Obesity

Obesity in pregnancy: What do recent trials deliver?

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Pre-existing obesity and excessive weight gain in pregnancy have significant consequences for maternal and fetal health and may also have consequences for the offspring and future generations. Potential complications include gestational diabetes, pre-eclampsia, caesarean delivery, maternal haemorrhage and infant mortality. Obesity also presents difficulties in the initiation and maintenance of breastfeeding, which has been suggested to be protective against future obesity.

A recent systematic review examined the impact of dietary interventions on excess weight and obesity in pregnancy (Flynn et al, 2016). The studies reviewed had different participant numbers, interventions, intervention delivery approaches and assessment tools. Although several of the studies were encouraging and reported beneficial maternal effects, the majority failed or were not powered to demonstrate an impact on neonatal outcomes.

Recently, prevention of excessive weight gain through lifestyle intervention and/or medication has been studied in randomised clinical trials. Dodd et al (2014) compared a dietary and lifestyle intervention against standard care in 2212 overweight or obese women across three centres in Australia. They reported improved maternal diet and activity in the intervention arm, as well as an 18% reduction in the risk of infants being born weighing more than 4 kg. However, only 40% of eligible women took up the programme.

UPBEAT (UK Pregnancies Better Eating and Activity Trial; *n*=1556) was conducted across eight centres in the UK and involved dietary and lifestyle sessions (Poston et al, 2015). Participants randomised to the intervention arm had a 0.55 kg reduction in mean gestational weight gain and improved diet and activity. Adherence was good, with 83% attending the majority of the sessions.

In EMPOWaR (Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial), the authors compared metformin (highest tolerated dose up to 2500 mg) with placebo in 449 obese women without diabetes (Chiswick et al, 2015). No difference in birth weight was observed. In a similar new study (summarised alongside), Syngelaki and colleagues examined the impact of metformin (maximum dose, 3000 mg) in obese pregnant women without diabetes across three centres in the UK. The study included a more ethnically diverse population than EMPOWaR. The participants were randomised to metformin (*n*=225) or placebo (*n*=225), with a total of 400 subjects included in the analysis.

Side effects were more common in the metformin group. Median maternal weight gain was lower in the metformin group compared to placebo (4.6 kg vs 6.3 kg; *P*<0.001), and the risk of pre-eclampsia was reduced (3.0% vs 11.3%; *P*<0.001). There were five stillbirths and miscarriages in the placebo group, compared to one stillbirth in the metformin group. Metformin had no significant effect on birth weight.

Both this study and EMPOWaR generally show benefits of metformin in terms of several outcomes, although many of the differences did not reach significance because of insufficient statistical power.

Both lifestyle intervention and metformin may have a role in reducing maternal weight gain in pregnancy, but further study is required. Lifestyle advice may also have an impact on birth weight, but the optimal content and delivery of the lifestyle intervention need to be determined. At best, the evidence only shows modest effects on pregnancy weight outcomes. However, maternal weight gain is complex, involving many factors beyond adiposity (e.g. fluid shifts). The potential impact of metformin on pre-eclampsia is promising, but has not been consistently observed. No significant harm from metformin has been observed, although side effects are more common, and longer-term outcomes in the offspring are unknown. The best approach for avoiding the complications of obesity is yet to be determined, but focus should be on avoiding excessive weight gain during pregnancy through lifestyle intervention, and also concentrating on tackling overweight and obesity prior to conception. ■

References on opposite page

N Engl J Med

Metformin versus placebo in obese pregnant women

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 In this study, the effects of metformin on neonatal birth weight and other pregnancy outcomes were compared with placebo in obese pregnant women without diabetes.

2 Obese women (BMI >35 kg/m^2) at 12–18 weeks' gestation were randomised to metformin (titrated up to a maximum dose of 3000 mg; *n*=202) or placebo (*n*=198) until delivery.

3 There was no significant difference in neonatal birth weight z-score, incidence of large-for-gestational-age newborns or incidence of adverse fetal or neonatal outcomes between metformin and placebo.

4 In the mothers, median gestational weight gain was significantly lower in the metformin group (4.6 kg vs 6.3 kg; *P*<0.001); however, there was no difference in other maternal outcomes, including the incidence of gestational diabetes, hypertension, pre-eclampsia and caesarean delivery.

5 Other neonatal outcomes, including death and preterm birth, were similar between the groups.

6 In the overall cohort, there was a significant association between maternal gestational weight gain and pre-eclampsia (*r*=0.17; *P*=0.001).

7 Side effects, including nausea, diarrhoea and headache, were more common in the metformin group; however, there was no significant between-group difference in the incidence of serious adverse events.

8 The authors conclude that prophylactic metformin therapy in obese pregnant women reduces gestational weight gain but does not improve other outcomes.

Syngelaki A, Nicolaides KH, Balani J et al (2016) Metformin versus placebo in obese pregnant women without diabetes mellitus. *N Engl J Med* **374**: 434–43

Diabetologia

HIIT improves cardiac structure and function in T2D

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 In this randomised controlled trial, the authors sought to define the effects of high-intensity interval training (HIIT) on cardiac function and structure, visceral fat levels and glycaemic control in people with T2D.

