Received: 24 January 2025 | Revised: 2 March 2025 | Accepted: 12 March 2025

DOI: 10.1111/dom.16361

SPECIAL ISSUE ARTICLE

WILEY

A narrative review of metformin in pregnancy: Navigating benefit and uncertainty

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Abstract

Metformin is well-established as a treatment for type 2 diabetes in non-pregnant individuals. The low cost, acceptability and broad tolerability of metformin have also made it an attractive option for research into the treatment of other conditions associated with insulin resistance. Despite almost 50 years of clinical experience with the use of metformin to treat diabetes in pregnancy, many questions remain regarding its precise effectiveness in different maternal subgroups, as well as potential short-term and long-term effects on the offspring. In this narrative review, we present the current evidence for the use of metformin during pregnancy in various maternal subgroups, including women living with overweight and obesity, women at risk of gestational diabetes, women diagnosed with gestational diabetes and women with pregestational diabetes, including type 2 diabetes. Our specific focus is on the impact of metformin on short-term maternal, fetal and neonatal outcomes. We also consider the evidence for other emerging indications for metformin in pregnancy, such as the prevention and management of pre-eclampsia.

Plain Language Summary

This article looks at research on how metformin use in pregnancy affects mothers and newborns in the short term. Doctors have prescribed metformin since the 1970s for the treatment of diabetes in pregnancy. Despite years of use, there are still questions about how safe and effective metformin is for mothers and their children. Metformin taken during pregnancy moves through the placenta into the foetus's bloodstream. The short-term and long-term effects of metformin on offspring need careful attention. The studies that have looked at the link between metformin use and birth defects have not found any strong link between taking metformin in pregnancy and birth defects, however close attention will continue to be paid in this area. Some large studies have examined the use of metformin in pregnant women who do not have diabetes, but who do live with overweight or obesity. The studies are difficult to compare. Some, but not all, of these studies have shown less weight gain for the mother if metformin is taken by these women during pregnancy. Other large studies have looked at

whether metformin can prevent gestational diabetes. The results are mostly disappointing. They suggest that metformin does not stop gestational diabetes from developing. However, the participants in these studies were mostly from white backgrounds and metformin may help prevent gestational diabetes in women of different ethnic backgrounds. However, more research is needed. Metformin has been widely studied as an alternative to insulin for the treatment of gestational diabetes. Because different countries diagnose and treat GDM differently, this makes comparing study results difficult. Women with gestational diabetes seem to gain less weight during pregnancy if they use metformin rather than insulin. Using metformin instead of insulin may result in lower average birth weights for babies from these pregnancies. Also, the use of metformin may lead to fewer babies being born abnormally large. Similarly, large trials have examined the use of metformin in pregnant women who are living with type 2 diabetes. These studies show that metformin can lower a mother's insulin needs. It can also help control weight gain and reduce the risk of having a large baby. One study found that metformin use in women living with Type 2 diabetes might increase the risk of having smaller babies. This was especially true if the mother had high blood pressure or kidney disease. This finding requires further investigation. Metformin might help prevent pre-eclampsia, but this is still unclear. Research is ongoing into a potential role for metformin in the treatment of pre-eclampsia. In conclusion, metformin has been studied in many groups of pregnant women. Women with gestational diabetes or type 2 diabetes may see benefits like less weight gain and better blood sugar/glucose control. Current evidence suggests that metformin shouldn't be used if there are foetal growth issues. It is also not recommended for mothers with high blood pressure or kidney disease. Future studies might find specific groups of pregnant women who would benefit the most from metformin.

