Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2023, 13, 214-240
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Obesity: Impact and Outcome on Infertility—A Literature Review

Samar Zia

Specialty Trainee in Obstetrics and Gynarcology, Kings College and Hospital, London, UK
Email: samar.zia1@nhs.net

How to cite this paper: Zia, S. (2023) Obesity: Impact and Outcome on Infertility—A Literature Review. *Open Journal of Obstetrics and Gynecology*, **13**, 214-240.
https://doi.org/10.4236/ojog.2023.132023

Received: January 8, 2023
Accepted: February 18, 2023
Published: February 21, 2023

Abstract

Background: The health risks of obesity are a forever growing concern for societies worldwide. With the advent of Assisted reproductive technology more couples can achieve fertility which includes overweight and obese men and women. The review intends to explore the impact of overweight and obesity on human reproductive potential and explores ways of optimising outcome and minimising risk through development of sound recommendations. **Aim:** To determine the impact of obesity on infertility in men and women and recommendations to optimise reproductive outcome. **Method:** Relevant published reviews on the subject were searched on the PubMed, Google scholar, Medline, and Cochrane library within the past 10 years, from 2011 to 2021. **Results:** Thirty-six articles met the criteria. Twenty-six of these were qualitative studies and ten were quantitative. The main themes were increasing prevalence and burden of disease, impact on male and female obesity and assisted reproductive outcomes. **Conclusion:** Overall, it is evident that overweight and obesity negatively effects reproductive health of both men and women. It has numerous sequalae in men and women of reproductive age group with lasting impact on following progeny. These risks are minimised both in short and long term by weight loss strategies and there is need for more literature on the subject.

Keywords

Obesity, Infertility, Sub-Fertility, BMI, Lifestyle Interventions

1. Introduction

Obesity is defined as a medical condition in which excess body fat has accumulated to an extent that it may have a negative impact on health. The World Health Organization (WHO) defines the body mass index (BMI) equal to or is greater than 25 kg/m^2, overweight, whereas if the BMI equals to or is greater

than 30 kg/m^2, it is considered obesity [1].

The Global Burden of Disease study, 2017, estimates that 4.7 million people died prematurely in 2017 because of obesity [2]. The current prevalence of overweight and obese adults in UK is 67% for men and 60% for women [3]. This included 26% of men and 29% of women who were obese. In England 1 in 3 children leaving primary school are overweight or living with obesity with 1 in 5 living with obesity [3].

The Health Survey for England (HSE) that, monitors trends in the nation's health and care found that 43% of adults aged 16 and over had at least one long-standing medical condition and 16% of children aged up to 15 years old had at least one longstanding medical condition. The above data not only highlights the significant burden of obesity but also the risks it is associated with. It is likely to be the biggest cause of preventable death the near future [4].

1.1. Obesity and Infertility

National Institute for Health and Clinical Excellence (NICE) defines Infertility as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [5]. In the UK, infertility affects approximately 1 in 7 couples. There is evidence that higher the BMI, greater the risk of comorbidities such as diabetes mellitus, high blood pressure, dyslipidaemia, cardiovascular disease, obstructive sleep apnoea, various types of cancer and over-all mortality [6]. Furthermore, there is evidence that a high BMI is also associated with infertility [7] [8].

In women of childbearing age, the risk of infertility is increased by 78% and 27% with obesity and overweight, respectively, as compared with women of normal weight (BMI 18.5 - 25) [9]. Obesity negatively affects both menstrual [10] and ovulatory [11] functions in women of reproductive age group. They also indicated impact on development of oocytes. Studies have also discussed detrimental effect of obesity and overweight on quality of oocyte [12] [13] [14]. Broughton and Jungheim, 2016, discussed in their paper that obese women have disruption of hypothalamic pituitary axis (HPO) and impairment of pre-implantation trophoblasts [15]. Most women with PCOS are overweight, with estimates of the prevalence of obesity in PCOS ranging from 35% to 63% [16]. Higher serum leptin levels can result in negative impact on endometrial receptivity and embryo implantation [17] [18].

The effect of obesity on male fertility is thought to be multifactorial and may be modulated by genetic, endocrinal, and environ-mental influences [19]. Male obesity is suspected to cause alterations in semen parameters, especially sperm concentration, total sperm count, total motile sperm count, total progressively motile sperm count, sperm morphology and DNA fragmentation [20] [21]. Increase in BMI also increases seminal macrophage activation. This leads to decreased sperm motility, increased sperm DNA damage, decreased acrosome reaction and lower embryo implantation rates following IVF [19]. Obese men

have 1.3-fold higher risk of erectile dysfunction [22]. Salleman *et al.*, 2006, reported, odds of infertility increase by 10% for every 9 kg a man is overweight [23].

The growing rates of obesity have resulted in increased demands of Assisted Reproductive technology (ART) and raises significant clinical and ethical dilemmas. Obese and overweight women respond poorly to clomiphene stimulation and usually require higher doses of gonadotrophins for ovulation induction. Ovarian stimulation results in fewer follicles for harvest [24]. The preimplantation embryo is also affected by an obese environment [25]. Comparison of human IVF cycles in obese women have been shown to be more likely to result in poor quality embryos [12] [13]. Pregnancy rates have been found to be lower and increased early pregnancy loss rates.

It has significant negative impact on maternal and perinatal morbidity. Evidence looking at the impact of maternal obesity at conception on offspring has shown significantly higher odds of antenatal complications like gestational diabetes, pre-eclampsia, caesarean delivery, postpartum depression, and lower live birth rates [26]. New-born of obese mothers are at higher risk of preterm birth, macrosomia, congenital anomalies, and early development of obesity and diabetes. Given the fertility problems and the substantial risk to maternal and foetal health some countries restrict assisted reproduction treatments until women have achieved sufficient weight loss [24].

In the United Kingdom, public funding for fertility service is limited and strict guidance exists for who can be offered treatment under National Health Services (NHS). BMI is a universal criterion that is adopted by both public and private sector [27]. Though the referral criteria for IVF in United Kingdom is based on individual NHS clinical commissioning groups (CCGs), most CCGs recommend, women who are overweight or underweight will be offered referral to dieticians to improve their BMI before referral to ART. Women with a BMI less than 19 and greater than 30 will not be funded [28].

Obesity is modifiable risk factor. Its negative influence on reproductive health and outcomes can be optimised by weight loss and life changes. In, 2010, European Society of Reproduction and Embryology (ESHRE) recommended that the goal of 5% weight loss should be mandatory before accessing fertility treatment. This was based on the improved success with treatments, prevention of pregnancy complications and neonatal complications with lifestyle modifications and weight loss. In this literature review, we aim to review evidence of effects of obesity on the reproductive health of both men and women, its association with infertility and ART outcomes, benefits accrued from weight loss and lifestyle modification and management to improve fertility and pregnancy outcomes. The review will also explore impact, success, and complications of ART in overweight and obese couples [29].

1.2. Cost analysis of Obesity

It is estimated that the NHS spent £6.1 billion on overweight and obesity-related

ill-health in 2014 to 2015. Obesity has a serious impact on economic development. The overall cost of obesity to wider society is estimated at £27 billion. The UK-wide NHS costs attributable to overweight and obesity are projected to reach £9.7 billion by 2050, with wider costs to society estimated to reach £49.9 billion per year [3] [4].

2. Aims and Objective

The current literature review has systematically looked at published literature with aim to determine the impact of obesity on infertility in men and women. The review identified various methodologies utilised, potentials for future research and comment on the literature on the subject. We have developed recommendations for optimising reproductive health outcomes in overweight and obese men and women.

3. Method

A systematic review of literature was performed to identify the effects and impact of obesity on male and female infertility and optimising outcomes with weight loss and lifestyle modifications.

3.1. Search Strategy

Relevant published reviews on the subject were searched on the PubMed, Google scholar, Medline, and Cochrane library within the past 10 years. A priori review protocol was followed. A review of both published and grey literature was also carried out. Language was restricted to English. Keywords to cover all types of studies on obesity and infertility ["BMI "OR "obese" OR "overweight"] AND ["infertility" OR "Subfertility" OR "Subfecundity" male/female] AND ["IVF" OR "ART" OR "ICSI"] AND ["Intervention" OR "Weight loss" OR "weight Management" OR "Lifestyle modifications"] AND ["outcomes" OR "Live birth rate" OR "pregnancy complications" OR "physiology"].

3.2. Inclusion and Exclusion Criteria

Inclusion criteria were all male and female in reproductive age group >= 18 years and data reported on BMI ≥ 25 kg/m^2 seeking fertility. Use of interventions like lifestyle modification and weight loss to achieve fertilisation. All studies reporting effect of BMI on ART outcomes. Exclusion criteria were known systemic illness, advanced age, smoking or those not trying to conceive. Studies that used any alternate parameters for overweight and obese like waist hip ratio will also be excluded.

Due to qualitative nature of the review, no discrimination was made between qualitative and quantitative data. There were many published reviews on the obesity and infertility. Expert opinions, unsystematic reviews, editorials, overview articles, commentaries, recommendation articles, and perspectives could result in bias, therefore, they were excluded. Individual case studies were also not

be included.

3.3. Outcome Measures

The outcome of interest would be likelihood of infertility, pregnancy rate, live birth rate.

4. Results

The search strategy returned a total of 17,400 electronic citations from 2011 to 2021. A total of 151 full manuscripts were retrieved following removal of duplicates and exclusion by title and abstracts. After application of inclusion and exclusion criteria, 36 articles were included in this literature review. Twenty-six of these were qualitative studies and ten were quantitative. The main themes identified from the analysis are discussed in the review.

