Chapter

Reproductive Consequences of Obesity

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Abstract

With increasing global obesity, there is a growing body of research looking at the impact of this on reproduction. Both male and female fertility are impacted on by being overweight or obese. Although the pathophysiology is not clear, it appears that obesity impacts endocrine function in men and women, oocyte and sperm quality, embryo quality, endocrine receptivity, and implantation. Miscarriage, pregnancy, and live birth rates and the risk of congenital malformations are all influenced by obesity. Transgenerational health is also affected, with metabolic, endocrine, and reproductive outcomes in the offspring being negatively affected by both paternal and maternal obesity. It appears that weight loss results in improvements in these outcomes and various strategies have been employed including lifestyle and behavior modification, pharmacological agents, and also bariatric surgery. This chapter aims to explore the reproductive outcomes of obesity and how this can be best managed to improve outcomes.

Keywords: obesity, IVF, embryos, bariatric, fertility, offspring, reproduction, lifestyle, oocyte, sperm

1. Introduction

Overweight or obesity is defined as an accumulation of excess body fat that poses a risk for health [1]. A measure often used in assessment of this is the body mass index (BMI), which is a person's weight in kilograms divided by height in meters squared (kg/m^2). Obesity is a BMI greater than 30 and overweight is a BMI greater than 25, although in South East Asian populations, it is generally accepted that the upper limit of normal is a BMI of 23.

Globally, 39% of adults over 18 years are overweight and 13% are obese, and worldwide, obesity has tripled since the 1970s [2]. Being overweight or obese is directly linked to a greater risk of mortality and disease than being underweight.

Infertility is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [3]. Globally, at least 50 million couples worldwide experience infertility, with the burden affecting up to one in four couples in developing nations. The overall prevalence of infertility does not appear to have changed since the 1990s.

Overweight or obesity is understood to impact on both female and male reproductive health, and mounting research demonstrates that this impact will extend to the health and reproductive outcomes of future generations.

2. Effects of obesity on female reproduction

2.1 Hormonal effects of obesity

Menstrual irregularities occur more frequently in women who are overweight. This is due to a functional alteration to the hypothalamic-pituitary-ovarian (HPO) axis from various factors. Firstly, obesity induces a hyperinsulinemic state, separate to polycystic ovarian syndrome (PCOS). Hyperinsulinemia leads to a suppression in serum hormone binding globulin (SHBG), which results in an increase in bioactive androgens. These androgens are subsequently aromatized within body fat to estrogen, which suppresses gonadotrophins produced by the pituitary [4].

Elevated androgens in PCOS also lead to an increased deposition of visceral fat, exacerbating insulin resistance and hyperinsulinemia, further stimulating androgen production and perpetuating the cycle of pituitary suppression [5].

Additionally, adipokines, cytokines produced from adipose tissue, are known to impact on ovulation. Obese women have higher levels of circulating leptin, a cell-signaling protein from adipose tissue, than normal weight women, and this can therefore mean a chronic downregulation of the receptor in the hypothalamus, [6] resulting in suppression of the HPO axis activity. A study of eumenorrheic obese women demonstrated that the amplitude of luteinizing hormone (LH) pulses was significantly reduced compared with normal weight women, again pointing to a central defect [7].

Obese women remain subfertile even if they are ovulatory. Two studies in large cohorts of Danish women showed a decline in fecundability ratios with increasing BMI [8, 9]. Another large American cohort [10] along with a Dutch cohort of over 3000 women [11] also demonstrated a linear decline in spontaneous conception rates with rising BMI.

Consequently, there are other factors at play that affect fertility in overweight and obese women.

2.2 Effects of obesity on oocyte quality

Data show that being overweight or obese can have profound impact on oocyte quality. A study of over 45,000 assisted reproduction transfers demonstrated that a higher BMI resulted in a lower likelihood of successful pregnancy when autologous oocytes were used but not when oocytes from lean donors were used [12]. This has been demonstrated in other research as well [13].

Studies also suggest that obese women in in vitro fertilization (IVF) cycles require higher levels of gonadotrophin stimulation and longer treatment to achieve an oocyte retrieval [14]. This is also the case in superovulation for intrauterine insemination cycles [15]. Obese women also have a greater risk of cycle cancelation, lesser oocytes collected, and lesser oocyte maturity than normal weight women [16–18].

Several mechanisms are believed to impact on the oocyte quality in obese women.

