

Review

The impact of obesity on male fertility

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ABSTRACT

Obesity in men of reproductive age is globally on the increase. There is clear evidence from epidemiological studies that obesity impacts negatively on male fertility; it is associated with hypogonadism, although it is less consistently linked to impaired spermatogenesis and tests of sperm function, including DNA fragmentation. Sperm from obese men used for in vitro fertilisation/intra cytoplasmic sperm injection is associated with a greater number of pregnancy losses and is less likely to result in live births. There are also increasing data from animal studies that paternal obesity may impact negatively on the reproductive and metabolic health of offspring and grand-offspring. It has been suggested that high-fat dietary exposures could affect the epigenetic content of sperm or the endocrine content of seminal fluid and thus impact early fetal development. Experimental and epidemiological data show that male fertility, and offspring health, can be improved by weight loss in obese and overweight males.

Key words: Fertility, Hypogonadism, Infertility, Metabolic syndrome, Overweight, Paternal, Sperm

INTRODUCTION

The prevalence of obesity worldwide has doubled since 1980; 65% of the global population now live in countries where overweight and obesity results in more morbidity than underweight, while the combined medical costs associated with obesity have increased by an estimated £2 billion/year.¹⁻³ In examining the impact of overweight and obesity on male reproductive functioning it needs to be appreciated that fertility is a complex multifactorial process involving the female partner as well and, therefore, while robust endpoints such as pregnancy and live birth are the

key outcomes, surrogate endpoints such as analysis of spermatogenesis are often required. Furthermore, obesity affects male fertility via multiple mechanisms including obesity-associated hypogonadism, its impacts on sperm production and function and its atherogenic effect on peripheral vasculature which may also cause erectile dysfunction.^{4,5}

OBESITY AND HYPOGONADISM

Male obesity is associated with hypogonadism. This may be as a result of a combination of hypogonadotropic hypogonadism, a reduction in sex hormone binding globulin (SHBG) production by the liver, and greater adipocyte aromatase activity resulting in an increase in the conversion of testosterone to estradiol leading to altered hypothalamic and pituitary negative feedback. The EMAS analysis of older men (ages 40 to 80) confirms the substantial effect of increas-

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ing BMI on total testosterone, free testosterone, and SHBG at all ages.⁶ A relationship between degree of obesity and effect is very apparent. A meta-analysis of these relationships confirmed the clear impact of increasing BMI on low testosterone, low free testosterone, and SHBG, though study results of the effects on estradiol have been much less consistent.⁷ Most studies moreover did not find any effect on LH levels, although an early study suggested a reduced LH pulse amplitude but not pulse frequency in obese men.⁸ This may reflect the now well-recognised impact of energy sensing pathways on the kisspeptin/neurokinin B pathways in the hypothalamus, which drive GnRH pulsatile secretion.⁹

Longitudinal data from the EMAS study provide evidence of the impact on weight gain or loss on male reproductive endocrinology. Importantly, these data show that weight loss is associated with rises in total testosterone, free testosterone, and SHBG, the latter exhibiting the clearest size effect relationship. The rise in SHBG with modest weight loss therefore tends to obscure any effect on free testosterone until weight loss is more substantial. These studies also indicate a rise in LH with more marked weight loss.^{10,11} Overall, the abovementioned analyses therefore point to the potential benefit of weight loss measures in hypogonadal obese men, and indeed studies assessing lifestyle change and bariatric surgery confirm the beneficial effects of weight loss on male reproductive function. A meta-analysis of 24 studies also pointed to a relationship between reductions in BMI and rise in testosterone, with the testosterone rise being greater in younger and more obese men.¹²

OBESITY, SPERMATOGENESIS, AND FERTILITY

While results demonstrating the endocrine effects of obesity on male reproductive function are largely robust, those indicating effects on fertility, and particularly on spermatogenesis are less consistent. Any analysis of the impact of the rising prevalence of obesity also needs to give serious consideration to the known background changes in male fertility that have occurred over the past few decades. Registry-based studies indicate US fertility rates (births/1000 men) have declined from 57 in 1980 to 45.8 in 2013,¹³ and in Denmark the number of offspring per man at age

45 dropped from 1.9 to 1.7 between 1990 and 2005,¹⁴ an effect partially compensated for by increasing rates of IVF.¹⁴ In many countries, the prevalence of male reproductive disorders has been steadily rising, this is most robustly demonstrated in the rising incidence of testicular cancers.¹⁵ Concerns over declining spermatogenesis are more controversial but appear well established in some,^{16,17} if not all, populations.¹⁸

