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Review

Effect of obesity on assisted reproductive treatment outcomes and its management: a literature review

Mohammed Khairy MD MRCOG,[a,*] **Madhurima Rajkhowa** MD MRCOG[b]

[a]Subspecialty Trainee of Reproductive Medicine and Surgery, Birmingham Women's Fertility Centre, Birmingham Women's NHS Foundation Trust, Birmingham, West Midlands B15 2TG, UK
[b]Consultant of Reproductive Medicine and Surgery, Birmingham Women's Fertility Centre, Birmingham Women's NHS Foundation Trust, Birmingham, West Midlands B15 2TG, UK
*Correspondence: Mohammed Khairy. Email: mohammed.mahmoud@bwnft.nhs.uk

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Key content

- Obesity is associated with infertility and poor obstetric outcomes.
- The current trends of advanced maternal age and rising obesity rates contribute indirectly to the growing demand for fertility treatment and assisted reproduction treatment (ART), posing clinical and ethical dilemmas for fertility service providers.
- The live-birth rate, after ART, is significantly lower in obese women than non-obese women, possibly due to impaired oocyte quality and/or defective endometrial receptivity. Poor ART outcomes correlate positively with the severity of obesity.
- Management of obesity-related infertility should include diet, exercise, cognitive behavioural interventions and possibly adjunctive pharmacotherapy. Bariatric surgery may benefit morbidly obese women who struggle to lose weight otherwise.
- Randomised controlled trials are required to clarify the effects of various therapeutic interventions for obesity on ART outcomes.

Learning objectives

- To understand the association of obesity and infertility with ART outcomes.
- To learn the principles of obesity-related infertility management.

Ethical issues

- To understand the ethical challenges in the provision of ART for obese women and to inform the stance of professional bodies, such as the British Fertility Society and the European Society of Human Reproduction and Embryology.

Keywords: assisted reproduction treatment (ART) / bariatric surgery / infertility / pregnancy / obesity

Linked resource: Single best answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

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Introduction

Obesity is a major risk factor for many systemic conditions and has become a major public health problem as its prevalence has reached epidemic proportions. It is estimated that currently 26.1% of the adult female population in the UK are obese with body mass index (BMI) >30 kg/m^2 as compared to 16.4% two decades ago.[1]

It has been shown consistently that obesity has a strong association with subfertility[2–4] and is also a major risk factor for serious pregnancy complications in mothers.[5–8] Moreover, there is an increase in the risk of early fetal loss,[9–11] congenital malformations[12,13] and poor perinatal outcomes as well as stillbirth and neonatal death.[14–16]

Concurrent with this rising trend in obesity and obesity associated subfertility, is a trend of delaying childbearing. It is believed that this has led to increasing reliance on fertility treatment to achieve pregnancy. This means that an increasing number of overweight and obese women as well as older women will seek fertility interventions and may require assisted reproductive treatment (ART). This places strains in terms of resources and finances on the fertility and obstetric services, in addition to raising the issue of ethics regarding the eligibility of these patients for fertility treatment in the face of finite resources and potential harm to both mother and baby.

In this article, we review the current evidence relating to different grades of obesity (overweight: BMI 25–29.9 kg/m^2; obese class I: BMI 30–34.9 kg/m^2; class II: 35–39.9 kg/m^2; and class III: >40 kg/m^2) and ART and seek to answer the following questions:

1. What is the evidence for the clinical outcomes of obese women having ART?
2. How can obesity modify fertility and ART outcomes?
3. What are the potential interventions that may modify the outcomes?

4. Is it cost-effective to offer ART treatment to obese, subfertile women?
5. Is it ethical to refuse obese women fertility and ART treatment options?

The clinical outcomes of ART in obese women

Information regarding the effect of obesity on ART outcomes is derived mainly from retrospective observational studies. The largest meta-analysis to date, that reported on 47 967 treatment cycles from 33 studies, concluded that overweight or obese women had significantly lower clinical pregnancy rates (CPR) (relative risk [RR] = 0.90, $P < 0.0001$) and live-birth rates (LBR) (RR = 0.84, $P = 0.0002$) and significantly higher miscarriage rates (RR = 1.31, $P < 0.0001$) compared with women with a BMI <25 kg/m^2.[17] A subgroup analysis of overweight and obese women separately confirmed this conclusion, with a lower chance of LBR (RR = 0.91, 95% confidence interval [CI] 0.85–0.98) and (RR = 0.80, 95% CI 0.70–0.90) in the overweight and obese groups of women, respectively.[17]

The main strength of the findings of this meta-analysis is the consistency of results across studies showing worse clinical outcomes in obese women as compared with normal weight women. The meta-analysis, however, did not adjust for the effect of potential confounders, such as age and polycystic ovary syndrome (PCOS), both of which are strongly associated with obesity, as well as other factors, such as smoking. Furthermore, the included studies had considerable heterogeneity in classifications of obesity and ovarian stimulation.