Obesity is an inflammatory state where women have higher circulating levels of C-reactive protein (CRP), which is an inflammatory biomarker. Adipose tissue produces many proinflammatory adipokines including leptin, tumor necrosis factor alpha (TNFα), and interleukin (IL) 6. The reproductive tissues, like all tissues, are negatively affected by inflammation. The follicular environment is altered in an obese woman. Follicular fluid contains higher levels of insulin, triglycerides, leptin, and markers of inflammation such as lactate and CRP [6]. Leptin affects steroidogenic pathways in granulosa cells, thus affecting estrogen and progesterone production. This could therefore have impact downstream on endometrial receptivity and implantation [6].

In obese mouse models, the ovaries demonstrate more apoptotic follicles and the oocytes themselves are smaller and less likely to be mature. These oocytes reveal high rates of meiotic aneuploidy due to fragmented and disorganized meiotic spindles and chromosomes that are not properly aligned on the metaphase plate [6].

Independent from this, obesity alters mitochondrial function in the oocyte. In an obese mouse model, the mitochondria have a disordered architecture with fewer cristae, more vacuoles, and evidence of swelling [19]. These abnormal mitochondria show evidence of metabolic stress, which leads to a compensatory increase in mitochondrial DNA copy number in obese mice [6, 20]. Obese mice also demonstrate evidence of endoplasmic reticulum (ER) stress where their cumulous-oocyte complexes have increased ER stress markers and increased granulosa cell apoptosis [21].

A possible cause for this cellular and organelle damage in obesity is lipotoxicity. Lipotoxicity is a condition where fatty acids from the diet that exceed the storage ability of the adipocytes can accumulate in other tissues and cause toxic effects.

Obese women have higher circulating free fatty acids (FFAs), which increase reactive oxygen species (ROS) that induce mitochondrial and ER stress and leads to apoptosis. Studies have shown that the oocytes of mice have significant increased production of ROS along with depleted glutathione levels, which is an important intracellular antioxidant defense against ROS [22]. Oocytes exposed to maternal obesity or to high levels of FFA in vitro have demonstrated perturbed mitochondria with reduced mitochondrial function, which then fail to support normal cleavage and embryo development [21].

2.3 Effects of obesity on embryo quality

The preimplantation embryo is also affected by an obese environment. Given that the early embryonic development is largely driven by the oocyte, it is not unexpected that if the oocyte is negatively affected, then the embryo development would be too.

In a mouse model, embryos of obese females have demonstrated slower preimplantation development and disordered differentiation to inner cell mass and trophectoderm lineage [20].

In an IVF model with autologous oocytes, obese women are more likely to create poor quality embryos [23, 24]. One study noted that embryos from women with a BMI > 25 kg/m^2 were less likely to develop after fertilization and those that did reached the morula stage more rapidly. Those that reached the blastocyst stage had fewer cells in the trophectoderm and demonstrated poor glucose uptake and increased levels of triglycerides along with altered amino acid metabolism compared with embryos from normal weight women (BMI < 25 kg/m^2) [25].

Much like oocytes, embryos may also be susceptible to lipotoxicity. Murine embryos that are cultured in palmitic acid, the most common FFA present in human serum, have fewer nuclei and altered IGF-1 receptor expression [26]. This negatively affects insulin sensitivity and glucose transport at a critical stage in development. This study also demonstrated that the trophoblastic cells that are exposed to the palmitic acid proliferate less and undergo apoptosis in a dose-dependent fashion.

Elevated leptin levels also have a direct negative effect on the developing embryo. In vitro studies have demonstrated that leptin has a stimulating effect on human trophoblastic cell growth and inhibition of leptin decreases that proliferation and induces apoptosis [27]. Much like its effect in the brain, tonically elevated leptin levels in an obese state may decrease the sensitivity of trophoblastic cells to its effect, altering their development.

However, there are studies in human models that have not demonstrated a negative effect of obesity on embryo quality, showing no significant difference in the quality of transferred embryos between the different BMI groups [28–31]. Although it is worth noting that despite the quality of transferred embryos being similar, other studies have suggested a reduction in the overall quality of all embryos created in an IVF cycle [14, 24], with fewer surplus embryos cryopreserved in an obese population compared to women with a normal BMI [14]. A retrospective analysis of IVF/ICSI cycles observed that in young women, obesity led to a significant reduction in average embryo quality, cryopreservation, and also embryo utilization [24]. A large retrospective analysis of over 6500 IVF cycles demonstrated no difference in embryo quality but did comment that there were poorer outcomes in the obese women [31]. Certainly, large prospective trials are required to further elucidate the effect of obesity on the embryo.

2.4 Effects of obesity on endometrial receptivity and implantation

There are conflicting data as to whether or not obesity affects endometrial receptivity and implantation of embryos, and there are several suggested mechanisms.

