REVIEW

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

Rebecca M Reynolds¹ and Adrienne Gordon²¹University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK²Charles Perkins Centre, University of Sydney, Sydney, AustraliaCorrespondence should be addressed to R M Reynolds: r.reynolds@ed.ac.uk

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.

Key Words

- ▶ obesity
- ▶ fertility
- ▶ pregnancy
- ▶ intervention

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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 (Kanagalingam *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

(Guzzardi *et al.* 2017). 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 was 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 Eating 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.

Why have interventions not ‘worked’?

The lack of clinical benefit on pregnancy outcomes of lifestyle and pharmacological interventions is intriguing.

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.

Figure 1
Schematic diagram of opportunities for intervention in maternal obesity to improve outcomes for mothers and babies.

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.

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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References

- Arendas K, Qiu Q & Gruslin A 2008 Obesity in pregnancy: pre-conceptional to postpartum consequences. *Journal of Obstetrics and Gynaecology Canada* **30** 477–488. ([https://doi.org/10.1016/S1701-2163\(16\)32863-8](https://doi.org/10.1016/S1701-2163(16)32863-8))
- Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, Aagaard K, Thornburg KL, Catalano PM, Galan HL, *et al.* 2018 A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. *American Journal of Obstetrics and Gynecology* **219** 367.e1–367.e7. (<https://doi.org/10.1016/j.ajog.2018.06.013>)
- Best D, Avenell A & Bhattacharya S 2017 How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. *Human Reproduction Update* **23** 681–705. (<https://doi.org/10.1093/humupd/dmx027>)
- Blackmore HL & Ozanne SE 2015 Programming of cardiovascular disease across the life-course. *Journal of Molecular and Cellular Cardiology* **83** 122–130. (<https://doi.org/10.1016/j.yjmcc.2014.12.006>)
- Cheney K, Berkemeier S, Sim KA, Gordon A & Black K 2017 Prevalence and predictors of early gestational weight gain associated with obesity risk in a diverse Australian antenatal population: a cross-sectional study. *BMC Pregnancy and Childbirth* **17** 296. (<https://doi.org/10.1186/s12884-017-1482-6>)
- Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, Walker BR, Quenby S, Wray S, Weeks A, *et al.* 2015 Effect of

