

## NEW DEBATE

# The preconceptual contraception paradigm: obesity and infertility

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**Obesity is a major health problem across the world. Recent editorials suggest that obese patients should be denied treatment of any kind aimed to improve ovulation rates and achieve pregnancy until they have reduced their BMI. We propose that this approach is not a resolution of the problem, but indeed may amplify the maternal and perinatal complications attributed to fertility centres. Obesity independent of polycystic ovary syndrome (PCOS) is associated with anovulation, and minimal weight loss alone is an effective therapy for induction of ovulation in both obese women and obese PCOS women. Consequently, lifestyle programmes encouraging weight loss should be considered to be an ovulation induction therapy and due consideration for a potential pregnancy in an obese woman given. We propose that women with a BMI in excess of 35 kg m<sup>2</sup> should lose weight prior to conception—not prior to receiving infertility treatment. Therefore, clinicians undertaking the management of infertility in obese women should adopt measures to reduce their body mass prior to exposing them to the risks of pregnancy. We advocate that this approach should be aggressively managed including pharmacological strategies; intrinsic in this programme is the use of contraception and high-dose folic acid during that period of preconceptual weight reduction.**

*Key words:* infertility/pregnancy outcomes/obesity/contraception

### Introduction

Obesity has become a major health problem across the world. In the UK, obesity affects one-fifth of the female population, with 18.3% of the female population in the reproductive age group (16–44 years) being classed as obese (Department of Health, 2004). Similar rises have been observed in the pregnant population, with one in five women booking for antenatal care being clinically obese (Kanagalingam *et al.*, 2005). The relationship between female obesity and reproductive success is complex. Reduction in pregnancy potential has been reported for various infertility treatment procedures, but the effect is not universal, as one study demonstrated that implantation may even be promoted by obesity. In general, deleterious effects have been revealed to be modest. Furthermore, the outcome of pregnancy in obese women is also highly complex, as nulliparous mothers are more profoundly affected than multiparous. As infertility treatments are generally effected in nulliparous women, observations of potential adverse outcomes related to obesity should influence clinical practice in these patients. It should be borne in mind that many women undertaking infertility treatment are prepared to get pregnant at all costs with little consideration of perinatal consequences, as seen in the

recent single embryo transfer debates. There is an inherent conflict between their desire to achieve pregnancy while optimizing the maternal environment for fetal development. Failure to appreciate and convey these risks to patients may amplify the maternal and perinatal complications attributed to fertility centres.

### Fetal risks attributable to maternal obesity

Maternal obesity (BMI  $\geq$  30 kg m<sup>2</sup>) has significant detrimental impacts on fetal development with an increased risk of isolated fetal anomalies: anencephaly and spina bifida [OR 3.3 (95% confidence interval (CI) 1.4–8.1)], spina bifida [OR 3.5 (95% CI 1.2–10.3)], exomphalos [OR 3.3 (95% CI 1.0–10.3)], atrial septal defect or ventricular septal defect cardiac defects [OR 3.5 (95% CI 1.0–10.3)], orofacial clefts [OR 1.3 (95% CI 1.11–1.53)] and also multiple anomalies [OR 2.0 (95% CI 1.0–3.8)] (Cedergren and Kallen, 2003; 2005; Watkins *et al.*, 2003). Furthermore, the association of obesity with neural tube defects is not completely abolished by folic acid fortification of food and it has a reduced benefit in the prevention of neural tube defects in obese women [OR 0.52

(95% CI 0.28–0.96)] compared to non-obese [OR 0.32 (95% CI 0.14–0.73)] (Ray *et al.*, 2005). Accurate estimates for morbid obesity are limited; however, there does appear to be ~7% increase in risk of fetal anomaly for each 1 unit incremental increase in BMI above a 25 kg m<sup>2</sup> (Watkins *et al.*, 2003). A potential over-estimate of risk due to termination of pregnancy has been discounted by examination of postmortem and birth records (Callaway *et al.*, 2006). Maternal choice with respect to antenatal management may also be limited, as prenatal diagnosis of congenital anomalies is reduced in obese women despite repeated examinations (Hendler *et al.*, 2005) and advanced ultrasound equipment (Hendler *et al.*, 2004b), with 10% of obese women having suboptimal four-chamber views at 22–24 weeks gestation (Hendler *et al.*, 2004a).