KEYWORDS
gestational diabetes, metformin, pregnancy, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Metformin is a biguanide that has been in therapeutic use since the 1950s.[1] It is widely considered to be a cheap, safe and effective glucose-lowering treatment, and is frequently used in non-pregnant adults with diabetes.[2] Research interest in metformin has surged in recent years for its therapeutic potential in other insulin-resistant states such as polycystic ovary syndrome (PCOS), pre-diabetes and gestational diabetes (GDM), and diverse investigational uses have been proposed in cancer prevention, Alzheimer's disease and healthy ageing.[3,4]

Although metformin has been used to treat diabetes in pregnancy since the 1970s,[5] its use remains controversial. It is noteworthy that metformin bioavailability, volume of distribution and clearance are increased during pregnancy and there is a lack of guidance on the optimal dosing strategy throughout pregnancy.[6] Metformin has been shown to cross the human placenta, with fetal serum concentrations equivalent to or higher than maternal serum concentrations.[7] Mouse models identify organic cation transporter 3 (OCT3) as key to fetal metformin uptake and distribution.[8] Placental expression of this transporter increases with gestational age, implying that peak fetal exposure may occur in later gestation.[9] However, while metformin use has not been observed to increase the risk of major congenital malformations,[10] safety concerns have been raised regarding potential long-term impacts on offspring, outside of the neonatal period.[11]

Several potential mechanisms for fetal harm from metformin have been proposed.[12] Activated AMPK signalling and inhibition of placental mTOR signalling by metformin could adversely affect fetal growth and differentiation. For example, stimulation of AMPK inhibits expression of Pax3 in mice, a gene essential for neural tube closure.[13] Metformin has a known association with vitamin B_{12} deficiency and antifolate action that could disrupt DNA methylation and intrauterine epigenetic programming, although the effects of maternal vitamin B_{12} supplementation when using metformin during pregnancy have not been studied.[14] In long-term follow-up studies of children exposed to metformin in utero, some,[15,16] but not all,[17–19] have shown increased rates of obesity and markers of adverse cardiometabolic health. Nevertheless, in many countries, metformin continues to be used off-label during pregnancy for the treatment of GDM and other insulin-resistant states, due to its cost-effectiveness, acceptability and broad tolerability compared with insulin or sulphonylurea therapy.[20,21]

The aim of this article is to review the evidence for the efficacy and safety of metformin in the various subgroups of pregnant women in which it has been studied, specifically women living with overweight and obesity, GDM, and pregestational diabetes mellitus (PGDM). Other emerging indications for metformin in pregnancy are also considered. This review focuses on maternal, fetal and neonatal outcomes only; the longer-term effects on maternal offspring are considered in a separate article in this Special Supplement.

2 | METHODS

During December 2024, the authors searched the online databases PubMed, EMBASE, the Cochrane Library, MEDLINE and CINAHL, using combinations of a selection of keywords including 'metformin', 'biguanide', 'oral antidiabetic', 'pregnant', 'pregnancy', 'overweight', 'obesity', 'diabetes', 'GDM', 'PGDM', 'T1DM', 'T2DM', 'HDP', 'gestational hypertension', 'pre-eclampsia', 'renal failure', 'nephropathy', 'MASLD' and 'NAFLD' We focused primarily on evidence published since January 2020 from systematic reviews, meta-analyses and randomized controlled trials (RCTs) pertinent to the efficacy and safety of metformin during pregnancy. Bibliographies of relevant studies were also reviewed to identify further important literature.

3 | METFORMIN AND THE RISK OF CONGENITAL MALFORMATIONS

Decades of clinical experience with metformin use during pregnancy have not yielded concerns regarding an increased risk of congenital malformations, and this is supported by limited data from observational studies.

