INTRODUCTION

Metformin is a biguanide which has been used in the treatment of hyperglycaemia for more than 60 years. Over 80 million adults in the United States have been prescribed metformin and it remains first line for many patients with type 2 diabetes. Although the exact mechanism of action for metformin is incompletely understood,
it acts primarily on the mitochondria to reduce hepatic gluconeogenesis and glucagon-mediated hepatic function. In addition, it has a multitude of other actions on protein kinase A signalling, lipid metabolism and the mechanistic target of the rapamycin (mTOR) pathway.\textsuperscript{3,4}

Metformin has been used in pregnancy since the 1970s.\textsuperscript{5} It was initially preferred over insulin due to its lower cost and ease of administration and its use became widespread in lower-income countries. Though metformin is considered acceptable by patients\textsuperscript{6} and has demonstrated benefits including reduced maternal gestational weight gain (GWG) and reduction in numbers of infants born large for gestational age (LGA),\textsuperscript{7} its use remains controversial. Metformin crosses the placenta at levels equal to that of the maternal circulation.\textsuperscript{8} Follow-up studies have demonstrated that small subgroups of children exposed to metformin in utero are heavier in childhood\textsuperscript{9} and many have raised the concern that the potential long-term effects of metformin on offspring are unknown.

On the other hand, neither human insulin nor its analogues cross the placenta\textsuperscript{10} and some would suggest that it is unnecessary to consider metformin in pregnancy when a safe alternative is available. However, insulin has the associated risks of maternal hypoglycaemia and excessive GWG both of which are unacceptable to women and need to be considered.\textsuperscript{6} As the rates of obesity,\textsuperscript{11} GDM and type 2 diabetes in pregnancy are all increasing,\textsuperscript{12} the need for effective, affordable and safe therapies has never been greater.

The aim of this article is to review the benefits and potential pitfalls of metformin use in pregnancy. To conduct this review, the authors performed a search of web-based databases (including PubMed, CENTRAL via the Cochrane Library and EMBASE) using the keywords listed above. We read the full texts of any relevant texts published in English and searched clinicaltrials.gov for relevant unpublished trials. We included randomised controlled trials (RCTs), cluster RCTs, pilot and feasibility studies in our review. We excluded conference abstracts, case reports and case series. Observational data which were deemed to be of high quality were also considered. Additionally, we searched bibliographies for all relevant publications to identify other studies.

\section{IMPACT OF METFORMIN ON THE MOTHER}

\subsection{Pregnancy}

Metformin is used for a variety of reasons during pregnancy. It is used in obese non-diabetic women and in women with polycystic ovarian syndrome (PCOS) in an effort to prevent GDM, and as a glucose-lowering treatment in GDM and in type 2 diabetes (in addition to insulin).

\subsection{Pregnancy complicated by obesity}

The number of pregnancies affected by obesity has increased substantially worldwide.\textsuperscript{13} Obesity during pregnancy is associated with an increase in complications for both mother and infant and studies suggest that maternal obesity may impact offspring cardiovascular health and cognition in the long term.\textsuperscript{14} While this effect of maternal obesity is multifactorial, it may be influenced by the higher glucose levels observed in obese non-diabetic women compared to normal weight women.\textsuperscript{15}

Metformin has been evaluated in a number of trials of overweight and obese pregnant women to see whether the associated pregnancy-related morbidities can be modified.

The GROW RCT\textsuperscript{16} examined the use of metformin compared to placebo alongside dietary interventions in 500 women with a body mass index (BMI) of \(\geq 25\) kg/m\(^2\). Metformin was commenced between 10 and 20 weeks of gestation and continued throughout pregnancy. The GROW investigators found no change in the number of infants born with a birth weight >4 kg, or born LGA or SGA. Women in the metformin group were more likely to gain less weight compared to institute of medicine (IOM) recommendations but overall GWG was similar and rates of GDM were unchanged between the two groups. The significant findings from this trial include fewer deliveries requiring Caesarean section in the metformin group (due to more elective repeat Caesarean sections in the placebo
group) and an unexplained 0.5 cm decrease in the infant abdominal circumference in the metformin group. This finding has since been replicated in other studies and is potentially significant for the long-term health of infants exposed to metformin.

