REVIEW

Obesity, fertility and pregnancy: can we intervene to improve outcomes?

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Abstract

Rates of obesity among women of reproductive age have risen dramatically in recent decades. Obesity impacts on health of women across their reproductive lifespan with adverse effects on not only fertility and short-term complications of pregnancy, but also on longer term health outcomes for both women and their children. This places considerable burden and cost on health services. Here, we review the evidence linking maternal obesity to adverse fertility, pregnancy and longer term health outcomes for women and their children. We discuss the outcomes of recent lifestyle, pharmacological and surgical intervention studies. As many of these studies have not shown a significant improvement in clinical outcomes, we discuss the need for better study design in future trials.

Background

Within the current global crisis of obesity (BMI ≥30 kg/m²), women of reproductive age represent a group with the steepest rises in obesity rates over recent decades (NCD Risk Factor Collaboration 2016). In the United Kingdom, it is estimated that one in five women are now obese at the time of antenatal booking (Kanagalalingam et al. 2005, Heslehurst et al. 2007, 2010), with similar estimates in developed countries (LaCoursiere et al. 2005, Goldstein et al. 2017). Obesity impacts on health of women across their reproductive lifespan with adverse effects on not only fertility and short-term complications of pregnancy, but also on longer-term health outcomes for both women and their children. Here, we describe the evidence linking maternal obesity to adverse outcomes for women and their children and discuss the options for interventions that have been tested and that should be considered, to improve clinical outcomes.

Obesity and fertility

Obesity is increasingly recognised as a key factor influencing fertility (Vahratian & Smith 2009). Available data suggest that increased BMI in both men (Sallmen et al. 2006) and in women (Wise et al. 2010) is associated with delayed conception in a dose-dependent manner, with longer time and inability to conceive observed in those of greater BMI or if both partners are obese (Ramlau-Hansen et al. 2007). Mechanisms are multifactorial and not completely understood. For example, in women, obesity is associated with anovulation and menstrual irregularity but also with impaired oocyte development and quality (Metwally et al. 2007, Zain & Norman 2008, Klenov & Jungheim 2014). For men, there are less available data, though observational studies have suggested possible contributing factors may be increased testicular temperature with sitting (Hammoud et al. 2012), increased oestrogen production in adipose tissue (Shukla et al. 2014) and reduced sperm count and motility (Sermondade et al. 2013).
Obesity and maternal health in pregnancy and in the longer term

Numerous studies have documented the associations between maternal obesity and increased risk of multiple serious pregnancy complications for the mother in both the short and long term. These risks include hypertension and preeclampsia, gestational diabetes, antenatal depression and thromboembolic events (Kalliala et al. 2017). Women with obesity are more likely to experience induction of labour and caesarean section, with up to one in seven caesareans attributable to maternal obesity (Sebire et al. 2001, Dodd et al. 2011, Kalliala et al. 2017). Compared to normal weight women, obese women are also more likely to have a stillbirth (odds ratio 5.2, 95% CI 2.5–10.9) or perinatal death, particularly in later gestations (Hazard ratios (95% CI) for foetal death before week 14: 0.8 (0.5–1.4), weeks 14–19: 1.6 (1.0–2.5), weeks 20–27: 1.9 (1.1–3.3), weeks 28–36: 2.1 (1.0–4.4), weeks 37–39: 3.5 (1.9–6.4) and weeks 40+: 4.6 (1.6–13.4) (Nohr et al. 2005). There is a dose–response relationship between maternal pre-pregnancy weight and severe maternal morbidity or mortality (Lisonkova et al. 2017). The absolute increases in numbers of deaths or cases of serious morbidity per 10,000 women were 17.6 for overweight women, and 24.9, 35.8 and 61.1 for women with obesity classes 1, 2 and 3, respectively. This places a considerable burden and health cost on antenatal services (Galtier-Dereure et al. 2000, Denison et al. 2009, 2014).

