Human Fertility

an international, multidisciplinary journal dedicated to furthering research and promoting good practice

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ihuf20

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To cite this article: Firass Abiad, Johnny Awwad, Hussein A. Abbas, Dina Zebian & Ghina Ghazeeri (2017) Management of weight loss in obesity-associated male infertility: a spotlight on bariatric surgery, Human Fertility, 20:4, 227-235, DOI: 10.1080/14647273.2017.1317369

To link to this article: https://doi.org/10.1080/14647273.2017.1317369

Published online: 02 May 2017.

HUMAN FERTILITY, 2017
VOL. 20, NO. 4, 227–235
http://dx.doi.org/10.1080/14647273.2017.1317369

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REVIEW ARTICLE

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Management of weight loss in obesity-associated male infertility: a spotlight on bariatric surgery

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ABSTRACT
In recent years, there has been a paralleled increase between male obesity and infertility rates. Obesity is associated with impaired hypothalamic-pituitary-gonadal axis, aberrant semen parameters, and subfertility or infertility. Weight loss is strongly recommended for the management of obesity-associated infertility. Lifestyle modifications that include caloric restriction and increased physical activity have a short-lived impact. Bariatric surgery is a better and more durable weight loss alternative. Comprehensive information about the benefits of weight loss on obesity-associated male infertility following bariatric surgery is still emerging. In this review, we discuss the hormonal, physical and environmental mechanism contributing to obesity-associated infertility. We then assess weight loss approaches, which include lifestyle modification, medical and surgical approaches, that can improve fertility in obese men. This review focuses also on bariatric surgery for the management of obese men seeking fertility treatment. Anecdotal evidence suggesting that bariatric surgery can impair fertility is also discussed.

ARTICLE HISTORY
Received 15 May 2016
Accepted 3 October 2016

KEYWORDS
Infertility; obesity; bariatric surgery; weight loss; sperm parameters; male reproductive function

Introduction

Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse. In 2010, 48.5 million couples worldwide were unable to conceive after five years of trying, a figure that has been increasing throughout time (Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012). In the United States, ~1 in every 13 couples suffers from infertility (Stephen & Chandra, 2006). Male-related infertility comprises 30% of all cases and contributes to another 30% of mixed male and female infertility (Katib, 2015). The decline in male reproductive function has gained much attention in the past 50 years and several studies reported a link between poor male reproductive function and obesity (Davidson, Millar, Jones, Fatum, & Coward, 2015; Hammoud, Gibson, Peterson, Meikle, & Carrell, 2008). In 2014, the World Health Organization (WHO) reported that more than 1.9 billion adults aged 18 years and over were overweight or obese. Despite the preventable nature of obesity and its dire consequences such as cardiovascular disease, type 2 diabetes and psychiatric problems, rates of obesity and overweight have more than doubled among individuals of reproductive age since 1980 (Colquitt, Picot, Loveman, & Clegg, 2009; DeMaria, 2007; Haslam & James, 2005; Practice Committee of the American Society for Reproductive Medicine, 2015). The increase of obesity rates worldwide can be attributed to environmental, lifestyle and genetic factors (Du Plessis, Cabler, McAlister, Sabanegh, & Agarwal, 2010). Unfortunately, obesity as early as in adolescence can still significantly impact adult male's reproductive outcomes. For instance, the number of children at adulthood for normal weight, overweight and obese adolescent males was 1.46, 1.4 and 0.90 in adulthood, respectively (Jokela et al., 2007). Also, a 3-unit increase in male body mass index (BMI) is significantly, though modestly, associated with infertility (Sallmen, Sandler, Hoppin, Blair, & Baird, 2006). Hence, early intervention to prevent and manage obesity in adolescence may lead to a significant impact on male's adult fertility.

Obesity is well studied as a major cause of anovulation and infertility in women of reproductive age (Abiad, Abbas, Hamadi, & Ghazeeri, 2016). Reproductive dysfunction in obese males can manifest as poor semen quality, erectile dysfunction or hormonal disturbances. A review by Davidson et al. (2015) in a previous issue of

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Human Fertility assessed the role of obesity in male infertility, and the hormonal and molecular mechanisms that ultimately lead to obesity induced infertility (Davidson et al., 2015). Therefore, in this review, we will discuss some of the mechanical and hormonal mechanisms influencing fertility in obese men. Further, we will discuss weight loss management in the treatment of obesity-induced male infertility with special focus on bariatric surgery.