Several studies have demonstrated an increased risk of miscarriage in obese women undergoing ART, with estimates of risk of fetal loss before 20 weeks gestation of 27% [OR 1.71 (95% CI 1.20–2.43)] for obese women, increasing to 31% if morbidly obese (BMI ≥ 35 kg m<sup>2</sup>) [OR 2.19 (95% CI 1.27–3.78)] (Wang *et al.*, 2002). However, in spontaneous conceptions, obesity is also associated with an increased risk of early miscarriage (6–12 weeks gestation) [OR 1.20 (95% CI 1.01–1.46)] and recurrent miscarriage [OR 3.51 (95% CI 1.03–12.01)] (Lashen *et al.*, 2004). The risk of fetal death is not, however, restricted to early pregnancy, as the risk of late fetal death increases consistently with increasing pre-pregnancy BMI. A series of 167 750 births from Sweden demonstrated that, among nulliparous women, the risk of fetal death after 28 weeks gestation is approximately doubled among women with a normal BMI, when compared with lean women, tripled among those who were overweight and quadrupled among those who were obese [OR 4.3 (95% CI 2.0–9.3)] (Cnattingius *et al.*, 1998). Among parous women, the risk of fetal death is only increased in obese women [OR 2.0 (95% CI 1.2–3.5)] (Cnattingius *et al.*, 1998). A later study from Sweden with 805 275 women provided similar estimates of risk of late fetal death for obese and morbidly obese women, but also demonstrated that 1 in 121 women with a BMI > 40 had a stillbirth (Cedergren, 2004). These risks are startlingly high; however, they may be even potentially higher in obese women undergoing ART, as a meta-analysis of singleton IVF pregnancies suggested a significance of the risk of stillbirth due to ART as compared to spontaneous conception [OR 4.3 (95% CI 2.0–9.3)] (Jackson *et al.*, 2004). The risk of death of the child is not restricted to the antenatal period, with obesity having a significant impact on neonatal and infant mortality. The risk of early neonatal death (within the first 7 days of life) after adjustment for maternal age, parity smoking status and year of birth was [OR 1.59 (95% CI 1.25–2.01)] in obese women, with further increments in risk if the BMI was >35 [OR 2.09 (95% CI 1.50–2.91)] or >40 [OR 3.41 (95% CI 2.07–5.63)] (Cedergren, 2004). A study of 84 701 nulliparous women in Scotland showed that morbid obesity was associated with a significant increase in the risk of death within the first 28 days of life [OR 2.77 (95% CI 1.54–4.99)]; however, the risk was not increased in multiparous women (Smith *et al.*, 2006).

Preterm birth can either be due to preterm labour or due to elective preterm delivery. An interaction between parity and obesity has previously been noted in multiparous women not at increased risk of preterm delivery (Cnattingius *et al.*, 1998). Among nulliparous women, the risk of elective preterm birth increases with BMI: overweight [OR 1.15 (95% CI 1.03–1.27)], obese [OR 1.52 (95% CI 1.31–1.77)] and morbidly obese [OR 2.13 (95% CI 1.75–2.58)], whereas the risk of spontaneous preterm birth decreased: overweight [OR 0.89 (95% CI 0.82–0.98)], obese [OR 0.85 (95% CI 0.73–0.99)] and morbidly obese [OR 0.81 (95% CI 0.64–1.03)] (Smith *et al.*, 2006). The net effect of obesity depends, therefore, on the balance between the increased risk of elective preterm birth and the decreased risk of spontaneous preterm birth. This study demonstrated that morbidly obese (BMI > 35) nulliparous women had a greater than 2-fold risk of elective preterm birth but only a 20% lower risk of spontaneous preterm birth, leading to an increased risk of all-cause prematurity [OR 1.34 (95% CI 1.15–1.56)] (Smith *et al.*, 2006). Furthermore, 40% of morbidly obese nulliparous women who had an elective preterm delivery had a diagnosis of pre-eclampsia compared with only 2.6% of the rest of the population (Smith *et al.*, 2006). Therefore, the increase in iatrogenic preterm delivery is most likely due to the strong association between nulliparity, increasing BMI and pre-eclampsia.

