The impact of obesity on male fertility

Val Bullen, Simran Judge

While the majority of research into the effects of obesity on reproductive health focusses on women, the latest evidence shows that a large number of complications can also occur in obese men. This article summarises the effects of obesity on male reproductive health across a man's entire lifespan, from the *in utero* environment, through puberty and adulthood, to the putative epigenetic effects on the offspring. Treatment options are also discussed, although this remains a somewhat overlooked area of research.

As the obesity epidemic continues to spread, more and more people are being affected both in the short term and in the long term by the consequences. While obesity is associated with reproductive dysfunction in both men and women throughout their lifespan, the impact on female reproductive health has been studied more, given the consequences of obesity on both mother and child. Although the impact of obesity on male fertility is only now being evaluated in depth, Hammoud et al (2008) refer to the writings of Avicenna from the 16th century on the health disadvantages of excessive weight, in which he describes the obese man as infertile and unable to impregnate women. This is being borne out in current research, with obese men demonstrated to have erectile dysfunction (ED) and low sperm counts (Hammoud et al, 2012). This article will consider the impact of obesity on all phases of the reproductive lifespan of men, from the production of the reproductive organs *in utero* to the impact a man's obesity may have on his children.

The intrauterine environment

The male gonads develop early on in gestation, producing the testosterone crucial for formation of the male genitalia and movement of the testes from the abdomen into the scrotal sac. In recent years, evidence has been accumulating that exposure at critical developmental periods to environmental compounds with oestrogenic activity causes reproductive disorders (Delbès et al, 2006). In males, exposure to these endocrine disruptors has been said to cause a spectrum of symptoms known as testicular dysgenesis syndrome, including lower sperm count, hypospadias, testicular cancer and cryptorchidism (Skakkebaek et al, 2001). However, in a review of current published studies, Storgaard et al (2006) found no strong epidemiological evidence that prenatal exposure to oestrogens was linked to disturbed development of male reproductive organs. However, a study by Swan et al (2007) suggested that maternal beef consumption, and the possible xenobiotics in the beef, may alter a male's testicular development *in utero*. The debate goes on, with protagonists (Andersson et al, 2008) and antagonists (Nohynek et al, 2013), and with more recent animal research suggesting that endocrine disruptors have epigenetic effects (Manikkam et al, 2013).

In obese women, adipose tissue produces oestrogen; however, whether the excess oestrogen levels that are found in obese pregnant woman

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Article points

1. Current research suggests that obesity has negative effects on male reproductive health throughout all stages of a man's life.
2. In addition to putative effects of maternal obesity on the fetus's gonadal development, obesity has been shown to delay pubertal development in adolescent boys and increase the likelihood of fertility problems in adult men.
3. The underlying mechanisms principally consist of disruption of the hypothalamic–pituitary–gonadal axis and reduction of testosterone levels.

Key words

- Male reproductive health
- Obesity

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Page points

1. Obesity in boys has been found to delay puberty by disrupting the release of hormones that induce pubertal development and, possibly, by suppressing Sertoli cell proliferation.
2. Overweight and obese men have a 50% greater chance of fertility problems compared with normal-weight men as a result of impaired spermatogenesis, reduced testosterone levels, erectile dysfunction and poor libido, as well as obesity-related comorbidities such as type 2 diabetes and hypertension.

can cause similar effects as exogenous oestrogen in disrupting testicular development is somewhat more controversial. An initial investigation by Ramlau-Hansen et al (2007) suggested that high pre-pregnancy BMI may be associated with low semen quality in the offspring, but this has not been confirmed. Nonetheless, we do know that the *in utero* environment is a critical window for programming, and some studies have hypothesised that maternal obesity could cause semen abnormalities in male offspring by having a programming effect on testicular development during fetal life (Teerds et al, 2011).

Pubertal development

In contrast to girls, in whom obesity has contributed to a lowering of the age of menarche, in boys obesity is associated with delayed puberty and/or diminished gonadal function (Wang, 2002). The ontogeny of puberty is similar in both boys and girls, in that there is a nocturnal increase in pulsatile release of luteinising hormone (LH), which is thought to be affected by the hormone leptin. How obesity disturbs different hormonal aspects of pubertal development remains unclear but, in boys, the increased adipose tissue mass is known to cause an increase in the activity of the cytochrome P450 enzyme aromatase, resulting in increased conversion of oestradiol from testosterone, a phenomenon often termed the "testosterone–oestradiol shunt" (Saboor Aftab et al, 2013). This not only reduces testosterone levels but also gives rise to the preferential deposition of fat within abdominal depots, in the so-called "hypogonadal–obesity cycle" (Cohen, 1999).