Mechanisms by which obesity leads to male infertility

Hypothalamic-pituitary-gonadal axis disruption in obese patients

Obesity deregulates the hypothalamic-pituitary-gonadal axis responsible for the hormones in the reproductive cycle in men (Davidson et al., 2015). This is plausibly mediated via increased oestradiol levels due to aromatization of androgens in adipocytes and peripheral tissues, obesity-induced insulin resistance and sleep apnoea (de Boer, Verschoor, Ruinemans-Koerts, & Jansen, 2005; Du Plessis et al., 2010; Hammoud et al., 2008; Hammoud, Carrell, Gibson, Peterson, & Meikle, 2012; Katib, 2015). Elevated oestradiol levels induced by augmented aromatase activity and the abnormally elevated endorphins can suppress gonadotropin releasing hormone (GnRH) pulses from the hypothalamus. These events reduce follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary, and ultimately, lead to a decline in testosterone production from the testicular Leydig cells (de Boer et al., 2005). Experimentally, GnRH stimulation failed to illicit a normal pituitary response in obese insulin-dependent diabetic patients (Ballester et al., 2004). Obesity is also associated with sleep apnoea and deprivation that can also disrupt the normal nocturnal testosterone rhythm and the HPG axis (Luboshitzky, Lavie, Shen-Orr, & Herer, 2005). These findings support that the HPG axis in obese patients can be significantly impaired.

Impairment of Sertoli and Leydig cells by obesity

Male fertility is dependent on the optimal functioning of the Sertoli and Leydig cells of the testis. The Sertoli cells are under the control of the hypothalamus and pituitary gland, which regulate spermiogenesis (de Kretser et al., 2001). The Sertoli cells exclusively secrete inhibin B, a testicular peptide that negatively regulates FSH secretion and is associated with spermatogenic activity, testicular volume and total sperm count (Anawalt et al., 1996; Pierik, Vreeburg, Stijnen, De Jong, & Weber, 1998). Noteworthy, in sub-fertile males, inhibin B is considered a potential endocrine marker of spermatogenesis due to its high diagnostic accuracy (95%) (Globerman, Shen-Orr, Karnieli, Aloni, & Charuzi, 2005). However, inhibin B and FSH levels are low in obese or overweight men (Globerman et al., 2005; Pierik et al., 1998). It is plausible that obesity plays a role in suppressing Sertoli cells' function to produce inhibin B and eventually lead to impaired spermatogenesis (Giagulli, Kaufman, & Vermeulen, 1994; Jensen et al., 2004; Kerr, Millar, Maddocks, & Sharpe, 1993; Vermeulen, Kaufman, Deslypere, & Thomas, 1993). Also, high homocysteine and leptin levels and low vitamin D levels in obese patients can suppress testosterone production, and negatively affect semen quality (Hausman, Barb, & Lents, 2012; Katib, 2015). Yet, the definitive sequence of events that lead to these perturbations is not yet deciphered.

Insulin resistance and hyperinsulinemia in obesity can impair fertility

In addition to the aberrant HPG axis function in obese patients, insulin is positively correlated with obesity and plays an important role in regulating testosterone secretion. Insulin resistance promotes a pro-inflammatory state that can suppress HPG axis, whereas hyperinsulinaemia in obese patients can impair sperm quality and quantity (Bhasin et al., 2010). Moreover, obese men have reduced sex-hormone-binding globulin (SHGB) levels due to the mediated alteration of insulin level and insulin resistance (Stellato, Feldman, Hamdy, Horton, & McKinlay, 2000). Yet, the effect of insulin resistance or type 2 diabetes on sperm function and hypothalamic-pituitary-gonadal axis in the obese male remain contentious.

Toxin, environmental, genetic factors and psychological factors

Fat cells provide a nourishing milieu for several environmental toxins such as nematocide, 1,2-dibromo-3-chloropropane, and reactive oxygen species to accumulate and disrupt male fertility (Ivell, 2007; Oliva, Spira, & Multigner, 2001). Excess scrotal adiposity can alter sperm production by elevating testicular temperature, whereas removal of scrotal fat significantly improves sperm quality (Shafik & Olfat, 1981). Genetic conditions such as Klinefelter and Prader-Willi exhibit certain levels of obesity as well as infertility (Cabler, Agarwal, Flint, & du Plessis, 2010). However, the underlying cause of infertility in these patients is more likely attributed to the nature of the disease and mutations more than obesity *per se*. Additionally, obese men can have sexual dysfunction, manifested by decreased libido, low self-confidence and avoidance of sexual encounters. Noteworthy, erectile dysfunction is insufficient to explain infertility in obese patients.