This study also highlighted the risk of nulliparous morbidly obese women delivering an infant of <1000 g, which was still alive at 1 year of age [OR 3.36 (95% CI 1.89–5.98)] (Smith *et al.*, 2006). This group of children has a 40–45% risk of severe neurodevelopmental delay in childhood and, therefore, was used as a proxy measure of severe long-term morbidity (Ohls *et al.*, 2004). Other delivery-related fetal outcomes have also been related to BMI: the risk of fetal distress: obese [OR 1.61 (95% CI 1.53–1.69)], morbidly obese [OR 2.13 (95% CI 1.93–2.35)] and BMI > 40 [OR 2.52 (95% CI 2.12–3.58)], meconium aspiration: obese [OR 1.64 (95% CI 1.30–2.06)], morbidly obese [OR 2.87 (95% CI 2.13–3.85)] and BMI > 40 [OR 2.85 (95% CI 1.60–5.07)]; shoulder dystocia: obese [OR 2.14 (95% CI 1.83–2.49)], morbidly obese [OR 2.82 (95% CI 2.1–3.71)] and BMI > 40 [OR 3.14 (95% CI 1.86–5.31)] (Cedergren, 2004).

These studies collectively demonstrate a strong association between maternal obesity in early pregnancy and a number of severe fetal complications during early and late development, delivery and the neonatal period. Increased odds ratios of rare complications describe events that remain rare. However, the statistical increases in the major events described above (stillbirth, neonatal death and prolonged morbidity) are tangible elements. Given that the subfertile population generally experiences poorer perinatal outcomes than the population as a whole, the role of obesity in infertility treatment clinics must be considered seriously. These complications are quite separate from the well-established maternal complications related to obesity, in particular, the hypertensive disorders of pregnancy, gestational diabetes, thromboembolism, infection and the anaesthetic and obstetric problems associated with delivery and the post-partum period.

### Weight loss in the anovulatory woman

The effects of weight loss, by dint of calorie restriction and/or exercise, have been studied in a relatively small number of cases, but with reasonable agreement among the studies. Weight loss, with or without exercise, results in improved insulin sensitivity and increased ovulation frequency with relatively minor degrees of absolute weight reduction. Kiddy *et al.* (1992) described 11 anovulatory obese women losing  $>5\%$  of their pretreatment weight. About 9 of these 11 showed improvement in reproductive function, as they either conceived (5) or experienced a more regular menstrual pattern. In contrast, the group losing  $<5\%$  of their initial weight recorded little improvement in reproductive function. Hollman *et al.* (1996) reported that in 35 women undergoing a weight reduction programme over 32 weeks who recorded a weight loss of  $<10\%$ , there was menstrual period improvement in 80% and pregnancy in 29%. One study in overweight women diagnosed with polycystic ovary syndrome (PCOS) showed similar benefits of weight loss (Huber-Buchholz *et al.*, 1999). About 18 infertile anovulatory women with PCOS and normal glucose tolerance (BMI 27–45 kg m<sup>2</sup>), underwent a 6-month diet and exercise programme. The patients, who responded with improved ovulation frequency, showed an 11% reduction in central fat, whereas mean weight loss was between 2 and 5% of starting weight over the programme. These data indicate that lifestyle modification, leading to improved insulin sensitivity with relatively modest degrees of weight loss, commonly result in improved ovulation rates and conception. These programmes should therefore be considered to be effective ovulation-induction therapies.