Few studies have attempted to address these weaknesses. In one study, obesity and age interaction was a significant predictor. At younger ages, a high BMI had a pronounced negative influence on fertility and this effect diminished as the women aged.[18] The finding of a greater effect of obesity on fertility in younger women was corroborated by another study in which obesity did not affect embryo development in women aged <38 years, although the CPR and LBR were reduced.[19]

A comprehensive regression analysis of 4609 women stratified according to BMI categories in their first in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) cycles and adjusted for multiple confounders, including age, ovarian reserve and response parameters, embryo quality and number of embryos transferred, showed significantly decreased odds of implantation, clinical pregnancy, and live birth in women with BMI >30 kg/m^2. The adjusted odds ratio (AOR) for live birth was significantly lower across all categories of high BMI compared with the normal weight cohort, with AOR and 95% CI for live birth of 0.63 (0.47–0.85) for BMI 30.00–34.99 kg/m^2, 0.39 (0.25–0.61) for BMI 35.00–39.99 kg/m^2 and 0.32 (0.16–0.64) for BMI ≥40.0 kg/m^2.[20] Based in the results of this study, it was concluded that women with BMI >30 kg/m^2 have up to 68% lower risk of having a live birth following their first ART cycle compared with women with BMI <30 kg/m^2.[20]

The obstetric outcomes in obese pregnant women after IVF have been reported using data for 60 232 singleton and 24 111 twin live births from the clinical outcome reporting system of the Society of Assisted Reproductive Technology (SART).[21] There was a 1.5–2-fold increase in the risk of very early (<28 weeks) and early (<32 weeks) preterm birth (VEPTB/EPTB) among singletons and a 2–3-fold higher risk of VEPTB/EPTB among conception of twins in obese women (BMI >35 kg/m^2) after IVF compared with similar conceptions in normal weight women.[21]

How can obesity affect fertility and ART outcome?

The association between obesity and infertility has long been recognised and several possible causative mechanisms have been suggested.

Energy homeostasis and reproduction

Research has shown that gut and adipose tissue hormones, which are the main controls of caloric intake, have a significant role in regulation of reproductive function. The most widely studied of the pancreatic and gut hormones are insulin, ghrelin and glucagon like peptide-1 (GLP-1), while among the adipose tissue hormones, leptin and adiponectin are the best characterised.

In cases of high caloric intake with increased adipose tissue, the gut hormones (primarily insulin and GLP-1) and the adipose tissue hormone leptin act centrally in the hypothalamus leading to a satiety response by inhibiting neuropeptide Y (NPY). This inhibition of NPY together with stimulation of proopiomelanocortin (POMC) neurons relieves the effects of the inhibitory signals on the gonadotropin releasing hormone (GnRH) pulse generator in the hypothalamus. Leptin also stimulates the hypothalamic GnRH pulse generator directly through kisspeptin (an essential neuropeptide involved in the direct activation of GnRH neurons) with subsequent increases in gonadotropin levels, mainly luteinising hormone.[22]

Insulin and leptin seem to act synergistically, with the latter hormone being the main mediator of the stimulatory functions. Both insulin and leptin also act peripherally on the ovaries, where leptin potentiates insulin-induced theca cell proliferation and intra-ovarian androgen production.[22]

On the other hand, circulating levels of the gut hormone ghrelin and the adipose tissue hormone adiponectin increase in cases of fasting, low caloric intake and malnutrition, while insulin and leptin levels plummet leading to inhibition of the GnRH pulse generator in the hypothalamus and stimulation of feeding behaviour.[22] Teleologically, this mechanism helps conserve energy during times of famine, while encouraging reproduction when food is more readily available.