In 2018, Given et al. carried out a case–control study using data from European registries, including 50 167 infants with congenital anomalies, 168 of whom had been exposed to metformin during the first trimester.[22] The authors found no evidence of an overall increased risk of all major congenital anomalies combined, but did note an association between metformin use and the risk of pulmonary valve atresia (adjusted odds ratio [OR] 3.54, 95% confidence interval [CI] 1.05–12.00, compared with non-genetic controls). However, the authors concluded that this finding was no more than would be expected by chance. In 2023, Abolhassani et al. published a systematic review and meta-analysis of the risk of major congenital malformations following first-trimester exposure to metformin in women with PCOS or PGDM.[10] The point estimates for the rates of major congenital malformations in metformin-exposed women with PCOS were not significant in either randomized controlled trials (OR 0.93; 95% CI 0.09 to 9.21; $I^2 = 0\%$) or observational studies (OR 1.35; 95% CI 0.37 to 4.90; $I^2 = 65\%$). Similarly, the observational studies included in their meta-analysis did not demonstrate an increased rate of major congenital malformations in metformin-exposed women with PGDM (OR 1.05; 95% CI 0.50 to 2.18; $I^2 = 59\%$). However, the authors noted a general paucity of data in this area, due to the practice of discontinuing metformin in these patients once pregnancy is confirmed. Furthermore, poorly controlled PGDM is itself known to significantly increase the risk of major congenital malformations,[23] and it is difficult to control for this confounding effect when studying the effect of metformin, as data regarding glycaemic control are often unavailable in these studies.

In recent years, paternal use of metformin in the preconception period has also come under scrutiny. In 2022, Wensink et al. used Danish registry-based data to examine the association between major birth defects and paternal use of anti-diabetic drugs during spermatogenesis, excluding the offspring of women with diabetes or essential hypertension.[24] Of 1 116 779 offspring included, 3.3% had one or more major birth defects. Regression analysis found that among the offspring of metformin-exposed fathers, birth defects were more common (adjusted OR 1.4; 95% CI 1.08 to 1.82; $p = 0.012$), specifically genital birth defects, all in male offspring (adjusted OR 3.39; 95% CI 1.82 to 6.30), and the proportion of male offspring was lower (49.4% vs. 51.4%; $p = 0.073$). However, this analysis did not adjust for paternal comorbidities such as metabolic syndrome or diabetes, which may have led to confounding by indication.[25] Conversely, in 2024, Meng et al. published the results of a population-based, cross-national cohort study including 619 389 Norwegian infants and 2 563 812 Taiwanese infants.[26] When restricted to men with type 2 diabetes mellitus only, analysis using overlap propensity score weighting showed that paternal metformin use was not associated with an increased relative risk (RR) of congenital malformations in either Norway (RR 0.98; 95% CI 0.72 to 1.33) or Taiwan (RR 0.87; 95% CI 0.74 to 1.02).

In summary, the limited available data are reassuring regarding maternal and paternal use of metformin and the risk of congenital malformations. Ongoing surveillance using detailed population-based registries is required to increase the sample size available for future analysis.

4 | METFORMIN USE IN DIFFERENT MATERNAL SUBGROUPS

4.1 | Metformin for non-diabetic pregnant women living with overweight or obesity

Rates of obesity are increasing worldwide, and women of childbearing age are at particular risk of obesity and weight gain.[27,28] Maternal obesity is associated with adverse maternal and fetal outcomes,[29,30] childhood obesity,[31] and has impacts on the long-term cardiometabolic health of offspring.[32] While these adverse outcomes occur in obesity independent of glucose intolerance, obesity further increases the risk of pregnancy complications in women with GDM.[33]

A summary of randomised and observational studies is detailed in Table 1. Metformin has been evaluated at doses of between 1000 and 3000 mg/day for its potential to impact gestational weight gain (GWG), limit fetal overgrowth and reduce the rates of GDM in women living with obesity.

Reduced maternal weight gain has been found in some[34–36] but not all studies.[37–39] Some but not all of these differences may be

TABLE 1 Studies evaluating the impact of metformin on pregnant women with overweight or obesity.

