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Effect of metformin in addition to dietary and lifestyle advice for pregnant women who are overweight or obese: the GRoW randomised, double-blind, placebo-controlled trialGlobal

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Methods: Pregnant women at 10+0 to 20+0 weeks gestation with body mass index (BMI) ≥25kg/m2 were recruited from three public maternity units in South Australia. Women were randomised using a computer-generated schedule and received either metformin to a maximum dose of 2000mg per day, or an identical appearing placebo. All women received an antenatal dietary and lifestyle intervention. The primary outcome was the proportion of infants with birth weight >4000 grams. Statistical analyses adopted intention to treat principles. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001277831). A post-hoc analysis was performed to incorporate the trial findings in the current Cochrane Systematic Review and meta-analysis.
Findings: 524 women were randomised (261 Metformin; 263 Placebo). There was no significant difference in the proportion of infants with birth weight >4000 grams (15·63% Metformin versus 14·34% Placebo; adjusted Risk Ratio (aRR) 0·97; 95% Confidence Intervals (CI) 0·65-1·47; p=0·899). Women receiving metformin had lower average weekly gestational weight gain (GWG) (p=0·007), and were more likely to gain below recommendations (p=0·008). Total GWG, pregnancy and birth outcomes were not statistically significantly different.
Update of the available Cochrane Systematic Review identified a modest impact on GWG, with no evidence of an impact on clinical pregnancy and birth outcomes.
Interpretation: For pregnant women who are overweight or obese, metformin as an adjuvant to dietary advice does not improve pregnancy and birth outcomes.

TITLE:

Metformin as an adjuvant therapy to dietary advice for pregnant women who are overweight or obese: the GROW randomised, placebo controlled trial.

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ABSTRACT:

Background: Maternal overweight and obesity is associated with well-recognised pregnancy complications. While antenatal dietary and lifestyle interventions modestly impact gestational weight gain with no effect on pregnancy outcomes, the role of metformin as an adjuvant therapy is unclear.

Methods: Pregnant women at 10^{+0} to 20^{+0} weeks gestation with body mass index (BMI) $\geq 25 kg/m^2$ were recruited from three public maternity units in South Australia. Women were randomised using a computer-generated schedule and received either metformin to a maximum dose of 2000mg per day, or an identical appearing placebo. All women received an antenatal dietary and lifestyle intervention. The primary outcome was the proportion of infants with birth weight >4000 grams. Statistical analyses adopted intention to treat principles. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001277831). A post-hoc analysis was performed to incorporate the trial findings in the current Cochrane Systematic Review and meta-analysis.

Findings: 524 women were randomised (261 Metformin; 263 Placebo). There was no significant difference in the proportion of infants with birth weight >4000 grams (15·63% Metformin versus 14·34% Placebo; adjusted Risk Ratio (aRR) 0·97; 95% Confidence Intervals (CI) 0·65-1·47; p=0·899). Women receiving metformin had lower average weekly gestational weight gain (GWG) (p=0·007), and were more likely to gain below recommendations (p=0·008). Total GWG, pregnancy and birth outcomes were not statistically significantly different.

Update of the available Cochrane Systematic Review identified a modest impact on GWG, with no evidence of an impact on clinical pregnancy and birth outcomes.

Interpretation: For pregnant women who are overweight or obese, metformin as an adjuvant to dietary advice does not improve pregnancy and birth outcomes.

Funding: Australian National Health and Medical Research Council

Introduction:

The world-wide prevalence of overweight and obesity continues to climb.[1] Across developed nations, approximately 50% of women enter pregnancy with a body mass index (BMI) in excess of 25kg/m^2,[2] placing both the woman and her infant at risk of a range of well-documented adverse pregnancy and birth outcomes.[3] Furthermore, high maternal BMI significantly predicts infant birth weight above 4000 grams, which in turn is recognised as an independent predictor of childhood obesity, increasing the risk by more than 2-fold.[4]

There has been considerable research and clinical interest in the provision of antenatal dietary and lifestyle interventions for pregnant women, particularly women who are overweight or obese, as a strategy to limit gestational weight gain (GWG), and thereby improve maternal pregnancy and birth, and infant outcomes. An individual participant data meta-analysis incorporating data from 36 randomised trials, and more than 12,500 pregnant women globally who received an antenatal dietary and/or lifestyle intervention[5] indicates a modest effect on GWG (mean difference -0.7kg), but very little effect on clinical pregnancy outcomes,[5] findings consistent with other recent reports.[6] Together these findings highlight the need for the evaluation of additional strategies.

Metformin has been considered for use in pregnant women who are overweight or obese, recognising the associations between high maternal BMI and gestational diabetes, and a similar intrauterine milieu of insulin resistance, hyperglycaemia, hyperlipidaemia, and chronic inflammation.[7] Metformin has insulin sensitising properties, reducing hepatic glucose production and increasing peripheral glucose utilisation,[8] and is used increasingly in the treatment of women with gestational diabetes.[9]

Recent studies[10,11] evaluating the use of metformin among obese pregnant women, have reported conflicting findings with regards to the effect on GWG and some pregnancy outcomes. Importantly, women participating in these randomised trials[10,11] were not provided with a dietary and lifestyle intervention. Furthermore, as the risk of adverse pregnancy outcomes increases with increasing maternal BMI,[3] there may be clinical benefit in providing treatment for women who are overweight, as well as for those who are obese.

The aim of this randomised trial was to evaluate the effects of antenatal metformin as an adjuvant therapy to dietary and lifestyle advice among overweight and obese pregnant women on maternal and infant outcomes.