The effect of metformin on maternal and foetal outcomes in obese pregnant women (EMPOWaR) RCT\textsuperscript{17} studied the effect of metformin on over 400 women with a BMI $\geq 30 \text{ kg/m}^2$ who were randomised to take either metformin or placebo from 12 to 16 weeks of gestation until the end of pregnancy. The authors found no change in infant birthweight, z score, rates of LGA births, Caesarean delivery or rates of maternal hypertensive disorders. At 28 weeks of gestation, women in the metformin group had lower levels of insulin resistance (defined by the homeostatic model assessment of insulin resistance [HOMA-IR] scores); however, this did not persist to 36 weeks. In total, 18% of women treated with metformin developed GDM compared to 24% in the placebo group (non-significant). The average GWG in women treated with metformin was 6.7 kg which is within the IOM recommendations of 5–9.1 kg for women with BMI $\geq 30 \text{ kg/m}^2$ and was not statistically different to the GWG seen in women receiving placebo.

The Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus (MOP) RCT included women with a BMI $\geq 35 \text{ kg/m}^2$. In this trial, metformin was associated with a reduction in GWG (4.3 kg compared to 6.1 kg in the placebo group, $p < 0.001$). There was also a reduction in the rate of PET in those receiving metformin with a strong association between PET and weight gain; however, by the authors’ own admission, the study was underpowered to evaluate this. Once again, the rate of GDM remained similar in both groups and birth weight was unchanged.\textsuperscript{18}

In all three RCTs, women reported mild gastrointestinal side effects and medication compliance ranged from 60% to 80%.

Unlike the MOP study, EMPOWaR and GROW failed to show a reduction in GWG and EMPOWaR did not show a reduction in PET. The different results observed in these RCTs are potentially explained by a number of factors. First, the EMPOWaR study included mostly Caucasian women who took metformin at a maximum dose of 2500 mg, whereas the MOP trial had more ethnic diversity and participants received metformin to a maximum dose of 3000 mg. Women in the GROW study received 2000 mg of metformin and had a lower BMI (32.5 kg/m$^2$, compared to 38 kg/m$^2$ in EMPOWaR and 38.6 kg/m$^2$ in MOP) than the other studies. Adherence was also higher in the MOP study compared to EMPOWaR. Such differences in patient characteristics, medication dosage and adherence may explain some of these findings. A summary of these differences and maternal and foetal outcomes is shown Tables 1 and 2.

The effect of metformin on PET is promising in these studies and although not replicated in studies of metformin for other indications, metformin is being studied in those at high risk for PET (NCT04855513). A 2018 Cochrane review concluded that there was insufficient evidence to suggest that metformin improved maternal or foetal outcomes in obesity\textsuperscript{19}; however, it is likely that those with greater levels of obesity are most likely to benefit from metformin therapy.

### 2.1.2 b) Pregnancies in women with PCOS

PCOS can affect up to 20% of women and is associated with an increase in pregnancy-related morbidity including GDM, miscarriage, hypertensive disorders, pre-term delivery (PTD) and delivery of babies born SGA.\textsuperscript{20,21}

It was anticipated that metformin, through its role as an insulin sensitiser, could be used to prevent many of these complications. This was supported by observational data which demonstrated a reduction in early pregnancy loss, preterm labour and a reduction in rates of GDM.\textsuperscript{22} Unfortunately, many of these benefits were not replicated in RCTs.

The first RCT completed in women with PCOS evaluated the effect of 2000 mg of metformin commencing in the first trimester in 247 Caucasian women.\textsuperscript{23} In this RCT, the authors used the Rotterdam criteria to diagnose PCOS and up to 30% of women had some metformin exposure prior to commencement of the trial. The authors did not identify any reduction in PET or PTD (primary outcomes), macrosomia, SGA or GDM in the metformin-exposed group. They did however show a reduction in GWG of 2.2 kg in the metformin group and in the per-protocol analysis, there was a reduction in PTD from 10 to 2% ($p < 0.05$). This study did not assess pregnancy loss and was ultimately underpowered to detect changes in GDM rates.