Lead author, country, year	Inclusion criteria mean BMI (kg/m^2)	Daily dose (mg)	No. of participants	Placebo control	Significant maternal weight change	Other maternal outcomes	Offspring outcomes
Nascimento,[44] Brazil, 2020	>30 37.4	1000	357 pregnant women, <20 weeks' gestation	No	Not reported	No difference in GDM rates Reduced pre-eclampsia with metformin	Fewer Caesarean deliveries ARR 23.1 (95% CI 13.0 to 33.24) No difference in LGA
Dienstmann,[37] Brazil, 2020	>30 38.3	1000	424 pregnant women, <20 weeks' gestation (confirmed normal glucose tolerance)	No Dietary guidance in both arms	No	No change in BMI or lipid levels	Not documented
Dodd[36] (GRoW), Australia, 2019	>25 32.5	2000	525 pregnant women, 10–20 weeks' gestation	Yes Dietary guidance in both arms	Lower weekly weight gain with metformin, but total weight gain similar		No difference in macrosomia 0.5 cm decrease in infant abdominal circumference in metformin group No difference in adiposity measures on ultrasound[45]
Sales,[39] Brazil, 2018	>30 37.5	1000	164 pregnant women, <20 weeks' gestation	No	No	No difference in OGTT	Not reported
Syngelaki[34] (MOP), United Kingdom, 2016	>35 38.5	3000	300 pregnant women, 12–18 weeks' gestation	Yes	4.6 kg versus 6.3 kg in placebo arm ($p < 0.001$)	Reduced pre-eclampsia with metformin	No difference in birthweight
Fattah,[35] Egypt, 2016	>35 36.4	1000	200 pregnant women, 12 weeks' gestation	Yes	6.55 kg versus 11.61 kg in placebo arm ($p = 0.00$)	No change in hypertension or glucose levels	Not reported
Chiswick[38] (EMPOWaR), United Kingdom, 2015	>30 38	2500	449 pregnant women, 12–16 weeks' gestation (confirmed normal glucose tolerance)	Yes	No	No change in glucose or lipid metabolism (18% vs. 24% developed GDM, $p = 0.27$)	No difference in birthweight centile

Abbreviations: ARR, absolute risk reduction; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; LGA, large for gestational age; OGTT, oral glucose tolerance test.

explained by differences in the ethnicity of participants, mean body mass index (BMI) at randomisation, and dose of metformin.[34,37] Systematic reviews evaluating GWG have reported high rates of heterogeneity; however, metformin appears to reduce GWG by 1.49–2.93 kg.[40–43] Two studies found a reduction in the rates of hypertensive disorders,[34,44] and this is further discussed in Section 4.7.1.

Metformin does not impact fetal overgrowth or size in studies to date.[34,36,38,40,41] No increase in the rates of small for gestational age (SGA) deliveries has been reported, although one trial, the GRoW trial, did find an unexplained reduction of 0.5 cm in neonatal abdominal circumference in the metformin group.[36] Similarly, there is no evidence from systematic reviews that metformin reduces Caesarean delivery or preterm birth,[40,41] not included in these systematic reviews was a 2020 study of 357 obese women randomized on average at 11 weeks' gestation to receive either placebo or 1000 mg/day of metformin.[44] This study found a reduction in Caesarean delivery from 62.9% to 39.8% (absolute risk reduction 23.1%; 95% CI 13.0 to 33.24; $p < 0.01$) and number needed to treat of 4.

Between studies, there is a large variation in adherence, with over 70% of women in both the placebo and metformin arms reporting side effects in one study with metformin doses up to 2000 mg/day[36] and only 4% reporting side effects at 1000 mg/day.[44] This large difference may account for some of the differences in outcomes observed.

4.2 | Metformin for pregnancies affected by PCOS

Pregnancies in women with PCOS are associated with an increased risk of miscarriage, higher GWG, GDM, gestational hypertension, pre-eclampsia, induction of labour and Caesarean delivery.[46] Given its insulin-sensitising properties, metformin has the potential to improve outcomes in women with PCOS who are pregnant or are trying to conceive.[47] This role of metformin is reviewed in a separate manuscript in this Special Supplement.

