In the past 5–10 years, obesity has become a worldwide epidemic that has brought attention to learning more about the various causes, effects, and treatments. A combination of an increasingly acceptable sedentary lifestyle and unhealthy diet in the Western world has resulted in an increasing number of overweight and obese children and adults. According to the WHO, approximately 1.6 billion adults were classified as being overweight and 400 million adults were obese in 2005 [1]. It is predicted that globally, in the next 5 years, more than 700 million adults will suffer from obesity [1]. Once considered a problem only in high-income countries, overweight and
obesity are now dramatically on the rise in all countries. Evidence of this is the five unit increase in body mass index (BMI) for the period 1997–2006 in the 95th percentile BMI level among children aged 6–9 years in China. These children in the 95th percentile have a BMI of 24.8, which is surprisingly higher than that of the USA (22.2), Australia (20.1), and the UK (20.1) [2].

Parallel to the global increase in obesity is the reported world decrease in male fertility and fecundity [3]. Interestingly, men with increased BMI were significantly more likely to be infertile than normal-weight men, according to research conducted at the National Institute of Environmental Health Sciences (NIEHS) [4]. According to Carlson et al., the quality of semen has substantially declined, which has subsequently lead to decreased male fertility [5]. This could likely contribute to overall reduced male reproductive potential. Some studies estimate that male sperm counts continue to decrease at a rate of approximately 1.5% per year in the USA and similar findings have been found in other Western countries as well [3]. In addition, there is also a significant increase in the incidence of obesity in patients with male factor infertility, and couples with obese male partners are more likely to experience subfecundity, a correlation that seems necessary to address [6]. Due to the fact that this decline has occurred in close parallel with increasing rates of obesity, it is necessary to focus on the possibility of obesity as an etiology of male infertility and reduced fecundity. The “obesity pandemic” seen in many countries is a serious threat to public health, and a reduced capacity to reproduce is a potential but less well-known health hazard that can often be attributed to obesity.

It is therefore necessary to explore the links between obesity and male infertility, as well as to explain how it disrupts the male reproductive system at a mechanistical level. Treatment and prevention of obesity and associated fertility disorders will also be discussed in a clinical context.

What Is Obesity?

Obesity is a medical condition in which excess body fat, or white adipose tissue, accumulates in the body to the extent that the excess fat adversely affects health, often reducing life expectancy. The fundamental cause of obesity and overweight is an energy imbalance, where the energy consumed exceeds the energy expended. Global increases in overweight and obesity are attributable to a number of factors, including a shift in diet toward increased intake of energy-dense foods that are high in fat and sugars, and a trend toward decreased physical activity, resulting from increasingly sedentary nature of work, changing modes of transportation, and increasing urbanization.

Currently, overweight and obesity are defined more broadly as abnormal or excessive fat accumulation that may impair health. However, there are other specific requirements that qualify an individual as obese. The most accurate measures are to weigh a person underwater or to use an X-ray test called dual energy X-ray absorptiometry. These methods are not practical for the average individual and are conducted only in research centers with special equipment. There are simpler methods to estimate body fat such as BMI, skin fold measurements, waist-to-hip ratio (WHR), waist circumference, and also methods such as bioelectrical impedance analysis, risk factors and comorbidities [7]. The two tools that are most commonly used to identify obese patients are BMI, a waist-to-height ratio, and waist circumference. An individual is normally defined as being overweight if their BMI is between 25 and 30 kg/m² and obese if it exceeds 30 kg/m² [8]. A problem with this method is that individuals with a high BMI may be mesomorphic and have a high amount of muscle mass. Therefore, BMI may not be the most accurate marker for total body fat percentage and is an even less suitable tool to assess body fat distribution.

Waist circumference is a slightly less common method used to predict obesity in an individual, but may be more accurate in predicting obesity-related health issues. For females, a waist circumference of 88 cm or greater is considered unhealthy. For men, a waist circumference of 102 cm or greater is considered unhealthy. If waist circumference is used as the criterion, then according to a study conducted in 2006, the prevalence of being overweight among Australian adults, and probably other Caucasian populations, may be significantly greater than indicated by surveys relying on self-reported height and weight. The development of valid self-reported measures of waist circumference for use in population surveys may allow more accurate monitoring of overweight and obesity and should be considered instead of BMI [9]. A WHR can also be used to predict unhealthy consequences as a result of increased body fat (normal WHR: males=<0.9; females=<0.85), especially related to the risk of coronary heart disease as it relates to obesity [10]. WHR may be the most useful measure of obesity and the best simple anthropometric index in predicting a wide range of risk factors and related health conditions [11].

