problem in germ cells or is due to lack of support from the Sertoli cells (Lanfranco, 2004).

Prader-Willi syndrome is characterized by diminished fetal activity, hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, and morbid obesity. It is the most common syndromal cause of



Potential mechanisms for hypoandrogenism and erectile dysfunction in obese males.

human obesity (Farooqi, 2005). This is an imprinting disease caused by the absence of the paternal segment 15q11.2-q12, either through deletion (75%) or through loss of the entire paternal chromosome with presence of 2 maternal homologues (22%). Prometaphase banding examination can visualize deletions of chromosome 15 that account for 70%–80% of cases (Goldstone, 2004). Cryptorchidism is found in 80%–100% of patients with this syndrome (Suzuki et al, 2002). Testicular biopsy shows undifferentiated Leydig cells and arrested spermatogenesis at the late spermatid level (Diemer and Desjardins, 1999).

Other genetic entities resulting in male obesity and infertility are the Laurence-Moon and Bardet-Biedl syndromes. These are rare autosomal recessive disorders. The differentiation between these 2 syndromes is not unanimous. For many they constitute different expressions of a single entity "Laurence-Moon-(Bardet-)Biedl syndrome" (Yamada et al, 2000). They include common multiple defects, including mental retardation, retinal pigmentary dystrophy, hypogonadism, and morbid obesity (Mohsin et al, 2003). Polydactylia is found mainly in Laurence-Moon syndrome. Known genetic abnormalities include defects in the 4 loci BBS1 to BBS4. Infertility is frequent, but some patients have normal testicular function and spermatogenesis (Diemer and Desjardins, 1999).

Summary

The parallel change in obesity and sperm count suggests a potential link between obesity and male fertility. Obesity is associated with altered spermatogenesis and erectile dysfunction. The altered spermatogenesis is mainly due to hypoandrogenism and the deleterious effect of increased levels of estrogens. All these factors can affect the ability of a male to participate in the conception of a child (Figure). This review is a call for more focused studies to unveil the extent of the correlation between obesity and decreased sperm count and to quantify the contribution of obesity to male infertility. In the absence of clinical trials, treatment options for obese infertile males are limited and should be targeted toward reversing the hormonal profile and the erectile dysfunction.

References

Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. *Am J Public Health*. 2001;91:642–644.

Akingbemi BT. Estrogen regulation of testicular function. *Reprod Biol Endocrinol*. 2005;27:3–51.

Aquila S, Gentile M, Middea E, Catalano S, Morelli C, Pezzi V, Ando S. Leptin secretion by human ejaculated spermatozoa. *Clin Endocrinol Metab*. 2005;90:4753–4761.

Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med*. 2003;139:161–168.

Bonde JP, Ernst E, Jensen TK, Hjollund NH, Kolstad H, Henriksen TB, Scheike T, Giwercman A, Olsen J, Skakkebaek NE. Relation between semen quality and fertility, a population-based study of 430 first-pregnancy planners. *Lancet*. 1998;352:1172–1177.

Bottner A, Kratzsch J, Muller G, Kapellen TM, Bluher S, Keller E, Bluher M, Kiess W. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. *J Clin Endocrinol Metab*. 2004;89:4053–4061.

Boutin P, Froguel P. Genetics of human obesity. *Best Pract Res Clin Endocrinol Metab*. 2001;15:391–404.

Chehab FF, Lim ME, Lu RH. Correction of the sterility defect in homozygous obese female mice is treatment with the human recombinant leptin. *Nat Genet*. 1996;12:318–320.

Chung WS, Sohn JH, Park YY. Is obesity an underlying factor in erectile dysfunction? *Eur Urol*. 1999;36:68–70.

Coviello AD, Bremner WJ, Matsumoto AM, Herbst KL, Amory JK, Anawalt BD, Yan X, Brown TR, Wright WW, Zirkin BR, Jarow JP. Intratesticular testosterone concentrations comparable with serum levels are not sufficient to maintain normal sperm production in men receiving a hormonal contraceptive regimen. *J Androl*. 2004;25:931–938.