Evidence for an association between obesity and fertility rates comes from epidemiological studies examining correlations between BMI and fertility, and also from comparisons of sperm counts in obese and normal-weight men. Epidemiological studies have consistently demonstrated an impact of obesity on male reproductive function. The Danish National Birth Cohort reported in 2007 an analysis of 47,835 couples. Increasing BMI in males was associated with subfertility (time to pregnancy of >12 months) with an adjusted odds ratio (AOR) (95% confidence interval) of 1.53 (1.32-1.77) in obese men (BMI >30 kg/m²), an effect which increased to 2.75 (2.27-3.30) where the female was also obese.¹⁹ Comparable data were obtained in the Norwegian Mother and Child Cohort of 26,303 planned pregnancies where the adjusted OR for infertility at 12 months was 1.2 (1.04-1.38) in overweight men and 1.36 (1.13-1.63) for obese men relative to those of normal weight, likely a conservative estimate given that couples failing to conceive were excluded from the analysis.²⁰ The results were similar when only couples where the female had a normal BMI were analysed. Data from the Agricultural Health Study in the United States also showed increasing BMI to be associated with infertility at 12 months: in this study, a 3kg/m² increase in BMI was associated with increased risk of subfertility of 1.21 (1.07-1.38).²¹ All of these studies used self-reported weight and height and collected the data retrospectively; the Scandinavian studies also excluded unplanned pregnancies, all of which factors may have affected the accuracy of the results, although the data are remarkably consistent.

Studies assessing the impact of obesity on spermatogenesis have been less consistent. The major confounding factor in many studies is that samples are often drawn from populations presenting to infertility centres, resulting in bias. An exception is a study of military recruits from Denmark where men

with a BMI of over 25kg/m² showed 21% and 23.9% reductions in sperm concentration and total sperm count, respectively.²² Underweight men (BMI <20kg/m²) also showed a reduced sperm concentration and total sperm count. In neither group were percentages of normal or motile spermatozoa different.²² This analysis included a large number of individuals (1,558); however, their median age was only 19. An American cohort of 468 men, also recruited outside a fertility setting, found BMI and waist circumference to correlate only with ejaculate volume and not with any other sperm parameters, although the number of recruits with BMI <25 (the reference group) was relatively small (n=83).⁴ A meta-analysis in 2010 concluded that there was no evidence for a relationship between BMI and sperm concentration or total sperm count,⁷ with only 5 of 31 studies identified being able to be pooled for analysis. A subsequent larger meta-analysis, in which 21 studies reporting on over 13,000 men were included, did however find evidence of a significant impact on spermatogenesis, with OR for oligospermia or azospermia of 1.11 (1.01-1.21) for overweight and 1.28 (1.06-1.55) for obese men, rising to 2.04 (1.59-2.62) for morbidly obese men.²³ There was strong heterogeneity between studies, impacted upon by multiple factors, for example, operator variability, time of abstinence, and time of year that the sample was taken.

Evidence of abnormal sperm function derives from analyses of IVF and ICSI outcomes in obese males where the live birth rates per embryo transfer are reduced in obese men when compared to those of healthy BMI.^{24,25} The suggestion of an increased risk of pregnancy loss after assisted conception²⁶ embryo development and pregnancy, and live birth outcomes after assisted reproductive technology (ART is intriguing and may also indicate abnormal sperm function. One potential mechanism possibly accounting for this is through increased sperm DNA fragmentation. Analysis of chromatin integrity suggests that both overweight and obese men show increased sperm chromatin damage.^{4,7,27,28} Methods for assessing sperm DNA integrity however remain debated.²⁹ While an initial meta-analysis (not addressing BMI) suggested that sperm DNA damage was associated with increased pregnancy loss, a more recent update from the same group failed to find a consistent link to embryo quality

and/or development.^{30,31} A further factor of relevance to disrupted sperm function in obese men is the presence of reactive oxygen species (ROS), an indicator of perturbed mitochondrial function.³² Increased ROS were present in the semen of obese men, which appeared to originate from macrophages.³³ In rodent studies, high fat diet exposure also increased reactive oxygen species in sperm,^{34,35} an effect which also perturbed embryonic development.³⁶

IS THERE A TRANSGENERATIONAL IMPACT OF PATERNAL OBESITY?

Epidemiological and experimental studies suggest that paternal obesity may also impact on the metabolic health of offspring and grand-offspring. Offspring of obese parents are more likely to be obese and suffer from adverse metabolic health, with some studies showing the strongest effect exerted by paternal obesity.^{37,38} Data collected in Överkalix at the end of the 19th and in the early 20th century in Sweden suggest that paternal nutrition impacts on mortality and risk of cardiovascular disease in grandsons.³⁹ However, comparison of multiple studies does not provide conclusive evidence that there is a clear maternal or paternal effect of obesity that can be differentiated; rather, the conclusion is that it is difficult to control for the presence of environmental and genetic confounding, which thus makes interpretation complex.³⁸ For this reason, experimental studies in which postnatal and genetic factors can be controlled have been useful to determine if effects can be transmitted from father to offspring after which the potential mechanisms may be investigated. Evidence showing the transmission of diet-induced phenotypes through the male line is supportive of the concept that transmission may be mediated by non-genetic inheritance,⁴⁰⁻⁴⁴ with some evidence suggesting a perturbed 'epigenome' in the sperm.⁴⁰⁻⁴⁴ These studies are summarised in the Table. It should be borne in mind, however, that paternal behaviour and the constituents of semen may also influence maternal behaviour and/or pre-implantation development and thus might also have a part to play.⁴⁵⁻⁴⁸