How Does Obesity Affect Male Fertility?

The relationship between male infertility and obesity has more concrete evidence than solely studies showing reduced fecundity among couples, one of whom is an obese male. Although spermatogenesis and fertility are not impaired in a majority of obese men, a disproportionate number of men seeking infertility treatment are obese. There have been a number of studies analyzing the relationship between semen quality and obesity, with a common finding that there is an inverse correlation between BMI and quality of semen parameters.
Abnormal Semen Parameters

Altered semen parameters attributed to obesity include decreased sperm concentration, abnormal morphology, compromised chromatin integrity, and abnormal motility. Although there is a convincing amount of evidence to demonstrate the adverse affect of excess body fat on spermatogenesis, not all studies have come to the same conclusions. Individual studies are conflicting in evidence, but a recent meta-analysis by MacDonald et al. [12] combined 31 studies containing data and information relating to obesity and male infertility. Reproductive hormones studied included testosterone, free testosterone, estradiol, FSH, LH, inhibit B, and sex hormone-binding globulin (SHBG). This meta-analysis was conducted to investigate sperm concentration and total sperm count but found no evidence for a relationship between BMI and sperm concentration or total sperm count. Examination of further studies may present more insight in the relationship between obesity and semen quality.

Decreased Sperm Count and Concentration

Obese men are three times more likely than healthy men of normal weight to have a sperm count of fewer than 20 million/ml, an indicator of oligospernia [13]. In one of the largest studies on male fertility and obesity, done on Danish men, Jensen et al. measured BMI in relation to semen quality and reproductive hormones and found significant relationships between sperm concentration and BMI. A lower sperm concentration was observed in not only obese and overweight males, but also in males who were significantly underweight. This could serve as an indication that there may be an ideal range of BMI for normal spermatogenesis. Subjects whose BMI was within the normal range showed a higher sperm concentration as well as a higher total sperm count, and a lower percentage of abnormal spermatozoa [14]. According to a study by Chavarro et al., men with a BMI greater than 25 kg/m² had a lower total sperm count than men of normal weight, and the measured volume of ejaculate decreased steadily with an increasing BMI [15]. These findings have been corroborated by other studies as well [16, 17]. Although several reports exist indicating a considerable negative effect of BMI on sperm count and concentration, some discrepancies have been noted. In these studies, a correlation between sperm count and concentration in obese men compared to controls was demonstrated but was not deemed significant [18–20].

DNA Fragmentation

Kort et al. found that an increase in the DNA fragmentation index (DFI) accompanied an increase in BMI, demonstrating that obesity might compromise the integrity of sperm chromatin, their only genetic material [24].

DFI is the percent of sperm in a semen sample that have increased levels of single or double strand breaks in their nuclear DNA. A young and healthy man has about 3–5% of sperm with fragmented DNA while a level of 25–30% DFI places a man attempting natural conception at a statistical risk for infertility [25]. An increase in the BMI above 25 kg/m² causes an increase in sperm DFI and a decrease in the number of normal chromatin-intact sperm cells per ejaculate, relative to the degree of obesity [24]. Men with type 2 diabetes also present with a significantly higher number of severe structural defects in sperm compared with sperm from controls (p<0.05) [47]. Typically, males presenting with a high DFI will have reduced fertility, and their partners will display an increased incidence of miscarriage as a consequence [26].

A new breakthrough in gel electrophoresis has been used to identify obesity-associated changes of the sperm proteome. Semen samples from obese males differed from those of normal-weight men with 12 spots seen after running their “difference gel electrophoresis” (DIGE) of fluorescently labeled human sperm proteins. Tryptic digestion of the 12 spot proteins and mass spectrometric analysis of the corresponding peptides identified nine sperm proteins associated with obesity. This can now be considered a noninvasive experimental tool in the diagnosis of male infertility and monitoring device for fertility-restoring therapy in obese males [27]. This finding clearly demonstrates the differences or changes in the protein composition of spermatozoa in obese men.