Work-up of infertility in obese patients

Work-up of infertility includes full medical history, physical examination, and semen analysis. In recent years, there has been more emphasis on the DNA content and integrity of sperm concluding that DNA fragmentation index should be examined in the work-up of infertility (Esteves, 2016; Practice Committee of the American Society for Reproductive Medicine, 2015; Rao et al., 2016). Only few studies have linked obesity to aberrations in DNA fragmentation index and many of those studies were conducted in rodents and are reviewed in McPherson and Lane (2015). Recently, sperm binding and sperm mitochondrial health are being considered in the assessment of sperm quality despite conflicting results. However, the significance of these studies in association to infertility and obesity has not yet been addressed. Assessment of fertility in the partner is also necessary.

Semen parameters in obese patients

Semen analysis is usually one of the initial studies requested in the management of infertility. The increase in obesity rates is paralleled with increased reports of poor semen quality causing male infertility. One of the earliest large studies conducted in Denmark found that low testicular volume and abrogated semen quality as measured by sperm concentration and count were strongly associated with BMI levels lower than 19 kg/m^2 or more than 30 kg/m^2 (Jensen et al., 2004). Several other studies replicated the Danish group's findings and found that male obesity can indeed confer aberrations in total sperm count, sperm concentration (oligozoospermia), sperm motility (asthenozoospermia), sperm morphology as well as sperm DNA fragmentation index (Fejes, Koloszar, Szollosi, Zavaczki, & Pal, 2005; Kort et al., 2006; MacDonald, Herbison, Showell, & Farquhar, 2010; Martini et al., 2010; Palmer, Bakos, Fullston, & Lane, 2012). Noteworthy, not all studies have found a correlation between semen analysis abnormalities and obesity (Alshahrani, Ahmed, Gabr, Abalhassan, & Ahmad, 2016; MacDonald et al., 2010; McPherson, & Lane, 2015). Variation in findings among studies can be attributed to differences in study designs, semen analysis parameters reported, and environmental and genetic factors. Many conducted studies did not account for smoking, alcohol consumption, diet, supplements, and recreational drug use, which could significantly alter semen parameters. However, in the Chemicals and Pregnancy Study (CHAPS) UK study even after controlling for many modifiable and non-modifiable confounding variables like these no impact of obesity was seen on motile sperm concentration (Povey et al., 2012) or sperm morphology (Pacey et al., 2014). Inaccuracies in reporting extent of sexual dysfunction are also expected among participants. Further, the degree of aberrant findings with respect to BMI increase or decrease was not assessed in many studies. Nevertheless, despite some conflicting results, there is sufficient evidence from large studies to suggest that obesity can indeed influence semen quality in men and contribute to infertility in obese men.

Management of obesity in infertile men

Weight loss should be implemented in obese men seeking fertility treatment

While obesity induces noticeable disruptions in men's fertility rates, these changes can be reversed. Weight loss is one of the most effective measures to improve fertility in subfertile obese men and should be strongly recommended to improve reproductive hormone profile and increase the chances of successful conception (Du Plessis et al., 2010; Niskanen et al., 2004). The reversal and or improvement of male infertility are dependent on the extent of weight loss and the patient's ability to maintain the lost weight. Weight reduction approaches include lifestyle modifications, medical treatment and surgical intervention.

Lifestyle modifications

Traditionally, the management of obesity consisted of lifestyle modifications targeted at dietary restriction and physical activity. Dietary interventions that result in a daily energy deficit of 500–1000 kcal/day can lead to a weight loss of ~0.5–1 kg per week. In reality, overweight and obese individuals require a reduction of at least 5–10% of their body weight to achieve a healthy BMI of less than 25 kg/m^2, thus a plan for a steady weight loss of 0.5–1 kg/week is not usually successful in achieving sustainable weight loss goal in the long term (Jakicic et al., 2001). Unfortunately, lifestyle modifications that lead to at least 10% weight loss for more than 1 year is only successful in 20% of patients