Methods:

Study Design and Participants

Between June 2013 and April 2016, women were recruited from the three major public maternity hospitals in metropolitan Adelaide, South Australia. Eligible women had a live singleton pregnancy between 10^{+0} and 20^{+0} weeks gestation, and were overweight (BMI 25·0-29·9kg/m^2) or obese (BMI $\geq$30·0kg/m^2) at their first antenatal visit. Women with a multiple pregnancy, type 1 or 2 diabetes diagnosed prior to pregnancy, or with significant renal or hepatic impairment such that metformin therapy was contraindicated, were excluded.

The study protocol[12] (Supplementary File 1) was approved by the Women's and Children's Health Network Human Research Ethics Committee with local institutional approval at each site, and registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001277831). Participating women provided written informed consent.

Randomisation and Masking

All women presenting for antenatal care at the participating centres had their height and weight measured, and BMI calculated at their first antenatal appointment. Eligible women were then counselled by a research assistant. Those women who consented to participate were randomised to the Metformin Group or Placebo Group, by using the central online randomisation service. The computer generated randomisation schedule utilised blocks of four, in the ratio 1:1, and was prepared by an investigator not involved with recruitment or clinical care. Stratification occurred for parity (0 versus 1 or more), BMI at antenatal booking visit (25·0-29·9kg/m^2 versus $\geq$30·0kg/m^2), and collaborating centre.

Metformin tablets 500 mg and identically appearing placebo tablets were packaged by an independent pharmaceutical packaging company (Pharmaceutical Packaging Professionals, Victoria) and coded according to the randomisation schedule. Women, their caregivers and research staff, including outcome assessors, were blinded to the allocated treatment (Metformin or Placebo).

Procedures

All women received a 16-week supply of tablets (metformin 500 mg or an identical appearing placebo), and a further 12-week supply at 28 weeks gestation. Women commenced tablets from randomisation, starting with one tablet daily for one week, and increasing to a maximum of two tablets twice daily (maximum dose metformin 2000 mg daily) over four weeks as tolerated, and then continuing until birth.

At 36 weeks gestation, women completed a questionnaire to ascertain compliance with medication and the occurrence of any side effects.

All women received dietary and lifestyle advice delivered over three face-to-face sessions (two with the dietitian, shortly after trial entry and at 28 weeks, and one with a research assistant at 36 weeks) and three telephone calls from the research assistant at 20, 24, and 32 weeks. Dietary advice was consistent with Australian standards. Women were advised to maintain a balance of carbohydrates, fat and protein, while specifically encouraging a reduction in the intake of energy dense and non-core foods high in refined carbohydrates and saturated fats, increased intake of fibre, and consumption of two servings of fruit, five servings of vegetables, and three servings of dairy each day.[13,14]

Tailoring of the intervention was informed by stage theories of health decision making.[15] Initially, there was a planning session with a research dietitian, in which women were provided with written information, an individual diet and physical activity plan, recipe book and example menu plans. Women were encouraged to set achievable goals for dietary and exercise change, supported to make these lifestyle changes and to self-monitor their progress, using a SMART (Specific, Measurable, Achievable, Relevant, and Timely)-goals approach. These principles were reinforced at subsequent face-to-face visits with the dietitian and research assistant, and during the telephone contacts.

All women completed a food frequency questionnaire, exercise diary, and quality of life assessments at trial entry, 28 and 36 weeks gestation. Consistent with state-wide clinical practice guidelines, all women were screened for gestational diabetes at approximately 28 weeks gestation.[16] During the course of the trial, diagnostic criteria for gestational diabetes changed across the state from a positive 75g oral glucose tolerance test with fasting blood glucose ≥5·5mmol/L, or 2-hour ≥7·8mmol/L, to fasting blood glucose ≥5·1mmol/L, 1-hour ≥10·0mmol/L, or 2-hour ≥8·5mmol/L.[16] Women diagnosed with gestational diabetes

remained in the study and were offered treatment with further dietary modification and metformin or insulin added as required to maintain appropriate glycaemic control.[16] All other care during pregnancy and birth was according to local hospital practices.[16]

Outcomes

The primary outcome was the proportion of infants with birth weight above 4000 grams.

A range of secondary outcomes were assessed, and included the following:

1) *Maternal weight gain outcomes* including total GWG (defined as the difference between pregnancy weight obtained at 36 weeks gestation or nearest to birth and early pregnancy weight); average weekly GWG; and GWG below, within, or above the Institute of Medicine (IOM) recommendations according to early pregnancy BMI (defined as 7·0 to 11·5kg for women who were overweight and 5·0 to 9·0kg for women who were obese).[17]

2) *Maternal diet and physical activity* as measured by questionnaires completed at trial entry, 28 and 36 weeks gestation (using the Harvard Semi-quantitative Food Frequency Questionnaire,[18] and the Short Questionnaire to Assess Health-enhancing physical activity)[19].

3) *Maternal pregnancy and birth outcomes* including hypertension (defined as a systolic blood pressure $\geq$140mmHg and / or diastolic $\geq$90mmHg on two occasions four or more hours apart) and pre-eclampsia (using the Australasian Society for the Study of Hypertension in Pregnancy criteria);[20] clinical diagnosis of gestational diabetes;[16] antepartum haemorrhage; preterm prelabour ruptured membranes; chorioamnionitis; induction of labour; caesarean section; postpartum haemorrhage (defined as blood loss >600 mL); perineal trauma; wound infection; endometritis; thromboembolic disease; and maternal death.