Sperm Motility

Some consensus on the effects of obesity on sperm motility has been established, but there is no overall agreement.
differences in what is classified as “normal” morphology and high individual variability within individual patient samples. However, most studies have shown no correlation between obesity and abnormal sperm morphology [14, 15, 19, 21]. In the large retrospective study of Danish military recruits, no association between obesity and poor sperm motility or morphology was reported [14]. Identifying the specific hormones, proteins, and mechanisms involved in regulating sperm morphology might help to explain how and why obesity affects normal spermatogenesis.

**What Are the Proposed Mechanisms?**

Although environmental and lifestyle factors might help to explain the growing numbers of obese adults and children, there is less evidence explaining how obesity causes male infertility. The mechanisms responsible for effects on male infertility are mostly ambiguous and undefined. Several mechanisms have been proposed, all of which are described below (Fig. 33.1). Most of these mechanisms contribute to the dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis, one of the most important functions of which is to regulate aspects of reproduction.

**Genetic Link**

Despite there being a known effect of obesity on infertility, many obese males are fertile and have normal reproductive function and fecundity. However, because obesity can result from an unfavorable genotype and because obesity can cause infertility, a genetic link between these two factors might explain this discrepancy. Patients with Klinefelter, Prader–Willi, or Laurence–Moon–Bardet–Biedel syndromes all display, to varying degrees, both obesity and infertility. In addition, men who are both infertile and obese show significantly lower testosterone levels than obese fertile men [28]. Although the specific genes involved and mechanism(s) explaining these syndromes are quite well understood, it is possible that other, less severe genetic mutations exist. These small mutations might explain the discrepancies between obese fertile and infertile men and shed light upon a possible genetic link between obesity and infertility.

Also, mutations in the human ALMS1 gene are responsible for Alström syndrome, a disorder in which key metabolic and endocrinological features include childhood-onset obesity, metabolic syndrome, and diabetes, as well as infertility [29]. Scientists still need to accurately establish which particular genes are involved in these different syndromes, but the linkage of obesity and infertility in extreme genetic cases points to some degree of genetic linkage. Hammoud et al. [30] recently discovered that an aromatase polymorphism modulates the relationship between weight and estradiol levels in obese men. This could explain why only certain obese men experience this rise in estradiol and subsequent fertility problems, while others experience no fertility issues. It seems possible that there are other less severe genetic markers than chromosome 15 abnormalities and ALMS1 mutations that may clarify the discrepancies between obese fertile and infertile men and give explanation to a possible genetic link between obesity and infertility.

**Hormonal Mechanisms**

Abdominal or visceral fat is more likely to lead to changes in hormone levels and to cause inflammation than fat stored in other parts of the body. This is predominantly due to the fact that white adipose tissue, found in high levels in obese men, exhibits elevated aromatase activity and secretes adipose-derived hormones, as well as adipokines.

**Reproductive Hormones**

The reproductive hormonal profiles of most obese men deviate from what is considered the norm. Obese men tend to present with elevated estrogen and low testosterone and FSH levels. Androgen deficiency or hypogonadism found in males who are obese or have metabolic syndrome can account for problems with erectile dysfunction and spermatogenesis. However, many other hormones associated with obesity may alter the male reproductive potential. In morbidly obese individuals,
reduced spermatogenesis associated with severe hypotestosteronemia may contribute to infertility [31, 32]. This estrogen excess is explained by overactivity of the aromatase cytochrome P450 enzyme, which is expressed at high levels in white adipose tissue and is responsible for a key step in the biosynthesis of estrogens. High levels of estrogens in obese males result from the increased conversion of androgens into estrogens, owing to the high bioavailability of these aromatase enzymes [33]. Visceral obesity can serve as a major endocrine disrupter and can also influence the endocrine interactions by reducing the levels of luteinizing hormone (LH) and testosterone, resulting in hypogonadotropic hypogonadism, a condition which contributes to male infertility. Although abnormal levels of reproductive hormones could be the source of fertility problems in obese males, Qin et al. [34] established that the associations between BMI and semen quality were found statistically significant even after an adjustment for reproductive hormones, thereby demonstrating that reproductive hormones cannot fully explain the association between BMI and semen quality [35]. Perhaps, altered hormone levels themselves do not explain poor semen quality but instead a deregulation of the normal HPG axis. Regardless, studies indicate that the association between BMI and semen quality is clearly more complex than what can be accounted for simply by reproductive hormones. Instead, it may be a result of other factors such as one’s lifestyle and increased adipokine release.