(Wing & Hill, 2001). Weight loss via lifestyle modifications is generally perceived as too slow by the obese patient, and is often insufficient to be beneficial in improving the hormone profile of sub-fertile men (Hammoud et al., 2012). Further, almost all patients regain the lost weight within 5 years (Practice Committee of the American Society for Reproductive Medicine, 2015). Yet, several studies showed a significant improvement in fertility hormones, semen analysis and inflammatory markers after lifestyle interventions (Du Plessis et al., 2010; Michalakis, Mintziori, Kaprara, Tarlatzis, & Goulis, 2013; Niskanen et al., 2004). One study involving 43 obese men during a 14-week weight loss programme (diet and exercise) found that semen parameters have significantly improved after a median weight loss of 15% (range of 3.5–25.4%) (Hakonsen et al., 2011). Also, changes in BMI were inversely linked to total testosterone level, inhibin B, total sperm count, semen volume and SHBG (Hakonsen et al., 2011; Weigle & Brunzell, 1990). In a randomized controlled study, a group of 38 obese men were randomly assigned to weight-loss programmes including low calorie diet and behavioural changes (Kaukua, Pekkarinen, Sane, & Mustajoki, 2003). After eight months of follow-up, the intervention group experienced increases in SHBG and testosterone levels and decreases in serum insulin and leptin levels, but without significant changes in sexual function (Kaukua et al., 2003). These studies indicate that weight loss can improve the reproductive hormone parameters and semen parameters. However, longitudinal studies are required to address whether the reproductive hormone profile improvements can also lead to successful pregnancies. Also, since most patients regain their lost weight, lifestyle modifications may be insufficient to endure a long-lasting effect on fertility.

Medical intervention

Treatment of infertility secondary to hypogonadal hypogonadism can be attained via administration of GnRH pumps, LH analogs or aromatase inhibitors (Du Plessis et al., 2010). Medical options that merely lead to weight loss are limited. Orlistat is approved for long-term management of obesity but its common gastrointestinal side effects may hinder its usage (Practice Committee of the American Society for Reproductive Medicine, 2015). The Food and Drug Administration (FDA) has recently approved a new formulation of phentermine for weight loss but it is contraindicated for individuals with cardiovascular disease and hypertension, which commonly occur in obese patients (Practice Committee of the American Society for Reproductive Medicine, 2015). Several other drugs have been considered in the treatment of obesity and include phentermine and topiramate combination, buproprion and naltrexone combination, lorcaserin, sibutaramine and metformin. Different formulations of testosterone replacement were also used although exogenous testosterone use in hypogonadal men can impede spermatogenesis (Ramasamy, Armstrong, & Lipshultz, 2015). While patients had significant improvement in lipid profiles and sexual function, weight reduction was minimal (Isidori et al., 2005). Nevertheless, the success of these drugs in inducing weight reduction has not been assessed in relationship to optimization of men's fertility and successful conception. Also, the side effects of these medications can result in early discontinuation. Hence, the utilization of medical therapy for the management of weight loss in obese patients is not effective in the long term.

Bariatric surgery

Long-term compliance of weight loss programmes is an essential component. A large proportion of obese people fail to adhere to a weight loss programme and quickly regain the lost weight (Weigle & Brunzell, 1990). Surgery is a long-lasting treatment for obesity particularly among obese people with concomitant morbidities (Adams et al., 2007). Scrotal lipectomy was one of the earliest surgical interventions to manage infertility in obese patients. Specifically, Shafik and Olfat (1981) aimed at relieving elevated testicular temperature and preventing accumulation of toxins by removing the scrotal adipose tissues. Almost 20% of infertile patients who underwent scrotal lipectomy could impregnate their partners (Shafik & Olfat, 1981). Also, more than 60% of these patients had improvement in semen quality (Shafik & Olfat, 1981). Nevertheless, such an approach does not manage obesity *per se* and scrotal adiposity can relapse. Bariatric surgery emerged as an effective procedure that remodels the gastrointestinal tract anatomy and led to reduced caloric intake. Bariatric surgery is recommended for obese patients who have a BMI of 35 or more with coexisting medical condition or who have a BMI of 40 or more (DeMaria, 2007; Foster, Burton, & Hubbard, 1992). Ultimately, bariatric surgery can prevent the complications of obesity, which include diabetes, cardiovascular risk, and increase in overall mortality (Adams et al., 2007; Sjöström et al., 2004). It is well known that bariatric surgery can significantly improve ovulation and fertility among women (Abiad et al., 2016). Bariatric surgery is also being considered for the management of male infertility induced by obesity.