Leukemia inhibitory factor (LIF) has been implicated in the regulation of implantation, and a significant negative correlation between endometrial glandular LIF and BMI has been observed [32]. It has also been suggested that a state of relative hyperestrogenemia that is seen in obese women (due to aromatization of androgens to estrogen in adipose tissue) may also have a detrimental effect on receptivity [32].

Obesity is associated with insulin resistance and hyperinsulinemia. Elevated insulin levels have been associated with a reduction on glycodelin and insulin-like growth factor binding protein 1 (IGFBP1). Low levels of glycodelin have been associated with recurrent pregnancy loss, and IGFBP1 is an integral molecule involved in adhesion during implantation [32]. Derangement in these molecules may contribute to reduced receptivity in obese women.

As noted previously, obesity is an inflammatory state and obese women have been observed to have elevations in proinflammatory cytokines (IL6, TNFα), and these inflammatory markers are thought to exert negative effects on implantation [14].

Obese women also have a different pattern of endometrial gene expression during implantation than lean women [33], which is more pronounced when examined in the context of infertility. It is postulated that this is due to all or some of the abovementioned factors and the change in the intrauterine milieu of the obese women.

Although there are several plausible mechanisms as to how obesity impacts negatively on endometrial receptivity and implantation, the data for impact on infertility are inconsistent and contradictory. The best model for discriminating between the obesity effects on oocyte/embryo and endometrium is the oocyte donation model [34]. A retrospective review of over 2500 oocyte donation cycles demonstrated a negative trend in pregnancy rates with a rising BMI and a statistically significantly lower pregnancy rate in overweight and obese women compared to normal weight women [35]. However, the implantation rates were considered similar, suggesting the difference between groups was due to an increased pregnancy loss rate in the obese women. Another study also demonstrated lower live birth rates among obese surrogates compared to normal weight women [36]. Other smaller studies have suggested no difference in outcomes in obese oocyte recipients [37].

A case-controlled trial looking at IVF with autologous oocytes observed that women with a BMI > 25 kg/m^2 had reduced implantation and pregnancy rates along

with increased miscarriage rates [38]. Once again, large well-designed prospective studies using this model are required to further examine the effect of obesity on endometrial receptivity and implantation.

2.5 Effects of obesity on miscarriage

The role of obesity and miscarriage is also debated. Given the recognized impact of obesity on both the embryo and the endometrium, it is a reasonable assumption that miscarriage rates would be higher in an overweight and obese population.

Several studies have demonstrated ever-increasing odds of miscarriage with increasing BMI, in ovulation induction for anovulatory infertility, as well as in IVF cycles in both fresh and frozen cycles [28, 17, 39, 40]. A large meta-analysis of over 47,000 cycles confirmed that overweight or obese women have a higher rate of miscarriage compared with normal weight women [41]. This has also been demonstrated in donor oocyte cycles, with higher miscarriage rates in obese recipients than in normal weight women [42].

Interestingly, however, a larger follow-up study of over 2600 donor oocyte cycles by the same group [43] did not demonstrate a difference in miscarriage rates. There was a trend toward a negative impact; however, it was only when a composite measure of ongoing pregnancy rate per cycle was calculated that this was shown to be significantly lower in the obese population.

A meta-analysis looking at both spontaneous and assisted reproduction pregnancies showed that women with a BMI > 25 kg/m^2 had a significantly higher rate of miscarriage <20 weeks gestation. Subgroup analysis confirmed this to be in the donor oocyte cycles but not across all patients in the studies [44]. Another study demonstrated that in a group of women with a history of recurrent pregnancy loss (RPL), obesity is a well-recognized risk factor for miscarriage in a subsequent pregnancy [45].

A striking study looking at the chromosomal make-up of miscarried specimens from patients with RPL demonstrated that obese women had a much higher rate of euploid pregnancy loss compared to normal weight women. This supports the theory of the impact of obesity on embryo quality and endometrial receptivity.

3. Effects of obesity on male reproduction

Historically, the impact of obesity on reproduction has largely been researched in female populations with very little examination of the impact of male obesity. There is, however, a growing body of research to indicate that obesity in the male is a cause for concern. A systematic review of 30 studies with over 115,000 participants found that obese men were more likely to experience infertility and that clinical pregnancy and live birth rates per assisted reproduction cycle were reduced.

3.1 Hormonal effects of male obesity

Much like in the female, the hypothalamic-pituitary-gonadal (HPG) axis is dysregulated in the setting of male obesity. There is strong evidence of a negative effect of obesity on total testosterone, SHBG, and free testosterone [46] as well as reduced inhibin B concentrations and diminished luteinizing hormone (LH) pulse amplitude [4]. It is well understood that suppression of SHBG by hyperinsulinemia in obese men increases androgen availability for aromatization to estrogen in adipose tissue, which may then lead to negative feedback and reduction in gonadotrophin secretion [4]. Consequent to this is a decreased Leydig cell testosterone secretion, which ultimately affects spermatogenesis.