In humans, only about 10% of the adult complement of Sertoli cells in the testes is present at birth (Cortes et al, 1987). Proliferation of the cells takes place in the perinatal period and at puberty. Winters et al (2006) measured the levels of inhibin B, an indicator of Sertoli cell numbers that is strongly correlated with high testicular volume and sperm counts, in healthy adult men and prepubertal boys. Inhibin B levels were found to be reduced in obese compared with normal-weight men; however, there was no difference between the obese and normal-weight prepubescent boys. Based on these findings, the authors proposed that obesity suppresses Sertoli cell proliferation during puberty, which may contribute to the contemporary decline in sperm production that has been observed (Jouannet et al, 2001).

Adult effects

The rate of obesity in men of reproductive age has almost tripled in the past 30 years and correlates with an increase in male infertility. Overweight and obese men have been shown to have a 50% higher chance of encountering fertility problems compared to normal-weight men (Kay and Martins da Silva, 2013). A study by Sallmén et al (2006) showed that for every 3-kg/m^2 increase in the man's BMI, couples were 12% more likely to be unable to conceive. However, the aetiology of this is multifactorial, with obese men at greater risk of impaired spermatogenesis, reduced circulating testosterone levels, ED and poor libido, together with comorbidities such as hypertension and type 2 diabetes, which will also have effects of their own. Many studies have linked obesity to ED and impotence, and men with a BMI over 28.7 kg/m^2 are 30% more likely to have ED (Esposito et al, 2008).

Even though the link between obesity and ED is not clear, it is thought that the effects of visceral adiposity on inflammatory and vascular endothelial function may be responsible. However, low testosterone levels, as well as confounding variables such as smoking, alcohol intake, vascular disease, type 2 diabetes and psychological factors, may also play a part in the pathogenesis (Esposito et al, 2008).

The highly complex process of spermatogenesis is kept under strict control by LH, follicle-stimulating hormone and testosterone, which are regulated by the hypothalamus, pituitary gland and Leydig and Sertoli cells in the testes (Palmer et al, 2012). Although various altered semen parameters, such as decreased sperm concentration, abnormal morphology, compromised chromatin integrity and abnormal motility, have been associated with obesity in various studies, not all research has come to the same conclusion (Cabler et al, 2010). Such discrepancies are frequently seen in human studies and may result from a variety of confounding factors, such as lifestyle and pre-existing conditions (Palmer et al, 2012). Men produce a large number of sperm, far more than

needed for conception, but studies have shown that a sperm count below 40 × 10^6/mL can be associated with an increased length of time to pregnancy and even subfertility (McPherson and Lane, 2015). Humans are also unusual in that the majority (up to 96%) of sperm in any ejaculate is abnormal according to World Health Organization parameters (Cooper et al, 2010), giving less room for error than in other species (Sharpe, 2010).

Reproductive hormone changes

Most studies on the impact of obesity focus on the hypothalamic–pituitary–gonadal (HPG) axis and endocrine changes in which we see various changes in the levels and pulse frequency of the gonadotrophins (particularly LH); decreases in sex hormone-binding globulin (SHBG), testosterone and inhibin B levels; and an increase in oestradiol levels. Aggerholm et al (2008) showed that serum testosterone levels were 25–32% lower in obese men than in normal-weight men, whereas oestrogen concentrations were 6% higher. Adipose tissue is an important site for hormone production; therefore, increased amounts of body fat lead to abnormal hormone regulation of testicular function (Teerds et al, 2011). Excessive visceral fat, more so than subcutaneous fat, is positively associated with increased oestradiol levels due to increased activity of aromatase, which is produced by adipose tissue and converts testosterone to oestradiol, thus deregulating the HPG axis (Gautier et al, 2013). Low levels of inhibin B are associated with seminiferous tubule dysfunction (Shukla et al, 2014). Levels of LH, SHBG and, thus, testosterone are also known to be affected by hyperinsulinaemia and hyperglycaemia, with increased insulin levels decreasing SHBG and LH levels (Palmer et al, 2012).