Types of bariatric surgery operations

There are different bariatric surgeries that are carried out on patients and include adjustable gastric banding (gastroplasty), Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG). Bariatric surgery can be classified as either restrictive, malabsorptive, or a combination of the two. Restrictive procedures such as gastroplasty promote early satiety via creating a small gastric reservoir that delays food emptying (DeMaria, 2007). Malabsorptive procedures bypass several portions of the small intestine where food absorption occurs (DeMaria, 2007). RYGB is considered a combination of both restrictive and malabsorptive pattern. The effectiveness of these methods has varied considerably among different studies and depends on the patient population, compliance with lifestyle changes and degree of complications (Abiad et al., 2016; DeMaria, 2007; Sjöström et al., 2004; Sjöström et al., 2012). Bariatric surgery can now be performed under guided laparoscopy, which results in decreased postoperative hospital stay and quicker return to normality for the patient. Caloric restriction and increased physical activity are still recommended to enhance and maintain weight loss after bariatric surgery.

Adverse effects and considerations for bariatric surgery

Bariatric surgery operation has a 0.1–2% risk of death depending on the procedure, degree of obesity (BMI >50), advanced patient age, patient comorbidities and expertise of surgeons (Adams et al., 2007; Bult, van Dalen, & Muller, 2008; DeMaria, 2007). Pulmonary embolism and anastomotic leaks are reported as causes of death. Other non-fatal surgical complications include infections, bleeding, hernia, and venous thromboembolisms (Adams et al., 2007; Bult et al., 2008; DeMaria, 2007). Bariatric surgery is associated with various deficiencies (such as proteins, iron, calcium and the Vitamins D and B12) due to anatomical changes in the digestive system tract. This is a major disadvantage of bariatric surgeries and can only be circumvented by supplementation with multivitamins. Hence, the pros and cons of bariatric surgery should be discussed at length with patients prior to operation.

Impact of bariatric surgery on obesity related male infertility

Bariatric surgery has demonstrated long-term effective weight loss in obese men (Adams et al., 2007; Sjöström et al., 2004; Sjöström et al., 2012). Furthermore, it has shown an improvement in cardiovascular and metabolic complications in addition to hormonal factors associated with infertility (Adams et al., 2007; Sjöström et al., 2004; Sjöström et al., 2012). Obesity is clearly associated with reduced serum testosterone levels and sperm quality, both of which lead to male infertility. Thus, weight loss following bariatric surgery is expected to increase testosterone levels, restore reproductive function in men and improve the chances of fertility.

Unfortunately, few studies assessed the hormonal and clinical parameters of infertility in relation to surgical weight loss. Hammoud et al. (2009) conducted one of the relatively large and earliest studies to address this issue. They found that in comparison to the control obese cohort, the 22 morbidly obese men that underwent gastric bypass surgery had a significant decrease in their BMI (-16.6 ± 1.2 vs. -0.46 ± 0.51 kg/m^2) and serum oestradiol (-8.1 ± 2.4 vs. 1.6 ± 1.4 pg/ml), while free testosterone (45.2 ± 5.1 vs. -0.4 ± 3.0 pg/ml) and total testosterone (310.8 ± 47.6 vs. 14.2 ± 15.3 ng/dl) levels increased significantly 2 years after surgery (Hammoud et al., 2009). The authors also reported significant improvement in sexual quality of life among obese men who underwent the surgery. The hormonal alterations, and the physical and psychosocial sexual dysfunction were related to the degree of obesity (Hammoud et al., 2009). Other studies have also reported that bariatric surgery was associated with increased FSH, total testosterone and SHBG, and a significant decrease in oestradiol levels (Bastounis et al., 1998; Globerman et al., 2005; Kaukua et al., 2003; Legro et al., 2015). Globerman et al. (2005) found that although inhibin B levels normalized, FSH levels remained low post bariatric surgery (Globerman et al., 2005). Further, despite improvement of testosterone and SHBG levels, sexual function did not improve for some patients (Kaukua et al., 2003). Importantly, Facchiano et al. (2013) found that younger obese patients can have significantly better hormonal profiles following bariatric surgery. Specifically, total testosterone and free testosterone were significantly more increased in patients below who are younger than 35 years of age (total testosterone: 10.54 [4.4 to 15.42] vs 4.15 [1.16 to 6.57] nM; $p = 0.04$, and free testosterone: 0.156 [0.063 to 0.177] vs 0.024 [-0.91 to 0.058] nM, $p = 0.005$) (Facchiano et al., 2013). These findings indicate that bariatric surgery can indeed improve the reproductive hormone profiles and that early weight loss intervention in the management of infertility can have a bigger impact.

