Diminished fertility in men with increased BMI

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ABSTRACT

The incidence of obesity as a risk factor for normal life is increasing worldwide. Its impact on hypertension, cardiovascular diseases, osteoporosis, insulin resistance and diabetes mellitus, is well recognized. Previous studies have proved the association between female obesity and infertility and several linked genes have been worked out. However, a little is known about the effect of obesity on male reproductive system and infertility. Recently some clinical studies have reported diminished semen parameters like sperm count, sperm motility and vitality and changing in reproductive hormones in over weight and obese men. Lack of such study in Asian countries and particularly in Indian population who are genetically more prone to obesity necessitates picking up this research to achieve robust findings in this regard.

Key words: Obesity; Azoospermia; BMI; Erectile dysfunction.

INTRODUCTION

The obese male is generally characterized as having greater than 25% body fat of total body mass with a BMI in excess of 30 kg/m2 [1]. BMI is used as the chief indicator of obesity, with stratified BMI categories as follows: 18.5–24.9 kg/m2 (normal), 25 kg/m2 and above (overweight) and 30 kg/m2 and above (obese). Other more accurate methods to assess obesity include measurement of skin fold thickness [2], hydrostatic weighing, dual-energy x-ray absorptiometry or whole-body adipose tissue computed tomography (CT) and MRI combined with waist:hip ratio measurements [3].

The potential effects of increased BMI in men on fertility have not been subject to the same degree of scrutiny as female obesity [4]. Obesity in women is known to contribute to anovulation, a reduced conception rate and an increased risk of miscarriage and prenatal complication [5]. Over the years, a number of population-based studies have highlighted a trend towards deterioration in semen quality [5], showing that overweight and obese men have an up to 50% higher rate of sub-fertility when compared with normal weight men [4,6]. Hypotheses put forward to explain this decline include increased use of pesticides [7], environmental pollutants [8,9], lifestyle factors [10], and increasing male obesity.[11]. Table1 shows the Criteria for a normal semen analysis [12]**.** Apart from these some more tests done in specialized laboratory are Super oxide dismutase (SOD), lipid peroxidase, Sperm nuclear chromatin decondensation (NCD), Reactive oxygen Species (ROS),and sperm function tests like Hypo osmotic swelling test (HOS), estimation of seminal fructose and zinc, Immunobed tests etc (Table2). In this review article, we aim to focus on the association between obesity and male fertility, and discuss present treatment or management options for this common problem.

Link between male obesity and fertility challenges based of evidences

Obesity and semen parameters

Obesity has been shown to be linked to reduced spermatogenesis. In a study of 1,558 military conscripts the total sperm count per ejaculate was reduced by 24% in men with a BMI > 25 kg/m^2. The percentage of normal sperm morphology was also shown to be adversely effected by either high or low BMIs in this study. Further, an associated decrease in testosterone, follicle stimulating hormone, Inhibin B and sex hormone binding globulin was observed in the overweight group [11]. A retrospective analysis of data from 390 men suggested that high BMI was associated with reduced sperm concentration and motility [13]. A recent World Health Organization surveillance study confirmed that obese men had significantly lower total sperm count than non-obese men, although other sperm parameters were not shown to be affected [14]. However, this effect on sperm count may be marginal, with analysis of a database of 2,139 men finding only a slightly lower total sperm count among overweight men and non-significant change in obese men [15]. A further study among men attending an infertility clinic showed that despite major changes in reproductive hormones, total sperm counts were lower only in cases of extreme obesity [16].

A study of 520 Danish men showed a significantly reduced number of normal motile sperms (normal BMI 18.6 x 10^6, overweight 3.6 x 10^6, obese 0.7 x 10^6) and importantly an increase in sperm DNA fragmentation in overweight and obese men [17]. DNA fragmentation index (DFI) is the percent of sperm in the semen sample that have increased levels of single or double strand breaks in nuclear DNA. Kort et al (2006) showed an increase in the DFI in men with high BMI, suggesting that obesity might compromise the integrity of sperm chromatin. The reference value for a young and healthy man is about 3-5% of sperm with fragmented DNA while this level is of 25-30% DFI in a man with high risk for infertility [18]. An increase in BMI above 25 kg/m^2 causes an increase in sperm DFI and a decrease in the number of normal chromatin-intact sperm per ejaculate, relative to the degree of obesity [17].