The function of the Sertoli cell, which provides both physical and nutritional support to the developing germ cell, is also impacted. Adhesion of the Sertoli cell is dependent on testosterone, and a reduction in these levels can lead to retention and phagocytosis of mature spermatids and ultimately reduced sperm counts. Other hormones that influence Sertoli cell function, FSH, LH, inhibin B, and SHBG are all lower in obese men [47].

3.2 Effects of obesity on spermatogenesis

The best markers to assess the impact of obesity on spermatogenesis are the sperm parameters from the semen analysis (count, motility, and morphology). Rodent models clearly demonstrate that diet-induced male obesity leads to reduced sperm motility, decreased sperm count, and decreased percentage of sperm with normal morphology [47], though some argue that this is indirectly due to altered hormonal stimulation.

The impact of male obesity on sperm parameters in humans is more controversial, with many contradicting studies. A review of studies [47] demonstrated varying results for the impact of male obesity on sperm concentration, morphology, and motility. The reviewers commented that there were several significant confounders including lifestyle factors such as smoking and alcohol consumption as well as cofactors such as the metabolic syndrome, which have all been shown to impact on sperm parameters. Most of the cohorts studied come from fertility centers and so are biased toward subfertile men, who may differ from the background population. Additionally, many studies rely on self-reporting, which can lead to inaccuracies.

A recent systematic review that evaluated 21 studies demonstrated a J-shaped correlation between male obesity and sperm count, whereby overweight and obesity is associated with higher rates of oligozoospermia and azoospermia [48].

3.3 Effects of obesity on sperm DNA integrity

In addition to sperm parameters, sperm DNA integrity has been found to be an important factor for the ability of a sperm to generate a healthy pregnancy [49]. Reactive oxygen species (ROS), commonly elevated in subfertile men, have been found to impair sperm DNA integrity. This is likely due to the fact that sperm are highly susceptible to ROS in the later stages of spermiogenesis as they lose the majority of their antioxidant defenses when they shed cytoplasm (**Figure 1**).

Studies have demonstrated that there is a positive correlation between increasing adiposity and higher sperm and seminal plasma ROS levels [50–52]. Oxidative stress is highly correlated with cumulative damage in the body induced by free radicals that are inadequately neutralized by antioxidant mechanisms. Antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione S-transferase (GST). A recent study in an obese mouse model showed decreased SOD in the testicular tissues of obese rats [53].

Studies have also confirmed that male obesity is associated with higher levels of sperm DNA damage [47], due to the oxygen-free radical damage, and a direct thermal effect on the testicles due to obesity. It is therefore a reasonable assumption that male obesity negatively impacts on sperm DNA integrity via high ROS levels within the testis. DNA fragmentation has been proven to reduce male fertility, possibly reduce success with assisted reproduction, and increase pregnancy loss.

Although not directly impacting on testicular function, obesity leading to reduced testosterone results in a reduction in libido and negatively impacts on erectile and ejaculatory function, which all lead to a reduction in fecundity [54].