5. Impact of Male Obesity on Infertility

5.1. Epidemiology of Male Infertility and Obesity

It is estimated that one in seven couples in the UK has trouble conceiving [5]. Male infertility underlies or contributes to up to 50% of infertility cases. Data from the Human Fertilisation and Embryology Authority, indicate that male

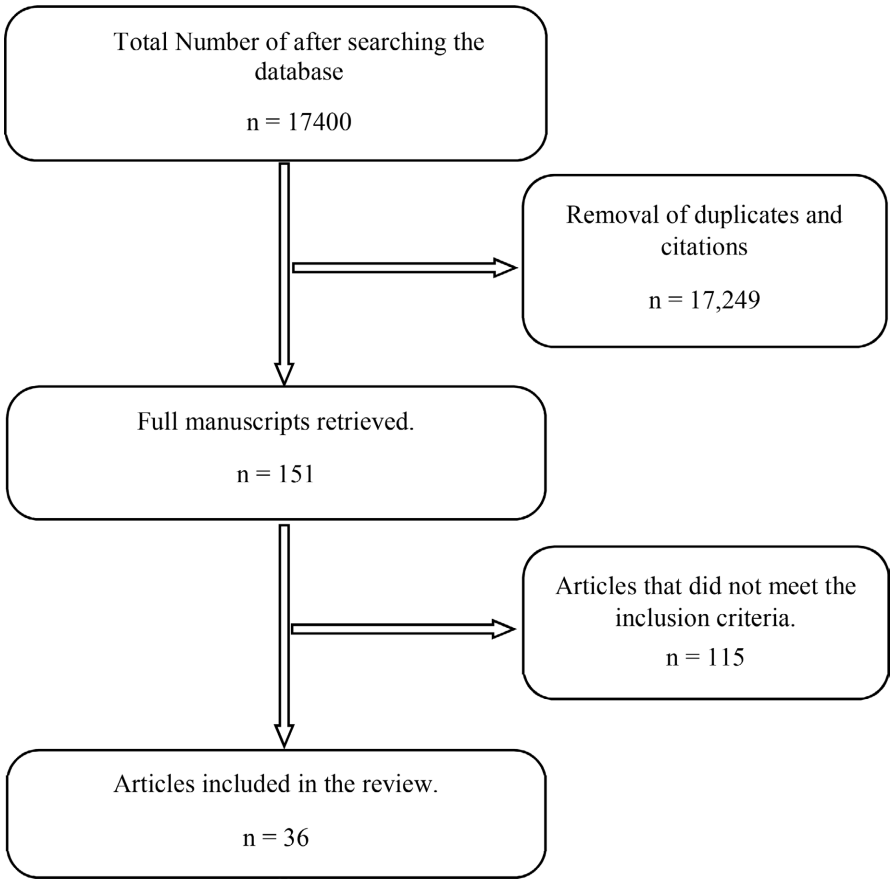

Figure 1. Flow chart for literature search and study selection.

infertility accounts for 37% of *in vitro* fertilisation (IVF) treatments, usually in combination with intracytoplasmic sperm injection (ICSI). Although over 50% of cases of male infertility are idiopathic or unexplained there are several other causes attributed one of which is obesity. According to Karavolos *et al.*, 2020, recent data has shown statistically significant relationship between overweight and obesity, with sperm parameter analysis showing more likely oligo-zoospermic or azoospermia compared with men who are within a normal weight range [30]. With the rise in rates of obesity its impact on infertility can become far more concerning (**Figure 1**).

5.2. Relationship between Overweight or Obesity and Male Infertility

Several studies have looked at the impact of overweight and obese on male reproduction and alteration in normal sperm parameters. Shukla *et al.*, 2014 and Chambers, 2015 discuss that the current scientific literature suggest the disturbance of multilevel complex physiological system [31] [32]. These disturbances are summarised below as evident from the review.

5.2.1. Hypogonadism

Hypogonadism is defined as decreased or absent gonadal function in males and is characterized by reduced testosterone levels [33]. Hammoud *et al.*, found that BMI is the most powerful predictor of male hypogonadism. Study conducted by Camacho *et al.* 2013, recruiting men for the European Male Aging Study, found a longitudinal relationship between body weight and hypogonadism [34]. They also describe the hormonal profile specific to obese men characterised by decreased total and, often, free T levels, decreased gonadotropin levels, and increased circulating oestrogen levels [35]. The decrease in testosterone is proportionate to level of obesity as established by historic studies and is the basis of Cohen's hypothesis. De Vincenzo *et al.*, 2018 discuss that obesity and, particularly, visceral adipose tissue expansion represents a strong risk factor for the development of male hypogonadism and this state is referred to as male obesity secondary hypogonadism (MOSH) [36]. Sultan *et al.*, 2020, in their review, quantified the risk of developing secondary male hypogonadism, increases by 8.7-fold for patients with BMI > 30 kg/m^2 [37]. Interestingly, further data explored by Sultan *et al.*, 2020, show that men with BMI of 35 - 40 kg/m^2 can have up to 50% less free and total testosterone when compared to age matched peers with a normal BMI [37].

5.2.2. Effect on HPG Axis

It has been long established that, decreased testosterone and increased oestrogen interferes with HPG axis. Katib *et al.*, 2015 discuss the disruption of negative feedback loop of HPG axis [19]. Overweight and obese men have higher adipose tissue which results in increased production of hormone adipokine. This results in increased aromatase cytochrome P450 enzyme activity, which then causes in-

creased aromatisation of testosterone to oestrogen [19]. Increased oestrogen has negative effect on the hypothalamus that alters the gonadotropin-releasing hormone (GnRH) pulses and suppresses gonadotropin (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) secretion [35]. Leisegang *et al.*, 2020 in their review discuss the role of Kisseptin, secreted by KISS1neurons by the hypothalamic arcuate nucleus. They theorize that based on evidence supplied by Wolfe & Hussain, 2018, there is decreased hypothalamic expression of kisseptin which leads to suppressed pulsatile release of hypothalamic GnRH, causing hypothalamic hypogonadism [38] [39].

5.2.3. Metabolic and Hormonal Disturbances

Increased adipose tissue in overweight and obese men, function not only as passive storage organs but also has endocrine functions. It secretes two main classes of molecules known as adipocytokines and adipose-derived hormones [40]. Hormones released by adipose tissue are ghrelin, leptin, orexin, adiponectin, obestatin and other metabolic hormones, all of which play a role in regulation of male reproductive function [41].

1) Role of Adipocytokines

Adipocytokines are the proteins secreted by the adipose tissues. The two main adipokines are interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) [40]. Both are implicated in creating a chronic state of inflammation and hyperinsulinemia which is associated with abnormal reproductive function. Increased insulin resistance and hyperinsulinemia reduces plasma concentration of sex hormone binding globulin (SHBG) which results in decreased testosterone and suppression of HPG axis [19]. More recent study by Laines *et al.*, 2019 determined low-grade, chronic inflammation caused by obesity affects GnRH neurons, resulting in reduced levels of LH in circulation and repression of *GnRH* mRNA in the hypothalamus [42]. Both IL-6 and TNF-α promote leucocyte production of Reactive Oxygen Species (ROS) [43]. High levels of ROS are implicated in erectile dysfunction [31]. ROS also alter sperm function and increase sperm damage. Interestingly, IL-6 and TNF-α both cause impaired penetration of ova [31].

2) Role of Leptin

Leptin is a protein hormone secreted by adipocytes and regulates several neuroendocrine functions, one of which is HPA [44]. One of the main functions of leptin is to control energy homeostasis and decrease food intake [45]. Due to its anti-obesity function, it is now an FDA approved medication for therapeutic effect in several medical condition [45] [46]. More recent studies have shown, positive correlation between abnormal sperm morphology and serum leptin and BMI and a negative correlation with sperm motility and concentration [47]. Obese men have more serum leptin levels that influence kisseptin receptors that modulate pulsatile GnRH release. Martin *et al.*, 2015 established the presence of leptin receptors in human Sertoli cells (hSCs) [45]. Thus, a more direct impact of leptin is on spermatogenesis. Acetate is needed for spermatogenesis. Martin *et*

al., 2015 showed that acetate production by hSCs is severely decreased after exposure to all concentrations of leptin [45]. Although, more studies are needed the overall impact is impaired sperm production.

3) Role of Inhibin B and Sex Hormone Binding Globulin

Inhibin B and Sex Hormone Binding Globulin are involved in the regulation of Sertoli cell function and spermatogenesis. Inhibin B is growth like factor secreted by Sertoli cells and mediates feedback inhibition of FSH production. It also stimulates testosterone synthesis by the Leydig cells. Several reports have shown that inhibin B levels are altered in obese men [35]. Suppressed inhibin B production in obese men may be due to high oestrogen level or any other mechanism indicating a direct disruptive effect of obesity on Sertoli cells [41]. Sex Hormone Binding Globulin (SHBG) is a glycoprotein produced by the liver. Increased male BMI is associated with reduced plasma concentrations of sex hormone binding globulin (SHBG) and testosterone with a concomitant rise in plasma concentration of oestrogen. The main disruption of SHBG comes as a part of metabolic syndrome characterised by hyperinsulinemia and hyperglycaemia. Both lower inhibin B and SHGB levels cause targeted disruption of FSH signals and receptors leads to aberrant gametogenesis and hormonal imbalance.

4) Role of orexin, vaspin, ghrelin and resistin

There are very few studies exploring the role of above hormones in obesity and male reproduction. Orexin is an adipose tissue hormone that stimulates testosterone production by inducing steroid synthesis in Leydig cells. It also has anti-oxidative effect [41]. Vaspin is an adipokine that has metabolic dysfunctional effect and insulin resistance. Its expression correlates with the percentage of body fat and BMI [41]. Resistin in an adipokine that again is found in significant concentrations in obese men and is implicated in development of insulin resistance [48]. Ghrelin is a neuropeptide secreted by gastrointestinal tract and influences testosterone production. However, direct role in spermatogenesis is disputed. Its overproduction can generate ROS and result in oxidative stress and alter normal testicular functions [41].

5.2.4. Alteration in Sperm Physiology and Sperm Parameters

The impact of male obesity on the reproduction and normal sperm physiological and sperm parameters has been long studied. The disruption is due to a complex interplay of factors discussed above. Several studies have evaluated the impact of obesity on the sperm characteristics that include motility, morphology, viability, concentration, count, and DNA damage. Although most studies agree that obesity has impact on sperm physiology but its detrimental effect on sperm characteristics is still contentious. Sharma *et al.*, 2013, obese men are three times more likely to exhibit a reduction in semen quality than men of a normal weight [49]. Abnormal semen parameters attributed to obesity include decreased sperm concentration, abnormal morphology, compromised chromatin reliability, and abnormal motility [50]. This literature review revealed there are very few recent studies exploring impact of obesity on sperm parameters. Older studies by Jen-

sen *et al.*, 2004 as discussed by Hammoud *et al.*, 2012 and Khullar *et al.*, 2012 reported a lower sperm concentration, count, and percentage of normal, spermatozoa for men with a BMI higher than 25 [35] [40]. Similarly, Magnusdottir *et al.*, 2005 found significant negative correlation between BMI and both sperm concentration (r 1/4 - 0.33; P 1/4.02) and total sperm count (r 1/4 - 0.30; P 1/4.04) [35]. Later studies by Hofny *et al.*, 2010 found negatively correlated with sperm concentration and motility [51]. Martin *et al.*, 2010 and Hammoud *et al.*, 2010 found evidence of oligospermia and low progressively motile sperm concentration [31] [35] [45]. This in contrast to findings by Huang *et al.*, 2017 and Palmer 2012 who found no association between BMI and sperm parameters [52] [53]. More recent studies by Belloc *et al.*, 2014 found that in morbidly obese patients (BMI > 40 kg/m^2) there was reduced semen volume, concentration, total sperm count, and reduced motility [54]. Similarly, Sermondade *et al.* 2012 carried out a systemic review investigating the effect of BMI on sperm count. They found that compared to men of normal BMI, those in the obese or morbidly obese categories had an odds ratio of 1.28 (1.06 - 1.55) and 2.04 (1.59 - 2.62) for oligozospermia and azoospermia, respectively [55]. A cross sectional study by Rufus *et al.*, 2018 that elevated BMI did not have a significant effect on semen quality [56]. It's therefore clear that no consensus on impact of obesity on sperm parameters and more studies are needed.