It is possible that obesity, as a state of prolonged hyper-caloric intake, leads to persistent activation of the GnRH and LH pulses centrally and theca cell proliferation peripherally, leading to PCO/PCOS phenotypes. Alternatively, obesity may be the result of a state of leptin resistance, leading to lack of the satiety response. The associated hyper-insulinaemia in these cases might lead peripherally to theca cell proliferation, hyper-androgenaemia and PCO/PCOS.

A minority of morbidly obese patients have mutations in the leptin or leptin receptor genes leading to a complete lack of response to leptin with phenotypic features of obesity and hypogonadotrophic hypogonadism.[23]

Obesity and inflammation

Another potential mechanism linking obesity and infertility is the effect of bidirectional communication between the immune cells in adipose tissue and adipocytes leading to release of free fatty acids (FFA) and various cytokines, as well as the induction of a systemic inflammatory response. This, together with intracellular accumulation of FFAs in various tissues, including ovarian tissues, leads to overproduction of reactive oxygen species (ROS) and intracellular stress reactions, with associated damage and dysfunction of the mitochondria and endoplasmic reticulum leading to molecular defects of oocytes.[24]

The outcomes of ART cycles in obese women have provided some insight into the effect of obesity on fertility.

Lower embryo implantation rates have been reported in obese women compared with those of normal weight women, despite a lack of differences reported in oocytes and embryo quality and the percentage of blastocyst transfers. This suggests the existence either of molecular or genomic defects in the oocytes or embryos of obese women, or an effect of obesity on endometrial receptivity.[10] Analysis of implantation rates among recipient women in different BMI categories following oocyte donor IVF cycles using good quality embryos has shown a trend of lower implantation rates in women in the higher BMI group, suggesting an endometrial effect.[11]

In support of the endometrial effect, multivariable regression analysis of the results of a study of healthy term births following single blastocyst transfer revealed that increasing BMI and smoking are significant negative predictors of healthy term births independent of maternal age.[25] Similarly, a retrospective analysis of fresh and cryothawed single blastocyst transfers showed that women with a BMI of >25 kg/m^2 have double the risk of miscarriage at <23 weeks compared with women with a normal BMI (38% versus 20%; odds ratio [OR] 2.4, 95% CI 1.6–3.8).[26] Furthermore, after adjusting for potential confounders, it was found that having a BMI of >25 kg/m^2 significantly increased the risk of miscarriage after both fresh and cryothawed blastocyst transfer by 2 and 6 fold, respectively.[26]

It was also shown that women with a BMI of >30 kg/m^2 had significantly higher numbers of endometrial polyps compared with women with a BMI of <30 kg/m^2 (52% versus 15%). The degree of obesity was positively correlated with the occurrence and size of the polyps, as well as the occurrence of multiple polyps.[27]

Furthermore, an analysis of miscarriage karyotypes led to the conclusion that overweight and obese women aged <35 years were less likely to have aneuploid miscarriages than women in a healthy weight range, suggesting alternative mechanisms for miscarriage in this population.[28] However, in other studies, higher incidence of oocyte morphological abnormalities,[29,30] poorer response to ovarian stimulation, a requirement for higher dose of gonadotropins, lower fertilisation rates and higher cancellation rates[31–33] were found to be more common in obese women compared with normal weight women. Another study showed that obese women under the age of 35 years have lower quality embryos with lower embryo utilisation rates and higher numbers of discarded embryos compared with age-matched normal weight women.[34] These findings lend support to the theory of lipotoxicity of oocytes and ovaries by accumulation of FFA and ROS and associated systemic inflammatory responses, suggesting the possibility of molecular/genomic defects in the oocytes of obese women.

A recent systematic review reported on the outcome of ART cycles in obese oocyte recipients with a BMI of >30 kg/m^2. This study has shown no significant effect of obesity on the rates of clinical pregnancy, implantation or miscarriage. This may imply a predominant role of oocyte dysfunction over endometrial receptivity in obese women.[35]

Potential interventions in obese women prior to ART

There is a paucity of randomised controlled studies of interventions aimed at improving outcomes in obese women pursuing fertility treatment in general and ART in particular. Here, we address the therapeutic interventions to optimise outcomes in obese women undergoing infertility treatment under the following subheadings: diet and lifestyle, medical management, and surgery.