In another retrospective study of 526 infertile men in which the incidence of oligozoospermia and low progressive motile sperm concentration was higher in overweight and obese men than in normal weight men [12]. However, it is important to note that many obese men have been shown to have normal semen quality and fertility, suggesting that the effect of obesity may not be consistent, as suggested in a study by Pauli et al (2008) in which there was no association between obesity and semen quality [2]. However, a recent study by Najafi et al (2011) showed a decrease in fertility parameters like sperm count and motility among overweight and obese men [19].

Reproductive hormones imbalance in adult obese men

The endocrine abnormalities associated with obesity in women are well known with an increase in androgen metabolism and elevated oestrogen levels [20]. Obese males usually express a characteristic hormonal profile described as "hyperestrogenic hypogonadotropic hypogonadism." Total body fat, intra abdominal fat, and subcutaneous fat have all been associated with low levels of total and free testosterone with a decreased ratio of testosterone to estrogen in obese men which is due to over activity of the aromatase cytochrom P450 enzyme (a product of CYP10 gene) which is highly expressed in white adipose tissue [21, 22]. The aromatization of C19 androgens such as testosterone and androstenedione is a key step in the biosynthesis of estrogens [23]. Central obesity in particular appears to be associated with a decrease in circulating androgen levels proportional to the degree of obesity [24].

In a recent observational study, despite demonstrating relative hypogonadotropic hypoandrogenism in obese men, semen analysis parameters were unaffected [2] while others have shown obesity to be associated with a decrease in testosterone and total sperm count [11]. These opposing results, suggest that any effect of reduced testosterone on male infertility may be modest and that further studies are required to give definitive answers. Conversely, it has been suggested that rather than obesity causing impaired testicular function, defective spermatogenesis causes obesity

[14], with some supporting evidence, such as body fat increasing in men receiving therapy to reduce testosterone during treatment for prostatic cancer [25]. Insulin resistance also is the other suggested mechanism to be associated with obesity and is a cause of hypoandrogenism and negatively correlated with testosterone levels [21].

Table 1. World Health Organization criteria for normal semen analysis

Criteria	Parameters
Semen volume	**≥2 ml**
Semen PH	**≥ 7.2**
Sperm concentration	**≥ 20 × 10^6 per ml**
Motility	**> 50% with forward progression**
Total sperm count	**> 40 × 106 sperm**
Morphology	**> 15% normal**
Vitality	**50% or more live, i.e., excluding dye**
White blood cells	**1×10^6 per ml**

Age-adjusted fasting insulin and C-peptide were shown to be inversely correlated to total and free testosterone in men [21]. Sex hormone–binding globulin levels are reduced in obese men, an alteration principally mediated by the increased circulating insulin levels associated with the insulin resistance of obesity [26].

Another suggested cause of endocrine changes which is more common in obese individuals relates to sleep apnea. Since patients with sleep apnea often have fragmented sleep course owing to repeated episodes of airway obstructions and hypoxia, appears to decrease the nocturnal rise of testosterone, resulting in lower mean levels of testosterone and LH. Luboshitzky et al (2005) showed that sleep apnea in obese cases is associated with decreased pituitary-gonadal function, and that decreased testosterone concentration is due to obesity [27].

Inhibin B is the most accurate marker for regular spermatogenesis in all males [28]. Inhibin B marks normal Sertoli cell function and associated spermatogenic activity. So it can be used to predict the quality of sperm and fertility of obese men [29, 30]. It is reported that obese men have significantly (25-32%) lower levels of Inhibin B than normal levels in non obese men [30], indicates that the production of male gametes is seriously impaired in obese males [28].