A follow-up RCT by the same group (Pregmet2)\textsuperscript{24} randomised 487 Caucasian women to 2000 mg metformin or placebo. All patients were aware of their PCOS diagnosis, suggesting perhaps a more severe phenotype and higher rates of medication adherence were observed when compared to rates in other trials. The results of this RCT mirrored results from the previous trial demonstrating less GWG but similar rates of GDM in the metformin compared to the placebo group. An intention-to-treat post-hoc pooled analysis of nearly 800 women from both trials was performed and identified:

- A reduction in PTD from 8% to 4% ($p < 0.05$). This finding drove the composite endpoint of late miscarriage and PTD.
**TABLE 1** Maternal outcomes from metformin trials

| Trial (total study pop) | Population | Mean BMI (kg/m²) | Gestation at inclusion (weeks) | Dose of metformin | Comparator | GWG | GDM rates | PET | CS | Need for insulin/insulin dose | PTD |
|-------------------------|------------|-----------------|-------------------------------|------------------|------------|-----|-----------|-----|----|-----------------------------|-----|
| GROW (524)17            | BMI ≥25 kg/m² | 32              | 10–20                         | 2000 mg          | Placebo    | ⬇*  | →         | →   |    | →                          | →   |
| EMPOWaR (449)18         | BMI ≥3 kg/m² | 37.5            | 12–16                         | 2500 mg          | Placebo    | →   | →         | →   |    | →                          | →   |
| MOP (550)29             | BMI ≥35 kg/m² | 38.5            | 12–18                         | 3000 mg          | Placebo    | ↓*  | →         | ↓*  |    | →                          | →   |
| PREGMET (273)24         | PCOS       | 29              | 5–12                          | 2000 mg          | Placebo    | ↓*  | →         | →   |    | →                          | →   |
| PREGMET 2 (487)25       | PCOS       | 27              | 12–23                         | 2000 mg          | Placebo    | ↓*  | →         | →   |    | →                          | →   |
| MIG (751)7              | GDM        | 35              | 20–33                         | 2500 mg +/- insulin | Insulin alone | ↓*  | n/a    | →   |    | ↓* (spontaneous)          | →   |
| MeDiGes (100)27         | GDM        | 30              | 14–35                         | 2550 mg +/- insulin | Insulin alone | ↓*  | n/a    | →   |    | ↓*                        | →   |
| Tertti (217)29          | GDM        | 29              | 22–34                         | 2000 mg +/- insulin | Insulin alone | →   | n/a    | →   |    | →                          | →   |
| MiTy (482)8             | Type 2 diabetes | 35              | 6–23                          | 2000 mg + insulin | Insulin alone | ↓*  | n/a    | ↓*  | ↓* | →                          | →   |

Note: ↑ increased rates; ↓ decreased rates; → no statistically significant change.
PTD, pre-term delivery; CS, Caesarean delivery; PET, pre-eclampsia; GWG, gestational weight gain; BMI, body mass index.

*p < 0.05; **Significant on a per protocol analysis.
Larger head circumference (0.5 cm) in the metformin group (head circumference remained in the normal range and there was no increase in operative delivery).

The reduction in primary endpoints was more profound in women with a BMI ≥ 30 kg/m² and in those who underwent assisted reproduction technology (ART).

In summary, metformin may be useful in reducing GWG and PTD particularly in those with PCOS and obesity; however, it appears to have no effect on rates of GDM.

2.1.3 | c) Pregnancies complicated by GDM

GDM is defined as any hyperglycaemia first diagnosed during pregnancy that is not overt diabetes. It is characterised by increased rates of PET, caesarean delivery, LGA and an increased lifetime risk of type 2 diabetes. Incidence rate of GDM is contributed to by several factors including ethnicity, diagnostic criteria and screening methods; however, in 2019, the International Diabetes Federation (IDF) estimated that 1 in 6 pregnancies were impacted by GDM and 20.4 million livebirths globally were affected by diabetes.

In some countries, metformin has been used for decades to treat GDM and the first landmark RCT of metformin for the treatment of GDM was published in 2008. The Metformin versus Insulin for the treatment of Gestational Diabetes (MiG) study evaluated metformin (to a maximum dose of 2500 mg) against insulin therapy in >700 women in an open-label RCT. The primary composite outcome consisted of a combination of neonatal hypoglycaemia, neonatal respiratory distress (defined as need for at least 4 h of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during the first 24 h after delivery), need for phototherapy, birth trauma (of any type, including bruises and abrasions which resolved by 6 weeks), Apgar score at 5 min and birth before 37 gestational weeks.