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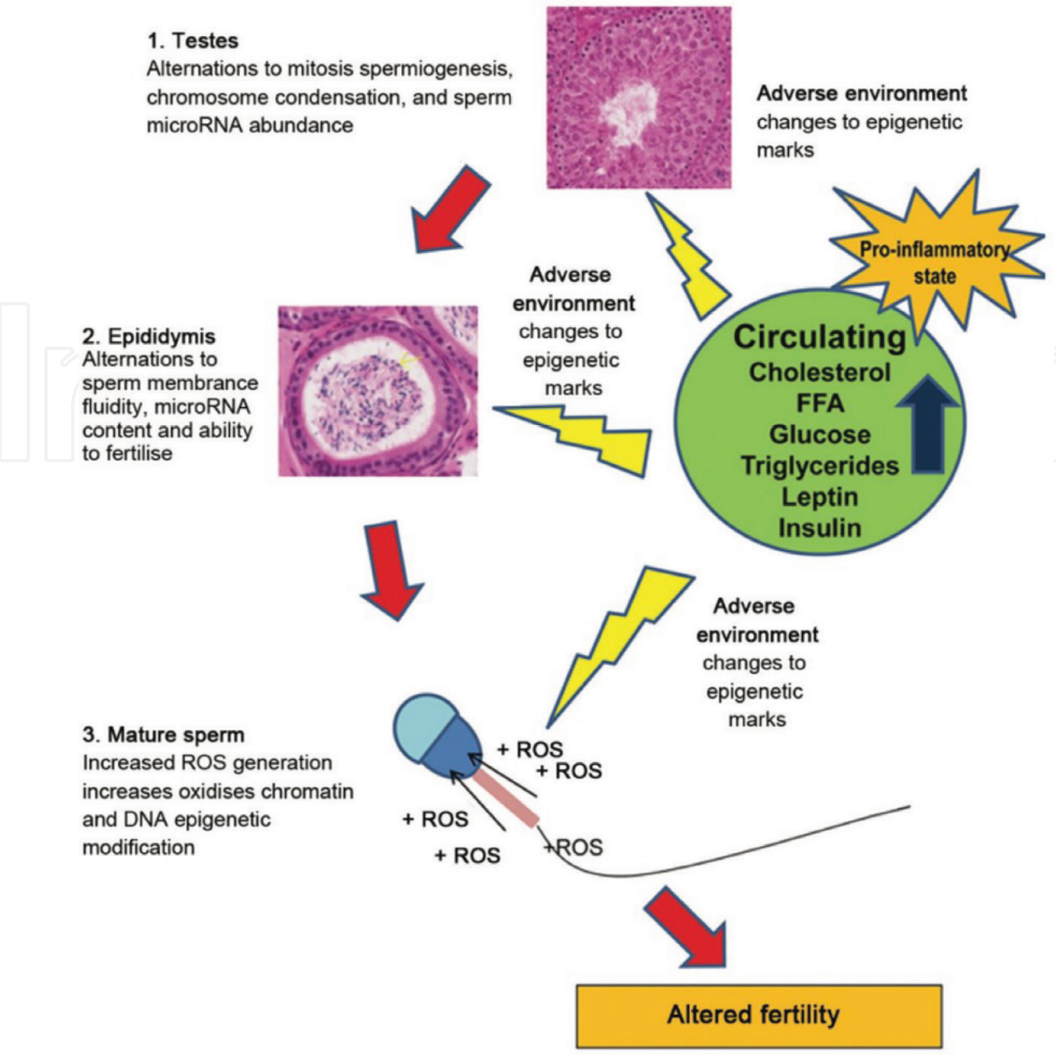

Figure 1.
Hypothesis on how epigenetic changes and impact of ROS due to an obese proinflammatory environment can occur at multiple different points along the development of the sperm, resulting in altered fertility [47].

4. Transgenerational effects of parental obesity

There is good evidence to show that maternal obesity during pregnancy is a risk factor for obesity in the offspring [55]. There is also an increasing body of evidence that obesity in males and females periconceptionally can impact on the metabolic health and even fertility of future generations. By using animal models, the impact of maternal and paternal obesity on offspring and future generations has been examined. Studies have demonstrated that obesity and other health conditions can be transmitted across multiple generations via epigenetic mechanisms down either the maternal or the paternal line.

An elegant murine study by Huypens and others [56] induced obesity in both male and female parents for 6 weeks with a high-fat diet (HFD) and then performed IVF. Embryos created from all combinations of parents were transferred into a lean dam, to negate the impact of obesity during pregnancy (**Figure 2**).

Female offspring born from both maternal and paternal obese parents gained more weight than the male offspring. The risk of female offspring obesity was reduced if only the female parent was obese, suggesting an additive effect.

Females from obese parents also had significant metabolic derangements. They demonstrated a delay in blood glucose clearance leading to hyperinsulinemia and increased fat mass. Male offspring demonstrated severe insulin resistance before