Being obese during pregnancy also has consequences for a woman’s health in later life. There is around a 50% greater odds of a woman developing diabetes (OR 1.47; 95% CI 1.11–1.94), chronic hypertension and cardiovascular disease during her lifetime, women with obesity during pregnancy have a 35% increased risk of premature mortality and increased risk of having a cardiovascular event (Hazard ratio (HR) for all-cause mortality 1.35, 95% CI 1.02–1.77; HR for cardiovascular events 1.32, 95% CI 1.02–1.68) (Lee et al. 2015). Maternal obesity also increases the likelihood of gynaecological cancers in later life including ovarian and endometrial cancer (Kalliala et al. 2017). While these observations have been noted from follow-up of women whose weight was measured during pregnancy, further work is needed to understand whether these adverse health effects are simply due to being obese in young adult life or whether the intersection of obesity and pregnancy confers additional adverse health risks for women compared to women who are obese but have not been pregnant.

Maternal obesity and consequences for the child

For the infant, risks of being born to an obese mother include macrosomia, stillbirth and neonatal death (Kalliala et al. 2017). Higher maternal BMI is the single largest predictor of being born large for gestational age (LGA) (Arendas et al. 2008), predisposing an individual to later life obesity and cardiometabolic disease. Babies born LGA are at 2- to 5-fold higher risk of childhood and adult obesity (Eriksson et al. 2001, Woo Baidal et al. 2016). Maternal obesity has been linked to increased risk of cardiovascular risk factors including glucose intolerance and insulin resistance, hypertension and dyslipidaemia in young adulthood (Hochner et al. 2012). We demonstrated increased risk of cardiovascular mortality in offspring of obese (HR 1.35, 95% CI 1.17–1.55), with a similar pattern in offspring born to overweight mothers, compared to normal-weight mothers (Reynolds et al. 2013). Offspring born to both obese and overweight mothers were also at significantly increased risk of a hospital admission with a cardiovascular event (Reynolds et al. 2013). This finding has been replicated in a population born to mothers who were overweight (Eriksson et al. 2014) suggesting these observations are robust.

While mechanisms underlying the link between maternal obesity and offspring cardiovascular disease are not completely understood, data from animal models, support a causal relationship between in utero exposure to maternal obesity and pathological left ventricular cardiac hypertrophy, hypertension and impaired systolic and diastolic function in the offspring (Fernandez-Twinn et al. 2012, Blackmore & Ozanne 2015). The limited data available in humans are consistent with these observations. Two human studies have demonstrated a link between maternal obesity and adverse changes in offspring cardiac structure and function which are detectable during foetal development from the first trimester of pregnancy and persist in early childhood (Ingul et al. 2016, Guzzardi et al. 2017). Foetuses of obese mothers compared to normal-weight mothers had reduced foetal biventricular global strain rate and strain from 14 weeks of gestation, lower systolic and late diastolic tissue Doppler velocities from 20 weeks of gestation and thicker foetal interventricular septum measured in late pregnancy (Ingul et al. 2016). Similarly, echocardiography in neonates born to obese mothers revealed thicker left ventricular posterior wall at birth and greater end-diastolic and stroke volumes at 1 year of age compared to those born to normal-weight mothers, independently of offspring adiposity.
Further follow-up studies are needed as the largest available data set following children at aged 8 years demonstrated that the findings of associations of maternal obesity with offspring increased cardiac ventricular mass were attenuated after adjusting for current childhood BMI (Toemen et al. 2016).

In addition to cardiometabolic outcomes, there is increasing evidence that maternal obesity is a key factor determining other offspring health outcomes including risk of allergies and asthma, as well as neuropsychiatric and neurodevelopmental problems (Godfrey et al. 2017, Mina et al. 2017a,b). More work is needed to dissect whether these findings persist into adult life and to understand the complex interplay between any phenotype which may be attributable to exposures in utero as opposed to the childhood postnatal environment. Importantly, being born LGA is associated with increased size at birth in the next generation, perpetuating a vicious cycle of high birthweight and obesity across generations (Cnattingius et al. 2012). Heavier birth weight is independently and linearly associated with increasing prevalence of obesity at age 7 years in the Avon cohort of children (n=8234) (Reilly et al. 2005). Specifically, infants defined as LGA (>90th percentile) at birth remained in the upper tertile of weight throughout early childhood (Glavin et al. 2014). Thus, any interventions that can optimise the health of women in pregnancy and reduce the risk of offspring being born LGA have potential to improve intergenerational health.