The trial found no difference in the composite endpoint between groups, but did find less severe neonatal hypoglycaemia (<1.6 mmol/L) and less GWG in the metformin-treated group (0.4 kg vs. 2 kg, \( p < 0.001 \)). The mean infant birth weight was lower in the metformin group; however, this did not reach statistical significance and there was no difference in the rates of SGA deliveries. There was a higher rate of PTD (spontaneous) in the metformin group which has remained unexplained. The authors showed that 46% of women treated with metformin also required insulin; however, their insulin requirements were lower than those treated with insulin alone. Those who required insulin were heavier at baseline and metformin therapy improved weight loss in the post-partum period.
In 2021, a Spanish group evaluated metformin treatment against insulin analogues in 200 women with GDM in an open label RCT. Their patient cohort was similar to the MiG trial participants in terms of age and BMI. As in the MiG trial, they found less maternal weight gain with metformin and found that metformin was more acceptable to patients. They similarly found no significant difference in birth weight, LGA or SGA rates. Unlike the MiG trial, they found metformin was associated with lower post-prandial readings after certain meals. Metformin also reduced the rate of delivery by Caesarean section from 52% to 27% \((p < 0.05)\) compared to those treated with insulin.

Other studies have evaluated the factors associated with suboptimal glucose control in women treated with metformin alone. Studies have consistently shown that older women with higher baseline glucose levels on the oral glucose tolerance test (OGTT), those who require treatment earlier in their pregnancy (<27 weeks) and those with more extreme obesity (BMI >30 kg/m²) were more likely to need insulin in addition to metformin.27,28

Since 2008, a number of RCTs have been conducted to evaluate the impact of metformin on infant size and rates of LGA.29 Like the MiG trial, many showed no significant difference in infant birthweight with metformin use.27–29 A 2019 meta-analysis of 19 RCTs concluded that metformin was associated with lower rates of macrosomia and LGA in mothers with GDM30 and an upcoming individual patient data meta-analysis should provide an illuminating insight into the outcomes of metformin therapy.31

All studies discussed so far have evaluated metformin against insulin. However, other oral hypoglycaemic agents, namely glyburide have also been used for treatment of GDM. Glyburide (previously used extensively in the United States for treatment of GDM) is no longer recommended by the American Diabetes Association unless other options have been exhausted. Compared to metformin glyburide is associated with higher rates of neonatal hypoglycaemia and macrosomia.32,33 The upcoming SUGAR-DIP trial14 will evaluate if glyburide has any potential as an additive agent in sequential therapy for the treatment of GDM.

Finally, an ongoing gap in metformin research is the lack of a double-blind randomized placebo controlled RCT in GDM. It has been previously noted that metformin may have a profound placebo effect as its addition is a strong indicator to patients that glycaemic control is suboptimal and that greater dietary and lifestyle measures are needed.

The EMERGE trial (NCT02980276) will evaluate the use of metformin in women of all BMI categories diagnosed by the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria against placebo. Its primary outcome is a composite of insulin initiation and fasting glucose levels >5.3 mmol/L at gestational weeks 32 or 38.

2.1.4 d) Pregnancies complicated by type 2 diabetes

Rates of type 2 diabetes in pregnancy are rapidly rising12 and type 2 diabetes now accounts for 36% and 50% of pregestational diabetes in Ireland and the United Kingdom, respectively.5,13 This group is particularly at risk for congenital anomalies, PET and macrosomia, and good glycaemic control is essential. Though extremely effective, insulin therapy is associated with excess GWG and neonatal hypoglycaemia, so alternative therapies are particularly attractive in this cohort.

There is significant interest in the use of metformin in this group but many trials to date evaluating insulin versus metformin have recruited only small numbers.37–39 Although these studies have demonstrated an increase in SGA births and a decreased rate of neonatal intensive care unit (NICU) admissions in the metformin groups, they are not large enough to conclusively guide decision-making.

Given that nearly half of metformin-treated GDM women required insulin, it was unclear from the available data if the addition of metformin was worthwhile for pregnant women with type 2 diabetes. This prompted the landmark Metformin in women with type 2 diabetes in pregnancy trial (MiTy): a multicentre, international, randomised, placebo-controlled trial.7 The MiTy trial randomised 502, mostly obese insulin-treated women with type 2 diabetes to either metformin or placebo. At a dose of 2000 mg daily, women in the metformin group had:

- A lower mean haemoglobin A1c (HbA1c) (41 vs. 43 mmol/mol (5.9% vs. 6.1%) at the last time of measurement before delivery
- A lower total daily insulin dose at 34 or 36 weeks of gestation
- Less use of short-acting insulins (fewer injections)
- A lower rate of birth by Caesarean section (63% vs. 53%)
- Less GWG (1.8 kg)