The more recent discovery of the hypothalamic peptide kisspeptin has added another dimension. Kisspeptin is now recognised as a crucial regulator of the onset of puberty, sex hormone-mediated secretion of gonadotrophins and control of fertility. It acts directly on gonadotrophin-releasing hormone (GnRH)-expressing neurones, determining the pulse amplitude and pulse frequency of LH. In women, oestrogen exerts its negative feedback action by inhibiting release of kisspeptin and therefore GnRH secretion, kisspeptin neurones being sensitive to sex steroid feedback and metabolic cues. The increased oestrogen in obese men will have the same effect, decreasing the pulsatile frequency of LH and hence testosterone production (Skorupskaite et al, 2014). The effects of obesity on reproductive hormones are summarised in *Figure 1*.

Qin et al (2007) established that the associations between BMI and semen quality were found to be statistically significant even after an adjustment for reproductive hormone levels, suggesting that there are other influencing factors. Other mechanisms that may contribute to obesity's effects on male fertility include an increased release of adipokines from adipose tissue; other physical problems, such as sleep apnoea, that may negatively affect morning serum testosterone levels (Luboshitzky et al, 2005); and increased scrotal temperature, due to increased fat deposition in the upper thighs and abdomen, which interferes with spermatogenesis (Jung and Schuppe, 2007).

Adipose tissue hormones

Adipose tissue is an active endocrine organ, producing adipokines, such as leptin, and pro-inflammatory cytokines, such as interleukin-6 (IL-6), that can affect spermatogenesis and sperm function (Shukla et al, 2014). For example, increased IL-6 levels can diminish the ovum-penetrating capability of spermatozoa and disrupt the penile endothelium by creating high levels of damaging reactive oxygen species. Leptin, although primarily responsible for satiety, has been shown to influence male reproduction both at the level of the testes and at the HPG axis. Leptin levels increase with fat mass and show an inverse relationship with serum testosterone levels in overweight and obese people (Shukla et al, 2014). High leptin levels can negatively influence Leydig cell testosterone synthesis by inhibiting the conversion of 17-OH progesterone into testosterone (Teerds et al, 2011). Furthermore, leptin receptors have been found on sperm plasma membranes and in ejaculate, suggesting a direct endocrine effect of the hormone on sperm (Aquila et al, 2005). Human adipose tissue also produces prolactin, and obese people often exhibit hyperprolactinaemia, which can inhibit secretion of GnRH as well as directly influencing

Page points

1. The effects of obesity on adult male reproductive health are primarily mediated through disruption of hormonal activity in the hypothalamic–pituitary–gonadal axis, as well as physical effects of excess fat such as sleep apnoea and increased scrotal temperature.
2. In addition, adipose tissue itself is an active endocrine organ, producing adipokines, pro-inflammatory cytokines and leptin, which can affect spermatogenesis and testosterone production.

"Although more research needs to be done in humans, there is evidence from animal models that paternal obesity can, through epigenetic changes, augment the susceptibility to obesity and diabetes in the offspring, implying another possible mechanism for the growing incidence of these chronic diseases."