Diet and lifestyle

The latest National Institute of Health and Care Excellence (NICE) guidelines on management of obesity recommends that the treatment of obese women should be tailored according to risk stratification based on BMI/waist circumference and associated comorbidities (e.g. diabetes, hypertension, dyslipidaemia, cardiovascular disease and obstructive sleep apnoea),[36] with female waist circumference of <80 cm considered low risk, 80–88cm categorised as high risk, and >88 cm as very high risk.

Dietary modification and regular exercise aimed at restriction of caloric intake and increased energy expenditure remain the first line and cornerstone of management of obesity in general. The main principle of dietary modification is a low caloric intake with a recommended daily caloric intake of 600 kcal less than caloric requirement to maintain a stable body weight. Very low-calorie diets (<800 kcal/day) should not be used routinely and if used in cases of emergency, the diet should be nutritionally complete and followed for a maximum of 12 weeks. Physical activity should be of moderate intensity for at least 60–90 minutes on five or more occasions each week. Furthermore, activities should be of a type that can be incorporated into the daily routine, such as brisk walking, cycling, gardening or supervised exercise programmes. The weight-loss target should be set realistically at no more than 0.5–1 kg/week and should be agreed individually with each woman.[36]

The main challenge is to introduce behavioural changes that lead to long-term adherence to the modified diet and exercise regimen as weight is inevitably regained when lifestyle changes are not sustained. Therefore, there may be a role for cognitive and behavioural interventions in combination with dietary and exercise modifications to achieve long-term effects. Cognitive behavioural strategies that have been suggested to help adults achieve weight control include self-monitoring of behaviour and progress, stimulus control, goal setting, slower eating, social support, problem solving and assertiveness, cognitive restructuring (thought modification) and reinforcement of change to prevent relapse.[36] The importance of a multidisciplinary approach to lifestyle interventions aimed at combating obesity has recently been re-emphasised, as no single intervention seems to be effective for long-term control.[37]

Two small-scale dietary trials on the effect of very low-calorie diet (VLCD) and low-calorie diet (LCD) before IVF have been reported. The former study included a very small number of women, precluding any meaningful conclusion.[38] The latter study compared LCD and exercise versus no intervention for a period of 6–8 weeks. Although weight reduction and BMI changes were statistically significant, there was no statistically significant difference between LBRs in the two arms of the study.[39]

One observational study has shown that the Preconception Dietary Risk Score (PDRS), which is a measure of nutritional habits and dietary quality (higher scores indicate higher dietary quality), is an independent predictor of ongoing pregnancy after IVF treatment.[40] In the same study, an adherence to the dietary recommendations with improvement of the PDRS by one point, was associated with a 65% increase in the ongoing pregnancy rate.[40]

It seems therefore, that there is scope for improving outcomes for overweight and obese women undergoing ART by lifestyle interventions; however, there is a gap in evidence from randomised controlled trials.

Medical management

Pharmacotherapy should be offered as an adjunct rather than as a substitute to diet and exercise management to women who have achieved partial success in losing weight and persevered with lifestyle changes for 6 months. There are several classes of medications used for weight loss and none have been shown to be superior to the others. The average net weight loss after 7–48 weeks of treatment achieved in one meta-analysis was 2–4 kg after subtracting weight loss associated with the placebo.[41] Combining medical treatment with lifestyle interventions may lead to greater weight loss.

A number of classes of medications can be used for weight loss. Anti-absorptive drugs include orlistat (Xenical), which is a potent inhibitor of pancreatic lipase leading to interference with the absorption of fat and fat soluble vitamins from the gut. The recommended dose is 120 mg taken immediately before, during, or up to 1 hour after each meal (maximum 120 mg three times daily). Common side-effects include flatulence, oily leakage from the rectum with steatorrhoea and fecal urgency. Prolonged administration can lead to malabsorption, and vitamin deficiency syndromes. Orlistat should, therefore, be used for longer than 12 weeks only if weight loss exceeds 5% of the initial bodyweight and after counselling patients about the potential risks and benefits.[42]

Insulin-sensitising agents, such as metformin, decrease circulating insulin and androgen levels and may be associated with a modest decrease in body weight and visceral fat. Two studies have shown benefit from combining metformin with a hypocaloric diet for reducing weight and visceral fat.[43,44] However, the effectiveness of metformin alone for reducing weight in obese PCOS patients has not been demonstrated.[45] Moreover, when metformin is used as adjunctive treatment for ovulation induction in PCOS patients, it is more effective in those that are lean than it is in obese PCOS patients. The recommended dose is 1500–2000 mg/day and the main side-effects are gastrointestinal upset and rarely, lactic acidosis in patients with hepatic and renal impairment. In the UK, metformin is not licensed as an anti-obesity drug and although it has been widely used in management of PCOS, this is still an unlicensed indication.