Infants experienced:

- Lower mean birthweight (3156 g vs. 3375 g)
- Lower rates of extreme LGA and macrosomia \((p < 0.05)\)
- But a higher rate of SGA births \((7% \text{ vs. } 13%; p < 0.05)\)

In total, there was a downward shift of birthweights in the metformin group and this effect was maintained regardless of maternal BMI. The findings of this study
have a number of implications as it provides some of the strongest evidence for the increased risk of SGA with metformin therapy (evidence which was not seen in some studies of women with GDM or in studies of women with obesity/PCOS). Due to high rates of birth trauma macrosomia and long-term cardiometabolic complications seen in macrosomia, 40 many viewed a decrease in infant size as a positive result. However, it is now apparent that SGA infants face cardiovascular disease, chronic kidney disease and type 2 diabetes 41 in adulthood and the risks and benefits of metformin treatment need to be carefully balanced.

In summary, metformin appears to confer benefits in terms of maternal GWG and reduced insulin doses in women with type 2 diabetes which may be of particular benefit to very insulin resistant women requiring large insulin doses. The lower rates of infant macrosomia and LGA is also an advantage (which may help to reduce birth trauma) but must be balanced against the increased number of healthy SGA infants and the impact this may have on long-term health of offspring.

2.2 Post-partum

It is firmly established that in addition to its other complications, GDM confers an increased risk of type 2 diabetes that is 10 times higher than the general population. 42 Alongside dietary and lifestyle measures, metformin has been evaluated for its ability to reduce progression to type 2 diabetes in this population.

Perhaps the most highly cited trial of type 2 diabetes prevention is the Diabetes Prevention Programme (DPP) which followed the trial population for 3 years. A prespecified subset of the study population included women with impaired glucose tolerance (IGT) and previous GDM. In the DPP, 350 women with previous GDM were compared to 1416 matched individuals without a history of GDM. Women with previous GDM lost less weight at 3 years and their overall weight loss was lower than those without GDM. 43 For women with previous GDM, metformin reduced the risk of type 2 diabetes by 50% compared to placebo; however, an impressive 53% reduction was also seen with intensive lifestyle therapy. Metformin was also significantly more effective than placebo in reducing rates of type 2 diabetes in the overall population. Metformin was especially effective in women with previous GDM where the number needed to treat to prevent 1 case of type 2 diabetes was 6.

At a 10-year follow-up study of the DPP, metformin continued to reduce the risk of type 2 diabetes in women with previous GDM by 40% 44 while intensive lifestyle changes reduced the risk by 35%. Once again metformin was significantly more effective in women with previous GDM compared to those without a history of GDM, independent of weight loss. While this finding is not entirely explained, it may be due to a higher baseline insulin secretion in at risk women who did not develop GDM.

3 | METFORMIN EFFECTS ON THE OFFSPRING

With the wealth of data on maternal benefits and safety, the residual concerns with metformin use centre around foetal and offspring health. Metformin crosses the placenta and concerns have existed over a potential link between metformin and congenital anomalies. A hyperglycaemic milieu also promotes congenital anomalies and it is difficult to know which factor has the greatest consequence on early foetal development. 45

3.1 a) Metformin exposure in the first trimester

It is now known that embryos have a primitive mitochondrial system and very low expression of cation transporters. This makes it difficult for metformin to enter the cell 46 and animal studies have demonstrated that embryonic changes observed in vitro are not replicated in vivo. 47

A large meta-analysis of over 50,000 infants with congenital anomalies, of which 168 had early metformin exposure, concluded that there was no overall increased risk of congenital anomalies with metformin exposure in the first trimester. 48 This meta-analysis also took into account which congenital anomalies had previously been associated with diabetes.

For women with pregestational diabetes and GDM on metformin, there was an increased risk of congenital anomalies (odds ratio (OR) 2.04, confidence interval (CI): 1.75–2.38); however, there was no increased risk of non-genetic anomalies in either PCOS (OR: 0.81, CI: 0.52–1.27) or infertility (OR: 0.89, CI: 0.66–1.19). When all indications (diabetes and non-diabetes related) were combined, the overall OR for congenital anomaly was 0.84 (CI: 0.55–1.3).