4.3 | Metformin for the prevention of GDM

The role of metformin for GDM prevention has been studied in several trials of at-risk groups, although mainly as a secondary outcome measure. Risk factors for the development of GDM include overweight or obesity, PCOS, advanced maternal age, non-European ethnicity, previous GDM and family history of diabetes.[48]

In pregnant women living with obesity, the EMPOWaR (Effect of metformin on maternal and fetal outcomes in obese pregnant women) randomized controlled trial assigned 449 women living in the UK with a body mass index (BMI) ≥30 kg/m^2 to either placebo or metformin from 12 to 16 weeks' gestation until delivery.[38] Metformin did not impact the secondary outcome of GDM prevalence (18% vs. 24%; OR 0.728; 95% CI 0.414 to 1.283; $p = 0.27$). The MOP (Metformin in Obese Non-diabetic Pregnant Women) trial assigned women with a body mass index ≥35 kg/m^2 to metformin or placebo from 12 to 18 weeks' gestation until delivery.[34] Again, there was no significant difference in the risk of developing GDM (12.4% vs. 11.3%; OR 1.11; 95% CI 0.60 to 2.04; $p = 0.74$). The GRoW randomized, double-blind placebo-controlled trial evaluated the effect of metformin versus placebo in 523 pregnant women with overweight or obesity from 10 to 20 weeks' gestation in Australia.[36] Metformin did not prevent GDM in this cohort (28% vs. 24%; adjusted treatment effect 1.19; 95% CI 0.88 to 1.62; $p = 0.253$).

The PregMet and PregMet2 trials evaluated metformin in women with PCOS.[49,50] In PregMet, the mean gestational length at randomisation was 74 days (standard deviation 13 days) in the metformin group and 75 (11) days in the placebo group. Similarly, in PregMet2, the median gestational length at randomisation was 74 days (interquartile range 55–93 days) in the metformin group and 75 (55–95) days in the placebo group. In PregMet, 22/125 (17.6%) developed GDM in the metformin group compared with 21 of 124 (16.9%) in the placebo group (risk difference 0.8%; 95% CI −8.6 to 10.2; $p = 0.87$). In PregMet2, the prevalence of GDM was a pre-specified secondary outcome, with 39/238 (16.4%) of the metformin group developing GDM during the study period, compared with 35 of 239 (14.6%) of the placebo arm (OR 1.15; 95% CI 0.68 to 1.95; $p = 0.61$). However, it should be noted that both PregMet and PregMet2 were ultimately underpowered for this outcome. In contrast, a smaller open-label RCT reported reductions in the risk of GDM when metformin was continued in pregnant women with PCOS (OR 12; 95% CI 6.20 to 18.08); however, this study is limited by small sample size ($n = 59$).[51]

Given the significant health risks associated with GDM, there has been a renewed interest in synthesizing the evidence for preventative measures from the literature, with three separate systematic reviews and meta-analyses published during 2024.[52–54] Diet, physical activity and myoinositol may play a role in reducing the incidence of GDM in at-risk women.[52,54] As illustrated in Table 2, the recent meta-analyses have reported contradictory conclusions regarding the protective role of metformin. Two meta-analyses incorporating non-randomized trials reported a reduced GDM risk with metformin, albeit with a high degree of heterogeneity.[52,53] The subgroup analysis of Yu et al. suggests that the factors of Asian ethnicity, PCOS and higher dose may be driving their finding of GDM risk reduction with metformin.[53] However, it should be noted that since the publication of these meta-analyses,[52,53] one of the included cohort studies has since been retracted from the literature.[55,56]

Overall, one can summarize that the results of trials of metformin in GDM prevention have been largely disappointing, and metformin is not currently recommended for GDM prevention. As most participants in prior studies were white, future work should include more diverse racial and ethnic populations, use double-blind, placebo-controlled study designs, and consider GDM prevention as a primary outcome.

4.4 | Metformin for pregnancies affected by GDM

GDM can be defined as glucose intolerance that develops during pregnancy in women without pre-existing diabetes.[61] Worldwide, GDM is estimated to affect 14% of pregnancies, with the highest

TABLE 2 Systematic reviews and meta-analyses of metformin use for the prevention of GDM, published in the last 5 years.