**Weight loss improves fertility outcomes**

A systematic review and meta-analysis including 40 studies, 14 of which were randomised controlled trials, examined the effectiveness of weight loss interventions in improving fertility outcomes (Best et al. 2017). The studies included randomised controlled trials of a combined diet and exercise intervention (typically calorie reducing and exercise increasing) versus control, of diet alone versus control and also nonrandomised trials of diet and exercise interventions versus control and motivational interviewing versus control. Bariatric surgery interventions were excluded. Participants were aged 25–35.4 years, with a BMI 24.5–44 kg/m², and duration of infertility ranging from 19.5 months to 11 years. Overall, the interventions were associated with a weight loss of −3.98 kg (95% CI −4.85 to −3.12) and weight loss was seen across all the interventions studied.

Overall there was a small but significant effect of improved pregnancy outcomes in the women who had received diet and exercise interventions (54.8 vs 49.9%, relative risk 1.59, 95% CI 1.01–2.5). There was some evidence that the combined intervention of diet and exercise was more effective than either diet alone or motivational interviewing. Overall the combined diet and exercise interventions were also associated with improved ovulation, menstrual irregularity and natural conception rates among women awaiting fertility treatment. There was no difference in miscarriage or IVF conception rate and no additional benefit of adding metformin to the intervention.

The review highlighted a striking lack of intervention studies to improve fertility in men with overweight and obesity. Two small cohort studies (Hakonsen et al. 2011, Faure et al. 2014) have assessed the impact of a nutrition focussed diet programme and a diet and exercise programme in 8 and 27 men, respectively. In one study, there were suggestions of improvements in sperm concentrations, motility and normal morphology as well as possible improvement in sperm DNA integrity (Hakonsen et al. 2011); however, no findings were statistically significant and neither study was adequately powered to assess these findings.

These findings prompted the authors of the systematic review to propose whether it is time for infertility weight loss programmes to be couple based? They argued that involving partners ‘may facilitate mutual support, behavioural change, weight loss and program continuation, at very little additional cost. A successful couple based intervention could improve the chances of achieving pregnancy and delivering a healthy baby, with a reduction in pregnancy complications. In the longer run both partners and their baby could benefit from maintained behaviour change with better health across the lifespan.’ While most interventions have focussed on optimising the woman’s health, this suggestion should be tested formally.

**Lifestyle interventions in pregnancy have limited effects on clinical outcomes**

Obese pregnant women often eat a diet that is energy dense, with high proportions of saturated fats and carbohydrates, but nutrient poor, with deficiencies in essential micronutrients including folic acid, iron, vitamin D and calcium (Mohd-Shukri et al. 2015). In addition, physical activity levels tend to decline in all women during pregnancy (Nascimento et al. 2015) with lower levels of physical activity in obese than lean women.
(Mohd-Shukri et al. 2015). It is known that pregnancy is a time when women may be more motivated to make lifestyle changes for example giving up smoking or reducing alcohol intake (Nowicki et al. 2018). A large number of studies have been designed to test whether diet and/or lifestyle interventions improve pregnancy outcomes for both mothers and babies. A very recent Individual Participant Data meta-analysis reviewed the evidence from 36 randomised controlled trials of diet and/or lifestyle interventions with data on over 12,000 women (Rogozinska et al. 2017). Overall, lifestyle interventions had a very modest impact on gestational weight gain with the pooled data showing only a 0.7 kg (95% CI 0.92–0.48 kg) reduction in gestational weight gain. There was no effect on any of the pregnancy clinical outcomes including birth weight, the incidence of LGA or small for gestational age infants. There was no effect on maternal composite outcomes of pregnancy complications including gestational diabetes and pre-eclampsia. A health economic evaluation concluded there was no evidence of cost benefit of these interventions. The authors concluded that further evaluation of the differential effects of lifestyle interventions on individual pregnancy outcomes is needed. This would be useful to understand the components of interventions that are effective and to explore the possible reasons for this, including factors such as adherence to the intervention. Further, the longer term potential benefits of a lifestyle intervention in pregnancy cannot be determined from this meta-analysis. For example, two large randomised controlled trials of lifestyle interventions, the LIMIT study conducted in Australia (Dodd et al. 2014) and the UPBEAT (UK Pregnancies: Better Easting and Activity Trial) study conducted in the UK (Poston et al. 2015) both demonstrated that the lifestyle interventions did result in improved diet quality and lifestyle among the women. If these behaviours persist into the postpartum period it is therefore plausible that the lifestyle intervention may have longer effects on the diet and lifestyle in the family which may impact on benefits for maternal and child health in the postpartum period. Indeed a recent Position Statement from the US Academy of Nutrition and Dietetics recommends that ‘Behavioral counseling to improve dietary intake and physical activity (PA) should be provided to overweight and obese women, beginning in the preconception period and continuing throughout pregnancy, for at least 12–18 months postpartum’ (Stang & Huffman 2016) because of the additional benefits to health of weight loss and exercise.