In unadjusted analyses, there was an increased risk of ano-rec tal atresia, atro-septal defect, pulmonary valve atresia and patent duc tus arteriosus. When adjusted for confounders (the strongest of which was diabetes), the only persistent risk was of pulmonary valve atresia (OR: 3.53, CI: 1.05–12 compared to non-genetic controls).

This large and well-conducted meta-analysis of registry data adds to the existing body of evidence and provides reassurance of the safety of metformin across multiple indications. 49
3.2 b) Metformin exposure in the second and third trimesters

As the pregnancy progresses, the placenta and foetal tissues begin to express metformin transporters and they have a higher rate of mitochondrial activity.

Metformin inhibits the action of the mitochondria (respiratory complex 1) and reduces adenosine tri-phosphate (ATP) levels. Increased adenosine monophosphate (AMP):ATP reduces gluconeogenesis and activates AMP-activated kinase (AMPK). Metformin also intercepts the mTOR pathway, which may restrict nutrient delivery to the placenta. This effect has certainly been witnessed in certain cancers and is thought to underly certain causes of intra-uterine growth restriction and prematurity in animal models.

In clinical practice, this is of relevance as the use of metformin for different indications has yielded different results. Women who receive metformin due to obesity or PCOS do not seem to demonstrate any change in infant size; however, lower infant birth weights have been observed in women with GDM and type 2 diabetes treated with metformin. This pattern raises the concern that the clinical community has misinterpreted a reduction in infant birthweight as a benefit of improved glycaemic control, rather than an effect of growth restriction with changes to the epigenetic profile, or genetic programming caused by metformin exposure.

A follow-up study of women with GDM treated with metformin (MiG) found that after 2 years infants exposed to metformin had larger upper-arm circumferences, subscapular and bicep skinfold thickness compared to those exposed to insulin. It should be noted that this cohort was smaller (crown-rump, triceps skinfold and subscapular skinfold) at birth compared to the general population. This suggests that while total fat concentration is similar for metformin- and insulin-treated infants, metformin may alter fat distribution.

Changes to weight, BMI and systolic blood pressure have also been found in other smaller studies of offspring at 18 months. In 2018, the results of a 7- to 9-year follow-up study of MiG offspring was published which reported on the outcomes of over 200 of the original participants. At age 7 years, no large changes in BMI, waist or hip circumference or total fat mass were observed. However, a further subset of this follow-up group (the Adelaide group) had worse glycaemic control in pregnancy compared to the entire study cohort, and had larger infants at birth. The children in this Adelaide group were not obese at 7 years, and the authors suggested that metformin exposure in utero had a protective effect in the immediate post-natal period.

| TABLE 3 | Long-term effects on offspring |
|---------|-----------------------------|
| Trial (total study population) | Pop | Follow-up | Comparator | BMI (kg/m²) | Total body fat (g) | Fat (%) | Upper arm circumference (mm) | Subscapular skinfold (mm) | Bicep skinfold (mm) | SBP (mmHg) | FPG (mmol/L) |
| MiG-TOFU (303) | 51 |
| GDM | 2 years | Insulin | ↑ |
| MiG-TOFU (109) | 54 |
| GDM | 7 years | Insulin | ↑ |
| MiG-TOFU (99) | 56 |
| GDM | 9 years | Insulin | ↑ |
| MiG-TOFU (99) | 56 |
| PCOS | 5-10 years | Placebo | ↑ |

Note: ↑ increased rates; ↓ decreased rates; → no change; $ weight/waist circumference was significantly higher in this group; $ higher rates of obesity.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure.
After 9 years, the metformin-exposed children in the Auckland group had higher weight, mid-upper arm and waist circumferences and waist to height ratios; the mothers of these infants had a greater BMI but gained less weight in pregnancy when compared to other groups.

Animal studies have suggested that the impact of metformin differs according to maternal BMI and offspring weight gain in the neonatal period is impacted by maternal weight changes, calorie intake of the mother during pregnancy and the gender of the infant. Higher BMI and larger waist circumferences are seen in the long term if the nutrient environment for the foetus is restricted. From a clinical perspective, this highlights the long-term importance of adequate and high-quality nutrition during pregnancy. Although debate continues on the best diet, nutrient intake should be balanced and carbohydrate should be of low glycaemic index. Weight gain should adhere closely to IOM recommendations based on current evidence.