Lead author, year	Studies included	Impact of metformin on the incidence of GDM
ADA/EASD PMDI group Takele,[52] 2024 Lim,[57] 2023	8 RCTs, 5 non-RCTs (*1 included cohort study*[55] *has since been retracted from the literature, weight 7.97%*)	Reduced risk (RR 0.66; 95% CI 0.47 to 0.93; $I^2 = 73.08\%$)
Yu,[53] 2024	15 RCTs, 5 cohort studies (*1 included cohort study*[55] *has since been retracted from the literature, weight 5.35%*)	Reduced risk (RR = 0.59; 95% CI 0.43 to 0.80; $I^2 = 76.2\%$)
Quotah,[54] 2024	11 RCTs	No significant effect (risk difference −0.00; 95% CI −0.04 to 0.03; $I^2 = 8.82\%$)
Tarry-Adkins,[58] 2021	7 RCTs	No significant effect (OR 1.07; 95% CI 0.87 to 1.33; $I^2 = 0\%$)
Doi,[59] 2020	11 RCTs	No significant effect (risk ratio 1.03; 95% CI 0.85 to 1.24; $I^2 = 20.2\%$)
Zhao,[60] 2020	3 RCTs, 1 non-RCT, 2 observational studies (*all women in these trials had PCOS*)	Reduced risk (log OR −1.27; 95% CI −2.24 to −0.30, $I^2 = 60.43\%$)

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; EASD, European Association for the Study of Diabetes; GDM, gestational diabetes mellitus; OR, odds ratio; PCOS, polycystic ovary syndrome; PMDI, Precision Medicine in Diabetes Initiative; RCT, randomized controlled trial; RR, relative risk.

prevalence in the Middle East, North Africa and South-East Asia,[62] although prevalence rates vary according to the screening approaches and diagnostic criteria used.[63]

Uncontrolled hyperglycaemia during GDM pregnancies independently increases the risk of Caesarean delivery and pre-eclampsia for the mother, while for the neonate there are increased risks of macrosomia, hypoglycaemia, hyperbilirubinemia, birth injury, preterm birth and neonatal intensive care unit (NICU) admission.[64] Treatment of GDM with glucose-lowering therapy has been shown to mitigate many of these risks,[65,66] though glycaemic treatment targets are debated.[67,68]

Following lifestyle modification, some guidelines recommend insulin as the first-line treatment for GDM.[11,69] The American Diabetes Association specifically does not recommend metformin as first-line treatment, citing concerns regarding long-term safety in the offspring.[11] In contrast, the Society for Maternal-Fetal Medicine has endorsed metformin as a 'reasonable and safe' first-line alternative to insulin in women with GDM requiring pharmacological treatment.[70] Similarly, the National Institute for Health and Care Excellence (NICE) in the UK recommends metformin as a first-line pharmacological treatment option for GDM.[71]

Several large randomized controlled trials have studied the short-term efficacy and safety of metformin use in GDM pregnancies. In 2008, Rowan et al. published the results of the MiG (Metformin In Gestational Diabetes) trial.[21] MiG was an open-label study, where 751 women with GDM (diagnosed using ADIPS 1998 criteria[72]) were randomly assigned in a 1:1 ratio to receive either metformin or insulin. Almost half (46.3%) of the women in the metformin arm also required supplemental insulin to achieve ADIPS 1998 targets.[72] The primary outcome was a composite neonatal safety outcome comprising hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-min Apgar score <7 or prematurity. The study authors did not find any difference in the primary outcome between the intervention and the control arms (RR 0.99; 95% CI 0.80 to 1.23; $p = 0.95$). Infants in the metformin arm experienced fewer episodes of severe hypoglycaemia (glucose less than 28.8 mg/dL or 1.6 mmol/L) (RR 0.41; 95% CI 0.21 to 0.78; $p = 0.008$). Preterm births were however more common in the metformin group (12.1% vs. 7.6%; RR 1.60; 95% CI 1.02 to 2.52, $p = 0.04$), comprising mainly spontaneous births (7.2% vs. 4.1%; RR 1.77; 95% CI 0.95 to 3.28, $p = 0.07$). Infants at term were also born on average slightly earlier in the metformin group (38.3 vs. 38.5 weeks, $p = 0.02$). Birthweight parameters such as the proportions of babies born SGA (7.2% vs. 9.7%; $p = 0.21$) or large for gestational age (LGA) (19.3% vs. 18.6%, $p = 0.83$) did not differ significantly between the groups. Mothers in the metformin group experienced less GWG on average (0.4 vs. 2.0 kg, $p < 0.001$), and had lost more weight at the 6–8 weeks post-partum visit (8.1 vs. 6.9 kg, $p = 0.006$).

