Male Infertility

Fertility Fears – Fate of the Fat

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Abstract
It is well known that being overweight or clinically obese can have adverse effects on health. In the past, little was known about the impact of obesity on male reproductive function. However, several recent studies clearly show that obesity is associated with reduced semen quality and erectile dysfunction, and therefore obesity can be regarded as a cause of male infertility. It is believed that excess fat leads to changes in hormone levels (e.g. adipocytes increase aromatisation of testosterone to oestrogen) as well as dysregulation of the hypothalamus–pituitary–gonadal axis. Higher levels of adipose-derived hormones and adipokines combined with physical disorders can further contribute to obesity-induced infertility. Several treatment options, e.g. lifestyle changes, pharmacological interventions and surgical options, are being explored for their ability to restore fertility in the obese. Urologists and fertility specialists must be more aware of the role obesity plays in the aetiology of male infertility.

Keywords
Obesity, male infertility, reproductive hormones, adipose-derived hormones, adipokines, sperm parameters, body mass index

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Evidence suggests that male fertility is decreasing not only in westernised societies but worldwide. This is evident from various population-based studies as well as from the increasing numbers of couples seeking infertility treatment.1–4 As yet, questions remain as to the cause of these findings. Several reports have focused on the possible link between obesity and male infertility.4–8 It is speculated that obesity disrupts male reproduction by impairing semen parameters and reducing secondary sex characteristics.9 It is thus of importance for urologists and fertility physicians to assess male body composition during the normal fertility work-up and to focus on obesity as an aetiology of male infertility.

Obesity – Definition and Prevalence
Obesity is a medical condition in which excess body fat, or white adipose tissue, accumulates in the body.6 Overweight and obesity are more broadly defined as abnormal or excessive fat accumulation that may impair health.

Only a few methods can accurately measure fat content, including underwater weighing and dual-energy X-ray absorptiometry (DEXA), but these methods are not practical and are performed only in research centres with specialised equipment. Therefore, the most commonly used method is the most simple to perform: body mass index (BMI), which is defined as weight in kilograms divided by the square of the height in metres (kg/m²). A BMI >25kg/m² is considered overweight and a BMI >30kg/m² is considered to be obese. Waist circumference and the waist-to-hip ratio (WHR) are less commonly used to diagnose obesity. In fact, they may be more accurate in predicting obesity-related health issues. For males, a waist circumference of 102cm or greater is considered to be unhealthy, while a WHR <0.9 is considered normal.10–12 Other anthropometrical measurements such as skin fold thickness, bioelectrical impedance analysis, risk factors and co-morbidities are also used to diagnose obesity.

Sedentary lifestyles and decreased physical activity combined with an increased intake of energy-dense foods high in fat and sugars lead to an energy imbalance whereby energy consumed exceeds energy expended.4 This lifestyle is the key cause of the global increase in overweight and obesity and the reason it is reaching epidemic proportions in several countries. In the US alone, more than 35–40% of the population is believed to have a BMI >30kg/m².13,14 Once considered to be a problem only of westernised countries, this phenomenon is now dramatically on the increase in developing countries and, specifically, in young children (six to nine years of age).15 The global prevalence of obesity has doubled in the past decade, and at this rate it is predicted that almost one billion people will suffer from obesity in the next five years.13

Obesity-linked Male Infertility – Evidence
The effects of obesity on reproductive function have been studied extensively in women, and it is well known that obesity negatively affects female fertility.16,17 Conversely, the effects of obesity on male fertility have not been comprehensively investigated in the past, and the affects are less apparent. However, recent studies have suggested that there is a connection between obesity and the hypothalamus–pituitary–gonadal (HPG) axis, semen parameters and sexual function.
In a noteworthy review article by Hammoud et al., the authors reviewed population studies and data obtained from couples seeking fertility treatment and found that obesity was associated with male infertility. One of the landmark studies that focused on the relationship between overweight and infertility was undertaken by Sallmen et al. Despite the several shortcomings of this study, male overweight and obesity as measured by BMI was shown to correlate with infertility with a maximal effect in the 32-43kg/m² group. Similar findings were observed in another epidemiological study. It was shown that the effect of BMI on infertility had a dose-response relationship. The odds ratio (OR) for men classified as overweight was 1.19 and for those defined as obese was 1.36. Another study found that if both partners are obese, they face a higher risk of fertility problems than if only one partner is obese. Hammoud et al. also highlighted studies of male partners from infertile couples. Some of these studies reported a definite relationship between male infertility and obesity as measured by BMI.

There appears to be no consensus in the literature on the effects of excess body fat and BMI on spermatogenesis and seminal parameters. Several semen parameters have been reported to be influenced by obesity: sperm concentration, morphology, chromatin integrity and motility. Jensen et al. found an association between sperm concentration and BMI in a cohort of males. Sperm concentration was significantly lower in obese and overweight males, whereas subjects whose BMI was within the normal range had a higher sperm concentration as well as a higher total sperm count and a lower percentage of abnormal spermatozoa. In this particular study, BMI was not associated with poor sperm morphology or motility.