2 Participants were randomised to either HIIT (n=12) or standard care (n=11) for 12 weeks. HIIT comprised five high-intensity pedalling intervals interspersed with 3-minute recovery periods comprising 90 seconds of rest, 60 seconds of band-resisted upper body exercise and 30 seconds of preparation for the next interval.

3 HIIT was found to increase left ventricular wall mass by 12% compared with baseline (P<0.05), while standard care resulted in a non-significant reduction. The HIIT group also had improvements in systolic function (stroke volume increased by 11 mL vs a reduction of 4 mL).

4 Within-group changes in body weight over the study were not significant; however, between-group comparisons showed a significant difference (a 1-kg reduction with HIIT vs a 1-kg increase in controls).

5 HIIT also resulted in a 39% reduction in liver fat, compared with an 8.5% increase in controls (P=0.01 for comparison), and a reduction in HbA_{1c} of 3 mmol/mol (0.3%) compared with an increase of 2 mmol/mol (0.2%; P=0.02).

6 The authors conclude that, while its effects on glycaemic control remain uncertain, HIIT is an effective therapy to improve cardiovascular risk and reduce levels of the visceral fat that is partly responsible for T2D.

Cassidy S, Thoma C, Hallsworth K et al (2016) High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* **59**: 56–66

ADA 2016

Dapagliflozin plus exenatide in obese adults

1 These authors sought to assess the effects of combined treatment with the sodium–glucose cotransporter 2 inhibitor dapagliflozin and the glucagon-like peptide-1 receptor agonist exenatide in obese adults without diabetes.

2 A total of 50 people with a BMI ranging from 30 to 45 kg/m^2 were randomised to treatment or placebo for 24 weeks. All were given general advice on diet and exercise.

3 Compared with placebo, the treatment group had a relative weight loss of 4.1 kg (4.2%). Overall, 41% of the treatment group lost ≥5% of body weight, compared with 5% of placebo recipients.

4 Assessment of adipose tissue volume using MRI suggested that most of the weight loss was attributable to reductions in fat.

5 HbA_{1c} reduced significantly in both groups, but to a greater extent in the treatment group (3.9 mmol/mol vs 1.6 mmol/mol [0.36% vs 0.15%]; P<0.05 for comparison). Fasting and postprandial glucose levels also fell significantly in the treatment group.

6 Mean systolic blood pressure fell by 9.6 mmHg (P<0.05) in the treatment group but not in the placebo group.

7 Nausea was more common in the treatment group (28% vs 12% of participants). Rates of other adverse events were similar between the groups, and two people discontinued in the treatment arm, compared with three in the placebo arm.

Lundkvist P, Amini SE, Pereira MJ et al (2016) Dapagliflozin + exenatide QW reduced body weight and improved glucose tolerance in nondiabetic obese adults: a randomized, placebo-controlled, phase 2 study. *American Diabetes Association 76th Scientific Sessions*: abstract 21-OR

ADA 2016

Effects of semaglutide in obese people without diabetes

1 In this double-blind, crossover trial, 30 obese people without diabetes were assigned to the once-weekly glucagon-like peptide-1 receptor agonist semaglutide and placebo, each for 12 weeks, in a randomised order.

2 The primary endpoint, *ad libitum* energy intake at lunch (after a standardised breakfast), was significantly lower after 12 weeks of semaglutide treatment compared with placebo (estimated treatment difference [ETD], –300 kcal; a relative difference of 35%).

3 *Ad libitum* energy intake was also significantly lower in the semaglutide group at dinner (ETD, –180 kcal) and with snacks (ETD, –246 kcal). Therefore, the total reduction in energy intake during *ad libitum* meals was 726 kcal (95% confidence interval, 446–1006 kcal), a relative difference of 24%, in the semaglutide group.

4 Mean body weight was reduced by 5.0 kg in the semaglutide group, compared to an increase of 1.0 kg in the placebo group, and proportionally more fat than lean body mass was lost.

5 Visual analogue scale scores of fasting overall appetite indicated reduced appetite with semaglutide (P=0.002), while scores for nausea were similar between the groups.

6 Scores on the Control of Eating Questionnaire indicated less hunger and fewer food cravings, and the Leeds Food Preference Task indicated a relatively lower preference for high-fat versus low-fat foods in the semaglutide arm.

Blundell J, Finlayson G, Axelsen MB et al (2016) Semaglutide reduces appetite and energy intake, improves control of eating, and provides weight loss in subjects with obesity. *American Diabetes Association 76th Scientific Sessions*: abstract 23-OR

"The authors conclude that, while its effects on glycaemic control remain uncertain, high-intensity interval training is an effective therapy to improve cardiovascular risk and reduce levels of the visceral fat that is partly responsible for type 2 diabetes."

References from commentary

Chiswick C, Reynolds RM, Denison F 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 Endocrinol* **3**: 778–86

Dodd JM, Turnbull D, McPhee AJ et al (2014) Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* **348**: g1285

Flynn AC, Dalrymple K, Barr S et al (2016) Dietary interventions in overweight and obese pregnant women: a systematic review of the content, delivery, and outcomes of randomized controlled trials. *Nutr Rev* **74**: 312–28

Poston L, Bell R, Croker H et al (2015) Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* **3**: 767–77