Coviello AD, Matsumoto AM, Bremner WJ, Hebst KL, Amory JK, Anawalt BD, Sutton PR, Wright WW, Brown TR, Yan X, Zirkin BR, Jarow JP. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. *J Clin Endocrinol Metab*. 2005;90:2595–2602.

de Boer H, Verschoor L, Ruinemans-Koerts J, Jansen M. Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. *Diabetes Obes Metab*. 2005;7:211–215.

Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89:5462–5468.

di Frega AS, Dale B, Di Matteo L, Wilding M. Secondary male factor infertility after Roux-en-Y gastric bypass for morbid obesity: case report. *Hum Reprod*. 2005;20:997–998.

Diemer T, Desjardins C. Developmental and genetic disorders in spermatogenesis. *Hum Reprod Update*. 1999;5:120–140.

Ding E, Song Y, Malik V, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2006;295:1288–1299.

Dunger DB, Ahmed ML, Ong KK. Effects of obesity on growth and puberty. *Best Pract Res Clin Endocrinol Metab*. 2005;19:375–390.

Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D. Effect of lifestyle changes on erectile dysfunction in obese men, a randomized controlled trial. *JAMA*. 2004;291:2978–2984.

Farooqi IS. Genetic and hereditary aspects of childhood obesity. *Best Pract Res Clin Endocrinol Metab*. 2005;19:359–374.

Fejes I, Koloszar S, Szollosi J, Zavaczki Z, Pal A. Is semen quality affected by male body fat distribution? *Andrologia*. 2005;37:155–159.

Fejes I, Koloszar S, Zavackcski Z, Daru J, Szollosi J, Pal A. Effect of body weight on testosterone/estradiol ratio in olgozoospermic patients. *Arch Androl*. 2006;52:97–102.

Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, McKinlay JB. Erectile dysfunction and coronary risk factors, prospective results from the Massachusetts male aging study. *Prev Med*. 2000;30:328–338.

Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. *J Clin Endocrinol Metab*. 1994;79:997–1000.

Goldstone AP. Prader-Willi syndrome, advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab*. 2004;15:12–20.

Goyal HO, Robateau A, Braden TD, Williams CS, Srivastava KK, Ali K. Neonatal estrogen exposure of male rats alters reproductive functions at adulthood. *Biol Reprod*. 2003;68:2081–2091.

Haffner SM, Valdez RA, Stern MP, Katz MS. Obesity, body fat distribution and sex hormones in men. *Int J Obes Relat Metab Disord*. 1993;17:643–649.

Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*. 2004;291:2847–2850.

Jarow JP, Zirkin BR. The androgen microenvironment of the human testis and hormonal control of spermatogenesis. *Ann N Y Acad Sci*. 2005;1061:208–220.

Jensen TK, Andersson AM, Jorgensen N, Andersen AG, Carlsen E, Petersen JH, Skakkebaek NE. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril*. 2004;82:863–870.

Jockenhovel F, Blum WF, Vogel E, Englaro P, Muler-Wieland D, Reinwein D, Rascher W, Krone W. Testosterone substitution normalises elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab*. 1997;82:2510–2513.

Kamischke A, Baumgardt A, Horst J, Nieschlag E. Clinical and diagnostic features of patients with suspected Klinefelter syndrome. *J Androl*. 2003;24:41–48.

Koloszar S, Fejes I, Zavacki Z, Daru J, Szollosi J. Effect of body weight on sperm concentration in normozoospermic males. *Arch Androl*. 2005;51:299–304.

Kort HI, Massey JB, Elsner CW, Mitchell-Leef D, Shapiro DB, Witt MA, Roudebush WE. Impact of body mass index values on sperm quantity and quality. *J Androl*. 2005;27:450–452.

Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet*. 2004;364:273–283.

Laron Z. Is obesity associated with early sexual maturation? *Pediatrics*. 2004;113:171–172.

Luboshitzky R, Lavie L, Shen-Orr Z, Herer P. Altered luteinizing hormone and testosterone secretion in middle-aged obese men with obstructive sleep apnea. *Obes Res*. 2005;13:780–786.

Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P, Lavie P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. *J Clin Endocrinol Metab*. 2001;86:1134–1139.

Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K. Persistent organochlorines, sedentary occupation, obesity and human male subfertility. *Hum Reprod*. 2005;20:208–215.

Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. *Int J Obes Relat Metab Disord*. 2002;26:1407–1433.