White Adipose Tissue as an Endocrine Organ

White adipose tissue is a major secretory and endocrine organ that secretes approximately 30 biologically active peptides and proteins that can be grouped as either adipose-derived hormones (e.g., leptin, adiponectin, resistin) or adipokines (immunomodulating agents). Adipose-derived hormones play a central role in body homeostasis including the regulation of food intake and energy balance, insulin action, lipid and glucose metabolism, angiogenesis and vascular remodeling, coagulation, and the regulation of blood pressure [35]. Due to an excess of white adipose tissue in obese men, levels of adipose-derived hormones are often elevated, and their action is thought to modify many obesity-related diseases, including reproductive functioning.

Leptin

One such adipose-derived hormone is leptin, which is best known as a regulator of food intake and energy expenditure via hypothalamic-mediated effects [36, 37]. Although normal levels of leptin are required for overall reproductive health, excess leptin may be an important contributor to the development of reduced androgens in male obesity [38]. In addition to a higher prevalence of infertility, obese individuals are reported to have higher circulating levels of leptin than nonobese individuals [39, 40]. An increasing body of data suggests that leptin is also involved in glucose metabolism as well as in normal sexual maturation and reproduction [16]. Leptin receptors are not only present in testicular tissue but also on the plasma membrane of sperm suggesting that leptin may directly affect sperm via the endocrine system, independent of changes in the HPG axis [38, 41]. Diet-induced obesity in mice caused a significant reduction in male fertility and resulted in a fivefold increase in leptin levels compared to control mice. Sperm from these obese males exhibited decreased motility and reduced hyperactivated progression compared to the lean mice.

Oxidative Stress and Reactive Oxygen Species

As mentioned previously, adipocytes secrete various adipokines (e.g., tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and tissue factor) [37]. A number of these adipokines have been connected to infertility and testicular cancer. Bialas et al. [42] found that changes in the activity of intratesticular cytokines may promote various distinct pathologies such as testicular cancer or infertility. Also, increased release of adipokines from excess white adipose tissue, resulting in inflammation, can have a toxic effect on spermatozoa through the release of excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) [43]. ROS and RNS are free radicals, highly reactive and unstable molecules that arise as a consequence of oxidative stress or inflammation that can induce significant cellular damage throughout the body. Two adipocyte-released adipokines, TNF-α and IL-6, significantly reduced human sperm progressive motility in a dose- and time-dependent manner by promoting the elevation of nitric oxide production to pathological levels [44]. Numerous authors have noted that obesity and several of its causative agents, namely insulin resistance and dyslipidemia, are associated with increased oxidative stress [45, 46]. This association is most likely the result of the elevated metabolic rates that are required to maintain normal biological processes and increased levels of stress in the local testicular environment, both of which naturally produce ROS. The local influences of biologically active substances (cytokines) released by activated leukocytes in the course of the inflammatory response to obesity may damage sperm and inhibit spermatogenesis. Agarwal et al. [47] found that abnormal patterns of increased ROS were associated with male factor infertility and are responsible for abnormal sperm concentration, motility, and morphology found in obese males.
Inhibin B

In a study by Winters et al. [48], the levels of inhibin B, another hormone involved in the HPG axis, declined with increasing obesity in young adult men, and values were 26% lower in men who were obese compared to normal-weight men. As it was shown that inhibin B is positively correlated with the number of Sertoli cells in normal adult rhesus monkeys, the reduced levels of inhibin B in the Winters study may indicate that obese men have fewer Sertoli cells than men of normal weight [49]. Since each Sertoli cell is thought to support a finite number of germ cells, fewer Sertoli cells as a result of obesity may result in a lower sperm count [48].

Resistin Secretion and Insulin Resistance

Resistin is another adipose-tissue-specific factor, which is reported to induce insulin resistance. Almost 80% of men with type 2 diabetes are also obese, and an increase in resistin secretion owing to a higher number of adipocytes links obesity to type 2 diabetes [37, 50]. As a consequence of insulin resistance in patients with type 2 diabetes, increased renin secretion was associated with increased oxidative stress [45, 46]. This association is most likely the result of the higher-than-usual metabolic rates required to maintain normal biological processes and an increased level of stress in the local testicular environment. Hyperinsulinemia, which often occurs in obese men, has an inhibitory effect on normal spermatogenesis and can be linked to decreased male fertility. In a group of diabetic men, semen parameters (concentration, motility, and morphology) did not differ from the control group, but the amount of nuclear and mitochondrial DNA damage in the sperm was significantly higher [51]. This sperm DNA damage can impair male fertility and reproductive health. In addition to inducing sperm DNA damage, high insulin levels also have been shown to influence the levels of sex hormone binding globulin (SHBG), a glycoprotein that binds to sex hormones, specifically testosterone and estradiol, thereby inhibiting their biologic activity as a carrier.