5.2.5. Oxidative Stress and Sperm DNA Fragmentation

Oxidative stress resulting in generation of free radicals is implicated in many diseases including infertility. ROS in excess can attack nuclear and mitochondrial DNA resulting in their fragmentation. According to Ruperez *et al.*, 2014, obesity results in a state of systemic oxidative stress [57]. The oxidative stress induced by excess amount of ROS which increases sperm DNA damage. The exact mechanisms by which ROS cause DNA damage are not well established. There are few studies in literature linking oxidative stress and sperm DNA fragmentation (SDF) and this probably is due to no consensus on accurate measurement of sperm fragmentation. Older studies by Kort *et al.*, 2006 who found positive association between SDF, and obesity used sperm chromatin assay [20]. Whilst more recent study by Fariello *et al.*, 2012 and Chavarro *et al.*, 2010 used gel electrophoresis to establish a similar link [58] [59]. A 3-year multi-centre study looking into association have also found positive link between obesity and SDF [60]. Though most evidence in literature indicate positive correlation more studies are needed to establish and verify link.

5.2.6. Erectile Dysfunction

Erectile dysfunction is a known cause of subfertility on its own. According to Hammoud *et al.*, 2012, in men reporting symptoms of erectile dysfunction, overweight or obesity are found in 79% of subjects [35]. They also reported that in a survey of health professionals, obesity was associated with a 1.3-fold relative risk for erectile dysfunction. ED in obese men results from interaction of several

factors like nervous, endocrine, metabolic and psychological factors. Obesity leads to a pro-inflammatory physiological state, which favours widespread arteriolar endothelial dysfunction and impaired activity of nitric oxide. Obesity is also known to cause both central and peripheral hypogonadism and testosterone deficiency thus further exacerbating erectile dysfunction [37]. Sultan *et al.*, 2020 report a 30% increased risk of erectile dysfunction in men with raised BMI than those of a normal BMI, and 96.5% of obese patients with metabolic syndrome report erectile dysfunction [37]. Katib *et al.*, 2015 also discuss lower sexual satisfaction, lack of sexual enjoyment, lack of sexual desire, difficulty with sexual performance, and avoidance of sexual encounters that further exacerbates erectile dysfunction [19].

5.2.7. Role of Obstructive Sleep Apnoea

One of the complications of obesity is sleep apnoea (SA). The exact pathological mechanism is not well established; however, it has been suggested that chronic hypoxia leads to dysfunction of the HPG axis and disruption of nocturnal testosterone rhythm due to sleep fragmentation [61]. Katib *et al.*, 2015 consider sleep apnoea to be associated with both low testosterone and erectile dysfunction independently [19]. SA is a modifiable risk factor and therefore its correction can improve overall reproductive potential.

5.2.8. Thermal Effects of Obesity

Optimal temperature in human range from 34˚C - 35˚C [19]. Obesity leads to excess lower abdominal, suprapubic, and medial thigh fat increases the intra-scrotal temperature altering the process of spermatogenesis. Rise in intra-scrotal temperature leads to increased DNA fragmentation and increased oxidative stress with subsequent alteration of semen parameters and sperm functions [61]. The deleterious effect of heat is associated with reduced sperm motility, increased sperm DNA fragmentation and increased sperm oxidative stress.

5.2.9. Genetic Control of Obesity

The genetic control of obesity is complex and polygenic as is evident from literature. The association of male obesity and genes was beyond the scope of this literature review.

5.3. Impact on ART

The current review supports the view that there is a negative impact of male obesity on ART in couples seeking fertility treatment. A recent meta-analysis and systematic review by Supramaniam *et al.*, 2018, looked at 49 articles investigating the role of obesity on assisted reproductive outcomes and concluded that raised BMI results in documented lower success rates and higher rates of miscarriages as well as higher total dosage of gonadotrophin usage [27]. The main reason for poor outcome is that obese men are significantly more likely to be oligo- or azoospermic [55], there is loss of mitochondrial membrane potential and increased DNA fragmentation in spermatozoa with associated high concen-

trations of reactive oxygen species (ROS) [62]. High ROS concentrations have been associated with reduced fertilization and impaired embryonic development [50] [62]. Importantly, ROS concentrations and DNA fragmentation are also associated with pregnancy loss [63]. Bakos *et al.*, 2011 conducted a retrospective analysis of 305 fresh ART cycles and concluded increased paternal BMI was associated with decreased blastocyst development, clinical pregnancy rates and live birth outcomes [64]. A more recent cohort study by Yuan *et al.*, 2017, of 1,463,597 men showed the corresponding ORs for men with high BMI (overweight 24 - 27.9 kg/m^2 [22%]; obese ≥ 28.0 kg/m^2 [5%]) versus men with normal BMI were as follows: preterm birth (1.12; 1.10 - 1.14 *vs* 1.24; 1.20 - 1.28), low birth weight (1.10; 1.05 - 1.15 *vs* 1.29; 1.20 - 1.40), macrosomia (1.19; 1.16 - 1.22 *vs* 1.34; 1.28 - 1.40), stillbirth (1.12; 1.02 - 1.23 *vs* 1.19; 1.00 - 1.41), and birth defects (1.12; 0.99 - 1.28 *vs* 1.32; 1.05 - 1.64) [65]. Despite the above available data there is paucity of studies looking at association of male obesity on ART outcomes.

5.4. Male Obesity and Embryo Development

There are very few published reports investigating the role of paternal obesity and human *in-vitro* embryonic development. Campbell *et al.*, 2015 reported that paternal obesity may reduce the live birth rate per assisted reproductive technology (ART) cycle and increases by 10% the risk of facing a non-viable pregnancy [66].

5.5. Epigenetic Effects of Paternal Obesity

Epigenetics refers to changes or modifications in a chromosome that affect gene activity and expression that can also be inheritable to offspring [61]. This epigenetic inheritance can lead to changes to the phenotype of the offspring and beyond generations. Obesity has been shown to directly drive transgenerational effects in successive generations [37]. Epidemiological and experimental studies suggest that paternal obesity may also impact on the metabolic health of offspring and grand offspring of obese parents are more likely to be obese and suffer from adverse metabolic health [32]. Evidence showing the transmission of diet-induced phenotypes through the male line, suggesting a perturbed "epigenome" in the sperm [32].

5.6. Management of Male Obesity

The main types of weight-loss interventions that can be proposed to male obese patients include modification of lifestyle habits, pharmacologic agents, and bariatric surgery.

5.6.1. Lifestyle Modifications

Weight loss achieved by lifestyle modifications is one of the main strategies that works by decreasing caloric intake and increasing energy expenditure. There is a lack in robust evidence to support the improvement in male reproductive functions following weight loss [61]. Some studies indicate improvement in andro-

gen and inhibin B levels as well as improved semen quality has been reported in obese individuals who used the natural methods of diet and exercise to lose weight [40]. Sultan *et al.*, 2020 use data from The European Male Aging Study (EMAS) has shown that changes in total body weight of ≥15% are correlated to changes in testosterone whereby gaining weight reduces testosterone levels and vice versa [37]. Hakonsen *et al.*, 2011 demonstrated an average weight loss of 15%, correlated to improvement in hormonal profile and an increase in total sperm count and semen volume [67]. It is also reported that physical activity is associated with 30% decreased risk of erectile dysfunction [22] [37]. The combined effect of improved hormonal and sperm parameters, improved spermatogenesis, reduction in ED and SA have the potential to significantly influence the male reproductive outcomes.

5.6.2. Pharmacological Treatment

Several therapeutic agents like aromatase inhibitors, phosphodiesterase inhibitors, androgen therapy, gonadotrophin therapy, metformin, orlistat, topiramate/phentermine, lorcaserin, bupropion/naltrexone, and liraglutide have been studied in relation to male obesity. These agents work by suppression of appetite, decreasing fat absorption from the gut, or increasing caloric expenditure [61]. Aromatase inhibitors inhibit aromatase P450 enzymes, thus normalizing the testosterone to estradiol ratio. Phosphodiesterase (PDE) inhibitors are considered the first line medical treatment of ED after lifestyle modification. Central hypogonadism is expected to be responsive to gonadotropin stimulation and expected to respond to gonadotrophin therapy. However, very few studies are available for evidence-based practice. Similarly, metformin improves insulin resistance and is expected to improve hypogonadism. Only one study by Ozata *et al.*, indicated reduction in total and free testosterone in obese men, following metformin therapy [68]. There are no studies conducted concerning the impact of above pharmacological agents' effect on semen parameters or male fertility. A recent study conducted by Cui *et al.*, 2016, showed improvement in sperm motility and sperm function with the usage of reservatol [69].

5.6.3. Surgical Interventions

The role of Bariatric surgery in treatment of obesity is well established. Its use in improving male reproductive functions needs further studies. Recent metanalysis by Sultan *et al.*, 2020 demonstrated benefits in improving hormonal, metabolic, sperm physiology and ED. It is noteworthy here that bariatric surgery could be an appropriate option for patients with a BMI > 40 kg/m^2 or those with a BMI of 35 - 40 kg/m^2 with co-morbid conditions [37]. Sultan *et al.* concluded from their metanalysis that sustained weight loss, demonstrated improvement in total testosterone, SHBG levels, insulin resistance, and several other metabolic parameters [37]. Wei *et al.*, 2018, showed no statistically significant difference pre- and post-bariatric surgery [70]. BARIASPERM study, assessing 46 male patients with no prior history of infertility, showed that sperm count at 6- and

12-months post operatively was significantly reduced [71]. One of the well documented impacts of bariatric surgery is improvement in ED.

6. Impact on Female Obesity on Infertility

6.1. Epidemiology of Female Infertility and Obesity

Several factors are responsible for female infertility. Estimates of the prevalence of ovulatory disorders vary from 21% to 32%, 14% to 26% for tubal disorders and 5% to 6% for endometriosis [72]. It is also well known that the prevalence of obesity is increasing worldwide. The World Health Organization, 2016 estimates with more than 600 million obese adults, including 15% of women, in 2014, double the prevalence reported three decades earlier [1].