4) *Maternal quality of life and emotional wellbeing* as measured by questionnaires completed by the woman at trial entry, 28 and 36 weeks gestation relating to quality of life (SF12 Health

Survey Questionnaire);[21] anxiety (Short Form Spielberger State Trait Inventory[22]) and depression (Edinburgh Postnatal Depression Scale[23]).

5) *Infant birth outcomes* including preterm birth before 37 weeks; perinatal mortality (defined as either an intrauterine fetal death after trial entry, and after 20 weeks gestation but prior to birth, or the death of a live born infant prior to hospital discharge, and excluding lethal congenital anomalies); infant birth weight (including weight below 2500 grams, and weight above 4500 grams); large for gestational age (defined as weight above the 90th centile for gestational age and infant sex); small for gestational age (defined as weight below the 10th centile for gestational age and infant sex); hypoglycaemia requiring treatment; infant admission to the neonatal intensive care unit, or special care baby unit; hyperbilirubinaemia requiring phototherapy; nerve palsy; fracture; birth trauma; shoulder dystocia; and newborn anthropometric measures (including biceps, triceps, abdominal, suprailiac, subscapular and thigh skinfold thicknesses, and head, chest, abdominal and right upper arm circumferences taken within the first days after birth according to a specifically developed protocol).[24]

6) *Fetal growth and adiposity measures determined by ultrasound* at 28 and 36 weeks gestation.

7) *Costs of health care* to determine the cost of the intervention per live birth.

Sample size

The primary clinical outcome was the proportion of infants born with birth weight above 4000 grams, which was estimated to occur in 15.5% of women eligible for this trial.[13] To detect a 47% difference from 15.5% to 7.35% (alpha 0.05; power 80%),[13] and accounting for a 5% rate of attrition (based on our experience with the LIMIT Study), we estimated a sample size of 524 women was required.

Statistical Analysis

All analyses followed a pre-specified statistical analysis plan (Supplementary File 2). Baseline characteristics of all randomised women were examined descriptively as an indication of comparable treatment groups, and included maternal age, parity, race, height, weight, smoking status, past obstetric history, and a diagnosis of previous gestational diabetes. Primary and secondary outcomes were analysed on an "intention to treat" basis, according to the treatment allocated (Metformin or Placebo) at the time of randomisation. Continuous outcomes were analysed using linear regression, and binary outcomes were analysed using log binomial regression. Outcomes measured at multiple time points included a time-by-treatment interaction term, with Generalised Estimating Equations used to account for correlation between repeated measures.

As specified in the Statistical Analysis Plan (Supplementary File 2), the primary analyses were adjusted analyses based on imputed data. Unadjusted analyses, and analyses on unimputed data (not presented), were also performed as secondary sensitivity analyses. Adjusted models included the stratification variables (centre, maternal BMI, and parity) as well as smoking, socio-economic status (as indicated by the Australian Bureau of Statistics' 2011 Socio-economic Index for Areas – Index of Relative Socio-economic Disadvantage (SEIFA IRSD) quintile), and maternal age at trial entry as covariates.

There were no missing values for the primary outcome or for other infant birth weight outcomes; many other outcomes (including infant anthropometry, infant and maternal delivery data) had less than 1% missing data, while infant SFTM and other maternal antenatal measures had between 20%-40% missing data. Multiple imputation by the fully conditional specification (chained equations) method was used to create 100 complete datasets for

analysis.[25] The imputation model included all outcomes, all stratification variables, maternal baseline height, weight and gestational age, and maternal weight at 36 weeks gestation. Estimates were derived in the standard manner by combining the estimates from each imputation using Rubin's Rules.[25] As there were no missing values for the primary outcome, no missing not at random (MNAR) sensitivity analyses were performed. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14 (StataCorp, Texas, USA).

Meta-analysis

Our published Cochrane Systematic Review adhered to standard Cochrane methodology.[26] In brief, randomised and quasi-randomised trials evaluating metformin use (compared with placebo or no metformin) in pregnant women who were overweight or obese, defined as an early or pre-pregnancy BMI $\geq$25.0kg/m^2 were identified and considered after searching the Cochrane Pregnancy and Childbirth's Trials Register. Two review authors independently assessed risk of bias for each study, with statistical analyses conducted using the Review Manager 5 software. A fixed-effect meta-analysis was used to combine data where trials were judged to be sufficiently similar, and a random-effects meta-analysis to produce an overall summary if substantial statistical heterogeneity was detected. For dichotomous data, results are presented as summary risk ratio (RR) with 95% CIs, while for continuous data, the mean difference (MD) was calculated. Available data from the GROW randomised trial were incorporated into the available published systematic review and meta-analysis.

Role of the funding source

The funder had no role in the study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to the data and final responsibility for

the decision to submit for publication.

Results:

Between June 2013 and April 2016, 3,546 eligible women were approached to participate, with 524 randomised, 261 (49·8%) to Metformin and 263 (50·2%) to Placebo (Figure 1). A total of 514 women and infants were included in the analyses. There were no maternal deaths. There were two stillborn infants, both in the placebo group, one secondary to acute chorioamnionitis, and the other due to early onset fetal growth restriction and pre-eclampsia. There was one neonatal death in the metformin group following extremely preterm birth.

The baseline characteristics of women in the two treatment groups were similar at trial entry (Table 1). The median BMI of the cohort was 32·32kg/m^2 (Inter-Quartile Range (IQR) 28·90 to 37·10kg/m^2), with 32·49% of women overweight, and 67·51% obese. Adequate data were available for 514 (100%) infants for the primary outcome of birth weight above 4000 grams.

Over 77% of participants completed the questionnaire assessing compliance with medication (Table S1) and experience of side effects (Table 2), with no differences between the two treatment groups. Of women who responded, almost 84% took the maximum of 4 tablets daily, with approximately 75% of women in both treatment groups reporting the occurrence of one or more side effects, most commonly fatigue, nausea or diarrhoea.