Bariatric surgery has harms as well as benefits

Others have looked at the outcomes of pregnancy post bariatric surgery, an intervention associated with significant weight loss. Conception during the year following bariatric surgery is not recommended due to the major weight changes that are occurring in the mother and the potential for malabsorption of micronutrients. The largest series (Johansson et al. 2015) showed that bariatric surgery was associated with a reduction in LGA infants (8.6 vs 22.4%, odds ratio (OR) 0.33, 95% CI 0.24–0.44). However, there were complications associated with pregnancies post bariatric surgery including a higher risk of small for gestational age infants (15.6 vs 7.6%, OR 2.2, 95% CI, 1.64–2.95) and shorter gestation at delivery (mean difference 4.5 days, 273.0 vs 277.5 days). Thus, women who have had bariatric surgery prior to pregnancy require close monitoring during pregnancy to ensure optimal nourishment and gestational weight gain.

Pharmacological interventions

Obese women are more insulin resistant than lean women, even as early as at antenatal booking, and they are more insulin resistant and have higher glucose levels throughout pregnancy (Forbes et al. 2015). Data from the HAPO (Hyperglycaemia and Adverse Pregnancy Outcomes) study, including 37,000 women who had a glucose tolerance test during pregnancy showed that a higher glucose as measured by a higher fasting glucose, 1-h glucose post the glucose challenge or 2 h post the glucose challenge was associated with an increased risk of birthweight greater than the 90th percentile (Metzger et al. 2008). Likewise higher glucose levels were associated with increased risk of primary caesarean section rate. It is plausible therefore that lowering glucose might be expected to be associated with less risk of being born LGA. While lifestyle and surgical interventions for weight loss in obese women will also lead to an improvement in insulin sensitivity, an alternative approach is to use a pharmacological intervention. Metformin is endorsed in national guidelines for lowering of maternal glucose levels in the treatment of GDM (https://www.nice.org.uk/guidance/ng3) and is widely used in clinical practice as a first line therapy when lifestyle interventions have failed (Stirrat et al. 2015).

The first clinical trial in obese pregnant women without gestational diabetes or pre-existing diabetes (‘EMPOWaR’) randomised 444 women to either
metformin or placebo from 12 to 16 weeks gestation until delivery (Chiswick et al. 2015). The primary outcome was birth weight of the baby, and there was no difference in the adjusted mean difference (95% CI of birthweight centile −0.029 (−0.217 to 0.158), P=0.7597). The trial indicated that women took their tablets during pregnancy as women who were treated with metformin were more likely to have the well-recognised GI side effects associated with metformin. A pooled analysis included data from EMPOWaR and a subsequent randomised controlled trial, MOPS, which had a similar intervention albeit with a slightly higher dose of metformin and a different ethnic background of the included women showed similar (lack of) effects on the primary outcome (Syngelaki et al. 2016). In the combined meta-analysis, there was no significant effect on birthweight and only a modest reduction in gestational weight gain (Elmaraezy et al. 2017). A subsequent Cochrane review including data from these two trials and one additional study from Egypt, with outcomes available for 1034 participants overall, concluded that there was insufficient evidence to support the use of metformin for women with obesity in pregnancy for improving maternal and infant outcomes (Dodd et al. 2018). Moreover, metformin was associated with increased risk of adverse effects, particularly diarrhoea. Whether metformin is safe in pregnancy is also under debate (Barbour et al. 2018). It is known that metformin freely crosses the placenta, and though a survey of 1.9 million births from 11 European population-based registries found no evidence of an association between metformin exposure in the first trimester and congenital anomalies (Given et al. 2018), there is currently uncertainty as to whether metformin may affect long-term health of the offspring. The longest follow-up of children exposed to metformin in utero as part of a randomised controlled trial of gestational diabetes treatment extends to 9 years. Children exposed to metformin had higher BMI, waist circumference, waist-to-hip ratio and abdominal fat than children exposed to insulin (Rowan et al. 2018), suggesting a potential for adverse metabolic effects of metformin on child health. Further research is needed to understand the role of metformin alone, or as an adjuvant to dietary and lifestyle advice in obese pregnant women.