6.2. Relationship between Overweight or Obesity and Female Infertility

Obesity can negatively affect women's fertility via menstrual and ovulatory disorders. The commonest type of ovulatory dysfunction is polycystic ovary syndrome (PCOS), the most common cause of female infertility, affecting 6% to 10% of women of child-bearing age [26]. Female obesity also causes alterations in the development [11] and quality of oocytes [11] [73] and the endometrium as well as higher miscarriage rates [74]. Moreover, obese women seeking fertility have poor assisted reproductive outcomes with decreased pregnancy and live birth rates [26].

6.2.1. Effect on HPO Axis and Neuroendocrine Dysfunction

Both central and peripheral fat accumulation in obese women impacts the function of the hypothalamus-pituitary-ovarian (HPO) axis [75]. In obese women, gonadotropin secretion is affected firstly, due to increased peripheral aromatization of androgens to oestrogens; and secondly due to insulin resistance and hyperinsulinemia which lead to hyperandrogenaemia. Furthermore, the sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) are decreased and leptin levels are increased. Thus, the neuro-regulation of the hypothalamic-pituitary-ovarian (HPO) axis may be severely deranged while the obese condition also increases the risk of miscarriage, poor pregnancy outcomes, and impaired foetal wellbeing [76]. There are metabolic mediators and pathways that directly or indirectly interact with the HPO axis in obesity and fertility [75]. Especially the role of few adipokines as described below:

1) Leptin

Obesity is characterized by leptin resistance, probably via a down-regulation of leptin receptor expression [25]. The ovaries, however, remain sensitive to leptin, therefore being exposed to the high circulating leptin levels, the ovary inhibits both granulosa and thecal cell steroidogenesis interfering with the process of ovulation [75]. The amplitude of LH pulsatility is significantly lower in eumenorrheic obese women, thus suggesting a central defect [76].

2) Adiponectin (APN)

APN receptors are abundantly present in female reproductive tissue. Circulating APN levels decrease with obesity and expression of APN receptors are reduced. This contributes to implantation failures and pregnancy loss in women with maternal metabolic conditions such as obesity and PCOS [76] [77].

3) Ghrelin

Ghrelin acts on hypothalamus and can decrease both GnRH secretion and pulsatility [78] [79]. Ghrelin can also affect ovarian steroidogenesis although the results are not consistent [80]. Muller *et al.*, 2015 discuss that ghrelin in connection to obesity, regulates insulin and insulin resistance where it decreases insulin secretion and sensitivity, ultimately leading to insulin resistance [81].

4) Resistin, visfatin, omentin and neuro-peptide Y

Resistin is an adipokine that has a possible role in HPA regulation. A randomized placebo-controlled study, by Spicer *et al.*, 2011, showed that treatment with the insulin sensitizer rosiglitazone significantly reduces the serum resistin levels in overweight women with PCOS, indicating its role in insulin sensitivity [82]. Visfatin is another protein found to be significantly elevated in obese women and that the gene expression and the circulating levels of visfatin are increased in women with PCOS [76]. Omentin is involved in insulin stimulated glucose transport but its role in reproductive physiology is unclear. A collection of neurons within the arcuate nucleus, which secrete the neuropeptide Y (NPY). During the ovulatory surge NPY concentration increases to potentiate the action of GnRH on pituitary gonadotropin secretion [78] [83]. Animal models have indicated an upregulated NPY activity in obesity leading to altered GnRH pulsatility and resultant oligo or anovulation [84]. The role and impact of the above described adipokines in obesity and female reproductive physiology remains still to be established.

5) Insulin resistance, hyperinsulinemia and hyperandrogenism

Obesity decreases SHBG production. This in turn leads to increased free circulating steroid hormone levels, such as oestrogens and androgens [78]. The androgen production is generated by two pathways. The first is by up-regulating cytochrome-P (CYP) 17A1 enzymes, which increase androgen production in both the adrenal gland and the ovary [85]. Second, insulin augments LH action on the ovary to increase androgen production and secretion [85]. The net effect of hyperandrogenism is premature follicular atresia thus favouring anovulation [75]. Goldsammler *et al.*, in their paper discussed studies indicating evidence of disruption of chromatin remodelling within mouse oocytes, thereby contributing to poorer oocyte quality with high insulin levels [78].

6.2.2. Impact on Ovarian Morphology, Function, and Oocyte Development

The impact of obesity on ovarian morphology and development is a cumulative result of altered HPO, steroidogenesis, neuroendocrine dysfunction and chronic inflammatory state induced by obesity. Hohos *et al.*, 2017 discuss the role of high fat diet on ovarian follicular development with decreased primordial follicle and

increased follicular atresia [86]. Increased levels of lipids in the ovary, characterised by increased lipid content in the cumulus cells and oocytes and is associated with increased lipotoxicity and increased rates of anovulation [86]. Lipotoxicity is known to cause increased markers of endoplasm reticulum (ER) stress, decreased mitochondrial membrane potential, and increased apoptosis and increased rates of anovulation [87]. There is also evidence that increasing BMI is associated with increasing triglycerides in the follicular fluid, and in a human granulosa cell line, treatment with saturated fatty acids induced apoptosis [86]. Enhanced steroidogenesis due to insulin and its interaction with LH, produces an unfavourable milieu that causes blockage of the follicle growth. Thus, the premature luteinization and the consequent follicular arrest result in menstrual cycle disorders and oligo-anovulation which appears strictly related to the obesity [76]. Apart from the above changes there is good evidence that obesity is an independent marker of poor oocyte quality. Animal studies conducted by Luzzo *et al.*, 2012 and Jungheim *et al.*, 2010 indicate that oocytes from obese mice are smaller, show delayed meiotic maturation and increased follicular apoptosis and have significant spindle or chromosome misalignment defects [88] [89]. Obese women have higher levels of circulating free fatty acids, which damage non adipose cells by increasing reactive oxygen species (ROS) that and induce mitochondrial and ER stress resulting in apoptosis of multiple cell types including oocytes [15].

6.2.3. Impact on Endometrium

Although there is evidence that obesity influences endometrial receptivity and alters decidualisation, there are few studies corroborating or refuting the impact. Desolle *et al.* 2009 published a retrospective review of 450 donor-oocyte frozen embryo transfer cycles and found BMI to be an independent predictor of clinical pregnancy [90]. More recently, Rhee *et al.*, 2016 showed that endometrial decidualization, the necessary step for uterine receptivity to occur, is impaired in the obese mice [91]. They also found decreased implantation sites and decreased response to hormonal stimulation in the endometrial stromal cells. These findings were reciprocated in human decidualization in primary cells from obese versus control women and found a decrease in obese women [15]. Decidualization and implantation defects may negatively affect the placentation process. In addition, in vitro studies have demonstrated that leptin can affect steroidogenic pathways in granulosa cells leading to downstream effects on endometrial receptivity and embryo implantation [15]. Robker *et al.*, 2008, suggested that a reduction in oocyte developmental competence may impair the developmental potential of the embryo, which may lead to an impaired implantation rate and subsequent abnormal implantation/trophoblastic invasion. More studies are needed to establish impact [92].

6.3. Impact on ART

Obesity not only affects the reproductive potential of women but also reduces

the success of ART. A recent metanalysis by Supramaniam *et al.*, 2018 clearly showed the negative impact of raised BMI on ART. The same metanalysis reported overweight and obese (BMI ≥ 25 kg/m^2) women have a statistically significant lower live birth following ART when comparisons are drawn to women with a normal BMI. An increase is also demonstrated in the number of miscarriages experienced by women with a BMI ≥ 30 kg/m^2 [27].

Several studies have indicated that obese women require significantly higher doses of gonadotropin than normal-weight women to produce a similar number of ovarian follicles during controlled ovarian hyperstimulation [84]. Furthermore, there is evidence that obese women are less likely to fertilize than oocytes from normal-weight women, suggesting that oocytes from obese women are of poorer quality [93]. A national study by Luke *et al.*, 2011, showed fewer oocytes collected, higher number of cycles cancelled for poor or high oocytes retrieved (overstimulation), higher miscarriage rates and reduced pregnancy and live-birth rates [94]. Jungheim *et al.*, 2013 attributed the above adverse pregnancy outcome to poor embryo quality and abnormal implantation [84]. When comparing whether conception was achieved with autologous or donor oocytes, study by Bellver *et al.*, 2013 demonstrated, lower implantation, clinical pregnancy, and live birth rate [95]. They concluded that female obesity impairs the reproductive outcome of ovum donation probably because of reduced uterine receptivity. Interestingly, very few studies have looked at ART outcomes in women with PCOS who need ART. A recent study by Sun *et al.*, 2020 reported increased spontaneous miscarriage rates women with raised BMI and PCOS seeking ART. They also reported from their systematic review that patients with PCOS may reduce the spontaneous abortion rate by losing weight before preparing for pregnancy, and the ideal target of weight control is within the normal BMI range. Obese patients may not benefit much if they have lost some weight but remain in the overweight status [96].

6.4. Impact on Embryo and Pregnancy Outcome

The preimplantation embryo is also affected by an obese environment [15] [25]. Leary *et al.* noted that embryos from women with BMI ≥ 25 kg/m^2 were less likely to develop after fertilization, and those that did reached the morula stage more quickly. In addition, those that reached the blastocyst stage had fewer cells in the trophectoderm and demonstrated poor glucose uptake and increased levels of triglycerides [25] [97]. DIO mice models have shown embryos demonstrated decreased insulin-like growth factor 1 receptor expression, suggesting decreased insulin signalling, and the resultant foetuses were growth restricted at midgestational [84]. Maternal and foetal complications are becoming more evident since the improvement in fertility service and more women with obesity becoming pregnant. Marchi *et al.*, 2015, conducted an extensive systematic review which showed higher odds of gestational diabetes (OR 3.01 to 5.55), preeclampsia (OR 2.93 to 4.14), antenatal (OR 1.43) and postpartum depression (OR

1.30), and caesarean delivery (OR 2.01 to 2.26), compared with normal-weight women. New-borns born to mothers with obesity are at a higher risk of preterm birth (<32 weeks' gestation; adjusted OR 1.33, 95% CI 1.12 - 1.57), macrosomia (>4500 g; OR 3.23, 95% CI 2.39 - 4.37), perinatal death (relative risk 1.34, 95% CI 1.22 - 1.47) and congenital anomalies including neural tube defects (OR 2.24, 95% CI 1.86 - 2.29) and cardiovascular anomalies (OR 1.30, 95% CI 1.12 - 1.51)—compared with new-borns born to mothers with normal prepregnancy weight [98].

6.5. Transgenerational Effects

There is concerning evidence that obesity has transgenerational and confers a risk of metabolic dysfunction through multiple generations [26]. It is long established that children of obese women are more at risk of obesity, type2 diabetes and cardiovascular disease [99]. More studies are needed to determine the impact.