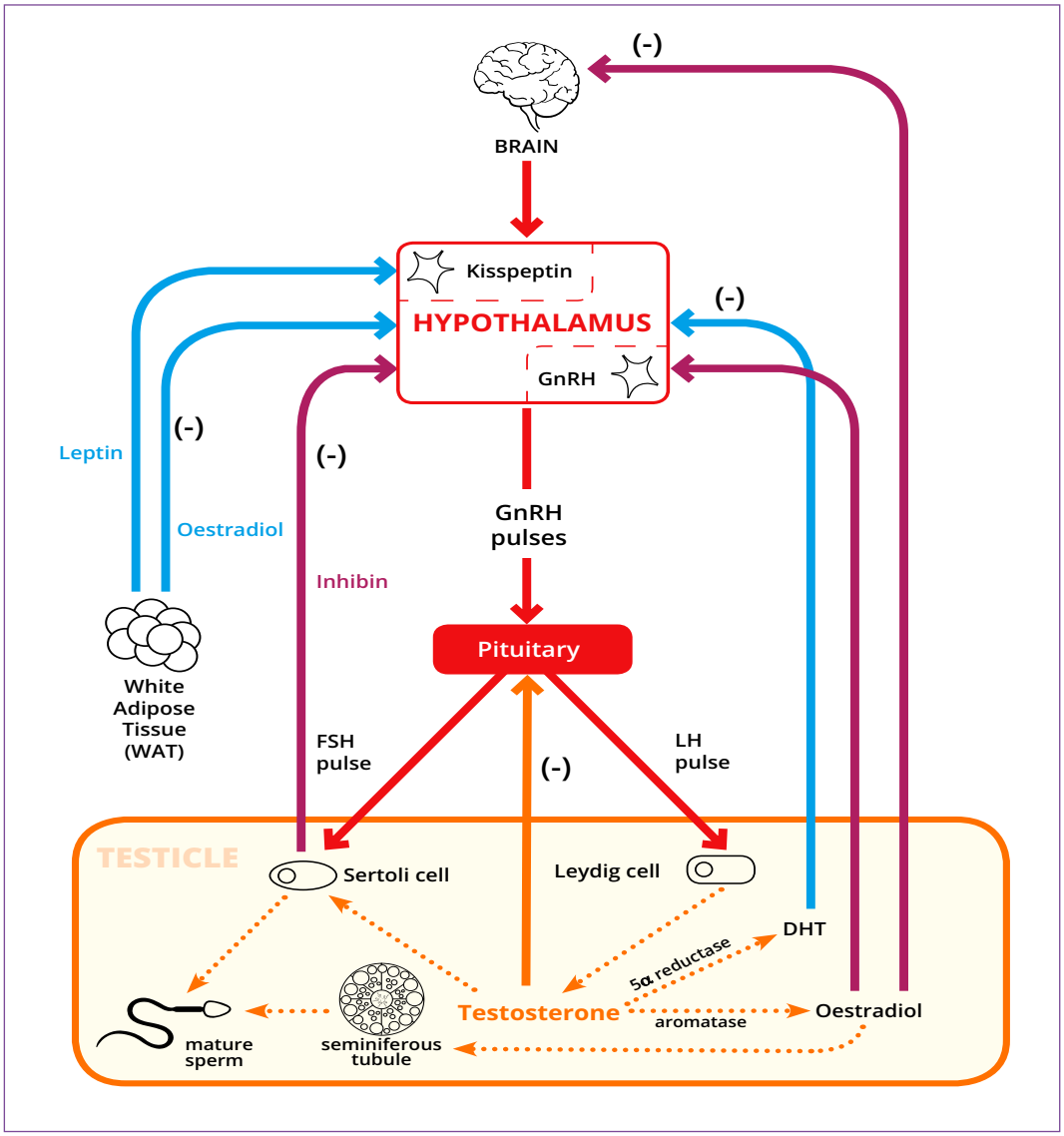

Figure 1. The effects of obesity on male reproductive hormones. Spermatogenesis is regulated by the gonadotrophins LH and FSH from the pituitary gland, and by testosterone, oestradiol and inhibin produced in the testes. In obesity, the increased levels of leptin and oestradiol, acting via kisspeptin neurones, interfere with the normal regulatory mechanisms of the hypothalamic–pituitary–gonadal axis.
DHT=dihydrotestosterone; FSH=follicle-stimulating hormone; GnRH=gonadotrophin-releasing hormone; LH=luteinising hormone.

spermatogenesis by acting on prolactin receptors on the Sertoli and Leydig cells, potentially causing infertility (Singh et al, 2011).

Impact on future generations

It has been known for some time that the uterine environment to which the fetus is exposed can have an impact later in life in terms of the diseases that are contracted, which has led to the "fetal and infant origins of adult disease" hypothesis (Robinson, 2001). There is now growing evidence that paternal health cues can be passed to the next generation as well as maternal ones (Skinner et al, 2010). Although more research needs to be done in humans, there is evidence from animal models that paternal obesity can, through epigenetic changes, augment the susceptibility to obesity and diabetes in the offspring, implying another possible mechanism for the growing incidence of these chronic diseases (Ozanne, 2015)

Treatment

An important point made by Teerds et al (2011) is that most overweight or obese men do not experience significant fertility problems despite the presence of lowered testosterone, although there is a higher prevalence of obesity among men with poor semen quality than in those with normal semen quality (Magnusdottir et al, 2005). However, identifying the subgroup who do develop these problems and finding effective treatment options will have a dramatic impact on the many couples for whom male infertility is a problem.