High circulating insulin levels inhibit SHBG synthesis in the liver, whereas weight loss has been shown to increase SHBG levels [52]. In obese males, the decrease in SHBG means that less estrogen will be bound, resulting in more biologically active, free estrogen. In addition to the conversion of testosterone to estrogen in obese patients, the decreased ability of SHBG to sustain homeostatic levels of free testosterone also contributes to abnormal testosterone levels [14]. This failure to maintain homeostatic levels might magnify the negative feedback effect of elevated total estrogen levels. Even when the presence of SHBG is accounted for, an independent relationship between insulin resistance and testosterone production can still be demonstrated [32]. Therefore, the levels of SHBG might be important only as a marker of altered hormone profiles in obese infertile men.

Environmental Toxins

Most environmental toxins are fat soluble and therefore accumulate in fatty tissue. Their accumulation not only around the scrotum and testes, but also elsewhere in the body may disrupt the normal hormone profile because they are proven endocrine disruptors in male fertility [21]. Since morbidly obese males present with excess scrotal fat, environmental toxins accumulating in white adipose tissue surrounding the scrotum may also have a direct localized effect on spermatogenesis in the testes. Lipophilic contaminants such as organochlorines, organic compounds containing at least one covalently bonded chlorine atom whose uses are controversial because of the often toxic effects of these compounds on the environment, are associated with decreased sperm production and thus decreased male reproductive potential, even if fat is not localized in the scrotal area [34]. Other toxic species that may induce abnormal spermatogenesis are ROS discussed in the previous section. Despite reports that certain toxins can negatively affect fertility, Magnusdottir et al. [6] found that poor semen quality was found to be associated with sedentary work and obesity, but not with increased plasma levels of persistent organochlorines.

Dysregulation of HPG Axis

Excess body weight can impair the feedback regulation of the HPG axis, and all of the factors above might contribute to or be a result of this dysregulation, contributing to apparent semen quality abnormalities. Sex steroids and glucocorticoids control the interaction between the hypothalamic–pituitary–adrenal (HPA) and the HPG axes, and any amount of disturbance might, in turn, affect spermatogenesis and male reproductive function. Men of normal weight with low levels of testosterone regularly present with elevated levels of LH and FSH, in contrast with obese men, who usually present with low LH and FSH levels [53]. Inhibin B, a growth-like factor, is produced by Sertoli cells in the testis and normally acts to inhibit both FSH production and stimulation of testosterone production by Leydig cells in the testis. Surprisingly, the expected compensatory increase in FSH levels in response to low levels of inhibin B is not observed in obese men. A low level of inhibin B might result from the suppressive effects of elevated estrogen levels. A study by Globerman et al. [54] also found that there was no increase in FSH levels in obese men whose inhibin B levels remained low after weight loss. Obese, infertile men exhibit endocrine
changes that are not observed in men with either obesity or infertility alone. This defective response to hormonal changes might be explained by partial or complete dysregulation of the HPG axis.

**Physical Mechanisms**

Many obese men face physical problems that could be related to their decreased fecundity and fertility, including erectile dysfunction, scrotal lipomatosis leading to increased scrotal temperatures, and sleep apnea that can cause disruptions in the nightly testosterone rise.

**Sleep Apnea**

Sleep apnea is a disorder affecting 4% of middle-aged men. The disorder is characterized by repetitive collapse of the pharyngeal airway during sleep resulting in hypoxia and hypercapnia. About two-thirds of middle-aged men with obstructive sleep apnea suffer from obesity, particularly central obesity [55]. Sleep apnea is characterized by a fragmented sleep course owing to repeated episodes of upper airway obstructions and hypoxia and is often diagnosed in obese and diabetic males. Patients with sleep apnea have a disrupted nightly rise in testosterone levels and, therefore, lower mean levels of testosterone and LH compared with controls. In a study analyzing sleep apnea in obese, control, and lean patients, Luboshitzky et al. [56] concluded that the condition is associated with decreased pituitary–gonadal function and that the accompanying decline in testosterone concentrations is the result of obesity and, to a lesser degree, sleep fragmentation and hypoxia. This disruption has been associated with abnormal spermatogenesis and male reproductive potential.