### The unfortunate conflict

There is an unfortunate conflict in these situations. Although the indicator for grade of obstetric/neonatal risk as outlined is absolute BMI, the critical factor for restoring ovulation appears to be percentage of weight lost and this may be relatively modest. Correspondingly, a reduction in BMI from 40 to 38 kg m<sup>2</sup> is likely to restore ovulation in a woman clearly at tangible obstetric/neonatal risk. Indeed, in exercise programmes, insulin sensitivity can be improved with even more modest absolute weight reduction, and ovarian function/fertility can be normalized by this means (Clark *et al.*, 1998). Although there is substantial evidence with respect to pregnancy that exercise can modify metabolic and vascular risk factors, it has yet to be determined whether exercise reduces the risk of adverse perinatal outcome. This collection of evidence means that simply advising weight loss or even putting a patient into a weight reduction (lifestyle modification) programme is actively putting a woman into a risk-prone situation, where the pregnancy-specific risks are now well quantified.

Balen *et al.* (2006) have proposed that obese patients with PCOS should be denied treatment of any kind aimed to improve ovulation rates and achieve pregnancy, including metformin, until they have reduced their BMI to 35 kg m<sup>2</sup>. We suggest that this position is flawed, on two grounds. The first is that obesity and the obstetrical/neonatal consequences are

not restricted to obese women with PCOS. The issues are obesity and ovulation. The second is that metformin treatment of obese women with PCOS is less efficacious than that of normal weight women (Fleming *et al.*, 2002) and that in the obese group, it is no more likely than weight loss itself to improve ovulation rates (Tang *et al.*, 2006). Therefore, the issue is not whether treatment with metformin should be discouraged, it is whether the patient should be protected from pregnancy during the time of weight reduction. In defence of metformin, it does reduce circulating androgens and hirsutism, and its use is associated with modest weight loss (Harborne *et al.*, 2003, 2005), with more consistent effects with the higher doses (Harborne *et al.*, 2005). However, the effect is time-consuming with an average of 5 kg over 8 months, with higher doses. In contrast, more profound effects may be achieved using weight-reducing drugs such as orlistat, which achieved a 5% reduction in weight in 3 months compared with 1% with metformin (Jayagopal *et al.*, 2005).

### Critical body mass criteria

Balen *et al.* (2006), somewhat arbitrarily, selected a BMI of 35 kg m<sup>2</sup> as the critical point above which fertility treatment should be withheld. However, there is substantial clinical evidence to support a BMI of  $<30$  kg m<sup>2</sup> from the world literature. With respect to the UK population and the specific risk of neonatal death and extremely low birth weight infants, the cut-off value of 35 kg m<sup>2</sup> has supportive evidence. However, we assert that programmes encouraging weight loss, through either diet or exercise or both, should be considered to be ovulation-induction therapies. Correspondingly, patients undertaking these measures should also be advised about contraception until that critical value of BMI 35 kg m<sup>2</sup> is achieved. Because of the associated risk of thromboembolism with combined oral contraception, the decreased efficacy of progesterone-only contraception, potential delays in return to ovulation with depot preparations and risk of pelvic inflammatory disease with intrauterine devices, the obvious choice during this at risk preconceptional period would be barrier methods.

### The unavoidable conclusion

Women with a BMI in excess of 35 kg m<sup>2</sup> should lose weight prior to conception—not prior to receiving infertility treatment. Therefore, clinicians undertaking the management of infertility in obese women should adopt measures to reduce their body mass prior to exposing them to the risks of pregnancy. We advocate that the approach should be aggressively managed using strategies that may include the drugs such as metformin or orlistat. Intrinsic in this programme is the use of barrier contraception during that period of weight reduction. The combination of weight loss, contraception and high-dose folic acid should become the standard preconceptional care for the obese woman. Women need to be made aware that any potential delay in therapy is in the best interests of mother and baby. In this context, we can potentially reduce the stigmatization of asking obese women to lose weight before treatment (Laredo, 2006).

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