6.6. Interventions to Improve Obesity and Reproductive Potential

6.6.1. Lifestyle Interventions

This literature review indicated that there is plenty of data indicating positive impact of diet and physical activity in improving fertility outcomes in obese women by altering the hormonal milieu and metabolic profile. ESHRE, 2018, states, lifestyle intervention (diet, exercise, and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity, and insulin resistance with an achievable target of 5% - 10% [100]. Silvestris *et al.* 2017, documented in their paper that available data suggest that the weight loss equal to 5% - 10% of the body weight may improve the fertility rate [76]. A systematic review by Mc Grei *et al.*, 2017 investigating the role of low carbohydrate diet on fertility hormones found that reducing carbohydrate load can reduce circulating insulin levels, improve hormonal imbalance, and resume ovulation to improve pregnancy rates compared to usual diet [101]. A randomised control trial (RCT) conducted by Mutsaerts *et al.*, 2016, using structured weight loss program and fertility outcomes in obese found significantly more women in the intervention group than in the control group had ongoing pregnancies that resulted from natural conception [102]. Sim *et al.*, 2014 found that the incidence of spontaneous pregnancy and live birth was increased in women allocated to a lifestyle intervention compared with controls [103]. A more recent meta-analysis conducted by Kim *et al.*, 2020, reviewed 21 RCTs, and concluded compared to the control group, nonpharmacological interventions significantly increased the pregnancy rate (relative risk (RR), 1.37; 95% CI, 1.04 - 1.81; $p = 0.03$; $I^2 = 58\%$; nine RCTs) and the natural conception rate (RR, 2.17, 95% CI, 1.41 - 3.34; $p = 0.0004$; $I^2 = 19\%$, five RCTs). However, they had no significant effect on the live birth rate (RR, 1.36, 95% CI, 0.94 - 1.95; $p = 0.10$, $I^2 = 65\%$, eight RCTs) and increased the risk of miscarriage (RR: 1.57, 95% CI, 1.05 - 2.36; $p = 0.03$; $I^2 = 0\%$) [104]. Therefore, nonpharmacological interventions could have a positive effect on the pregnancy and natural conception rates, whereas it is unclear whether they improve the live birth rate. It is to be

noted here that few studies exist exploring lifestyle measures as first line. Bivia-Riog *et al.*, 2020, have designed a study protocol for an RCT investigating the impact of internet-based lifestyle interventions in improving fertility outcomes in obese and overweight women [73]. It would be interesting to follow the results from the RCT. Zenaib *et al.*, 2015, reviewed literature on impact of lifestyle on ART outcomes. Their recommendations were assessment of lifestyle patterns of infertile couples, and design and implementation of healthy lifestyle counselling programs, before and during implementing assisted fertility techniques [105].

6.6.2. Pharmacological Approach

ESHRE guidance, 2018, on management of PCOS, recommends, anti-obesity medications in addition to lifestyle, could be considered for the management of obesity in adults with PCOS after lifestyle intervention. ESHRE also concludes that the role of anti-obesity pharmacological agents in PCOS remains unclear. Metformin which has been extensively studied in relation to PCOS, ESHRE recommends, its use in addition to lifestyle, to be considered in adult women with PCOS with BMI ≥ 25 kg/m^2 for management of weight and metabolic outcomes [100]. There is minimal literature on study of pharmacological intervention in obesity outside of PCOS and more research needs to be done in the area.

6.6.3. Surgical Intervention

Bariatric surgery as discussed previously is an effective form of treatment for morbid obesity with improvement in metabolic profile. Its impact on female fertility outcome is less studied. There is limited literature on fertility outcomes before and after the procedure. Butterworth, 2016 performed a systematic review and metanalysis of impact of bariatric surgery and fertility outcomes in PCOS [106]. They concluded that bariatric surgery results in postoperative conception rates varying from 33% to 100%. Casimiro *et al.*, 2019 reviewed literature and found improvement in fertility outcome in women with PCOS following bariatric surgery [107]. A recent metanalysis by Escobar-Morreale *et al.*, 2017, reported 96% improvement in gonadal dysfunction following bariatric surgery in females with PCOS [108]. However, data is limited and recommendations for surgical approach need to be balanced against bone-loss and reduction in hormones that can bring about perimenopausal state [107]. There is some evidence that though the bariatric surgery improves hypertension and diabetes in pregnancy, it is also has a higher risk of small for gestational age and a trend towards neonatal mortality [26] [109]. The American College of Obstetricians and Gynaecologists (ACOG) states that surgical weight-loss interventions should not be considered as a fertility treatment and recommends delaying the time of conception to at least 12 to 24 months after the procedure [110].

7. Conclusion

Overall, it is evident that overweight and obesity negatively effects reproductive

health of both men and women. It has numerous sequalae in men and women of reproductive age group with lasting impact on following progeny. These risks are minimised both in short and long term by weight loss strategies and there is need for more literature on the subject.

8. Recommendations from the Review

1) More comparative studies are needed to explore the impact of overweight and obesity on sperm parameters and benefits from reduction in weight.

2) Are neuro-endocrine hormones associated with improvement in sperm parameters? And can there be a direct or indirect role in improving fertility outcomes?

3) More evidence is needed to establish the role of overweight and obesity on endometrial receptivity and miscarriage.

4) Given the growing obesity pandemic is there a role of fat preventive hormones in management?

5) Can optimization of male obesity improve ART outcomes in isolation?

6) What is the role of weight loss in women with PCOS seeking ART?

7) Are lifestyle interventions the most cost effective and should be the first line approach?

8) Is using a weight loss protocol beneficial in improving care and service?

9) Anti-obesity medications their impact, role, and evidence in management of fertility.

10) Bariatric surgery in both men and women and fertility outcome before and after procedure.

11) What is the uptake of counselling and its role in optimizing outcomes in both overweight obese men and women?

12) Psychological health of overweight obese men and women trying to conceive, should this be part of standard care provision?

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] WHO (2021) Obesity and Overweight. World Health Organisation. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

[2] WHO (2019) Global Database on Body Mass Index. World Health Organization. http://www.assessmentpsychology.com/icbmi.htm

[3] Public Health England (2017) Health Matters: Obesity and the Food Environment. GOV.UK. Public Health England. https://www.gov.uk/government/publications/health-matters-obesity-and-the-food-environment/health-matters-obesity-and-the-food-environment--2

[4] NHS Digital (2019) Health Survey for England, 2018: Quick Guide. Health Survey for England 2018 [NS].

https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2018

[5] NICE (2013) Overview. Fertility Problems: Assessment and Treatment. Guidance,| NICE. Nice.org.uk. https://www.nice.org.uk/guidance/CG156

[6] Hensrud, D.D. and Klein, S. (2006) Extreme Obesity: A New Medical Crisis in the United States. *Mayo Clinic Proceedings*, **81**, S5-S10. https://doi.org/10.1016/S0025-6196(11)61175-0

[7] Castillo-Martínez, L., López-Alvarenga, J.C., Villa, A.R. and González-Barranco, J. (2003) Menstrual Cycle Length Disorders in 18- to 40-y-Old Obese Women. *Nutrition*, **19**, 317-320. https://doi.org/10.1016/S0899-9007(02)00998-X

[8] Bhattacharya, S., Porter, M., Amalraj, E., Templeton, A., Hamilton, M., Lee, A.J. and Kurinczuk, J.J. (2009) The Epidemiology of Infertility in the North East of Scotland. *Human Reproduction*, **24**, 3096-3107. https://doi.org/10.1093/humrep/dep287

[9] Ramlau-Hansen, C.H., Thulstrup, A.M., Nohr, E.A., Bonde, J.P., Sørensen, T.I. and Olsen, J. (2007) Subfecundity in Overweight and Obese Couples. *Human Reproduction*, **22**, 1634-1637. https://doi.org/10.1093/humrep/dem035

[10] Zain, M.M. and Norman, R.J. (2008) Impact of Obesity on Female Fertility and Fertility Treatment. *Women's Health* (*Lond*), **4**, 183-194. https://doi.org/10.2217/17455057.4.2.183

[11] Klenov, V.E. and Jungheim, E.S. (2014) Obesity and Reproductive Function: A Review of the Evidence. *Current Opinion in Obstetrics and Gynecology*, **26**, 455-460. https://doi.org/10.1097/GCO.0000000000000113

[12] Carrell, D.T., Jones, K.P., Peterson, C.M., Aoki, V., Emery, B.R. and Campbell, B.R. (2001) Body Mass Index Is Inversely Related to Intrafollicular HCG Concentrations, Embryo Quality and IVF Outcome. *Reproductive BioMedicine Online*, **3**, 109-111. https://doi.org/10.1016/S1472-6483(10)61977-3

[13] Metwally, M., Cutting, R., Tipton, A., Skull, J., Ledger, W.L. and Li, T.C. (2007) Effect of Increased Body Mass Index on Oocyte and Embryo Quality in IVF Patients. *Reproductive BioMedicine Online*, **15**, 532-538. https://doi.org/10.1016/S1472-6483(10)60385-9

[14] Reyes-Muñoz, E., Sathyapalan, T., Rossetti, P., Shah, M., Long, M., Buscema, M., Valenti, G., La Rosa, V.L., Cianci, S. and Vitale, S.G. (2018) Polycystic Ovary Syndrome: Implication for Drug Metabolism on Assisted Reproductive Techniques—A Literature Review. *Advances in Therapy*, **35**, 1805-1815. https://doi.org/10.1007/s12325-018-0810-1

[15] Broughton, D.E. and Jungheim, E.S. (2016) A Focused Look at Obesity and the Preimplantation Trophoblast. *Seminars in Reproductive Medicine*, **34**, 5-10. https://doi.org/10.1055/s-0035-1570032

[16] Balen, A.H., Dresner, M., Scott, E.M. and Drife, J.O. (2006) Should Obese Women with Polycystic Ovary Syndrome Receive Treatment for Infertility? *BMJ*, **332**, 434-435. https://doi.org/10.1136/bmj.332.7539.434

[17] Lin, Q., Poon, S.L., Chen, J., Cheng, L., HoYuen, B. and Leung, P.C. (2009) Leptin Interferes with 3',5'-Cyclic Adenosine Monophosphate (cAMP) Signaling to Inhibit Steroidogenesis in Human Granulosa Cells. *Reproductive Biology and Endocrinology*, **7**, Article No. 115. https://doi.org/10.1186/1477-7827-7-115