Maternal obesity is associated with altered insulin resistance, glucose homeostasis, fat oxidation and amino acid synthesis as reviewed in detail elsewhere (Nelson et al. 2010). Lifestyle and pharmacological interventions are targeted to ameliorate this metabolic disturbance, and have been shown, for example, to have demonstrable effects in improving insulin sensitivity and inflammatory markers in pregnancy (Chiswick et al. 2015). Yet, the window of gestation in which the foetus is exposed to the abnormal metabolic environment is likely critical. One possibility is that the foetal growth trajectory is already well established at the time of intervention. Women may be reluctant to engage with an intervention until after they have had their confirmatory booking scan and this means that interventions are likely not started until the second trimester. A study using routinely collected data of ultrasound scans conducted during pregnancy showed that at 20-week gestation offspring of obese mothers compared to lean mothers already had evidence of increased risk of the foetal abdominal circumference measuring greater than the 90th percentile (relative risk and 95% CI 1.63 (1.29–2.06)) (Sovio et al. 2016). Supportive of these data, early pregnancy weight gain also appears to have a stronger association with adverse outcomes and is more likely when women are obese prior to pregnancy (Cheney et al. 2017). These observations suggest that the studies to date have been conducted ‘too late’ and the results of ongoing preconception intervention trials are eagerly awaited.

**Conclusions**

The importance of health care across the life course was highlighted in the most recent annual report of the Chief Medical Officer of England (Davies 2014). This report recognised the importance of achieving a healthy weight prior to pregnancy and considering health across the life course. The WHO commission on ending childhood obesity has preconception and pregnancy care for women who are overweight or obese as one of six key recommendations (http://www.who.int/end-childhood-obesity/final-report/en/).

Despite this recognition, there is a lack of high-quality effectiveness research to support the recommendations. Ideally, future research would consist of large multi-centre RCTs that are adequately powered for both fertility and pregnancy outcomes (Fig. 1). Clearly, such large studies are a challenge and therefore to date have been run in clinics where fertility treatment is being offered.

**Why have interventions not ‘worked’?**

The lack of clinical benefit on pregnancy outcomes of lifestyle and pharmacological interventions is intriguing.
However, in settings where fertility treatment is expensive, this strategy will exclude women and couples of lower socio-economic status, who tend to have higher rates of obesity and pregnancy complications. Trials need to consider compliance and drop out as well as early pregnancy loss rates in a group with an already reduced chance of conception. This means significant inflation of the numbers of participants needed to show a significant difference in pregnancy rates, which necessarily requires more funding as well as multi-site collaboration.

Based on the science, it would be appropriate for future intervention trials to include men attending fertility clinics as well as women. This is not only to ensure partner support for weight loss programmes but because of the potential fertility benefit from weight reduction in overweight men. Trials that assess both men and women would ideally have mechanistic questions and biosamples integrated in to the trial design to both increase understanding in this area as well as testing the intervention.

Longer duration of follow-up for studies assessing weight loss and fertility is essential. There is potential for benefits for mothers and offspring well beyond conception that can only be assessed over time. Weight maintenance beyond interventions should also ideally be monitored (Fogelholm et al. 2017). In countries where data linkage to health outcomes is possible, this represents a very cost-effective method of ongoing follow-up and can include both maternal and offspring outcomes as well as impact on future pregnancies.

In addition to better designed trials of effectiveness, there remains a need for further research (Fig. 1) to better understand the maternal metabolic environment in obese pregnancy in order to design novel interventions to improve clinical outcomes for mother and child.

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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