There was no statistically significant difference in the proportion of infants with birth weight above 4000 grams between the Metformin and Placebo groups (40/256 (15·63%) Metformin versus 37/258 (14·34%) Placebo; adjusted risk ratio (aRR) 0·97; 95% confidence interval (CI) 0·65 to 1·47; p=0·899) (Table 3).

Women who received metformin when compared with women who received placebo, had lower average weekly GWG (0·38 ± 0·34 kg Metformin vs 0·47 ± 0·35 kg Placebo; aMD -0·08; 95% CI -0·14 to -0·02; p=0·007), and were more likely to have weight gain below the IOM recommendations (100 (39·20)% Metformin versus 70 (27·00%) Placebo; aRR 1·46; 95% CI 1·10 to 1·94; p=0·008) (Table 4). Total GWG was not statistically significantly different between the treatment groups (7·48 ± 6·95 kg Metformin versus 8·72 ± 6·91 kg Placebo; aMD -1·18; 95% CI -2·37 to 0·01; p=0·053). Dietary patterns and physical activity (Table S2) also did not differ between the two treatment groups at trial entry or over the course of pregnancy.

There were no statistically significant differences between the two treatment groups with regards to maternal risk of pregnancy (Table 4) complications, particularly a diagnosis of gestational diabetes, regardless of the diagnostic criteria used (Table S3). Furthermore, following diagnosis, there were no statistically significant differences between the treatment groups with regards use of either metformin or insulin therapy (Table S3).

The risks of maternal labour complications (Table 5) were not significantly different between the two treatment groups. While there was a reduction in risk of caesarean birth among women administered metformin as compared with placebo (87 (33·98%) Metformin versus 111 (43·02%) Placebo; aRR 0·78; 95% CI 0·62 to 0·97; p=0·025), this likely reflected differences in the number of women undergoing an elective repeat caesarean birth (44 (17·19%) Metformin versus 54 (20·93%) Placebo; aRR 0·72; 95% CI 0·52 to 1·00; p=0·053) (Table 5). Self-reported maternal quality of life did not differ between groups (Table S4).

The mean gestational age at birth was similar between the two groups (39·12 ± 1·64 weeks Metformin versus 38·93 ± 1·85 weeks Placebo; aMD 0·10; 95% CI -0·20 to 0·40; p=0·532), as was mean infant birth weight (3487·80 ± 531·37 grams Metformin versus 3471·80 ± 556·67 grams Placebo; aMD -13·01; 95% CI -106·45 to 80·44; p=0·785) (Table 3). There were no statistically significant differences between the two groups with regards to other infant outcomes (Table 3) or newborn anthropometric measures (Table S5). Although infant abdominal circumference at birth was 0·5cm smaller in the Metformin group (33·35 ± 2·72 cm Metformin versus 33·74 ± 2·87 cm Placebo; adjusted mean difference -0·48; 95% CI -0·97 to -0·00; p=0·049) this is likely a chance finding and the small difference of questionable clinical significance (Table S5).

A pre-specified secondary analysis identified some evidence of effect modification by maternal BMI category, the use of metformin being associated with a greater reduction in the proportion of infants with birth weight above 4000 grams, and a reduction in total GWG, among overweight, when compared with obese women (Table S6).

Fetal growth and adiposity measures determined by ultrasound will be reported in a subsequent manuscript. A detailed health economics cost analysis was not performed given that the intervention demonstrated no significant impact on clinical outcomes.

Meta-analysis

In a post-hoc analysis incorporating the findings of the GROW trial in the published Cochrane Systematic Review,[26] metformin was identified to have only a modest impact on GWG (Mean Difference -2·27 kg; 95% CI -4·45 to -0·08; 4 studies; 1,278 women). There

was no evidence of an impact on clinical pregnancy and birth outcomes, and particularly the risk of pre-eclampsia (RR 0·82; 95% CI 0·25 to 2·68; 3 studies; 1,355 women).

Discussion:

In our randomised trial, overweight or obese pregnant women who received metformin as an adjuvant therapy to dietary and lifestyle advice did not significantly differ in the chance of their infant having birth weight above 4000 grams, when compared with women who received placebo and dietary and lifestyle advice. Although there were no statistically significant differences in total GWG, women who received metformin were more likely to have weight gain below the IOM recommendations, and have lower average weekly GWG. However, these differences in GWG were not accompanied by a significant effect on maternal and infant pregnancy or birth outcomes.

Our randomised trial has a number of strengths, being the first to include both overweight and obese women, as the risk of adverse pregnancy outcomes increases with increasing maternal BMI. We utilised robust methods, including prospectively measured height, weight, and BMI in all participants, central randomisation, and appropriate blinding of participants, clinicians and outcome assessors. Furthermore, we had pre-specified outcomes of clinical relevance, followed a pre-specified analysis plan, and achieved a high rate of follow-up of participants.

Our trial is also the first to evaluate the effect of metformin as an adjuvant therapy to an antenatal dietary and lifestyle intervention. Following dietary intervention over the course of pregnancy, women across both treatment groups were successful in modifying their dietary intake, specifically reducing their overall energy intake and improving their healthy eating index score as an indicator of diet quality. These findings are consistent with those reported

previously from the LIMIT randomised trial,[13,27] highlighting the reproducibility of the intervention among overweight and obese pregnant women in producing dietary change. Together, these findings also suggest that many of the complex determinants of GWG may not be readily modifiable by changes to dietary intake and physical activity.