Other classes of anti-obesity drugs include appetite suppressants such as sibutramine and the cannabinoid receptor antagonists (e.g. rimonabant), have been withdrawn from the market in the UK due to concerns over cardiovascular effects (hypertension, palpitation) for the former class and neuro-psychiatric effects including depression and suicidal risks of the latter class.

The safety of exposure to anti-obesity drugs in early pregnancy has been assessed using the Swedish National Medical Register including the data for 392 126 infants. No evidence of any increase in the relative risk of major malformation was observed in women who used orlistat in early pregnancy (248 women) (RR = 0.42, 95% CI 0.11–1.07).[46] It is, however, recommended that anti-obesity drugs are stopped once pregnancy is achieved.

One small randomised controlled trial (RCT) comparing metformin and orlistat in obese anovulatory PCOS patients for 3 months showed no significant difference in ovulation rates between the two treatments, although significant reductions in BMI and androgen levels were observed in both arms of the study.[47] Currently, there are no reports of RCTs comparing anti-obesity drugs with placebo in an IVF setting.

Bariatric surgery

These operations are increasingly being used for the treatment of obesity and are classified into three categories.

- Restrictive surgery (vertical band gastroplasty, adjustable gastric banding, intragastric balloon, laparoscopic gastric plication, sleeve gastrectomy) is aimed at restricting gastric capacity and inducing early satiety.
- Largely restrictive/mildly malabsorptive surgery (e.g. Roux-en-Y gastric bypass) is aimed at both restricting gastric capacity and reducing the length of absorbing bowel.
- Largely malabsorptive/mildly restrictive surgery (e.g. biliopancreatic diversion duodenal switch). Although gastric capacity is reduced in these procedures the main effect of surgery is inducing a state of malabsorption.

The primary goal of bariatric surgery is to ameliorate medical problems related to obesity. These operations are therefore generally offered to women with a BMI of >40 kg/m^2 or >35 kg/m^2 with serious coexisting medical complications aggravated by obesity and who are highly motivated but have struggled to achieve their target body weight with conventional dietary and behavioural therapy. The NICE guidelines recommend early consideration of bariatric surgery in patients with a new diagnosis of type II diabetes and BMI 30–35 kg/m^2 and even lower BMI in patients of Asian origin.

The women selected should be fully aware of the complications associated with the operation, including an overall mortality rate of 1%.[48–50] Data from multiple meta-analyses indicate that women with a preoperative BMI of >40 kg/m^2 can be expected to lose 20–40 kg over 2 years and to maintain their reduced weight for 10 years.[48–50] Pregnancy is therefore generally not recommended for 12–18 months after bariatric surgery, when most of the weight loss occurs, to avoid nutritional deficiencies. These women should receive a follow-up care package for a minimum of 2 years, including monitoring of nutritional intake, physical activity and comorbidities and the provision of psychological support.[36]

Evidence of the effects of bariatric surgery on infertility and IVF is sparse, with only a small amount of data regarding IVF outcomes after bariatric surgery available from case–control studies of a small number of patients; therefore, more high-quality studies are needed.[51] There are no reports of RCTs assessing the impact of bariatric surgery in infertile populations generally or in patients undergoing ART; however, a recent observational study has shown an improvement in the number of oocytes retrieved in obese women after bariatric surgery.[52]

Is it cost-effective to offer ART to obese subfertile women?

The cost-effectiveness of ART treatment in obese women in the UK has been addressed by Scottish investigators who estimated the direct health service costs of live birth after a single cycle of IVF treatment among women in different BMI categories. They concluded that there is no statistically significant difference in the obstetric costs among the different BMI groups. The authors held this view mainly for class I obese women compared with the normal BMI group and maintained that the small number of women included in higher BMI groups led to uncertainty regarding their conclusion.[53]

Another study modelled the costs of achieving live birth in both ovulatory and anovulatory obese women using different modalities of infertility treatment as compared with women with normal BMIs. In their hypothetical model based on an extensive literature search of reported success rates of different treatments they included the direct costs of treatment and indirect costs of pregnancy complications. They concluded that the costs per live birth in anovulatory overweight and obese women were 54% and 100% higher, respectively, than those in their normal weight counterparts, and for ovulatory obese women the costs were 44% and 70% higher, respectively.[54]

Is it ethical to withhold fertility treatment and ART options from obese women?

