Implications of obesity on surgical management of infertility and heavy menstrual bleeding

Oonagh Keag
Tahir A Mahmood
Chu Lim

Abstract

This review on the impact of obesity on reproductive health will concentrate on two key areas: infertility and heavy menstrual bleeding. The pathophysiology involved in these common problems is discussed. The management of infertility is discussed, in particular the management of anovulation associated with polycystic ovarian syndrome. There is also a focus on the surgical management of infertile obese women in the form of diagnostic laparoscopy, highlighting the key concerns and risks involved. Medical and surgical management of heavy menstrual bleeding is discussed including the many varied issues involved in hysterectomy of the obese woman.

Keywords anovulation; assisted reproduction; heavy menstrual bleeding; hysterectomy; infertility; laparoscopy; menorrhagia; obesity; polycystic ovarian syndrome

Introduction

In the United Kingdom, more than half of all women are either overweight or obese. The World Health Organisation (WHO) defines a person with a body mass index (BMI) of 25–30 kg/m^2 as overweight and a BMI $>$ 30 kg/m^2 as obese. Obesity affects more than a billion people throughout the world in both western and developing countries and this epidemic has had a profound impact on all aspects of female reproductive health.

This review will focus on two important issues – fertility and heavy menstrual bleeding, looking in particular at the difficulties and complications of surgical management of these problems in women with obesity.

Oonagh Keag *MBChB is a Specialist Registrar in Obstetrics and Gynaecology at Victoria Hospital, Kirkcaldy, Fife, UK. Conflicts of interest: none declared.*

Tahir A Mahmood *MD FRCOG FRCPI MBA is a Consultant Obstetrician and Gynecologist at Victoria Hospital, Kirkcaldy, Fife, UK. Conflicts of interest: none declared.*

Chu Lim *MRCOG is a Consultant Obstetrician and Gynecologist at Victoria Hospital, Kirkcaldy, Fife, UK. Conflicts of interest: none declared.*

Fertility

Case 1

Gemma Smith is a 28-year-old nulliparous lady who attends the Infertility clinic with her husband Mark who is 32 years old. Gemma has no significant past medical history and does not take any regular medicines. She has no allergies. She is a non-smoker and takes 5–10 units of alcohol per week. She has a normal smear history. Menarche was aged 13 and initially her periods were regular but over the last 5 years she has only had around 3 periods per year, lasting for 2–3 days. She denies any dysmenorrhoea, menorrhagia or dyspareunia. She has only ever used condoms for contraception and her and Mark have been trying to conceive a pregnancy for two years. Gemma has no previous history of pelvic inflammatory disease and chlamydia testing is negative. She is rubella immune. Her BMI is 40.

Mark has no significant past medical history and does not take any regular medicines. He is a non-smoker and has a normal BMI. Semen analysis on two occasions is normal and reassuring.

It is estimated that infertility affects 1 in 7 heterosexual couples in the UK. Fertility rates are reduced in those couples where the female partner is overweight or obese, largely due to menstrual cycle irregularity or anovulation. When this is also associated with biochemical disturbances and/or symptoms of acne or hirsutism, polycystic ovarian syndrome (PCOS) is diagnosed. One mechanism for this is the presence of polycystic ovarian syndrome (PCOS) in obese patients.

The recently updated National Institute of Clinical Excellence (NICE) guideline on fertility recommends that women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive. One possible mechanism for this is that the increased body weight and fat tissue is associated with sex steroid imbalance. This is mainly due to the reduction of sex hormone-binding globulin (SHBG) levels in the circulation, resulting to an increased fraction of free androgens in blood. Hyperandrogenism may arrest folliculogenesis through inhibition of granulosa cell proliferation and maturation. Hyperinsulinaemia in the presence of obesity may also play a role in causing premature maturation of granulosa cells.

Adipokines secreted by adipose tissue may influence fertility in the presence of obesity and PCOS. For example, high levels of leptin may inhibit folliculogenesis and abnormal levels of leptin may interfere with embryo implantation. Reduced adiponectin levels in obesity contribute to insulin resistance and therefore infertility whilst also possibly having a direct effect on folliculogenesis. High levels of IL-6, another adipokine, inhibit ovulation and TNF-α may affect several levels of the reproductive axis: inhibition of gonadotrophin secretion, ovulation, steroidogenesis, corpus luteum regression and endometrial development.

A further contributing factor in the fertility of obese women include sexual dysfunction which could be related to physical or psychological disturbances.

Impact of obesity on fertility treatments

Not only does obesity affect ovulation, but increased BMI hinders the desired outcomes of fertility treatments. For this reason, diet and lifestyle changes are considered the first-line approach. According to NICE, women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception (NICE) and pregnancy rates

are highest in those who participate in group programmes involving exercise and dietary advice. Weight loss programmes applied to obese patients with PCOS result in the improvement of the abnormal biochemical and hormonal parameters. Especially, a reduction in serum-free testosterone and insulin concentrations and an increase in SHBG values have been reported, while in more than 50% of the cases regular ovulation and menstruation are re-established. A steady decrease of intra-abdominal fat is associated with restoration of ovulation. Evidence from studies suggests that diets with reduced glycaemic load may provide a better control of hyperinsulinaemia and the metabolic consequences as well as menstrual cyclicity. It is estimated that for the majority of women, a period of 3–6 months is required to lose 5–10 kg in body weight.