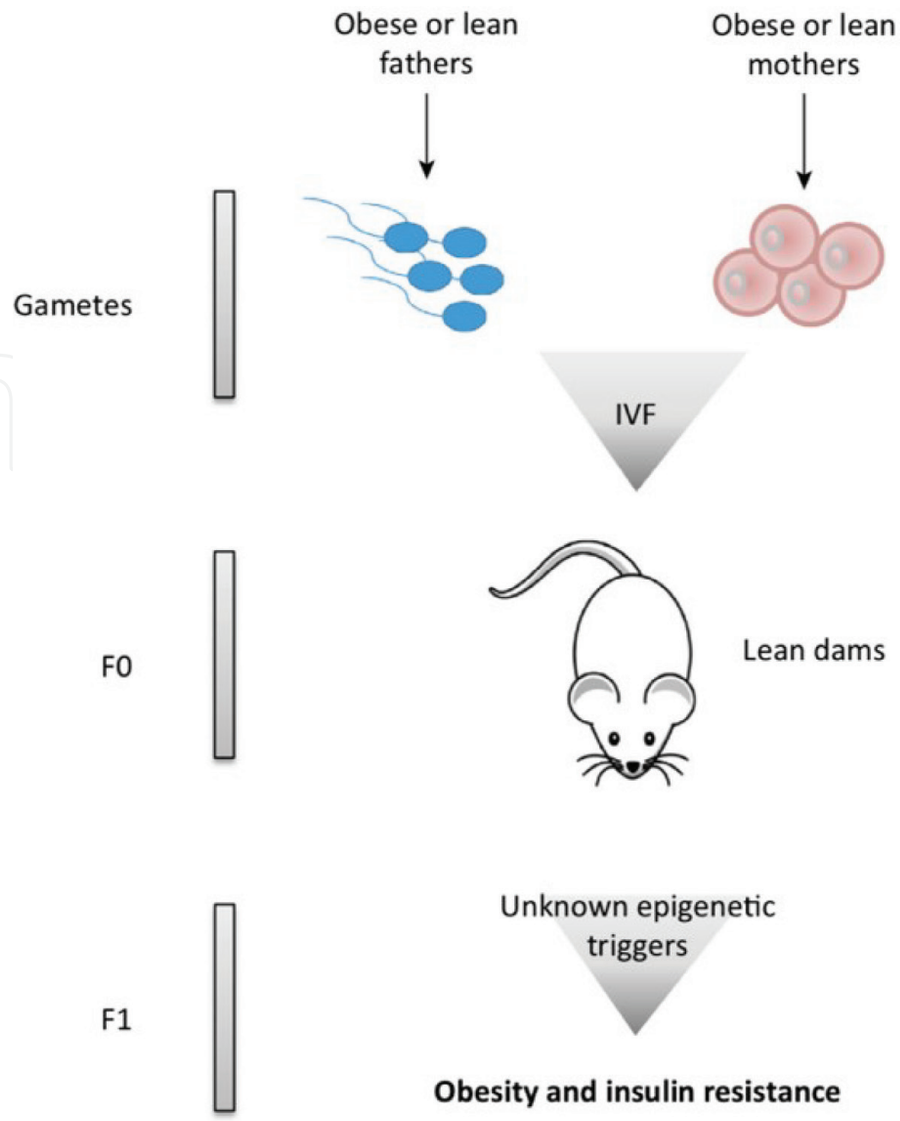

Figure 2.
Embryos created from different combinations of obese and lean parents were transferred into a lean surrogate dam, to determine the impact of overweight and obesity in male and female parents on the next generation [55].

any change in body weight. This insulin resistance was acquired in the offspring via the maternal line.

Another study by Fullston and others [57] demonstrated that paternal obesity initiated changes to metabolic health and obesity in multiple subsequent generations. Insulin resistance and obesity were transmitted to both the female and male first-generation offspring and then through both parental lineages to the second generation with amplified obesity in the female offspring in the first generation and in their sons in the second generation.

Epigenetics is the hypothesized mechanism for transgenerational disease patterns. It was thought that this was in utero exposure to epigenetic modification of offspring DNA or histone modification during developmental stages without alteration to the DNA itself. However, this has been broadened to include transgenerational (meiotic) alterations and occurs through several possible processes including DNA methylation, histone modification, DNA-binding proteins, and noncoding RNA [6] (**Figure 1**).

In the study by Fullston and others [57], they demonstrated that diet-induced paternal obesity leads to an alteration in mRNAs and microRNAs within the rodent testes, with alteration in the sperm microRNA content as well. They also detected

25% reduction in global methylation of germ cell DNA. These modifications are potential signals to program obesity and impaired metabolic health in offspring. These effects have also been demonstrated in humans with hypomethylation of sperm being associated with subfertility [58]. Another study [59] demonstrated, in a mouse model of diet-induced obesity, sperm tRNA-derived small RNAs impaired offspring glucose tolerance and induced insulin resistance. Other studies have also demonstrated that both maternal and paternal obesity can cause epigenetic changes that predispose offspring to obesity or metabolic disease later in life [60].

5. Effectiveness of weight loss strategies

There is no doubt that obesity contributes to significant periconceptional and perinatal morbidity and has been clearly associated with prolonged time to conception, increased pregnancy loss, and higher rates of adverse pregnancy outcomes such as preeclampsia and gestational diabetes along with preterm birth and in turn increased fetal morbidity and mortality. As mentioned previously, there is increasing information that it affects fertility and miscarriage rates so it is not unexpected that national and international guidelines focus on weight loss prior to either spontaneous conception or assisted reproduction [4, 32, 61] and that first-line management is ideally with lifestyle intervention and behavior modification.