In women with a history of PCOS, infants exposed to metformin were heavier and more likely to be overweight or obese at age 4 years. At 5–10 years, the children of mothers with PCOS exposed to metformin had a higher BMI and waist to height ratio and were more likely to be obese. Other cardiometabolic risk factors (C-peptide and cholesterol) were similar in the two groups. This follow-up study found that the risk of obesity in the offspring increased with a greater maternal pre-pregnancy BMI although the group was too small to draw any further conclusions. It should also be noted that although this original study group did not directly report on SGA rates, they did not find any difference in mean birth weight or numbers of infants born <2500 g lending further support to the complex interplay between childhood obesity, SGA delivery, maternal BMI and ante-natal nutrition.

This same group also published their findings on cognitive effects on the offspring. While they found no difference in the mean intelligence quotient (IQ) of children in the metformin and placebo groups, they found that a higher percentage of children with IQ 70–85 (borderline IQ) had been exposed to metformin compared to placebo. The authors conclude that these figures should be interpreted with caution and other studies have not identified this link.

Unfortunately, there is a paucity of long-term follow-up data on the infants of obese women exposed to metformin; however, a summary of studies conducted in GDM and PCOs is shown in Table 3.

### Table 4 Author recommendations

| Condition          | Suitable patient cohort                                                                 |
|--------------------|------------------------------------------------------------------------------------------|
| Obesity            | • Consider in the very obese (BMI ≥35 kg/m²) to minimise weight gain                      |
|                    | • Small evidence base                                                                     |
|                    | • Does not appear to affect infant size at birth                                           |
|                    | • Personalised decision with risks and benefits (particularly long-term foetal outcome and gastrointestinal side effects) discussed |
| PCOS               | • Consider continuing it especially in those with a BMI ≥30 kg/m²                        |
|                    | • Does not reduce infant size                                                             |
| GDM                | • Consider in very obese women who are likely to need insulin as metformin will reduce dose needed and GWG |
| Type 2 diabetes    | • In patients already on metformin consider continuing throughout pregnancy however stop if any evidence of foetus being SGA |
|                    | • Consider initiating treatment in obese women who are insulin naïve                      |
|                    | • Consider adding it to those on large dose of insulin to reduce dose                     |

Note: In all cohorts, avoid metformin in women who have had previous SGA infants in the past (not evidence based, authors personal recommendations); avoid metformin in women with GDM or type 2 diabetes if there is any suspicion patient may have type 1 diabetes.

Abbreviations: GDM, gestational diabetes; PCOS, polycystic ovarian syndrome.

In summary, metformin has many maternal advantages when taken during and after pregnancy, including reduced maternal GWG, PTD and insulin requirements, a reduction in operative delivery and possible reduction in hypertensive disorders and future type 2 diabetes. Some benefits are even greater for women with a BMI ≥30 kg/m². The infant also benefits from reduced rates of extreme weight, macrosomia, hypoglycaemia and need for neonatal unit care. This however must be balanced against the potential risk of SGA and its implications on long-term health, the potential for infant obesity and potential long-term cardiometabolic consequences which have not yet been studied.

We have outlined a potential guideline for starting metformin in each of the above conditions (Table 4).
To ensure that residual concerns regarding offspring health are addressed, future trials should be randomised and placebo controlled. Women should be consented for long-term follow-up of the maternal–infant pair and consideration should be given to bio-banking which has the potential to further interrogate our understanding of diabetes and other cardiometabolic conditions. Any future RCTs should also encompass core outcome sets (COS), which are a minimum set of outcomes that should be consistently measured and reported in all clinical trials. COSs improve the quality of meta-analysis and allow stronger conclusions to be drawn. COSs have been developed and are published for the treatment and follow-up of diabetes in pregnancy and have the ability to enhance evidence synthesis.

Until we can provide evidence-based answers to the remaining uncertainties surrounding metformin use, women should be well informed about the risks and benefits and a personalised, patient-centred approach should be employed to ensure the best outcome for both mother and child.

CONFLICTS OF INTEREST
Prof Fidelma Dunne and Dr Christine Newman are the principal investigators (PIs) and sub-PI for the Effectiveness of Metformin in addition to usual care in the Reduction of Gestational Diabetes Mellitus effects (EMERGE) randomised controlled trial.

ORCID
Christine Newman https://orcid.org/0000-0003-2387-4109
Fidelma P Dunne https://orcid.org/0000-0003-3682-9403

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