**Erectile Dysfunction**

Whereas the effects of sleep apnea on reproduction are confounding owing to obesity itself being a cause of infertility, erectile dysfunction is significantly associated with obesity. Patients who are overweight or obese make up of 76% of men who report erectile dysfunction and a decrease in libido [19]. Many studies have found an association between an increased incidence of erectile dysfunction and an increase in BMI; hormonal dysfunction is central to the connection between obesity and erectile dysfunction [57]. Erectile dysfunction is highly prevalent in men with both type 2 diabetes and obesity and might act as a forerunner to cardiovascular disease in this high-risk population. Conversely, improved diabetes control and weight loss have been found to improve erectile function [58].

**Elevated Scrotal Temperature**

An elevated BMI can impair or arrest spermatogenesis by causing an increase in scrotal temperature. Increased fat distribution in the upper thighs, suprapubic area, and scrotum in conjunction with the sedentary lifestyle often associated with obesity can result in increased testicular temperature [21, 28]. Studies of cyclists, truck drivers, and individuals that almost constantly experience elevated scrotal temperatures, like those with undescended testes demonstrate a negative influence of genital heat stress on spermatogenesis. Many studies have focused on genital heat stress as a potential cause of impaired semen quality in cases of sedentary occupations, the occurrence of frequent fever, and varicocele [59]. Hjollund et al. [60] concluded that even a moderate physiological elevation in scrotal skin temperature is associated with substantially reduced sperm concentrations. Additionally Magnusdottir et al. [6] found that the duration of sedentary posture correlated positively with increased scrotal temperatures, leading to a decrease in sperm density.

**Are There Solutions?**

From the preceding literature, it is evident that obesity is an influencing factor in male infertility. Many experts believe that overweight and obesity, as well as their related chronic diseases, are largely preventable and measures can be taken to reverse both the unhealthy consequences associated with obesity and the negative impacts on male fertility. Therefore, the treatment approach will predominantly focus on the management of obesity (Fig. 33.2). The rapid rise in the incidence of obesity has prompted researchers to not only look at natural treatment methods but also for new treatments in order to manage the pandemic and its subsequent comorbidities.

**Lifestyle Changes**

Lifestyle changes that can lead to weight loss can include diet modifications (eating smaller meals, cutting down on certain types of food) as well as making a conscious effort to exercise more in order to achieve a normal energy balance. Several studies showed that natural weight loss through diet and/or exercise resulted in an increase in androgen, inhibin B, and SHBG levels and decreased serum concentrations of insulin and leptin, thereby improving semen parameters in obese men [15, 28, 38, 61, 62]. In addition, reducing adipose tissue mass through weight loss in association with exercise or a low-energy and low-fat diet decreases levels of TNF-α, IL-6, and other inflammatory cytokines associated with infertility [63, 64].
Gradual weight loss is best achieved through a sensible eating plan that can be maintained over long periods of time. The likelihood of maintaining weight loss is increased when the diet is combined with regular exercise, cognitive behavior therapy, and connecting with a supportive group environment [65]. Therefore, adoption of these principles in a primary health-care setting can aid in the treatment of infertility related to obesity.

**Pharmacological Interventions**

Medication can be used to either treat obesity by addressing weight loss or dealing with the obesity-related effects on the male reproductive system. Currently, only two anti-obesity medications are approved by the Food and Drug Administration for long-term use [66]. One is orlistat (Xenical), which reduces intestinal fat absorption by inhibiting pancreatic lipase; the other is sibutramine (Meridia), which acts in the brain to inhibit deactivation of the neurotransmitters norepinephrine, serotonin, and dopamine, therefore decreasing appetite. However, weight loss with these drugs is modest.