The EMERGE (Early Metformin in Addition to Usual Care in the Reduction of Gestational Diabetes Effects) trial results were published by Dunne et al. in 2023.[73] EMERGE was the first double-blind placebo-controlled trial to examine the efficacy and safety of early metformin use from the time of GDM diagnosis.[73] The study authors randomized 535 pregnancies diagnosed with GDM (using WHO 2013 criteria[61]) before 28 + 6 weeks' gestation in a 1:1 ratio to either metformin (2500 mg) or placebo, in addition to usual care. The primary outcome was a composite efficacy outcome of insulin initiation or a fasting glucose level ≥5.1 mmol/L (91.8 mg/dL) at gestational weeks 32 or 38. The primary outcome was not significantly different between the metformin group and the placebo group (56.8% vs. 63.7%; relative risk 0.89; 95% CI 0.78 to 1.02; $p = 0.13$). Secondary analysis demonstrated a lower requirement for insulin initiation in the metformin group compared with the placebo group (38.4% vs. 51.1%; RR 0.75; 95% CI 0.62 to 0.91; $p = 0.004$). Women in the metformin group experienced less GWG on average (0.8 vs. 2.0 kg; difference −1.2 kg; 95% CI −1.99 to −0.42; $p = 0.003$), but there

was no difference in weight loss at the 12-week post-partum visit. There was no significant difference in the proportion of preterm births between the 2 groups. Infants in the metformin group had lower mean birthweights (3.393 vs. 3.506 kg; difference −113 g; 95% CI −201 to −24; $p = 0.005$) and there were fewer cases of macrosomia (7.6% vs. 14.8%; difference −7.2%; 95% CI −12.6% to −1.8%; $p = 0.02$) and LGA babies (6.5% vs. 14.9%; difference−8.4%; 95% CI −13.7% to −3.2%; $p = 0.003$) in the metformin group. The proportion of SGA infants in each group was not significantly different (5.7% vs. 2.7%; unadjusted RR 2.1; 95% CI 0.9 to 5.2; $p = 0.13$). Regarding neonatal anthropometrics, there was a statistically significant difference in crown-heel length between the metformin group and the placebo group (51.0 vs. 51.7 cm; difference −0.7 cm; 95% CI −1.3 to −0.2; $p = 0.02$), the clinical significance of which is unclear and will be determined in follow-up studies.