Our trial population was predominantly white Caucasian and from the highest areas of social disadvantage, with approximately 85% of eligible women declining to participate due to time constraints and lack of willingness to take medication during pregnancy. Together, these findings limit somewhat our generalisability and external validity. However, such rates of uptake of trial participation (15%) are within the range described by similar trials in the literature, which have varied from 13-47%.[10,11]

Our estimates of compliance indicate 84% of respondents took the maximum of 4 tablets daily, with no differences identified between the treatment groups. These figures are difficult to directly compare with other studies, which have used varying measures to assess treatment compliance,[10,11] although our assessment of adherence is comparable to the overall 80% reported by Syngelaki and colleagues,[11] and the 66% reported by Chiswick and colleagues.[10]

While metformin is increasingly used in pregnancy for the treatment of gestational diabetes,[9] and there is evidence to support its safety, longer-term childhood follow-up of the offspring of women who participated in this trial will be important. The primary findings from the MIG trial did not identify any differences in infant birth weight for women with GDM who were treated with insulin, as compared with metformin.[9] However, follow-up of child participants at 9 years of age indicates children exposed to metformin, as compared with insulin, were of

higher weight and BMI, with some suggestion of increased adipose tissue deposition evaluated by dual energy x-ray absorptiometry (DXA).[28]

As highlighted in our methods, during the course of the trial there was a change in the diagnostic criteria for GDM across the State.[16] However, the criteria were applied equally across the two treatment groups, and we demonstrated no significant differences in diagnosis or requirements for metformin or insulin between the two treatment groups. While the change in criteria may have resulted in an increase in the number of women being diagnosed with GDM, discussion of the relative merits and evidence base to support a range of different testing approaches and criteria is well beyond the focus and scope of this manuscript.

Our findings do not suggest that metformin impacts clinical pregnancy and birth outcomes, which is broadly consistent with the available literature.[10,11,29] Syngelaki and colleagues reported a significant reduction in the risk of pre-eclampsia following metformin administration. This was not evident when the current trial data are incorporated in the available published meta-analysis (RR 0·82; 95% CI 0·25 to 2·68; 3 studies; 1,355 women),[26] raising the possibility of a spurious finding of a secondary outcome.

We did not identify a statistically significant reduction in total GWG, although there was some evidence of effect modification, with a possible greater benefit from metformin in reducing the risk of infant birth weight above 4000 grams, and total GWG among overweight, as compared with obese women. While this secondary analysis was pre-specified, our findings should be interpreted cautiously, and warrants confirmation by others.

Our findings in relation to GWG are consistent with those of Chiswick,[10] but in contrast to those of Syngelaki[11] and Abd El Fattah.[29] Incorporation of our data into the Cochrane Systematic Review[26] indicates overall, metformin has a very modest impact on GWG (Mean Difference -2·27 kg; 95% CI -4·45 to -0·08; 4 studies; 1,278 women). While there are inherent variations in the study design of the randomised trials evaluating metformin conducted to date,[10,11,29] including the BMI of women recruited (overweight and obese in the current trial versus obese only[10,11,29]), the dose of metformin administered (1000mg[29] up to 3000mg[11] daily), and the inclusion of a dietary and lifestyle intervention for all women in the current trial, these differences appear insufficient to explain the overall observations of a limited reduction in GWG and lack of effect on clinical outcomes.

Such a limited effect of metformin is, however, consistent more broadly with the evidence relating to prenatal dietary and lifestyle interventions[5] for women who are overweight or obese, and raises important questions as to their modest at best reduction in GWG, and little evidence of effect on clinical outcomes. It is important to recognise that the IOM recommendations[17] are based on extensive observational literature identifying associations between GWG and pregnancy outcomes, with an underlying assumption that the observed associations are causal in nature. Furthermore, it has been assumed that GWG can be modified either through use of metformin, or via changes to diet and lifestyle during pregnancy, and that weight gain within the recommended range leads to optimal maternal and infant outcomes.

These prevailing assumptions need to be questioned in light of the mounting available clinical evidence from randomised trials. For pregnant women who are overweight or obese, intervention during pregnancy (whether through metformin, dietary or lifestyle modification,

or a combination of the two) may be "too little, too late", highlighting the need to target women, particularly those who are overweight or obese, prior to conception to improve their diet and lifestyle, and to encourage weight loss.[30] Not withstanding the logistical implications of intervention prior to conception, there is currently little evidence to support improved pregnancy outcomes following pre-conception weight loss, and robust evaluation of such an approach is urgently required.

Our findings indicate that the use of metformin as an adjuvant to a dietary and lifestyle intervention among pregnant women who are overweight or obese was associated with some evidence of reduced GWG measures, but did not impact clinical pregnancy and birth outcomes. Use of metformin in this clinical setting is not advocated.

Panel: Research in context

Evidence before this study

Antenatal dietary and lifestyle interventions for pregnant women, particularly those who are overweight or obese, have been evaluated as a strategy to limit gestational weight gain but demonstrate only a modest effect on weight gain in pregnancy and very little effect on clinical outcomes.

Metformin has been proposed as a possible agent for use among obese pregnant women, although recent studies have reported conflicting findings with regards to the effect on GWG and some pregnancy outcomes. Importantly, women participating in these randomised trials were not provided with a dietary and lifestyle intervention. Furthermore, as the risk of adverse pregnancy outcomes increases with increasing maternal BMI, there may be clinical benefit in providing treatment for women who are overweight, as well as for those who are obese.

Added value of this study

To our knowledge, this is the first trial to evaluate the effect of metformin as an adjuvant therapy to an antenatal dietary and lifestyle intervention, and to include women both who are overweight or obese.