Clomiphene is an anti-oestrogen indirectly leading to increased GnRH and gonadotrophin release thus causing follicle development and subsequent dominant follicle ovulation, and is used as first-line treatment in anovulatory infertile women with PCOS. Clomiphene resistance is attributed to several hormonal and clinical characteristics of the women including free androgen index, BMI and age. Hence, obese women with PCOS respond less well to clomiphene, and the chance of ovulation is reduced particularly in women with amenorrhoea as compared to those with oligomenorrhoea. Such women may need higher doses of clomiphene even up to 250 mg/day.

Aromatase inhibitors can be used for ovulation induction in PCOS. Letrozole is one of the third-generation aromatase inhibitors and based on evidence derived from a meta-analysis, it is equally effective compared with clomiphene in inducing ovulation in women with PCOS. However, the possible teratogenic effects of letrozole are still debated. FSH can be used for clomiphene failure or resistance, though moderate obesity is associated with a lower ovulation rate and a higher miscarriage rate. In the same study, significantly higher doses of gonadotrophins were required in the group of the obese than in the group of the lean women, a finding that was confirmed in a subsequent study.

Laparoscopic ovarian drilling (LOD) is a further management for anovulation. Regarding the influence of obesity in the effectiveness of LOD, a retrospective study including 200 patients with PCOS, who were treated unsuccessfully with clomiphene, showed that LOD applied to women with a BMI >35 kg/m^2 induced significantly lower ovulation and pregnancy rates as compared to moderately overweight and normal weight women. Nevertheless, once ovulation was achieved, BMI had no influence on the conception rates in agreement with previous reports. Several studies have shown a negative correlation between BMI and the response to various medical treatments including clomiphene and gonadotrophins. However, LOD has been shown to sensitize clomiphene-resistant patients to this drug.

It is known that about 40% of patients with PCOS are obese. Insulin resistance is one of the main characteristics of these women. Treatment with metformin would be expected to improve insulin sensitivity and the metabolic and reproductive functions. Several studies have demonstrated that obese but not lean women with PCOS may benefit from the treatment with metformin. A recent meta-analysis confirmed the initial observations that metformin treatment alone resulted in a greater reduction in BMI than placebo, but when added to a diet programme, it did not show any advantage over placebo. Two recent meta-analyses have demonstrated that metformin in combination with clomiphene might be useful only in cases of clomiphene resistance before moving to the second-line treatment of low-dose FSH protocols.

Assisted reproduction techniques

When using assisted reproduction techniques (ART), women with obesity pose increasing challenges. They will require higher dose of sedation, due to increased surface area, which potentially may lead to side effects due to a higher risk of exposure to the drugs utilized. Embryo transfer is technically more difficult and time-consuming due to poor views using abdominal ultrasound. Whether this leads to lower pregnancy rate remains unknown as there are no data in the literature to explore either difficulties with the procedure or lower pregnancy rates.

Results from ART demonstrate a reduction in pregnancy rates (RR 0.87, 95% CI 0.80–0.95, $P = 0.002$) in obese women (BMI $>$ 30 kg/m^2) when compared with those who have normal BMI ($<$25 kg/m^2). Live birth rates also reduced as BMI increases.

Of those who conceive after ART, there is a 30% increased risk of miscarriage if women are overweight (BMI $>$ 25 kg/m^2) compared to those with normal BMI (RR 1.33, 95% CI 1.06–1.68). This risk further increases to just over 50% when miscarriage rates are compared in those who are obese to those with a BMI $<$ 30 kg/m^2 (OR 1.53, 95% CI 1.27–1.84). Given that the success of ART clearly worsens as BMI increases, NICE recommend that a woman's BMI should ideally be in the range 19–30 kg/m^2 before commencing assisted reproduction.

Ethical considerations

As well as the reduced success rates of ART in obese women, there are ethical considerations in offering such techniques. There are many adverse maternal, foetal and neonatal outcomes known to be associated with obesity and many pregnancy-associated complications occur with greater frequency in obese women, for example, pregnancy-induced hypertension and gestational diabetes. The Confidential Enquiry into Maternal Death revealed that more than half of all maternal morbidity from direct or indirect causes was in women who were either overweight or obese. Furthermore, over 15% of all women who died were at least morbidly obese.

In addition, the long-term health of individuals born to obese mothers is a public health issue of concern. Children of obese women will grow up with greater risks of coronary heart disease, hypertension, glucose intolerance and diabetes as well as themselves being obese, thereby perpetuating the problem to the subsequent generation.

Successful pregnancies in obese women conceived through ART add to the obstetric workload through increased high-risk clinic and ultrasound scan appointments and a higher rate of operative deliveries, anaesthetic complications, perioperative morbidity and longer hospital stays. This in turn leads to rising economic costs. Therefore, patients have a responsibility to themselves but healthcare professionals also have a public responsibility to their offsprings and to society to promote healthy living.

Laparoscopic surgery and obesity

Laparoscopic surgery for obese women has clear benefits over open surgery affording advantages such as shorter hospital stay,