There are few studies addressing whether weight loss might improve fertility. However, an abstract presented at ENDO 2015 indicates that in a cohort of

Table. Summary of animal studies examining the effect of paternal diet or fasting on phenotypes offspring and grand-offspring. F1 indicates offspring of the exposed male. F2 indicates the grand-offspring of exposed males. ND Not reported, 'Yes' indicates parameter was significantly altered as a result of the male intervention, 'No' indicates was not significantly different

| Study | Species | Exposure | Exposure time | Exposure age from | Outcome | Effect in | | | |
|-------|-----------------------|-----------------------------|----------------|-------------------|-------------------------------|-----------|-----------|------------------|-----------|
| | | | | | | F1 male | F1 female | F2 male | F2 female |
| 44 | Drosophila | 30g/L vs. 300g/L sugar diet | 2 days | 4-5 day | Increased serum triglycerides | Yes | ND | No | ND |
| 40 | Mouse: Out bred Swiss | 24 hour fast | 6x over 3weeks | 8 week old | Serum glucose at 6wk | Yes | Yes | ND | ND |
| 43 | Rat: Sprague Dawley | Chow vs. 40.7-43% fat diet | 14 weeks | 4 weeks | Impaired glucose tolerance | ND | Yes | ND | ND |
| 41 | Mouse: C57/bl6 | 11% vs. 20% protein diet | 6-9 weeks | 21 days | Lower cholesterol esters | Yes | Yes | ND | ND |
| 42 | Mouse: C57/bl6 | 21% vs. 40% Fat diet | 10 weeks | 5 weeks | Increased weight | Yes | Yes | Yes (via female) | No |
| | | | | | Impaired glucose tolerance | Yes | Yes | Yes (via female) | No |

obese men, those whose partners conceived had lost more weight, and significant independent predictors of pregnancy were losing weight, eating more breakfasts weekly, and greater consumption of fruit and vegetables.⁴⁹ Studies in mice also provide evidence that sperm parameters and metabolic health in offspring can be improved by a switch from a high-fat to a low-fat diet, an effect additionally enhanced by exercise.^{50,51} A small study of men undergoing bariatric surgery for obesity found improvement in hormonal measures but no change in sperm parameters 2 years following the intervention.⁵² This is in contrast to case series which identified a fall in already perturbed sperm counts following bariatric surgery, with incomplete recovery at 2 years post-surgery.^{23,53} In contrast, diet and exercise induced weight loss may improve sperm parameters.⁵⁴

CONCLUSION

Obesity has multifactorial effects on male reproductive function, with clear evidence of endocrine disturbance in the form of hypogonadotropic hypogonadism, probably accompanied by hyperestrogenemia (Figure). The epidemiologic evidence for reduced fertility also appears clear, but the mechanisms for this, also likely to be multifactorial, are less appar-

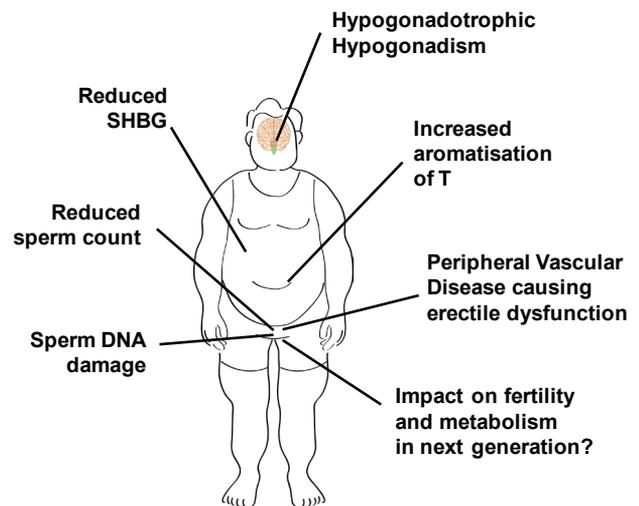


Figure. Factors contributing to reduced fertility in obese men.

ent. There is some evidence of abnormal Sertoli cell function/spermatogenesis, but not all studies have found this. These effects may be accompanied by reduced coital frequency and erectile dysfunction in some men. Importantly, however, evidence is starting to emerge that many, if not all, of these effects are reversible. Knowledge is also accumulating about the impact of obesity on spermatogenesis and its potential implications for subsequent generations.

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