Implications of all of the available evidence

The use of metformin as an adjuvant therapy to an antenatal dietary and lifestyle intervention in women who are overweight or obese did not impact the chance of infant birth weight above 4000 grams. There was no effect of metformin on total gestational weight gain or other clinical pregnancy and birth outcomes. The use of metformin in this clinical setting is not

advocated, and future strategies should focus on improving women's health and diet to encourage weight loss prior to conception.

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The authors declare they have no conflicts of interest to report.

Each author fulfils the requirements for authorship and in particular all have been involved equally in the development and design of the trial, the conduct of the trial, drafting of the manuscript and revision for intellectual content, and gives approval of the final submitted version.

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- Women's and Children's Hospital (229 women)

  Staff of the division of Women and Babies including: W Hague, A McPhee, H Purcell
- The Lyell McEwin Hospital (238 women)

  Staff of the Women and Children's Division including G Dekker
- Flinders Medical Centre (57 women)

  Staff of the Flinders Women and Children's Division including J McGavigan
- Staff of the University of Adelaide including:

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Data Sharing Statement:

Additional trial-related documents and requests for de-identified data (aggregate or individual participant level) may be requested by written application to the corresponding author, and will be considered on an individual basis by the trial steering committee.

FIGURE 1: Flow of trial participants

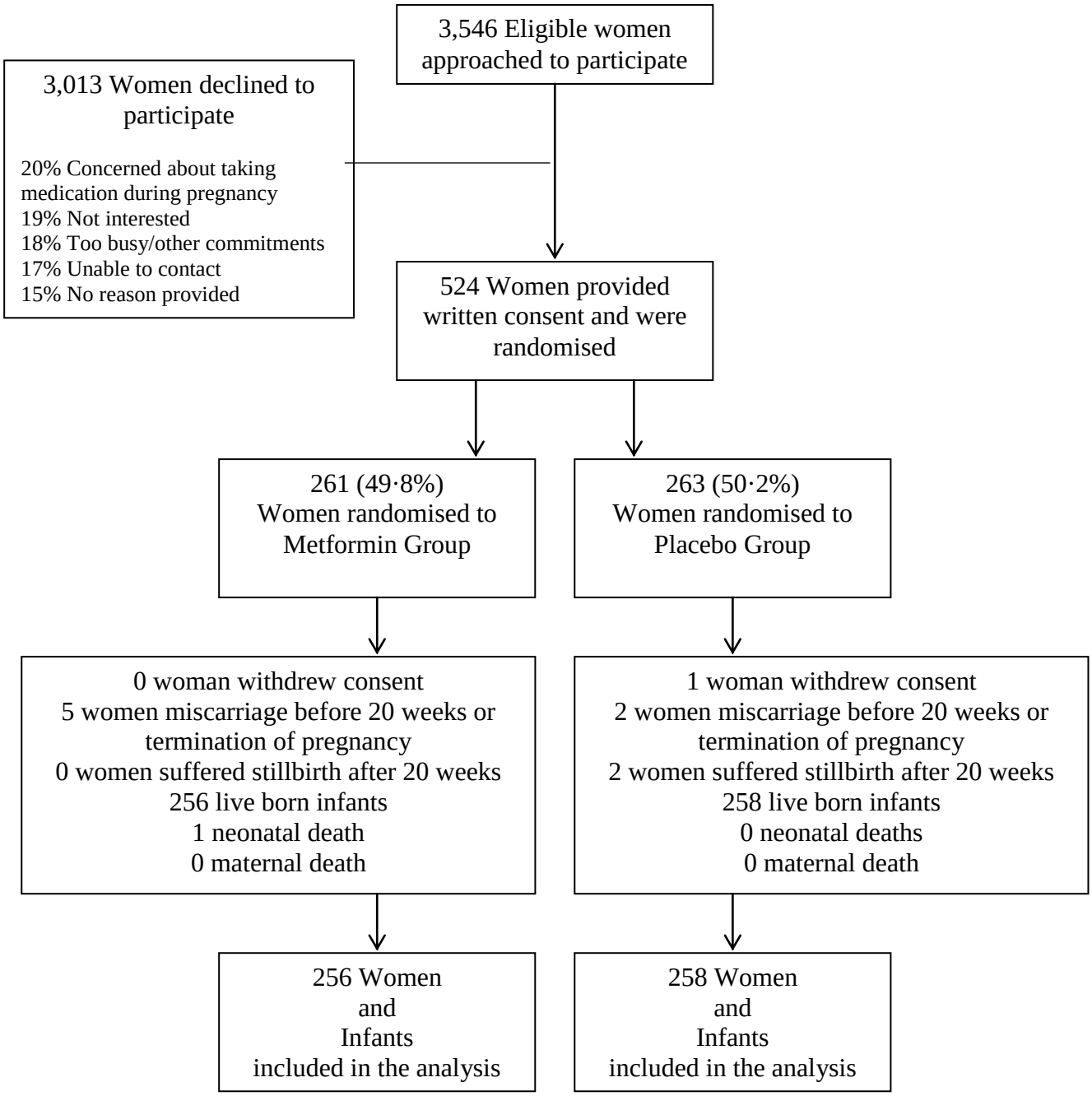

TABLE 1: Baseline characteristics of participants at trial entry

Characteristic	***Metformin (N=256**)***	***Placebo (N=258**)***
Maternal Age (Years)[*]	29·87 (5·54)	30·17 (5·37)
Study Centre[#]		
. Womens and Childrens Hospital	110 (42.97)	112 (43.41)
. Lyell McEwin Hospital	117 (45.70)	118 (45.74)
. Flinders Medical Centre	29 (11.33)	28 (10.85)
Gestational Age at Entry (Weeks)[+]	16·29 (14·43, 18·00)	16·29 (14·57, 18·14)
Body Mass Index (kg/m^2)[+]	32·50 (28·71, 37·54)	32·05 (29·10, 36·80)
Body Mass Index Category[#]		
. BMI 25.0-29.9 kg/m^2	83 (32·42)	84 (32·56)
. BMI $\geq$30.0 kg/m^2	173 (67·58)	174 (67·44)
Public Patient[#]	252 (98·44)	254 (98·45)
Weight (kg)[*]	92·89 (19·76)	91.80 (19·79)
Height (cm)[*]	165·27 (6·76)	164·87 (6·79)
Race[#]		
. Caucasian	210 (82·03)	221 (85·66)
. Asian	5 (1·95)	7 (2·71)
. Indian	12 (4·69)	6 (2·33)
. Other	29 (11·33)	17 (9·30)
Smoker[#]	24 (9·38)	43 (16·67)

Characteristic	*Metformin (N=256**)*	*Placebo (N=258**)*
Nulliparous[#]	88 (34·38)	92 (35·66)
Previous Preterm Birth[#]	13 (5·08)	13 (5·04)
Previous Pre-eclampsia[#]	13 (5·08)	10 (3·88)
Previous Stillbirth or Neonatal Death[#]	1 (0·39)	6 (2·33)
Previous Caesarean Section	48 (18·75)	67 (25·97)