- metformin on maternal and fetal outcomes in obese pregnant women (EMPOWar): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinology* **3** 778–786. ([https://doi.org/10.1016/S2213-8587\(15\)00219-3](https://doi.org/10.1016/S2213-8587(15)00219-3))
- Cnattingius S, Villamor E, Lagerros YT, Wikstrom AK & Granath F 2012 High birth weight and obesity – a vicious circle across generations. *International Journal of Obesity* **36** 1320–1324. (<https://doi.org/10.1038/ijo.2011.248>)
- Davies SC 2014 Annual Report of the Chief Medical Officer, 2014, The Health of the 51%: Women. London, UK: Department of Health. (available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/595439/CMO_annual_report_2014.pdf)
- Denison FC, Norrie G, Graham B, Lynch J, Harper N & Reynolds RM 2009 Increased maternal BMI is associated with an increased risk of minor complications during pregnancy with consequent cost implications. *British Journal of Obstetrics and Gynaecology* **116** 1467–1472. (<https://doi.org/10.1111/j.1471-0528.2009.02222.x>)
- Denison FC, Norwood P, Bhattacharya S, Duffy A, Mahmood T, Morris C, Raja EA, Norman JE, Lee AJ & Scotland G 2014 Association between maternal body mass index during pregnancy, short-term morbidity, and increased health service costs: a population-based study. *British Journal of Obstetrics and Gynaecology* **121** 72–81; discussion 82.
- Dodd JM, Grivell RM, Nguyen AM, Chan A & Robinson JS 2011 Maternal and perinatal health outcomes by body mass index category. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **51** 136–140. (<https://doi.org/10.1111/j.1479-828X.2010.01272.x>)
- Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, Crowther CA, Wittert G, Owens JA, Robinson JS, *et al.* 2014 Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* **348** g1285. (<https://doi.org/10.1136/bmj.g1285>)
- Dodd JM, Grivell RM, Deussen AR & Hague WM 2018 Metformin for women who are overweight or obese during pregnancy for improving maternal and infant outcomes. *Cochrane Database of Systematic Reviews* **7** Cd010564. (<https://doi.org/10.1002/14651858.CD010564.pub2>)
- Elmaraezy A, Abushouk AI, Emara A, Elshahat O, Ahmed H & I Mostafa M 2017 Effect of metformin on maternal and neonatal outcomes in pregnant obese non-diabetic women: a meta-analysis. *International Journal of Reproductive BioMedicine* **15** 461–470. (<https://doi.org/10.29252/ijrm.15.8.461>)
- Eriksson J, Forsen T, Tuomilehto J, Osmond C & Barker D 2001 Size at birth, childhood growth and obesity in adult life. *International Journal of Obesity and Related Metabolic Disorders* **25** 735–740. (<https://doi.org/10.1038/sj.ijo.0801602>)
- Eriksson JG, Sandboge S, Salonen MK, Kajantie E & Osmond C 2014 Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. *Annals of Medicine* **46** 434–438. (<https://doi.org/10.3109/07853890.2014.919728>)
- Faure C, Dupont C, Baraibar MA, Ladouce R, Cedrin-Durnerin I, Wolf JP & Levy R 2014 In subfertile couple, abdominal fat loss in men is associated with improvement of sperm quality and pregnancy: a case-series. *PLoS ONE* **9** e86300. (<https://doi.org/10.1371/journal.pone.0086300>)
- Fernandez-Twinn DS, Blackmore HL, Siggers L, Giussani DA, Cross CM, Foo R & Ozanne SE 2012 The programming of cardiac hypertrophy in the offspring by maternal obesity is associated with hyperinsulinemia, AKT, ERK, and mTOR activation. *Endocrinology* **153** 5961–5971. (<https://doi.org/10.1210/en.2012-1508>)
- Fogelholm M, Larsen TM, Westerterp-Plantenga M, Macdonald I, Martinez JA, Boyadjieva N, Poppitt S, Schlicht W, Stratton G, Sundvall J, *et al.* 2017 PREVIEW: prevention of diabetes through lifestyle intervention and population studies in Europe and around the world. Design, methods, and baseline participant description of an adult cohort enrolled into a three-year randomised clinical trial. *Nutrients* **9** E632. (<https://doi.org/10.3390/nu9060632>)
- Forbes S, Barr SM, Reynolds RM, Semple S, Gray C, Andrew R, Denison FC, Walker BR & Norman JE 2015 Convergence in insulin resistance between very severely obese and lean women at the end of pregnancy. *Diabetologia* **58** 2615–2626. (<https://doi.org/10.1007/s00125-015-3708-3>)
- Galtier-Dereure F, Boegner C & Bringer J 2000 Obesity and pregnancy: complications and cost. *American Journal of Clinical Nutrition* **71** 1242s–1248s. (<https://doi.org/10.1093/ajcn/71.5.1242s>)
- Given JE, Loane M, Garne E, Addor MC, Bakker M, Bertaut-Nativel B, Gatt M, Klungsoyr K, Lelong N, Morgan M, *et al.* 2018 Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies: exploratory case-control study. *BMJ* **361** k2477. (<https://doi.org/10.1136/bmj.k2477>)
- Glavin K, Roelants M, Strand BH, Juliusson PB, Lie KK, Helseth S & Hovengen R 2014 Important periods of weight development in childhood: a population-based longitudinal study. *BMC Public Health* **14** 160. (<https://doi.org/10.1186/1471-2458-14-160>)
- Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG & Broekman BF 2017 Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinology* **5** 53–64. ([https://doi.org/10.1016/S2213-8587\(16\)30107-3](https://doi.org/10.1016/S2213-8587(16)30107-3))
- Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, *et al.* 2017 Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. *JAMA* **317** 2207–2225. (<https://doi.org/10.1001/jama.2017.3635>)
- Guzzardi MA, Liistro T, Gargani L, Ait Ali L, D'Angelo G, Rocchiccioli S, La Rosa F, Kemeny A, Sanguinetti E, Ucciferri N, *et al.* 2017 Maternal obesity and cardiac development in the offspring: study in human neonates and minipigs. *JACC: Cardiovascular Imaging* [epub]. (<https://doi.org/10.1016/j.jcmg.2017.08.024>)
- Hakonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY, Bungum M, Ernst EH, Hansen ML, Ernst EH, *et al.* 2011 Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. *Reproductive Health* **8** 24. (<https://doi.org/10.1186/1742-4755-8-24>)
- Hammoud AO, Meikle AW, Reis LO, Gibson M, Peterson CM & Carrell DT 2012 Obesity and male infertility: a practical approach. *Seminars in Reproductive Medicine* **30** 486–495. (<https://doi.org/10.1055/s-0032-1328877>)
- Heslehurst N, Ellis LJ, Simpson H, Batterham A, Wilkinson J & Summerbell CD 2007 Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. *British Journal of Obstetrics and Gynaecology* **114** 187–194. (<https://doi.org/10.1111/j.1471-0528.2006.01199.x>)
- Heslehurst N, Rankin J, Wilkinson JR & Summerbell CD 2010 A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989–2007. *International Journal of Obesity* **34** 420–428. (<https://doi.org/10.1038/ijo.2009.250>)
- Hochner H, Friedlander Y, Calderon-Margalit R, Meiner V, Sagy Y, Avgil-Tsodik M, Burger A, Savitsky B, Siscovick DS & Manor O 2012 Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation* **125** 1381–1389. (<https://doi.org/10.1161/CIRCULATIONAHA.111.070060>)
- Ingul CB, Loras L, Tegnander E, Eik-Nes SH & Brantberg A 2016 Maternal obesity affects fetal myocardial function as early as in the first trimester. *Ultrasound in Obstetrics and Gynecology* **47** 433–442. (<https://doi.org/10.1002/uog.14841>)
- Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, Stephansson O & Neovius M 2015 Outcomes of pregnancy after bariatric surgery. *New England Journal of Medicine* **372** 814–824. (<https://doi.org/10.1056/NEJMoa1405789>)

- Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Mitra A, Terzidou V, Bennett P, Martin-Hirsch P, Tsilidis KK, *et al.* 2017 Obesity and gynaecological and obstetric conditions: umbrella review of the literature. *BMJ* **359** j4511. (<https://doi.org/10.1136/bmj.j4511>)
- Kanagalingam MG, Forouhi NG, Greer IA & Sattar N 2005 Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. *British Journal of Obstetrics and Gynaecology* **112** 1431–1433. (<https://doi.org/10.1111/j.1471-0528.2005.00685.x>)
- Klenov VE & Jungheim ES 2014 Obesity and reproductive function: a review of the evidence. *Current Opinion in Obstetrics and Gynecology* **26** 455–460. (<https://doi.org/10.1097/GCO.0000000000000113>)
- LaCoursiere DY, Bloebaum L, Duncan JD & Varner MW 2005 Population-based trends and correlates of maternal overweight and obesity, Utah 1991–2001. *American Journal of Obstetrics and Gynecology* **192** 832–839. (<https://doi.org/10.1016/j.ajog.2004.11.034>)
- Lee KK, Raja EA, Lee AJ, Bhattacharya S, Bhattacharya S, Norman JE & Reynolds RM 2015 Maternal obesity during pregnancy associates with premature mortality and major cardiovascular events in later life. *Hypertension* **66** 938–944. (<https://doi.org/10.1161/HYPERTENSIONAHA.115.05920>)
- Lisonkova S, Muraca GM, Potts J, Liauw J, Chan WS, Skoll A & Lim KI 2017 Association between prepregnancy body mass index and severe maternal morbidity. *JAMA* **318** 1777–1786. (<https://doi.org/10.1001/jama.2017.16191>)
- Metwally M, Cutting R, Tipton A, Skull J, Ledger WL & Li TC 2007 Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reproductive Biomedicine Online* **15** 532–538. ([https://doi.org/10.1016/S1472-6483\(10\)60385-9](https://doi.org/10.1016/S1472-6483(10)60385-9))
- Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, *et al.* 2008 Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine* **358** 1991–2002. (<https://doi.org/10.1056/NEJMoa0707943>)
- Mina TH, Lahti M, Drake AJ, Denison FC, Raikonen K, Norman JE & Reynolds RM 2017a Prenatal exposure to maternal very severe obesity is associated with impaired neurodevelopment and executive functioning in children. *Pediatric Research* **82** 47–54. (<https://doi.org/10.1038/pr.2017.43>)
- Mina TH, Lahti M, Drake AJ, Raikonen K, Minnis H, Denison FC, Norman JE & Reynolds RM 2017b Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children. *Psychologie Medicale* **47** 353–362. (<https://doi.org/10.1017/S0033291716002452>)
- Mohd-Shukri NA, Duncan A, Denison FC, Forbes S, Walker BR, Norman JE & Reynolds RM 2015 Health behaviours during pregnancy in women with very severe obesity. *Nutrients* **7** 8431–8443. (<https://doi.org/10.3390/nu7105403>)
- Nascimento SL, Surita FG, Godoy AC, Kasawara KT & Morais SS 2015 Physical activity patterns and factors related to exercise during pregnancy: a cross sectional study. *PLoS ONE* **10** e0128953. (<https://doi.org/10.1371/journal.pone.0128953>)
- NCD Risk Factor Collaboration 2016 Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* **387** 1377–1396. ([https://doi.org/10.1016/S0140-6736\(16\)30054-X](https://doi.org/10.1016/S0140-6736(16)30054-X))
- Nelson SM, Matthews P & Poston L 2010 Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. *Human Reproduction Update* **16** 255–275. (<https://doi.org/10.1093/humupd/dmp050>)
- Nohr EA, Bech BH, Davies MJ, Frydenberg M, Henriksen TB & Olsen J 2005 Prepregnancy obesity and fetal death: a study within the Danish National Birth Cohort. *Obstetrics and Gynecology* **106** 250–259. (<https://doi.org/10.1097/01.AOG.0000172422.81496.57>)
- Nowicki GJ, Misztal-Okonska P, Slusarska B, Rudnicka-Drozak E, Mlynarska M & Czekierdowski A 2018 Analysis of health behaviors and personal values of childless women, pregnant women and women who recently delivered. *International Journal of Environmental Research and Public Health* **15** E411. (<https://doi.org/10.3390/ijerph15030411>)
- Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, Hayes L, Khazaezadeh N, Nelson SM, Oteng-Ntim E, *et al.* 2015 Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinology* **3** 767–777. ([https://doi.org/10.1016/S2213-8587\(15\)00227-2](https://doi.org/10.1016/S2213-8587(15)00227-2))
- Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI & Olsen J 2007 Subfecundity in overweight and obese couples. *Human Reproduction* **22** 1634–1637. (<https://doi.org/10.1093/humrep/dem035>)
- Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A & Avon Longitudinal Study of Parents and Children Study Team 2005 Early life risk factors for obesity in childhood: cohort study. *BMJ* **330** 1357. (<https://doi.org/10.1136/bmj.38470.670903.E0>)
- Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, Sarwar N, Lee AJ, Bhattacharya S & Norman JE 2013 Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* **347** f4539.
- Rogozinska E, Marlin N, Jackson L, Rayanagoudar G, Ruifrok AE, Dodds J, Molyneux E, van Poppel MN, Poston L, Vinter CA, *et al.* 2017 Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. *Health Technology Assessment* **21** 1–158. (<https://doi.org/10.3310/hta21410>)
- Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S & Hague WM 2018 Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. *BMJ Open Diabetes Research and Care* **6** e000456. (<https://doi.org/10.1136/bmjdr-2017-000456>)
- Sallmen M, Sandler DP, Hoppin JA, Blair A & Baird DD 2006 Reduced fertility among overweight and obese men. *Epidemiology* **17** 520–523. (<https://doi.org/10.1097/01.ede.0000229953.76862.e5>)
- Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, Regan L & Robinson S 2001 Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *International Journal of Obesity and Related Metabolic Disorders* **25** 1175–1182. (<https://doi.org/10.1038/sj.ijo.0801670>)
- Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M, *et al.* 2013 BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Human Reproduction Update* **19** 221–231. (<https://doi.org/10.1093/humupd/dms050>)
- Shukla KK, Chambial S, Dwivedi S, Misra S & Sharma P 2014 Recent scenario of obesity and male fertility. *Andrology* **2** 809–818. (<https://doi.org/10.1111/andr.270>)
- Sovio U, Murphy HR & Smith GC 2016 Accelerated fetal growth prior to diagnosis of gestational diabetes mellitus: a prospective cohort study of nulliparous women. *Diabetes Care* **39** 982–987. (<https://doi.org/10.2337/dc16-0160>)
- Stang J & Huffman LG 2016 Position of the academy of nutrition and dietetics: obesity, reproduction, and pregnancy outcomes. *Journal of the Academy of Nutrition and Dietetics* **116** 677–691. (<https://doi.org/10.1016/j.jand.2016.01.008>)
- Stirrat LJ, Denison FC, Love CD, Lindsay RS & Reynolds RM 2015 Screening and management of gestational diabetes mellitus in Scottish obstetric units: a national survey. *Scottish Medical Journal* **60** 37–43. (<https://doi.org/10.1177/0036933014563458>)
- Syngelaki A, Nicolaides KH, Balani J, Hyer S, Akolekar R, Kotecha R, Pastides A & Shehata H 2016 Metformin versus Placebo in