In a more recent study, Rosenblatt and colleagues measured the long-term effect of bariatric surgery on androgenic hormones and erectile function more than six years after bariatric surgery (Rosenblatt, Faintuch, & Cecconello, 2013). They evaluated 51 patients of whom 23 undertook a bariatric surgery, 14 were obese controls and 14 were lean controls. The gastric bypass patients showed higher total free testosterone levels and SHBG in contrast to the obese controls but were comparable to the lean controls. Erectile dysfunction ($p = 0.015$) and overall sexual satisfaction ($p = 0.028$) were also higher in the bariatric surgery cohort than in the obese controls but not greater than the lean controls. These findings strongly support that bariatric surgery provide a significant long-term benefit with respect to biochemical, hormonal and overall sexual satisfaction. However, the ultimate effect on pregnancy outcomes has not been measured.

Controversy of bariatric surgery-induced infertility

A few anecdotal reports suggested that the weight loss post bariatric surgery could result in secondary infertility (di Frega, Dale, Di Matteo, & Wilding, 2005; Lazaros et al., 2012; Sermondade et al., 2012). Other studies showed that bariatric surgery has no effect on semen quality despite improvements of male fertility hormones (Reis et al., 2012). The earliest study to link bariatric surgery to worsening in sperm parameters was reported by Lazaros et al. (2012) on two obese patients. Another study later reported that six male obese patients who fathered at least one child prior to undergoing RYGB developed non-obstructive azoospermia with complete spermatogenic arrest despite the healthy appearance and normal sex hormone profiles (di Frega et al., 2005). Sermondade et al. (2012) reported that three obese male patients had severe worsening of semen parameters following bariatric surgery which was reversible two years later in one patient, while two patients later successfully conceived a child. Despite weight loss, sperm quality was worsened after bariatric surgery, possibly due to a severe decrease in the absorption of nutrients and release of toxins following surgical intervention (di Frega et al., 2005; Poitou Bernert et al., 2007). Also, the major and rapid weight loss may be interpreted by the body as an under-nutrition status, thus causing disruption to the normal pulsatile gonadotropin-releasing hormone secretion and hence leading to reproductive disorders (Tsutsumi & Webster, 2009). Noteworthy, these studies were based on a small sample size and did not report secondary causes of sperm reduction such as alcohol intake, smoking, malnutrition, medications, or lack of supplementations. Hence, the studies linking bariatric surgery to secondary sperm aberrations are inconclusive.

Conclusions

In recent years, it has become apparent that obesity is linked to decline in male reproductive function. The effect of obesity on male infertility is multifactorial and can be attributed to HPG axis disruptions, hormone deregulations, and environmental and genetic factors. Further, obesity confers major cardiovascular and metabolic burdens that can negatively impact male fertility. There is evidence that links obesity to impaired sperm parameters that ultimately lead to subfertility or infertility. Weight loss programmes should be strongly recommended for obese patients who are trying to conceive. Utilization of low calorie diet and increased physical activity can induce weight loss and improve fertility. However, the effects of these regimens are short lived and patients eventually gain the lost weight. Alternatively, bariatric surgery emerged as an effective procedure in the management of morbid obesity and its complications. The utilization of bariatric surgery to improve fertility has been supported by some studies. However, most of these studies investigated the effect of bariatric surgery on fertility hormones, while only few studies assessed semen parameters pre- and post- bariatric surgery. Nevertheless, compelling evidence is still lacking to recommend bariatric surgery for the sole management of male fertility. Instead, non-surgical weight loss programmes should be initiated first in obese men with subfertility or infertility. When non-surgical methods fail, considering bariatric surgery for weight loss should be based on the published guidelines for bariatric surgery, patient's risk factors, expected benefit, and the extent of reproductive hormone deregulation. Conclusively, bariatric surgery should not be considered for the sole indication of improving fertility in obese men due to lack of sufficient evidence. More studies are needed to assess whether bariatric surgery can indeed enhance male fertility.

Disclosure statement

All authors declare no conflict of interest.

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