Family History of Diabetes[#]	83 (32·42)	78 (30·23)
Family History of Hypertension[#]	105 (41·02)	104 (40·31)
Family History of Heart Disease[#]	58 (22·66)	61 (23·64)
Index of Socio-economic Disadvantage[^]		
. Quintile 1 (Most Disadvantaged)	76 (29·69)	95 (36·82)
. Quintile 2	78 (30·47)	74 (28·68)
. Quintile 3	31 (12·11)	30 (11·63)
. Quintile 4	52 (20·31)	43 (16·67)
. Quintile 5 (Least Disadvantaged)	19 (7·42)	16 (6·20)

*= mean and standard deviation

[+]= median and interquartile range

[#]= number and %

^= Socioeconomic index of relative social disadvantage as measured by SEIFA

**=Includes all women randomised who did not withdraw consent to use their data, and who did not suffer miscarriage or termination of pregnancy prior to 20 weeks gestation, or stillbirth

TABLE 2: Occurrence of side effects by treatment group

Measure	***Metformin N=256***	***Placebo N=258***
Overall Respondents	194	204
Experience of one or more side effects	140 (72·16)	158 (77·45)
- Nausea	65 (33·51)	73 (35·78)
- Vomiting	48 (24·74)	46 (22·55)
- Abdominal Pain	49 (25·26)	47 (23·04)
- Diarrhoea	52 (26·80)	52 (25·49)
- Fatigue	87 (44·85)	101 (49·51)
- Weakness	27 (13·92)	36 (17·65)
- Skin Rash	17 (8·76)	16 (7·84)
- Loss of Appetite	43 (22·16)	43 (21·08)

**Includes all women randomised who did not withdraw consent to use their data, and who did not suffer miscarriage or termination of pregnancy prior to 20 weeks gestation, or stillbirth

All values presented represent number and percent

TABLE 3: Pre-specified infant outcomes by treatment group

Outcome	*Metformin (N=256**)*	*Placebo (N=258**)*	*Unadjusted Treatment Effect (95% CI)*	*Unadjusted P-value*	*Adjusted Treatment Effect (95% CI)*	*Adjusted P-value*
Birth weight above 4000g[#]	40 (15·63)	37 (14·34)	1·09 (0·72, 1·65)	0·684	0·97 (0·65, 1·47)	0·899
Birth weight (grams)[~]	3487·80 (531·37)	3471·80 (556·67)	16·00 (-78·10, 110·09)	0·739	-13·01 (-106·45, 80·44)	0·785
Gestational Age at birth (weeks)[~]	39·12 (1·64)	38·93 (1·85)	0·19 (-0·11, 0·49)	0·222	0·10 (-0·20, 0·40)	0·532
Large for Gestational Age[#]	50 (19·53)	56 (21·71)	0·90 (0·64, 1·26)	0·543	0·87 (0·62, 1·23)	0·428
Small for Gestational Age[#]	10 (3·91)	8 (3·10)	1·26 (0·51, 3·14)	0·620	1·37 (0·55, 3·45)	0·502
Birth weight above 4500g[#]	5 (1·95)	7 (2·71)	0·72 (0·23, 2·24)	0·570	0·64 (0·21, 1·97)	0·433
Birth weight below 2500g[#]	4 (1·56)	11 (4·26)	0·37 (0·12, 1·14)	0·082	0·42 (0·13, 1·31)	0·135
Stillbirth[#^]	0 (0·00)	2 (0·77)	--		--	0·499[^]
Neonatal Death[#^]	1 (0·39)	0 (0·00)	--		--	0·496[^]
Admission to NICU or SCBU[#]	32 (12·55)	43 (16·67)	0·75 (0·49, 1·15)	0·189	0·78 (0·51, 1·20)	0·260
Hypoglycaemia Requiring Treatment[#]	19 (7·45)	24 (9·30)	0·80 (0·45, 1·43)	0·451	0·87 (0·49, 1·55)	0·632
Hyperbilirubinaemia Requiring Phototherapy[#*]	16 (6·27)	20 (7·75)	0·81 (0·43, 1·53)	0·513	0·76 (0·41, 1·40)	0·379
Nerve Palsy[#+]	0 (0·00)	0 (0·00)	--		--	
Fracture[#^]	1 (0·39)	0 (0·00)	--		--	0·497[^]
Birth Trauma[#^]	3 (1·18)	0 (0·00)	--		--	0·122[^]
Shoulder Dystocia[#]	7 (2·73)	7 (2·71)	1·01 (0·36, 2·83)	0·988	0·96 (0·34, 2·66)	0·935