5.1 Lifestyle intervention and behavior modification

It is controversial as to whether weight loss through dietary intervention, exercise programs, or behavior modification will impact significantly on spontaneous conception rates or success with assisted reproduction. There are a group of studies that suggest improved ovulatory frequency, pregnancy rates, and cost per pregnancy achieved in assisted reproduction [32, 62]. One randomized controlled trial demonstrated that a 12-week diet and exercise program resulted in a mean weight loss of 5.4 kg in the intervention group, a trend toward a higher clinical pregnancy rate and a significant difference in live birth rates [63]. A secondary analysis of two parallel randomized controlled trials in obese PCOS women also demonstrated that deferred ovulation induction treatment preceded by lifestyle modification resulted in significantly improved ovulation rates and live birth rates when compared with immediate treatment [62]. Weight reduction in an obese anovulatory population has been shown to improve pregnancy rates. A 6-month lifestyle intervention induced an average weight loss of 10 kg, which resulted in return of ovulation in 90% of participants and 78% conceiving. The miscarriage rate was 18% [64].

However, other studies suggest surprisingly little impact on conception and fertility outcomes. One large multicenter randomized controlled trial involving a 12-week intensive dietary intervention followed by IVF demonstrated a significant weight reduction in the intervention group, but this was not reflected in reproductive outcomes [65]. Live birth rates through IVF and miscarriage rates were not significantly different. The authors did note that the spontaneous pregnancy rates in the intervention group compared to the immediate treatment group were significantly higher. This may, however, have been due to having a longer time to achieve a spontaneous pregnancy, albeit they were then older at the time of IVF [65].

Firstly, lifestyle modification often results in only a modest weight loss. In a general population large-scale disease prevention programs including intensive counseling, support, and changes in diet and exercise, a 4–6 kg weight loss could be achieved but was sufficient to reduce the incidence of diabetes and metabolic syndrome [66]. Unfortunately, achieved weight loss is often regained relatively

quickly [61]. It is reported that weight loss through behavior modification and lifestyle change of greater than 10% and sustained for longer than 12 months occurs in only 20% of individuals who start a program [67].

Additionally, lifestyle modification has been attributed to positive effects on the endocrine and metabolic profile of an individual and that this, and not the weight loss, is the cause of the reported improved reproductive outcomes [68]. As such, there is a call for caution on delaying fertility treatment to allow lifestyle modification and weight loss to occur [69].

5.2 Pharmacological agents

Due to the modest weight loss from lifestyle intervention, pharmacotherapy is required as an adjunct to deliver better outcomes. There is good evidence to show that it can be used to help manage hypertension, diabetes, and cardiovascular disease in the obese population when used in addition to not replacing lifestyle intervention.

National and international bodies concur that these pharmacological agents can be used to help with weight loss prior to conceiving in those who are obese or those who are overweight with associated weight-related coexisting conditions [4, 32, 61]. It is important to note, however, that none of these drugs have been studied in men or women before conception and their effects on menstrual cycles, ovulation, or even pregnancy rates are unknown.

Phentermine is a sympathomimetic agent that suppresses appetite. Studies have indicated significant weight loss at 6 months compared to placebo [70]. There are side effects of dry mouth, agitation, insomnia, and tachycardia, and it is not recommended in patients with a history of cardiovascular disease. It is the most commonly used weight loss drug in Australia and the USA.

Orlistat inhibits pancreatic and gastric lipases and so reduces the absorption of dietary fats. It is found to be effective for weight loss [71] but has the side effects of fat malabsorption including steatorrhea, fecal incontinence, and fat-soluble vitamin deficiency [72].

Liraglutide is a glucagon-like peptide-1 agonist and controls hyperglycemia without causing hypoglycemia or weight gain. This drug was initially used to treat type 2 diabetes mellitus but its side effect profile of decreased appetite and subsequent weight loss led to its use as a weight loss agent. Studies demonstrate significant weight loss over placebo and improvement on cardiometabolic parameters [73]. Common side effects are nausea, vomiting, and diarrhea, which are dose related and diminish over time.

Topiramate, an anticonvulsant, has also been used to treat obesity due to the side effect of weight loss and is used as either monotherapy or in combination with phentermine. A naltrexone/bupropion combination has also been demonstrated to provide average weight loss over 12 months [74], and Lorcaserin, a selective 5-hydroxytryptamine 2c receptor agonist, also suppresses appetite with a 3.6% weight loss over a year [75].

All of these agents are contraindicated in pregnancy.

One agent not contraindicated in pregnancy is metformin. Metformin is a biguanide that inhibits hepatic glucose production and increases peripheral tissue sensitivity to insulin, resulting in a reduced circulating insulin and accompanying decreased body weight. Although not intended as a weight loss agent, it is known to reduce weight by 1–2 kg alongside a low-calorie diet and its safety in pregnancy is well studied [61].