[18] Greisen, S., Ledet, T., Møller, N., Jørgensen, J.O., Christiansen, J.S., Petersen, K. and Ovesen, P. (2000) Effects of Leptin on Basal and FSH Stimulated Steroidogenesis in Human Granulosa Luteal Cells. *Acta Obstetricia et Gynecologica Scandinavica*, **79**, 931-935. https://doi.org/10.3109/00016340009169237

[19] Katib, A. (2015) Mechanisms Linking Obesity to Male Infertility. *Central European Journal of Urology*, **68**, 79-85. https://doi.org/10.5173/ceju.2015.01.435

[20] Kort, H.I., Massey, J.B., Elsner, C.W., Mitchell-Leef, D., Shapiro, D.B., Witt, M.A. and Roudebush, W.E. (2006) Impact of Body Mass Index Values on Sperm Quantity and Quality. *Journal of Andrology*, **27**, 450-452. https://doi.org/10.2164/jandrol.05124

[21] MacDonald, A.A., Herbison, G.P., Showell, M. and Farquhar, C.M. (2010) The Impact of Body Mass Index on Semen Parameters and Reproductive Hormones in Human Males: A Systematic Review with Meta-Analysis. *Human Reproduction Update*, **16**, 293-311. https://doi.org/10.1093/humupd/dmp047

[22] Bacon, C.G., Mittleman, M.A., Kawachi, I., Giovannucci, E., Glasser, D.B. and Rimm, E.B. (2003) Sexual Function in Men Older than 50 Years of Age: Results from the Health Professionals Follow-Up Study. *Annals of Internal Medicine*, **139**, 161-168. https://doi.org/10.7326/0003-4819-139-3-200308050-00005

[23] Sallmén, M., Sandler, D.P., Hoppin, J.A., Blair, A. and Baird, D.D. (2006) Reduced Fertility among Overweight and Obese Men. *Epidemiology*, **17**, 520-523. https://doi.org/10.1097/01.ede.0000229953.76862.e5

[24] Pandey, S., Pandey, S., Maheshwari, A. and Bhattacharya, S. (2010) The Impact of Female Obesity on the Outcome of Fertility Treatment. *Journal of Human Reproductive Sciences*, **3**, 62-67. https://doi.org/10.4103/0974-1208.69332

[25] Broughton, D.E. and Moley, K.H. (2017) Obesity and Female Infertility: Potential Mediators of Obesity's Impact. *Fertility and Sterility*, **107**, 840-847. https://doi.org/10.1016/j.fertnstert.2017.01.017

[26] Belan, M., Harnois-Leblanc, S., Laferrère, B. and Baillargeon, J.P. (2018) Optimizing Reproductive Health in Women with Obesity and Infertility. *CMAJ*, **190**, E742-E745. https://doi.org/10.1503/cmaj.171233

[27] Supramaniam, P.R., Mittal, M., McVeigh, E. and Lim, L.N. (2018) The Correlation between Raised Body Mass Index and Assisted Reproductive Treatment Outcomes: A Systematic Review and Meta-Analysis of the Evidence. *Reproductive Health*, **15**, Article No. 34. https://doi.org/10.1186/s12978-018-0481-z

[28] NHS Choices (2019) Availability—IVF. NHS. https://www.nhs.uk/conditions/ivf/availability/

[29] ESHRE Task Force on Ethics and Law, including, Dondorp, W., de Wert, G., Pennings, G., Shenfield, F., Devroey, P., Tarlatzis, B. and Barri, P. (2010) Lifestyle-Related Factors and Access to Medically Assisted Reproduction. *Human Reproduction*, **25**, 578-583. https://doi.org/10.1093/humrep/dep458

[30] Karavolos, S., Panagiotopoulou, N., Alahwany, H. and Martins da Silva, S. (2020) An Update on the Management of Male Infertility. *The Obstetrician & Gynaecologist*, **22**, 267-274. https://doi.org/10.1111/tog.12688

[31] Shukla, K.K., Chambial, S., Dwivedi, S., Misra, S. and Sharma, P. (2014) Recent Scenario of Obesity and Male Fertility. *Andrology*, **2**, 809-818. https://doi.org/10.1111/andr.270

[32] Chambers, T.J. and Richard, R.A. (2015) The Impact of Obesity on Male Fertility. *Hormones* (*Athens*), **14**, 563-568. https://doi.org/10.14310/horm.2002.1621

[33] De Lorenzo, A., Noce, A., Moriconi, E., Rampello, T., Marrone, G., Di Daniele, N. and Rovella, V. (2018) MOSH Syndrome (Male Obesity Secondary Hypogonadism): Clinical Assessment and Possible Therapeutic Approaches. *Nutrients*, **10**, Article 474. https://doi.org/10.3390/nu10040474

[34] Camacho, E.M., Huhtaniemi, I.T., O'Neill, T.W., Finn, J.D., Pye, S.R., Lee, D.M.,

Tajar, A., Bartfai, G., Boonen, S., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Kula, K., Keevil, B., Lean, M.E., Pendleton, N., Punab, M., Vanderschueren, D. and Wu, F.C., EMAS Group (2013) Age-Associated Changes in Hypothalamic-Pituitary-Testicular Function in Middle-Aged and Older Men Are Modified by Weight Change and Lifestyle Factors: Longitudinal Results from the European Male Ageing Study. *European Journal of Endocrinology*, **168**, 445-455. https://doi.org/10.1530/EJE-12-0890

[35] Hammoud, A.O., Gibson, M., Peterson, C.M., Meikle, A.W. and Carrell, D.T. (2008) Impact of Male Obesity on Infertility: A Critical Review of the Current Literature. *Fertility and Sterility*, **90**, 897-904. https://doi.org/10.1016/j.fertnstert.2008.08.026

[36] Di Vincenzo, A., Busetto, L., Vettor, R. and Rossato, M. (2018) Obesity, Male Reproductive Function and Bariatric Surgery. *Frontiers in Endocrinology* (*Lausanne*), **9**, Article 769. https://doi.org/10.3389/fendo.2018.00769

[37] Sultan, S., Patel, A.G., El-Hassani, S., Whitelaw, B., Leca, B.M., Vincent, R.P., le Roux, C.W., Rubino, F., Aywlin, S.J.B. and Dimitriadis, G.K. (2020) Male Obesity Associated Gonadal Dysfunction and the Role of Bariatric Surgery. *Frontiers in Endocrinology* (*Lausanne*), **11**, 408. https://doi.org/10.3389/fendo.2020.00408

[38] Leisegang, K., Sengupta, P., Agarwal, A. and Henkel, R. (2021) Obesity and Male Infertility: Mechanisms and Management. *Andrologia*, **53**, e13617. https://doi.org/10.1111/and.13617

[39] Wolfe, A. and Hussain, M.A. (2018) The Emerging Role(s) for Kisspeptin in Metabolism in Mammals. *Frontiers in Endocrinology* (*Lausanne*), **9**, Article 184. https://doi.org/10.3389/fendo.2018.00184

[40] Khullar, K., Agarwal, A. and du Plessis, S. (2012) A Hormonal, Physical, and Proteomic View of Obesity-Induced Effects on Male Infertility and Possible Lifestyle Modifications. *Asian Pacific Journal of Reproduction*, **1**, 161-168. https://doi.org/10.1016/S2305-0500(13)60071-8

[41] Dutta, S., Biswas, A. and Sengupta, P. (2019) Obesity, Endocrine Disruption and Male Infertility. *Asian Pacific Journal of Reproduction*, **8**, 195-202. https://doi.org/10.4103/2305-0500.268133

[42] Lainez, N.M. and Coss, D. (2019) Obesity, Neuroinflammation, and Reproductive Function. *Endocrinology*, **160**, 2719-2736. https://doi.org/10.1210/en.2019-00487

[43] Doshi, S.B., Khullar, K., Sharma, R.K. and Agarwal, A. (2012) Role of Reactive Nitrogen Species in Male Infertility. *Reproductive Biology and Endocrinology*, **10**, Article No. 109. https://doi.org/10.1186/1477-7827-10-109

[44] Amjad, S., Baig, M., Zahid, N., Tariq, S. and Rehman, R. (2019) Association between Leptin, Obesity, Hormonal Interplay and Male Infertility. *Andrologia*, **51**, e13147. https://doi.org/10.1111/and.13147

[45] Martins, A.D., Moreira, A.C., Sá, R., Monteiro, M.P., Sousa, M., Carvalho, R.A., Silva, B.M., Oliveira, P.F. and Alves, M.G. (2015) Leptin Modulates Human Sertoli Cells Acetate Production and Glycolytic Profile: A Novel Mechanism of Obesity-Induced Male Infertility? *Biochimica et Biophysica Acta*, **1852**, 1824-1832. https://doi.org/10.1016/j.bbadis.2015.06.005

[46] Sinha, G. (2014) Leptin therapy gains FDA approval. *Nature Biotechnology*, **32**, 300-302. https://doi.org/10.1038/nbt0414-300b

[47] Einollahi, N., Dashti, N., Emamgholipour, S., Zarebavani, M., Sedighi-Gilani, M.A. and Choobineh, H. (2016) Evidence for Alteration in Serum Concentrations of Leptin in Infertile Men Categorized Based on BMI. *Clinical Laboratory*, **62**, 2361-2366.

https://doi.org/10.7754/Clin.Lab.2016.160516

[48] Flehmig, G., Scholz, M., Klöting, N., Fasshauer, M., Tönjes, A., Stumvoll, M., Youn, B.S. and Blüher, M. (2014) Identification of Adipokine Clusters Related to Parameters of Fat Mass, Insulin Sensitivity and Inflammation. *PLOS ONE*, **9**, e99785. https://doi.org/10.1371/journal.pone.0099785

[49] Sharma, R., Biedenharn, K.R., Fedor, J.M. and Agarwal, A. (2013) Lifestyle Factors and Reproductive Health: Taking Control of Your Fertility. *Reproductive Biology and Endocrinology*, **11**, Article No. 66. https://doi.org/10.1186/1477-7827-11-66

[50] Aitken, R.J. and Baker, M.A. (2013) Causes and Consequences of Apoptosis in Spermatozoa; Contributions to Infertility and Impacts on Development. *The International Journal of Developmental Biology*, **57**, 265-272. https://doi.org/10.1387/ijdb.130146ja

[51] Hofny, E.R., Ali, M.E., Abdel-Hafez, H.Z., Kamal, E.El-D., Mohamed, E.E., Abd El-Azeem, H.G. and Mostafa, T. (2010) Semen Parameters and Hormonal Profile in Obese Fertile and Infertile Males. *Fertility and Sterility*, **94**, 581-584. https://doi.org/10.1016/j.fertnstert.2009.03.085

[52] Palmer, N.O., Bakos, H.W., Fullston, T. and Lane, M. (2012) Impact of Obesity on Male Fertility, Sperm Function and Molecular Composition. *Spermatogenesis*, **2**, 253-263. https://doi.org/10.4161/spmg.21362