Obesity and erectile dysfunction

Another mechanism which has been reported in several studies to be more common among in men with increased BMI is erectile dysfunction [31, 32]. The relationship between erectile dysfunction and high BMI can be partly due to increased level of several proinfalamtory cytokines in obese persons. These inflammatory markers are positively associated with impaired endothelial function which is directly related to male erectile dysfunction. About 76% of men who report erectile dysfunction and decrease in libido are overweight and obese [2].

However, surprisingly when men with reduced coital frequency are excluded from the analysis, still it has been shown that overweight and obese men have increased incidence of sub-fertility [33].

Obesity and increased scrotal temperature

A high BMI has been postulated to increase in scrotal temperature and impair or arrest spermatogenesis. Many studies have focused on testicular heat stress as a potential risk factor of impaired sperm parameters. A study by Hjollund et al (2000) shown that even a moderate increase in scrotal temperature can be associated with substantially reduced sperm concentrations [34]. In addition, Magnusdottir et al (2005) concluded that increased duration of sedentary posture correlated positively with increased scrotal

temperature and ultimately a decrease in sperm quality [35].

Table 2. WHO references for optional tests of semen analysis

Test	Reference value
Hypo-osmotic swelling (HOS) test	**≥ 60% of the spermatozoa undergo tail swelling**
Papanicolaou staining	**≥15% normal**
Measurement of zinc in seminal plasma	**2.4 µmol or more per ejaculate**
Measurement of fructose in seminal plasma	**13 µmol or more per ejaculate**
Measurement of neutral α-glucosidase in seminal plasma	**20 mU per ejaculate (minimum)**

Treatment and management of obesity - induced infertility in men

Unlike in women, limited clinical data are available on treatment of infertility in obese men. However, if the changes that cause infertility by obesity are reversible, then change in life style and weight loss can be first step and is likely to be an effective treatment. Unfortunately, increasingly individuals fail to recognize that they are obese, and this is more so in men. A recent British survey by Johnson et al (2008) showed that 53% of the population was overweight or obese, yet in obese men only 67% recognized themselves to be overweight or obese[36]. Therefore, it is important that BMIs are measured in all men attending for advice on infertility. Overweight and obese men should be informed regarding the association between increased weight and infertility and strongly advised to aim for a BMI of below 25 kg/m2 before starting fertility treatment. However, it should be remembered that lean muscular men may have high BMIs and therefore infertility is not consequent to excess adiposity.

Obesity-induced hypogonadism in males may be treated by weight loss, which should reduce estrogen levels to normal and alleviate the HPT (hypothalamic-pituitary-testicular) feedback inhibition [1]. Roux-en-Y gastric bypass surgery, one option for the treatment of morbid obesity, has been shown in one study to seemingly reverse abnormal reproductive hormonal profiles, such that total testosterone is increased and serum estradiol is decreased [37]. Other treatment options for hypogonadism include supplementation with alternative or recombinant gonadotropins (e.g., human chorionic gonadotropin [hCG] and recombinant FSH), which stimulate testicular function, including testosterone production [38]. Finally, aromatase inhibitors, letrozole and anastrozole, can be used to prevent enzymatic conversion of androgens to estrogens in adipocytes and other tissues [23,38], thereby reducing serum estradiol and suppression of the HPT axis by interrupting the hypogonadal–obesity cycle [39]. Much more researches are required to evaluate the effect of these treatments on improvement of fertility in obese men.

CONCLUSION

There are an ever-growing number of reports concerning increasing number of overweight and obese men in the developed countries. The changes in sperm parameters and reproductive hormones (including testosterone, estrogen and Inhibin B) in obese men reported in recent studies emphasize on a link between obesity and spermatogenesis and erectile dysfunction. Though there is some inconsistency in the results of previous studies to measure semen parameters affected by obesity, the consistent increase in leptin levels and decrease in Inhibin B levels seen in all obese – infertile cases indicate a fault in normal spermatogenesis and sperm quality. We hope this review will be a call to launch genetic and molecular studies to unveil the molecular basis of obesity-induced infertility in men.

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