Aromatase inhibitors are an option for obese males facing infertility problems, especially if they have elevated estrogen and lowered testosterone levels. Aromatase inhibitors prevent the excess aromatase enzymes from converting testosterone to estrogen. They interfere with the aromatase p450 enzyme that is highly expressed in white adipose tissue. Currently available aromatase inhibitors include anastrozole, testolactone, and letrozole. Numerous case studies have found this to be an effective treatment in not only restoring normal hormone levels, but also fertility. Raman and Schlegel tested the effects of anastrozole on nonobstructive azoospermic patients who presented with normal or decreased levels of testosterone and elevated levels of estradiol. Anastrozole treatment normalized the testosterone-to-estradiol ratio and total testosterone levels and improved semen parameters [67]. Zumoff et al. [68] found that by inhibiting estrogen biosynthesis (through administration of the aromatase inhibitor testolactone), there was an alleviation of possible infertility as a result of hypogonadotropic hypogonadism in obese male subjects. In another case study, a patient diagnosed with infertility secondary to morbid obesity was treated with the aromatase inhibitor, anastrozole. This led to normalization of the patient’s testosterone, LH, and FSH hormone levels, as well as suppression of the serum estradiol levels and the normalization of spermatogenesis and fertility [33]. In a study including normal, overweight, and obese men, treatment with anastrozole led to an increase in testosterone-to-estradiol ratio that occurred in association with increased semen parameters. Anastrozole and testolactone have similar effects on hormonal profiles and semen analysis, but anastrozole appears to be at least as effective as testolactone for treating men with abnormal testosterone-to-estradiol ratio [67].

New directions in pharmacological treatment might include testosterone replacement therapy and maintenance and regulation of adipose-derived hormones, particularly leptin, which is produced by fat cells in the body and known to affect appetite and the body’s energy balance, and also reproductive function. Testosterone replacement therapy has been shown to suppress the levels of circulating leptin, although no information regarding the effect of the treatment on semen parameters was reported [16, 38]. Quennell et al. [69] discovered that leptin indirectly regulates gonadotropin-releasing hormone neuronal function, affecting forebrain...
neurons that induce infertility. By decreasing elevated leptin levels in obese patients, it might be possible to reverse some of the potential suppressive effects of excess leptin on the HPG axis and restore normal spermatogenesis and sperm function. Ghrelin, a hormone which is secreted by cells in the lining of the stomach, also affects appetite and the body’s energy balance. Further studies of these hormones may lead to the development of new medications to control appetite and provide an option for treating obesity-related health problems and infertility.

**Surgical Options**

In vitro fertilization may be an option for obese patients facing problems such as erectile dysfunction or other purely physical fertility problems. Although morbid obesity is associated with unfavorable IVF/ICSI cycle outcome as evidenced by lower pregnancy rates in females, there is no evidence for a contributing male factor when assisted reproductive methods are used [70]. It is recommended that morbidly obese patients undergo appropriate counseling before the initiation of this expensive and invasive therapy. Fortunately, studies show that obesity in men may not adversely affect the results of their partners who are undergoing in vitro fertilization or embryo transfer [71].

Scrotal lipectomy is a treatment option available for infertility in obese men whose excess fat accumulation may be contributing to their infertility, either through increased scrotal temperature or excess toxin accumulation. One-fifth of patients who were previously considered infertile and underwent scrotal lipectomy to remove excess fat were able to achieve a successful pregnancy [28]. For individuals who are severely obese, dietary changes and behavior modification may be accompanied by surgery to reduce or bypass portions of the stomach or small intestine. The risks of obesity surgery have declined in recent years, but it is still only performed on patients for whom other strategies have failed and whose obesity seriously threatens their health.

Bariatric surgery (“weight loss surgery”) is the use of surgical intervention in the treatment of obesity by reducing or bypassing portions of the stomach or small intestine. As it is a rather extreme intervention, it is only recommended for severely obese people (BMI > 40) who have failed to lose sufficient weight following dietary modification and pharmacological treatment [72]. Gastric bypass and banding surgeries are very effective in the treatment of morbid obesity and its comorbid conditions. One study reported that a significant decrease in estrogen, increase in testosterone, and normalization of other hormone and adipokine levels were experienced by patients who underwent vertical banded gastropasty [73]. However, others speculate that the drastic weight loss that accompanies this procedure might induce secondary infertility, even though natural weight loss has shown promising results in terms of restoring fertility [74]. Bariatric surgery should therefore not be recommended as a treatment for obesity-linked infertility until extensive, long-term studies have been performed to determine the definite effects on male fertility.