The diagnosis and treatment of reduced fertility observed in these obese men requires insight into the underlying pathology, which has hormonal, mechanical and psychosocial aspects (Hammoud et al, 2012). Natural weight loss and bariatric surgery are options for obese people and have shown promising results in restoring fertility and normal hormonal profiles in some individuals (Reis and Dias, 2012). The fact that these methods are not effective in all cases shows the complex aetiology that underlies the problem.

Although obesity is associated with low serum testosterone concentrations, treatment with exogenous testosterone is likely to adversely affect fertility as a result of the feedback mechanism influencing gonadotrophin release. Treatment of morbidly obese people with aromatase inhibitors has resulted in suppression of oestradiol and, in some cases, normalisation of spermatogenesis and fertility (Roth et al, 2008).

More simple measures may lie in reviewing the dietary constituents, along with smoking and alcohol, which are known to have adverse effects on spermatogenesis. According to Afeiche et al (2014), red meat, as a source of saturated fat, is related to low sperm concentration and total sperm count, whereas fish is an important source of long-chain omega-3 fatty acids, which appear to play an important role in spermatogenesis and have been associated with better sperm morphology.

Conclusion

As the number of obese men increases, and the potential impact of obesity on a man's fertility is becoming more widely recognised, it is important that more research is carried out, not only to ensure that the man's obesity does not impact a woman's chance of getting pregnant, but also to determine the mechanisms by which non-genetic transfer of paternal environmental information may cause long-term trans-generational effects (Soubry et al, 2014). ■

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Page points

1. Although there is a higher prevalence of obesity in men with poor semen quality than in those with normal semen quality, the majority of obese men do not have fertility problems depite their lower testosterone levels.
2. More research is required to examine the underlying pathology and provide treatment options in those men who do develop problems.
3. Natural and surgical weight loss, as well as treatment with aromatase inhibitors, has shown promise in restoring fertility in some but not all men, and administering exogenous testosterone is, counterintuitively, likely to exacerbate the problem as a result of feedback mechanisms.
4. More simple dietary measures involve reducing intake of alcohol and red meat, and increasing consumption of fish.

"The diagnosis and treatment of reduced fertility observed in these obese men requires insight into the underlying pathology, which has hormonal, mechanical and psychosocial aspects."

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1. Over the past 30 years the rate of obesity in men of reproductive age has:

   A. Almost tripled
   B. Doubled
   C. Halved
   D. Stayed the same

2. According to Kay and Martins da Silva (2013), by what percentage have overweight and obese men been shown to have an increased chance of encountering fertility problems when compared to normal-weight men?

   A. 10%
   B. 25%
   C. 50%
   D. 80%

3. It has been shown (Sallmén et al, 2006) that for every 3-kg/m^2 increase in a man's BMI, couples were more likely to be unable to conceive by:

   A. 5%
   B. 12%
   C. 22%
   D. 33%

4. Obese men are at greater risk of:

   A. Impaired spermatogenesis
   B. Reduced circulating testosterone levels
   C. Erectile dysfunction and poor libido
   D. All of the above

5. In a study by Aggerholm et al (2008), serum testosterone levels in obese men, when compared to normal-weight men, were:

   A. 10% lower
   B. 7% lower
   C. 15–20% lower
   D. 25–32% lower

6. In the same study by Aggerholm et al (2008), oestrogen concentrations in obese men, when compared to normal-weight men, were:

   A. 50% higher
   B. 6% higher
   C. 5% lower
   D. No difference

7. Studies have shown (McPherson and Lane, 2015) that an increased time to pregnancy and subfertility is associated with a sperm count below:

   A. 10×10^6/mL
   B. 40×10^6/mL
   C. 80×10^6/mL
   D. 10×10^7/mL

8. True or false? According to Teerds et al (2011), maternal obesity could cause semen abnormalities in male offspring by having a programming effect on fetal testicular development.

   A. True
   B. False

9. At birth, in humans, there are roughly X% of the adult complement of Sertoli cells in the testes present. The X% is:

   A. 5%
   B. 10%
   C. 25%
   D. 90%

10. True or false? According to Shukla et al (2014), leptin levels increase with fat mass and show an inverse relationship with serum testosterone levels in overweight and obese people.

    A. True
    B. False