**Includes all women randomised who did not withdraw consent to use their data, and who did not suffer miscarriage or termination of pregnancy prior to 20 weeks gestation, or stillbirth

[#] Number and percentage

[~] Mean and SD

* Poisson model with robust variance estimation used for adjusted analysis as binomial model did not converge

^ Insufficient events for analysis or imputation. p value from Fishers Exact test on un-imputed data.

+ There were no events in either group so no modelling was possible

TABLE 4: Pre-specified maternal antepartum outcomes by treatment group

Outcome	*Metformin (N=256**)*	*Placebo (N=258**)*	*Unadjusted Treatment Effect (95% CI)*	*Unadjusted P-value*	*Adjusted Treatment Effect (95% CI)*	*Adjusted P-value*
Total Gestational Weight Gain (kg)˜*	7·48 (6·95)	8·72 (6·91)	-1·23 (-2·45, -0·01)	0·048	-1·18 (-2·37, 0·01)	0·053
Average Weekly Gestational Weight Gain (kg)˜	0·38 (0·34)	0·47 (0·35)	-0·08 (-0·14, -0·02)	0·006	-0·08 (-0·14, -0·02)	0·007
Gestational Weight Gain Below Recommendations[#]	100 (39·20)	70 (27·00)	1·45 (1·09, 1·93)	0·010	1·46 (1·10, 1·94)	0·008
Gestational Weight Gain Above Recommendations[#]	83 (32·27)	101 (39·10)	0·83 (0·64, 1·07)	0·145	0·84 (0·65, 1·09)	0·185
Preterm birth before 37 weeks gestation[#]*	13 (5·08)	18 (6·98)	0·73 (0·36, 1·45)	0·368	0·79 (0·40, 1·58)	0·504
Hypertension[#]*	19 (7·42)	16 (6·23)	1·19 (0·63, 2·26)	0·592	1·25 (0·66, 2·35)	0·496
Pre-Eclampsia[#]*	13 (5·08)	11 (4·28)	1·19 (0·54, 2·60)	0·667	1·22 (0·56, 2·66)	0·618
Gestational Diabetes[#]	72 (27·93)	62 (23·95)	1·17 (0·85, 1·60)	0·335	1·19 (0·88, 1·62)	0·253
Antenatal Admission[#]	48 (18·75)	62 (24·03)	0·78 (0·56, 1·09)	0·146	0·82 (0·59, 1·15)	0·254
Antepartum Haemorrhage Requiring Admission[#]	1 (0·39)	7 (2·69)	--		--	0·068^
Preterm Prelabour Ruptured Membranes[#]^	5 (1·95)	3 (1·15)	--		--	0·502^

* Poisson model with robust variance estimation used for adjusted analysis as binomial model did not converge

^ Insufficient events for analysis or imputation. p value from Fishers Exact test on un-imputed data.

**Includes all women randomised who did not withdraw consent to use their data, and who did not suffer miscarriage or termination of pregnancy prior to 20 weeks gestation, or stillbirth

[#] Number and percent

˜ Mean and SD

TABLE 5: Pre-specified maternal labour and birth outcomes by treatment group

Outcome	*Metformin (N=256**)*	*Placebo (N=258**)*	*Unadjusted Treatment Effect (95% CI)*	*Unadjusted P-value*	*Adjusted Treatment Effect (95% CI)*	*Adjusted P-value*
Chorioamnionitis	3 (2·22)	5 (3·40)	--		--	0·725^
Induction of Labour	104 (40·63)	87 (33·72)	1·20 (0·96, 1·51)	0·107	1·19 (0·95, 1·49)	0·139
Antibiotics During Labour	135 (52·73)	147 (56·98)	0·93 (0·79, 1·08)	0·334	0·95 (0·81, 1·11)	0·493
Caesarean Section – All	87 (33·98)	111(43·02)	0·79 (0·63, 0·99)	0·037	0·80 (0·64, 1·00)	0·049
Elective Caesarean Section	44 (17·19)	54 (20·93)	0·82 (0·57, 1·18)	0·281	0·72 (0·51, 1·00)	0·053
Emergency Caesarean Section	43 (16·80)	57 (22·09)	0·76 (0·53, 1·09)	0·131	0·79 (0·56, 1·11)	0·168
Postpartum Haemorrhage Above 600mls	66 (25·79)	58 (22·55)	1·14 (0·84, 1·56)	0·393	1·15 (0·85, 1·57)	0·367
3rd/4th Degree Perineal Trauma	6 (2·34)	3 (1·15)	--		--	0·336^
Wound Infection	3 (1·17)	3 (1·16)	--		--	>0·999^
Endometritis	3 (1·17)	3 (1·16)	--		--	>0·999^
Thromboembolic Disease	1 (0·39)	0 (0·00)	--		--	0·497^

**Includes all women randomised who did not withdraw consent to use their data, and who did not suffer miscarriage or termination of pregnancy prior to 20 weeks gestation, or stillbirth

*Poisson model with robust variance estimation used for adjusted analysis as binomial model did not converge

All values presented are number and percent

^ Insufficient events for analysis or imputation. p value from Fishers Exact test on un-imputed data.

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