Many obese men and women also self-medicate with herbal supplements although their safety and effectiveness have not been demonstrated.

Unfortunately, much like with lifestyle intervention and behavior modification strategies, weight loss is modest at best, and dropout rates with these medications due to time and also side effects typically exceed 30% [76].

5.3 Bariatric surgery

There is an increasing number of bariatric surgical procedures being performed worldwide with nearly 200,000 cases being reported recently [77]. The surgeries vary between restrictive, such as the sleeve gastrectomy or the laparoscopic adjustable gastric banding and the malabsorptive procedures such as biliopancreatic diversion or a mixed restrictive/malabsorptive procedure such as the Roux en Y gastric bypass. Bariatric surgery is considered with morbid obesity (BMI > 40 kg/m^2) or with BMI > 35 kg/m^2 with concomitant medical conditions exacerbated by obesity [61].

The benefits of bariatric surgery include significant and long-term weight loss. The latest IFSO report demonstrated mean weight loss of 30% at 1 year postsurgery [77], and the Swedish Obese Study [61] showed significant weight reduction was maintained even after 10 years of follow-up [78]. Additionally, bariatric surgery has been shown to improve endocrine and metabolic profiles [61].

In women, bariatric surgery has been shown to improve menstrual regularity [79], correct ovulation [80], improve clinical and biochemical hyperandrogenism along with hyperinsulinemia and glycemic control, and improve both sexual function along with pregnancy rates [81–83].

In men, bariatric surgery improves hormone profiles by increasing testosterone and decreasing SHBG and estradiol [84]. Studies have not demonstrated an improvement in sperm quality, and in fact there have been case reports that have shown a deterioration on sperm parameters following surgery, likely due to nutritional deficiencies [48, 85]. This is in opposition to findings of longer-term stable sperm parameters following significant weight loss postbariatric surgery [86]. There is no doubt that more research needs to be done in this area to clarify this impact on male fertility.

The obstetric impact of bariatric surgery is profound with the risks of complications such as gestational diabetes, preeclampsia, and fetal macrosomia significantly reduced following surgery when compared to morbidly obese women [61]. Rare surgical complications (bowel obstruction, herniation, band events, and surgical line strictures) have been reported in pregnancy due to intra-abdominal pressure, displacement from the gravid uterus, and even hyperemesis [87, 88]. However, nutritional deficiencies due to malabsorptive-type surgery or noncompliance with long-term supplementation can have a significant effect on fertility and pregnancy outcomes. Deficiencies in iron, vitamin A, vitamin D, vitamin B12, vitamin K, and calcium can lead to maternal complications (e.g., anemia, osteopenia) and fetal complications (e.g., congenital abnormalities) [87]. Although there are no randomized prospective trials addressing time to conception after bariatric surgery, it is suggested to delay pregnancy 1–2 years postsurgery to avoid fetal exposure to nutritional deficiencies from rapid maternal weight loss [87, 89–91]. A large age and BMI-matched cohort study has demonstrated that the chance of preterm birth and small-for-gestational age (SGA) singletons were greater in women with a history of bariatric surgery than in women without such surgery and that the risk of still birth or neonatal death was slightly higher in the bariatric surgery group as well [92]. The median time from surgery to conception was 1.1 years. There does not appear to be any significant differences in obstetric or perinatal outcomes when comparing the different bariatric surgery procedures [93].

There are, however, studies comparing pregnancies conceived less than 1 year after bariatric surgery to those conceived greater than 1 year after surgery and found no difference in bariatric complications, pregnancy related, or perinatal outcomes [93, 94]. Therefore, when considering advanced age of the woman, the benefits of postponing pregnancy must be balanced against the risk of declining fertility due to age [4, 61].

6. Conclusion

Obesity is increasing globally in men and women, and the negative impact of overweight and obesity on reproductive health, fertility, pregnancy outcomes, and also transgenerational health is significant. Obesity impairs both natural and assisted conception and has been found to affect endocrine function, oocyte and sperm quality, embryo quality, and also endometrial receptivity and implantation. Pregnancy and live birth rates are lower, and miscarriage rates are higher in the setting of obesity. The metabolic and reproductive health of the offspring is also negatively affected by both maternal and paternal obesity.

Preconceptional weight loss is recommended for all women seeking fertility treatment, firstly through counseling, lifestyle intervention, and behavior modification and then with adjunctive pharmacological agents or bariatric surgery, with a delay to conception of at least 1 year following this. Careful consideration of the benefits of delaying conception for weight loss must be balanced against the possibility of declining fertility due to advancing age of the couple.

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Conflicts of interest

None.

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