Contrary to these findings, another study (n=794) found that obesity (BMI) correlated negatively with sperm motility and rapid motility, but not with sperm concentration. Sperm DNA fragmentation as measured by the DNA fragmentation index (DFI) has also been shown to be increased if BMI is >25kg/m². Increased DFI is correlated with reduced fertility and, furthermore, is indicative of overall poor spermatogenesis, which could also affect the concentration and motility of sperm.

Erectile dysfunction (ED) is another commonly reported cause of reproductive difficulty that has been significantly linked to obesity and increased BMI. Studies have shown that as the severity of obesity increases, so too does the severity of ED. It has been reported that up to 76% of men who are overweight or obese suffer from ED and lack of libido, while nearly 97% of males with metabolic syndrome displayed signs of ED.

It is well known that obesity is a chronic disease with several co-morbidities, including cancer, non-insulin-dependent diabetes, gallbladder disease, high cholesterol, atherosclerosis, heart disease, hypertension, stroke, psychological depression, sleep apnoea and renal failure, but, according to the recent studies cited above, it is also evident that it is a serious threat to male fertility.

Unravelling the Underlying Mechanisms

Central to the obesity epidemic is a sedentary lifestyle and an adverse genotype that can predispose people to obesity. Various mechanisms can serve as plausible explanations for male factor infertility in overweight and obese men, but the relationship is probably not that simple and more than likely multifactorial (see Figure 1). Most mechanisms involve hormonal alterations and dysregulation of the HPG axis or physical changes ultimately manifesting as impaired sperm production and function.

Obesity in males is characterised by visceral fat deposition. Over-accumulation of white adipose tissue can ultimately cause inflammation and hormonal changes as it is regarded not only as an endocrine organ but also as a very important mediator of inflammation and metabolism. White adipose tissue also displays aromatase activity, and it secretes more than 30 adipose-derived hormones and adipokines that are mostly of importance to energy balance and metabolism.

Figure 1: The Aetiology of Obesity-linked Male Infertility is Multifactorial

- Leptin: this is an adipose-derived hormone known for its role in regulating food intake via stimulation of the satiety centre. If over-secreted it can lead to reduced androgen levels in obese males. Leptin can also have a direct effect on spermatogenesis and sperm function, as leptin receptors are found in testicular tissue and on the sperm plasma membrane.
- Resistin: this is another adipose-tissue-specific factor. Increased secretion links obesity to insulin resistance and type 2 diabetes. Hyperinsulinaemia, on the other hand, has been linked to inhibition of normal spermatogenesis, sperm DNA damage and inhibition of sex-hormone-binding globulin synthesis in the liver, which thereby changes levels of biologically available testosterone and oestrogen.
- Aromatase: aromatase over-activity occurs when an abundance of the aromatase cytochrome P450 enzyme is expressed by white adipose tissue. This over-activity converts androgens to oestrogens, thereby leading to supraphysiological levels and disruption of the HPG axis in obese men. This increase in oestrogen and E2 levels inhibits gonadotrophin-releasing hormone (GnRH) pulses from the hypothalamus, thereby preventing secretion of follicle-stimulating hormone (FSH) and luteinising
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Obesity Management – Is There Hope?

Apart from genetic mutations and predispositions to obesity, it is believed that, in the general population, obesity is a preventable and/or reversible condition. Due to the fact that psychosocial influences also play a role in the manifestation of obesity, prevention is not necessarily the only treatment option, but alternative treatment modalities must be employed and explored to relieve obese patients from the burden of this pathology and its co-morbidities, including infertility.

When a urologist or fertility expert is faced with the obese patient, several approaches can be followed to induce weight loss and/or treat the specific resultant problems related to obesity (see Figure 2).

Weight loss can be achieved via lifestyle changes, pharmacological treatments or surgical interventions, and it is advised that the specific order from least to most invasive should be followed. Lifestyle changes include dietary modifications such as choosing healthy foods and eating smaller portions, as well as exercising more. The goal is initially to lose weight and ultimately to attain a normal energy balance and metabolism. Reducing weight via lifestyle changes has been shown to normalise androgen, sex-hormone-binding globulin, leptin and insulin levels and reduce inflammatory cytokine levels to a point where semen parameters improve in obese men.62–60

The final resort is bariatric surgery. With this type of surgery, the stomach size is reduced, either with a medical device (e.g. gastric banding) or by removing a portion of the stomach (e.g. sleeve gastrectomy) or portions of the stomach or small intestine are bypassed (i.e. gastric bypass surgery), which decreases the amount of nutrients that can be absorbed. Treatment of this nature is only advisable and justifiable in severely obese patients (BMI >40 kg/m²) and only after all other treatments have failed.62 With regard to weight loss, bariatric surgery is extremely effective, but very few studies have looked at whether it restores male fertility. In one study, hormone and adipokine levels returned to normal levels, whereas a second concluded that the procedure actually induced secondary infertility.63 It is evident that bariatric surgery as a treatment of obesity-induced infertility is still very much experimental and further research needs to be performed.