[53] Huang, Y.P., Liu, W., Liu, Y.D., Wang, H.X., Hu, K., Chen, B. and Lu, M.J. (2018) Right Testicular Volume Is a Dominant Predictor of Testicular Function Determined by Sperm Parameters and Total Testosterone. *Andrologia*, **50**, e12955. https://doi.org/10.1111/and.12955

[54] Belloc, S., Cohen-Bacrie, M., Amar, E., Izard, V., Benkhalifa, M., Dalléac, A. and de Mouzon, J. (2014) High Body Mass Index Has a Deleterious Effect on Semen Parameters Except Morphology: Results from a Large Cohort Study. *Fertility and Sterility*, **102**, 1268-1273. https://doi.org/10.1016/j.fertnstert.2014.07.1212

[55] Sermondade, N., Faure, C., Fezeu, L., Shayeb, A.G., Bonde, J.P., Jensen, T.K., Van Wely, M., Cao, J., Martini, A.C., Eskandar, M., Chavarro, J.E., Koloszar, S., Twigt, J.M., Ramlau-Hansen, C.H., Borges Jr., E., Lotti, F., Steegers-Theunissen, R.P., Zorn, B., Polotsky, A.J., La Vignera, S., Eskenazi, B., Tremellen, K., Magnusdottir, E.V., Fejes, I., Hercberg, S., Lévy, R. and Czernichow, S. (2013) BMI in Relation to Sperm Count: An Updated Systematic Review and Collaborative Meta-Analysis. *Human Reproduction Update*, **19**, 221-231. https://doi.org/10.1093/humupd/dms050

[56] Rufus, O., James, O. and Michael, A. (2018) Male Obesity and Semen Quality: Any Association? *International Journal of Reproductive BioMedicine*, **16**, 285-290.

[57] Rupérez, A.I., Gil, A. and Aguilera, C.M. (2014) Genetics of Oxidative Stress in Obesity. *International Journal of Molecular Sciences*, **15**, 3118-3144. https://doi.org/10.3390/ijms15023118

[58] Fariello, R.M., Pariz, J.R., Spaine, D.M., Cedenho, A.P., Bertolla, R.P. and Fraietta, R. (2012) Association between Obesity and Alteration of Sperm DNA Integrity and Mitochondrial Activity. *BJU International*, **110**, 863-867. https://doi.org/10.1111/j.1464-410X.2011.10813.x

[59] Chavarro, J.E., Toth, T.L., Wright, D.L., Meeker, J.D. and Hauser, R. (2010) Body mass Index in Relation to Semen Quality, Sperm DNA Integrity, and Serum Reproductive Hormone Levels among Men Attending an Infertility Clinic. *Fertility and Sterility*, **93**, 2222-2231. https://doi.org/10.1016/j.fertnstert.2009.01.100

[60] Dupont, C., Faure, C., Sermondade, N., Boubaya, M., Eustache, F., Clément, P.,

Briot, P., Berthaut, I., Levy, V., Cedrin-Durnerin, I., Benzacken, B., Chavatte-Palmer, P. and Levy, R. (2013) Obesity Leads to Higher Risk of Sperm DNA Damage in Infertile Patients. *Asian Journal of Andrology*, **15**, 622-625. https://doi.org/10.1038/aja.2013.65

[61] El Salam, M.A.A. (2018) Obesity, an Enemy of Male Fertility: A Mini Review. *Oman Medical Journal*, **33**, 3-6. https://doi.org/10.5001/omj.2018.02

[62] Zribi, N., Chakroun, N.F., Elleuch, H., Abdallah, F.B., Ben Hamida, A.S., Gargouri, J., Fakhfakh, F. and Keskes, L.A. (2011) Sperm DNA Fragmentation and Oxidation Are Independent of Malondialdheyde. *Reproductive Biology and Endocrinology*, **9**, Article No. 47. https://doi.org/10.1186/1477-7827-9-47

[63] Gharagozloo, P. and Aitken, R.J. (2011) The Role of Sperm Oxidative Stress in Male Infertility and the Significance of Oral Antioxidant Therapy. *Human Reproduction*, **26**, 1628-1640. https://doi.org/10.1093/humrep/der132

[64] Bakos, H.W., Henshaw, R.C., Mitchell, M. and Lane, M. (2011) Paternal Body Mass Index Is Associated with Decreased Blastocyst Development and Reduced Live Birth Rates Following Assisted Reproductive Technology. *Fertility and Sterility*, **95**, 1700-1704. https://doi.org/10.1016/j.fertnstert.2010.11.044

[65] He, Y., Xie, X., Tang, W. and Ma, X. (2017) Maternal and Paternal Obesity and Adverse Pregnancy Outcomes in China: A Cohort Study. *The Lancet*, **390**, S52. https://doi.org/10.1016/S0140-6736(17)33190-2

[66] Campbell, J.M., Lane, M., Owens, J.A. and Bakos, H.W. (2015) Paternal Obesity Negatively Affects Male Fertility and Assisted Reproduction Outcomes: A Systematic Review and Meta-Analysis. *Reproductive BioMedicine Online*, **31**, 593-604. https://doi.org/10.1016/j.rbmo.2015.07.012

[67] Håkonsen, L.B., Thulstrup, A.M., Aggerholm, A.S., Olsen, J., Bonde, J.P., Andersen, C.Y., Bungum, M., Ernst, E.H., Hansen, M.L., Ernst, E.H. and Ramlau-Hansen, C.H. (2011) Does Weight Loss Improve Semen Quality and Reproductive Hormones? Results from a Cohort of Severely Obese Men. *Reproductive Health*, **8**, Article No. 24. https://doi.org/10.1186/1742-4755-8-24

[68] Ozata, M., Oktenli, C., Bingol, N. and Ozdemir, I.C. (2001) The Effects of Metformin and Diet on Plasma Testosterone and Leptin Levels in Obese Men. *Obesity Research*, **9**, 662-667. https://doi.org/10.1038/oby.2001.90

[69] Cui, X., Jing, X., Wu, X. and Yan, M. (2016) Protective Effect of Resveratrol on Spermatozoa Function in Male Infertility Induced by Excess Weight and Obesity. *Molecular Medicine Reports*, **14**, 4659-4665. https://doi.org/10.3892/mmr.2016.5840

[70] Wei, Y., Chen, Q. and Qian, W. (2018) Effect of Bariatric Surgery on Semen Parameters: A Systematic Review and Meta-Analysis. *Medical Science Monitor Basic Research*, **24**, 188-197. https://doi.org/10.12659/MSMBR.910862

[71] Lee, Y., Dang, J.T., Switzer, N., Yu, J., Tian, C., Birch, D.W. and Karmali, S. (2019) Impact of Bariatric Surgery on Male Sex Hormones and Sperm Quality: A Systematic Review and Meta-Analysis. *Obesity Surgery*, **29**, 334-346. https://doi.org/10.1007/s11695-018-3557-5

[72] Wilkes, S., Chinn, D.J., Murdoch, A. and Rubin, G. (2009) Epidemiology and Management of Infertility: A Population-Based Study in UK Primary Care. *Family Practice*, **26**, 269-274. https://doi.org/10.1093/fampra/cmp029

[73] Biviá-Roig, G., Blasco-Sanz, R., Boldó-Roda, A., Vara, M.D., Escrivá-Martínez, T., Herrero, R., La Rosa, V.L., Baños, R.M. and Lisón, J.F. (2020) Efficacy of an Internet-Based Intervention to Promote a Healthy Lifestyle on the Reproductive Pa-

rameters of Overweight and Obese Women: Study Protocol for a Randomised Controlled Trial. *International Journal of Environmental Research and Public Health*, **17**, Article 8312. https://doi.org/10.3390/ijerph17228312

[74] Bellver, J., Martínez-Conejero, J.A., Labarta, E., Alamá, P., Melo, M.A., Remohí, J., Pellicer, A. and Horcajadas, J.A. (2011) Endometrial Gene Expression in the Window of Implantation Is Altered in Obese Women Especially in Association with Polycystic Ovary Syndrome. *Fertility and Sterility*, **95**, 2335-2341.E8. https://doi.org/10.1016/j.fertnstert.2011.03.021

[75] Gambineri, A., Laudisio, D., Marocco, C., Radellini, S., Colao, A. and Savastano, S., Obesity Programs of nutrition, Education, Research and Assessment (OPERA) Group (2019) Female Infertility: Which Role for Obesity? *International Journal of Obesity Supplements*, **9**, 65-72. https://doi.org/10.1038/s41367-019-0009-1

[76] Silvestris, E., de Pergola, G., Rosania, R. and Loverro, G. (2018) Obesity as Disruptor of the Female Fertility. *Reproductive Biology and Endocrinology*, **16**, Article No. 22. https://doi.org/10.1186/s12958-018-0336-z

[77] Kim, K.H., Lee, K., Moon, Y.S. and Sul, H.S. (2001) A Cysteine-Rich Adipose Tissue-Specific Secretory Factor Inhibits Adipocyte Differentiation. *Journal of Biological Chemistry*, **276**, 11252-11256. https://doi.org/10.1074/jbc.C100028200

[78] Goldsammler, M., Merhi, Z. and Buyuk, E. (2018) Role of Hormonal and Inflammatory Alterations in Obesity-Related Reproductive Dysfunction at the Level of the Hypothalamic-Pituitary-Ovarian Axis. *Reproductive Biology and Endocrinology*, **16**, Article No. 45. https://doi.org/10.1186/s12958-018-0366-6

[79] Kluge, M., Schüssler, P., Schmidt, D., Uhr, M. and Steiger, A. (2012) Ghrelin Suppresses Secretion of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) in Women. *The Journal of Clinical Endocrinology & Metabolism*, **97**, E448-E451. https://doi.org/10.1210/jc.2011-2607

[80] Rak-Mardyła, A., Wróbel, A. and Gregoraszczuk, E.L. (2015) Ghrelin Negatively Affects the Function of Ovarian Follicles in Mature Pigs by Direct Action on Basal and Gonadotropin-Stimulated Steroidogenesis. *Reproductive Sciences*, **22**, 469-475. https://doi.org/10.1177/1933719114549854