Matthiesson KL, Stanton PG, O'Donnel L, Meachem SJ, Amory JK, Berger R, Bremner WJ, McLachlan RI. *J Clin Endocrinol Metab*. 2005;90:5647–5655.

Mohsin N, Marhuby H, Maimani Y, Aghanishankar P, Al-Hassani M, Seth M, Daar AS. Development of morbid obesity after transplantation in Laurence Moon Biedle syndrome. *Transplant Proc*. 2003;35:2619.

Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. *JAMA*. 1999;282:1519–1522.

Narula A, Yi-Qun G, O'Donnell L, Stanton PG, Robertson DM, McLachlan RI, Bremner WJ. Variability in sperm suppression during testosterone administration to adult monkeys is related to follicle stimulating hormone suppression and not to intratesticular androgens. *J Clin Endocrinol Metab*. 2002;87:3399–3406.

National Center for Chronic Prevention and Health Promotion, Defining overweight and obesity. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/defining.htm. Accessed November, 2005.

O'Brien JH, Lazarou S, Deane L, Jarvi K, Zini A. Erectile dysfunction and andropause symptoms in infertile men. *J Urol*. 2005;174:1932–1934.

Oehninger S. Clinical and laboratory management of male infertility: an opinion on its current status. *J Androl*. 2000;21:814–821.

Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. *Hum Reprod*. 2001;16:1768–1776.

Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod Update*. 2003;9:359–372.

Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol*. 2002;167:624–629.

Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. *J Clin Endocrinol Metab*. 1979;48:633–638.

Seftel A. Male hypogonadism. Part II, etiology, pathophysiology, and diagnosis. *Int J Impot Res*. 2005 Epub ahead of print.

Semple PA, Graham A, Malcolm Y, Beastall GH, Watson WS. Hypoxia, depression of testosterone, and impotence in pickwickian syndrome reversed by weight reduction. *Br Med J.(Clin Res Ed)*. 1984;289:801–802.

Simpson E, Rubin G, Clyne C, Robertson K, O'Donnell L, Davis S, Jones M. Local estrogen biosynthesis in males and females. *Endocr Relat Cancer*. 1999;6:131–137.

Slama R, Eustache F, Ducot B, Jensen TK, Jorgensen N, Horte A, Irvine S, Suominen J, Andersen AG, Auger J, Vierula M, Toppari J, Andersen AN, Keiding N, Skakkebaek NE, Spira A, Jouannet P. Time to pregnancy and semen parameters, a cross-sectional study among fertile couples from four European cities. *Hum Reprod*. 2002;17:503–515.

Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men, prospective results from the Massachusetts male aging study. *Diabetes Care*. 2000;23:490–494.

Strain GW, Zumoff B, Kream J, Strain JJ, Deucher R, Rosenfeld RS, Levin J, Fukushima DK. Mild hypogonadotropic hypogonadism in obese men. *Metabolism*. 1982;31:871–875.

Sullivan ME, Thompson CS, Dashwood MR, Khan MA, Jeremy JY, Morgan RJ, Mikhailidis DP. Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res*. 1999;43:658–665.

Suzuki Y, Sasagawa I, Tateno T, Yazawa H, Ashida J, Nakada T. Absence of microdeletions in the Y chromosome in patients with Prader-Willi syndrome with cryptorchidism. *Int J Androl*. 2002;25:1–5.

Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996. *Environ Health Perspect*. 2000;108:961–966.

Tchernof A, Després JP, Belanger A, Dupont A, Prud'homme D, Moorjani S, Lupien PJ, Labrie F. Reduced testosterone and adrenal C19 steroid levels in obese men. *Metabolism*. 1995;44:513–519.

Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance, influence of sex hormone-binding globulin and body fat. *Diabetes Care*. 2004;27:861–868.

Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. *Pediatrics*. 2002;110:903–910.

World Health Organization Laboratory. *Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction.* 4th ed. Cambridge, MA: Cambridge University Press; 1999.

Yamada K, Miura M, Miyayama H, Sakashita N, Kochi M, Ushio Y. Diffuse brainstem glioma in a patient with Laurence-Moon-(Bardet-)Biedl syndrome. *Pediatr Neurosurg*. 2000;33:323–327.

Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA*. 2004;291:2013–2016.