Pharmacological treatment options can also be applied to address certain specific problems and underlying mechanisms of obesity-induced male infertility. Aromatase inhibitors have been prescribed with great success to those with elevated oestrogen levels, thereby effectively restoring testosterone and...

Figure 2: Various Treatment Modalities Can Be Explored to Treat Obesity-linked Male Infertility

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ART = assisted reproductive technologies.

Obese men also may experience some physical changes that can act as mechanisms for infertility. These include sleep apnoea, which disrupts the nocturnal rise in testosterone and thus affects the HPG axis.67–69 Scrotal lipomatosis (increased scrotal fat) and a sedentary lifestyle can lead to increased scrotal temperature and genital heat stress, which are associated with impaired spermatogenesis.69 Another physical factor is ED. Obesity may lead to ED by increasing the number of pro-inflammatory cytokines circulating in the bloodstream, which in turn causes endothelial dysfunction and release of nitric oxide, which is responsible for vasodilatation. Dysregulation of the HPG axis and decreased testosterone can also have an effect on ED.78–80

As initially stated, the human genotype can predispose people to obesity, which in turn can cause infertility. It is therefore not unrealistic to believe that a genetic link(s) may exist between these two pathways.7 Currently, the only evidence of such a link exists in conditions characterised by rare and severe genetic mutations (e.g. Prader Willi). However, other, less severe genetic mutations might exist that can shed light on chromosomal abnormalities that are typified by both obesity and infertility.80 Alstrom syndrome, for example, is a condition where a mutation in the ALMS1 gene is responsible for childhood-onset obesity as well as infertility.81 Obesity and delayed puberty, as well as hypogonadism, have also been characterised in humans with leptin deficiency or leptin resistance due to mutations in the leptin gene or leptin receptor gene.82 Recently, it was also shown that the absence of the histone demethylase JHDM2A gene (essential for spermatogenesis and critical for sperm nuclear condensation) gives rise to male obesity and infertility.83

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*Excerpt from the text*

Pharmacological interventions are the next step in the treatment of weight loss in the obese. There are only a few prescription medications currently approved by the US Food and Drug Administration (FDA) for weight loss: Xenical, which reduces intestinal fat absorption (Alli is a reduced-strength version that is sold over the counter [OTC]; and Phentermine, which acts as an appetite suppressant. Meridia, is currently under review by the FDA. However, these medications are not effective at inducing substantial long-term weight loss.84

The final resort is bariatric surgery. With this type of surgery, the stomach size is reduced, either with a medical device (e.g. gastric banding) or by removing a portion of the stomach (e.g. sleeve gastrectomy) or portions of the stomach or small intestine are bypassed (i.e. gastric bypass surgery), which decreases the amount of nutrients that can be absorbed. Treatment of this nature is only advisable and justifiable in severely obese patients (BMI >40 kg/m²) and only after all other treatments have failed.62 With regard to weight loss, bariatric surgery is extremely effective, but very few studies have looked at whether it restores male fertility. In one study, hormone and adipokine levels returned to normal levels, whereas a second concluded that the procedure actually induced secondary infertility.63 It is evident that bariatric surgery as a treatment of obesity-induced infertility is still very much experimental and further research needs to be performed.

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oestrone levels, normalising LH and FSH levels and restoring spermatogenesis and fertility.\textsuperscript{40,41} Various drugs are also available to treat ED in the obese patient.\textsuperscript{42,43}

Alternative surgical options may include scrotal lipectomy to reduce increased scrotal temperature and genital heat stress.\textsuperscript{35} Finally, assisted reproductive techniques such as in vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) remain viable options to treat male-factor infertility, despite morbid obesity in the male being associated with lower pregnancy rates in females after treatment.\textsuperscript{35}

In order to obtain the best treatment outcome and prognosis, it is advisable to motivate the morbidly obese to join support groups and undergo counselling/cognitive behaviour therapy before, during and after any of these treatments. For some patients, lifelong support may be needed.

**Conclusion**

The obesity pandemic is on the increase globally, and its associated co-morbidities are seriously affecting patients, nations and the global village as a whole. Data show that obesity is associated with lower pregnancy rates in females after treatment.\textsuperscript{68} In order to obtain the best treatment outcome and prognosis, it is advisable to motivate the morbidly obese to join support groups and undergo counselling/cognitive behaviour therapy before, during and after any of these treatments. For some patients, lifelong support may be needed.

The question of declining fertility-associated effects. Dysregulation of the HPG axis might manifest as altered sperm parameters and other possible infertility-associated effects. Dysregulation of the HPG axis might explain most of the changes seen in sperm parameters. Another potential cause of male infertility not discussed in this review is the accumulation of toxic substances in fatty tissue.\textsuperscript{44,45} A variety of treatment options are available, with weight reduction being the most successful at correcting hormonal imbalances. However, obesity treatment and therapeutic interventions need to be studied more extensively before they can be offered routinely.

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