[81] Müller, T.D., Nogueiras, R., Andermann, M.L., Andrews, Z.B., Anker, S.D., Argente, J., Batterham, R.L., Benoit, S.C., Bowers, C.Y., Broglio, F., Casanueva, F.F., D'Alessio, D., Depoortere, I., Geliebter, A., Ghigo, E., Cole, P.A., Cowley, M., Cummings, D.E., Dagher, A., Diano, S., Dickson, S.L., Diéguez, C., Granata, R., Grill, H.J., Grove, K., Habegger, K.M., Heppner, K., Heiman, M.L., Holsen, L., Holst, B., Inui, A., Jansson, J.O., Kirchner, H., Korbonits, M., Laferrère, B., LeRoux, C.W., Lopez, M., Morin, S., Nakazato, M., Nass, R., Perez-Tilve, D., Pfluger, P.T., Schwartz, T.W., Seeley, R.J., Sleeman, M., Sun, Y., Sussel, L., Tong, J. and Thorner, M.O., van der Lely, A.J., van der Ploeg, L.H., Zigman, J.M., Kojima, M., Kangawa, K., Smith, R.G., Horvath, T. and Tschöp, M.H. (2015) Ghrelin. *Molecular Metabolism*, **4**, 437-460. https://doi.org/10.1016/j.molmet.2015.03.005

[82] Spicer, L.J., Schreiber, N.B., Lagaly, D.V., Aad, P.Y., Douthit, L.B. and Grado-Ahuir, J.A. (2011) Effect of Resistin on Granulosa and Theca Cell Function in Cattle. *Animal Reproduction Science*, **124**, 19-27. https://doi.org/10.1016/j.anireprosci.2011.01.005

[83] Sutton, S.W., Toyama, T.T., Otto, S. and Plotsky, P.M. (1988) Evidence That Neuropeptide Y (NPY) Released into the Hypophysial-Portal Circulation Participates in Priming Gonadotropes to the Effects of Gonadotropin Releasing Hormone (GnRH). *Endocrinology*, **123**, 1208-1210. https://doi.org/10.1210/endo-123-2-1208

[84] Jungheim, E.S., Travieso, J.L. and Hopeman, M.M. (2013) Weighing the Impact of

Obesity on Female Reproductive Function and Fertility. *Nutrition Reviews*, **71**, S3-S8. https://doi.org/10.1111/nure.12056

[85] Wu, S., Divall, S., Nwaopara, A., Radovick, S., Wondisford, F., Ko, C. and Wolfe, A. (2014) Obesity-Induced Infertility and Hyperandrogenism Are Corrected by Deletion of the Insulin Receptor in the Ovarian Theca Cell. *Diabetes*, **63**, 1270-1282. https://doi.org/10.2337/db13-1514

[86] Hohos, N.M. and Skaznik-Wikiel, M.E. (2017) High-Fat Diet and Female Fertility. *Endocrinology*, **158**, 2407-2419. https://doi.org/10.1210/en.2017-00371

[87] Wu, L.L., Dunning, K.R., Yang, X., Russell, D.L., Lane, M., Norman, R.J. and Robker, R.L. (2010) High-Fat Diet Causes Lipotoxicity Responses in Cumulus-Oocyte Complexes and Decreased Fertilization Rates. *Endocrinology*, **151**, 5438-5445. https://doi.org/10.1210/en.2010-0551

[88] Luzzo, K.M., Wang, Q., Purcell, S.H., Chi, M., Jimenez, P.T., Grindler, N., Schedl, T. and Moley, K.H. (2012) High Fat Diet Induced Developmental Defects in the Mouse: Oocyte Meiotic Aneuploidy and Fetal Growth Retardation/Brain Defects. *PLOS ONE*, **7**, e49217. https://doi.org/10.1371/journal.pone.0049217

[89] Jungheim, E.S., Schoeller, E.L., Marquard, K.L., Louden, E.D., Schaffer, J.E. and Moley, K.H. (2010) Diet-Induced Obesity Model: Abnormal Oocytes and Persistent Growth Abnormalities in the Offspring. *Endocrinology*, **151**, 4039-4046. https://doi.org/10.1210/en.2010-0098

[90] Dessolle, L., Daraï, E., Cornet, D., Rouzier, R., Coutant, C., Mandelbaum, J. and Antoine, J.M. (2009) Determinants of Pregnancy Rate in the Donor Oocyte Model: A Multivariate Analysis of 450 Frozen-Thawed Embryo Transfers. *Human Reproduction*, **24**, 3082-3089. https://doi.org/10.1093/humrep/dep303

[91] Rhee, J.S., Saben, J.L., Mayer, A.L., Schulte, M.B., Asghar, Z., Stephens, C., Chi, M.M. and Moley, K.H. (2016) Diet-Induced Obesity Impairs Endometrial Stromal Cell Decidualization: A Potential Role for Impaired Autophagy. *Human Reproduction*, **31**, 1315-1326. https://doi.org/10.1093/humrep/dew048

[92] Robker, R.L. (2008) Evidence That Obesity Alters the Quality of Oocytes and Embryos. *Pathophysiology*, **15**, 115-121. https://doi.org/10.1016/j.pathophys.2008.04.004

[93] Shah, D.K., Missmer, S.A., Berry, K.F., Racowsky, C. and Ginsburg, E.S. (2011) Effect of Obesity on Oocyte and Embryo Quality in Women Undergoing *in Vitro* Fertilization. *Obstetrics & Gynecology*, **118**, 63-70. https://doi.org/10.1097/AOG.0b013e31821fd360

[94] Luke, B., Brown, M.B., Missmer, S.A., Bukulmez, O., Leach, R. and Stern, J.E., Society for Assisted Reproductive Technology Writing Group (2011) The Effect of Increasing Obesity on the Response to and Outcome of Assisted Reproductive Technology: A National Study. *Fertility and Sterility*, **96**, 820-825. https://doi.org/10.1016/j.fertnstert.2011.07.1100

[95] Bellver, J. (2013) Obesity and Poor Reproductive Outcome: Female and Male Body Weight Matter. *Fertility and Sterility*, **99**, 1558-1559. https://doi.org/10.1016/j.fertnstert.2013.01.142

[96] Sun, Y.F., Zhang, J., Xu, Y.M., Cao, Z.Y., Wang, Y.Z., Hao, G.M. and Gao, B.L. (2020) High BMI and Insulin Resistance Are Risk Factors for Spontaneous Abortion in Patients with Polycystic Ovary Syndrome Undergoing Assisted Reproductive Treatment: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology* (*Lausanne*), **11**, Article ID: 592495. https://doi.org/10.3389/fendo.2020.592495

[97] Leary, C., Leese, H.J. and Sturmey, R.G. (2015) Human Embryos from Overweight

and Obese Women Display Phenotypic and Metabolic Abnormalities. *Human Reproduction*, **30**, 122-132. https://doi.org/10.1093/humrep/deu276

[98] Marchi, J., Berg, M., Dencker, A., Olander, E.K. and Begley, C. (2015) Risks Associated with Obesity in Pregnancy, for the Mother and Baby: A Systematic Review of Reviews. *Obesity Reviews*, **16**, 621-638. https://doi.org/10.1111/obr.12288

[99] van Dijk, S.J., Molloy, P.L., Varinli, H., Morrison, J.L. and Muhlhausler, B.S., Members of EpiSCOPE (2015) Epigenetics and Human Obesity. *International Journal of Obesity* (*Lond*), **39**, 85-97. https://doi.org/10.1038/ijo.2014.34

[100] Polycystic Ovary Syndrome. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Polycystic-Ovary-Syndrome

[101] McGrice, M. and Porter, J. (2017) The Effect of Low Carbohydrate Diets on Fertility Hormones and Outcomes in Overweight and Obese Women: A Systematic Review. *Nutrients*, **9**, Article 204. https://doi.org/10.3390/nu9030204

[102] Mutsaerts, M.A., van Oers, A.M., Groen, H., Burggraaff, J.M., Kuchenbecker, W.K., Perquin, D.A., Koks, C.A., van Golde, R., Kaaijk, E.M., Schierbeek, J.M., Oosterhuis, G.J., Broekmans, F.J., Bemelmans, W.J., Lambalk, C.B., Verberg, M.F., van der Veen, F., Klijn, N.F., Mercelina, P.E., van Kasteren, Y.M., Nap, A.W., Brinkhuis, E.A., Vogel, N.E., Mulder, R.J., Gondrie, E.T., de Bruin, J.P., Sikkema, J.M., de Greef, M.H., ter Bogt, N.C., Land, J.A., Mol, B.W. and Hoek, A. (2016) Randomized Trial of a Lifestyle Program in Obese Infertile Women. *The New England Journal of Medicine*, **374**, 1942-1953. (Erratum in: N Engl J Med. 2018 Jun 28;378(26): 2546) https://doi.org/10.1056/NEJMoa1505297

[103] Sim, K.A., Partridge, S.R. and Sainsbury, A. (2014) Does Weight Loss in Overweight or Obese Women Improve Fertility Treatment Outcomes? A Systematic Review. *Obesity Reviews*, **15**, 839-850. https://doi.org/10.1111/obr.12217

[104] Kim, S.Y., Park, E.S. and Kim, H.W. (2020) Effectiveness of Non-Pharmacological Interventions for Overweight or Obese Infertile Women: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, **17**, Article 7438. https://doi.org/10.3390/ijerph17207438

[105] Zeinab, H., Zohreh, S. and Samadaee Gelehkolaee, K. (2015) Lifestyle and Outcomes of Assisted Reproductive Techniques: A Narrative Review. *Global Journal of Health Science*, **7**, 11-22. https://doi.org/10.5539/gjhs.v7n5p11

[106] Butterworth, J., Deguara, J. and Borg, C.M. (2016) Bariatric Surgery, Polycystic Ovary Syndrome, and Infertility. *Journal of Obesity*, **2016**, Article ID: 1871594. https://doi.org/10.1155/2016/1871594

[107] Casimiro, I., Sam, S. and Brady, M.J. (2019) Endocrine Implications of Bariatric Surgery: A Review on the Intersection between Incretins, Bone, and Sex Hormones. *Physiological Reports*, **7**, e14111. https://doi.org/10.14814/phy2.14111

[108] Escobar-Morreale, H.F., Santacruz, E., Luque-Ramírez, M. and Botella Carretero, J.I. (2017) Prevalence of "Obesity-Associated Gonadal Dysfunction" in Severely Obese Men and Women and Its Resolution after Bariatric Surgery: A Systematic Review and Meta-Analysis. *Human Reproduction Update*, **23**, 390-408. https://doi.org/10.1093/humupd/dmx012

[109] Carreau, A.M., Nadeau, M., Marceau, S., Marceau, P. and Weisnagel, S.J. (2017) Pregnancy after Bariatric Surgery: Balancing Risks and Benefits. *Canadian Journal of Diabetes*, **41**, 432-438. https://doi.org/10.1016/j.jcjd.2016.09.005

[110] (2009) ACOG Practice Bulletin No. 105: Bariatric Surgery and Pregnancy. *Obstetrics & Gynecology*, **113**, 1405-1413. https://doi.org/10.1097/AOG.0b013e3181ac0544