The results of economic analyses regarding the cost-effectiveness of ART treatment in obese women are conflicting. Furthermore, there is a paucity of data for the efficacy of ART outcomes in higher classes of obesity.

Consequently, it is still ethically contentious to justify declining ART treatment from this group of women based on current data.

There is a potential conflict between the patient's right of autonomy on the one hand and the societal perspective of justice as well as the physician's professional perspective of providing the highest level of care on the other.

Arguments for offering ART treatment to obese women include:

i. Respect for patient's autonomy if the woman is willing to accept an unfavourable outcome.
ii. Withdrawal of treatment from obese women is an act of injustice and discrimination compared with other obese women who conceive naturally.

The arguments against offering unconditional ART treatment are:

i. Physicians have an ethical duty to provide high-quality care and avoid harm in their professional capacity. Therefore, a requirement for weight loss is, in fact, in the interests of both the mother and the child and is in accordance with the principle of non-maleficence without violating the woman's autonomy.
ii. Requiring obese women to adopt a healthy lifestyle and achieve a certain weight target is neither impossible nor unfair as the success rate of ART can improve with BMI reduction. Furthermore, without these changes, these women will have high risk pregnancies as well as a high risk of short- and long-term health problems in their offspring. It is, therefore, professionally responsible to require lifestyle changes to reduce the risk of harm. It is also justifiable from a societal perspective to reduce the inevitably increased demand on resources. Supporters of the latter argument maintain that comparing women requiring ART with those who conceive naturally is not a valid argument because as all cases should be similar in all relevant aspects if differential treatment is to be called unjust. Although obese women who conceive naturally are advised to reduce weight and adopt a healthy lifestyle preconception, they do not require medical attention to achieve pregnancy.

As there is no hierarchy of evidence in ethical studies that inform practice, the collective opinion of professional bodies is regarded as the best available source of advice on offering fertility treatment.

In 2007, the British Fertility Society issued guidelines on offering fertility treatment to obese women, which recommended that women seeking fertility treatment should have a BMI of <35 kg/m^2. In addition, when clinical circumstances permit, treatment of younger women should be delayed until a BMI of <30 kg/m^2 is achieved.[55]

In 2010, The European Society of Human Reproduction and Embryology (ESHRE) also issued a statement regarding lifestyle factors and access to medically assisted conception. The position of the ESHRE is that it is not unethical for fertility specialists to insist on serious efforts to achieve weight loss before treatment can be considered.[56]

The NICE guidelines on fertility management recommend that women should have a BMI of 19–30 kg/m^2 before commencing ART as BMIs outside this range are likely to reduce the success of the treatment.[57]

In conclusion, it seems that a conditional offer of fertility treatment to obese women based on achievement of a target weight is justifiable. There are, however, a number of unresolved ethical questions. For instance, is it justifiable to require older women to achieve the same body weight targets as younger women given the decline in fertility with age? At what level of obesity should treatment be withheld? How would an infertility specialist decide if a woman has made genuinely serious efforts to lose weight? Furthermore, would it represent better use of resources to offer bariatric surgery to women who have struggled for years to lose weight and their fertility is in decline rather than to offer IVF treatment?

Conclusion

In summary, obesity has a significantly adverse effect on ART outcome independent of age and other confounders. This effect seems to be more pronounced in younger women (aged <35 years). The effect of obesity on ART outcome seems to be mediated by both molecular changes in oocytes leading to lower quality embryos as well as by impairment of endometrial receptivity.

Unfortunately, there is paucity of data from interventional studies that assess the effectiveness of different interventions on outcome in obese women undergoing fertility treatment. Thus, further well-designed studies in this area are required. There is also a need for a shared care pathway involving GPs or specialised bariatric units and infertility services.

The cost-effectiveness of ART in obese women is still an unresolved issue. However, as obesity is a modifiable risk factor, it would seem reasonable and ethically justifiable to require obese women to lose weight before receiving ART.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

MK reviewed the literature, wrote the manuscript and revised the final draft after critical appraisal by MR. MR reviewed the draft manuscript critically and revised the content before final approval.

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