- Obese Pregnant Women without diabetes mellitus. *New England Journal of Medicine* **374** 434–443. (<https://doi.org/10.1056/NEJMoa1509819>)
- Toemen L, Gishti O, van Osch-Gevers L, Steegers EA, Helbing WA, Felix JF, Reiss IK, Duijts L, Gaillard R & Jaddoe VW 2016 Maternal obesity, gestational weight gain and childhood cardiac outcomes: role of childhood body mass index. *International Journal of Obesity (Lond)* **40** 1070–1078. (<https://doi.org/10.1038/ijo.2016.86>)
- Vahratian A & Smith YR 2009 Should access to fertility-related services be conditional on body mass index? *Human Reproduction* **24** 1532–1537. (<https://doi.org/10.1093/humrep/dep057>)
- Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A & Hatch EE 2010 An internet-based prospective study of body size and time-to-pregnancy. *Human Reproduction* **25** 253–264. (<https://doi.org/10.1093/humrep/dep360>)
- Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME & Taveras EM 2016 Risk factors for childhood obesity in the first 1,000 days: a systematic review. *American Journal of Preventive Medicine* **50** 761–779. (<https://doi.org/10.1016/j.amepre.2015.11.012>)
- Zain MM & Norman RJ 2008 Impact of obesity on female fertility and fertility treatment. *Women's Health* **4** 183–194. (<https://doi.org/10.2217/17455057.4.2.183>)

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