**Conclusion**

Obesity is a modern-day pandemic with serious comorbidities, both physical and psychological. Studies clearly show that obese men have an increased chance of subfertility and subfertility due to various mechanisms (physical, genetic, hormonal, adipokine, cytokine) that ultimately lead to ED and abnormal semen parameters. The central factor behind these mechanisms is the abnormal regulation of the HPG axis. An abnormal hormonal profile, and more specifically increased adipose-derived hormones and adipokine levels, may explain the association between BMI, altered semen parameters, and infertility more accurately as it is clearly more complex than can be accounted for simply by abnormal levels of reproductive hormones.

New studies point to many causes for abnormal semen parameters, including genetic markers, excess adipose-derived hormone and adipokine release, as well as oxidative stress. The consistent decrease in inhibin B levels and increase in leptin levels, and specific proteomic sperm changes observed in obese infertile males, all may have negative impacts on spermatogenesis. Increased cytokines, such as IL-6, are connected with oxidative stress and impaired reproduction and could also contribute to abnormal semen parameters observed in obese men facing fertility issues. These markers point toward a true suppression of normal spermatogenesis and sperm quality despite some inconsistency in the results of studies performed to measure the effects of obesity on semen parameters.

In treating obesity-linked sperm disorders and male infertility, few controlled studies have been performed, and effective therapeutic treatments, advice for lifestyle changes, and surgical options should be explored further. In addition, determining the most accurate measure for qualifying patients as obese could more accurately clarify the cause of their infertility and other health issues that might accompany their state of obesity. Neither the reversibility of obesity-associated male infertility in response to weight loss nor effective therapeutic treatments or interventions have been extensively studied. The increasing prevalence of obesity worldwide in conjunction with a perceived declining male sperm count in modern man calls for more research and attention to obesity as an etiology of male infertility. Clinicians should consider obesity when a male patient with idiopathic infertility is confronted.
Expert Commentary

The purpose of this chapter was to discuss obesity as a newly discovered etiology of male infertility. The growing incidence of obesity and apparent decrease in male fertility makes this topic especially relevant when dealing with the infertile male. Although data on abnormal semen parameters and evidence of obesity as it affects male fertility is abundant, the specific mechanisms are not definite. Discovery and proof of significant mechanisms that contribute to this issue are important when treating infertility as it relates to obesity. The recognition of adipose tissue as an endocrine organ and discovery of adipokines have contributed greatly in explaining the mechanisms behind this problem, but it appears many other factors are involved. Further understanding of adipose tissue as an endocrine organ and obesity as a constant inflammatory state will allow in-depth studies of specific adipokines and cytokines involved.

In addition, controlled studies demonstrating all effects of aromatase inhibitors, weight loss, bariatric surgery, and other new therapeutic measures are needed to definitely recommend specific treatments. Lifestyle changes leading to weight loss appear to be of the greatest benefit, not only for male fertility issues but overall health. The pressing issue of obesity in not only the USA, but the whole world, has lasting effects that now appear to include male infertility. It is important, especially as the obesity epidemic grows, for clinicians to consider obesity as explanation to a male with idiopathic infertility or subfertility.

Key Issues

- Obesity is a medical condition in which excess body fat, or white adipose tissue, accumulates in the body to the extent that the excess fat often adversely affects health, often reducing life expectancy.
- The obesity epidemic is growing to concerning proportions, affecting an estimated 700 million people in the next 5 years.
- Altered semen parameters ascribed to obesity include decreased sperm concentration, abnormal morphology, compromised chromatin integrity, and abnormal sperm motility.
- The discovery of adipose tissue as an active endocrine organ secreting adipokines and adipose-derived hormones is an important mechanistic link explaining infertility in many obese men.
- Mechanisms that may explain abnormal semen parameters in obese men include genetic, hormonal, and physical mechanisms that may all contribute to the deregulation of the HPG axis that controls normal spermatogenesis.
- Physical problems that may contribute to decreased fertility include ED; scrotal lipomatosis, which leads to increased scrotal temperatures; and sleep apnea that can cause disruptions in the essential nightly testosterone rise.
- There are solutions that often lead to restoration of fertility that include lifestyle changes, pharmacological interventions, and surgical procedures.
- The rapid rise in the incidence of obesity has prompted researchers to not only look at natural or lifestyle changes as treatment methods but also for new therapies in order to manage the pandemic and its subsequent comorbidities.
- Clinicians should consider obesity when a male patient with idiopathic infertility is confronted.

References