Most recently, Rademaker et al. published the results of SUGAR-DIP[74]; a randomized, open-label non-inferiority trial comparing the combination of metformin and glyburide with insulin for the treatment of GDM. The diagnosis of GDM was made according to Dutch national guidelines, with a 75-g oral glucose tolerance test (OGTT) (using either WHO 1999 or WHO 2013 criteria), a 100-g OGTT, fasting glucose levels or daily glucose curves. Individuals with GDM were enrolled between 16 and 34 weeks' gestation if their glycaemic control was inadequate (fasting glucose level >5.3 mmol/L, 1-h post-prandial glucose >7.8 mmol/L, or 2-h post-prandial glucose >6.7 mmol/L) after 2 weeks of dietary modification. In total, 820 participants were randomized in a 1:1 ratio to receive either sequential metformin (2000 mg) and glyburide (2.5–5.0 mg), or insulin. In the metformin arm, 55% (224/406) of participants met glycaemic targets with metformin monotherapy, and 79% (320/406) with dual oral therapy. The proportion of LGA babies (which was the primary outcome) was not different between the oral therapy and insulin groups (23.9% vs. 19.9%; absolute risk difference 4.0%; 95% CI −1.7% to 9.8%; $p = 0.09$) and did not meet the pre-specified threshold of non-inferiority. Maternal hypoglycaemia was more common in the oral therapy group (20.9% vs. 10.9%; absolute risk difference 10%; 95% CI 3.7% to 21.2%), and exploratory analysis found that intravenous glucose therapy was administered more frequently to neonates from the oral therapy group (6.4% vs. 3.2%; absolute risk difference 3.2%; 95% CI 0.2% to 6.1%).

Other, smaller clinical trials have studied the short-term efficacy and safety of metformin versus insulin in GDM pregnancies.[75–82] Most have demonstrated a reduction in GWG with metformin use.[76,78–80,82] Some have mirrored the EMERGE findings of lower mean birthweights and fewer LGA infants in the metformin groups.[76,79] No other studies have replicated the increased preterm birth risk seen in the MiG trial. Comparisons between these studies are limited by the heterogeneity in inclusion criteria, ethnicities, GDM diagnostic criteria, treatment targets and outcome measures in each study.[83] Systematic reviews and meta-analyses continue to be published regularly in this area, though none have yet incorporated the results from the EMERGE or SUGAR-DIP trials. A summary of recently published systematic reviews and meta-analyses is given in Table 3.

4.5 | Metformin for the treatment of PGDM during pregnancy

The term PGDM refers to diabetes in pregnancy that existed prior to conception.[92] The main type of PGDM encountered in clinical practice is T2DM, with fewer living with type 1 diabetes mellitus (T1DM) or rarer forms of diabetes such as monogenic diabetes.[93] The prevalence of PGDM, and particularly T2DM, has increased substantially in recent decades amongst women of childbearing age.[94] Tight glycaemic management before and during pregnancy is required to mitigate the associated risks of adverse maternal and fetal outcomes including gestational hypertension, pre-eclampsia, congenital anomalies, LGA, preterm birth and perinatal mortality.[95]

4.5.1 | Metformin for the treatment of T1DM during pregnancy

As rates of overweight and obesity in adults living with type 1 diabetes approach 15%–30%, additive treatments are increasingly being studied.[96,97] For non-pregnant adults living with type 1 diabetes, metformin reduces insulin requirements and improves lipid profile.[98,99] The potential role of metformin in type 1 diabetes during pregnancy has been discussed as far back as 2011. Although to date only very small, real-world retrospective reports have been published,[100,101] metformin is being used in clinical practice with up to 5% of women living with type 1 diabetes in pregnancy using metformin in addition to insulin therapy.[102] A number of randomized controlled trials are currently in progress to further evaluate the role and potential benefits of metformin in pregnant women with type 1 diabetes (NCT03570632, NCT03928340, NCT03765359), and the results of these studies may contribute to changes in antenatal care.

4.5.2 | Metformin for the treatment of T2DM during pregnancy

After lifestyle and behavioural management, insulin therapy is recommended by the American Diabetes Association (ADA) as the preferred agent for the management of T2DM in pregnancy.[11] The ability to rapidly up-titrate doses makes insulin therapy highly effective at managing hyperglycaemia and countering the progressive insulin resistance of pregnancy. However, insulin therapy can be expensive and has been associated with excessive GWG, maternal and neonatal hypoglycaemia,[103] prompting interest in metformin as an adjunctive or alternative treatment. In 2022, based in part on evidence from the CLUE study,[104] an extension was granted to the label for metformin products in the European Union for use throughout pregnancy in women with pregestational Type 2 diabetes.[105] Despite the increasing prevalence of T2DM amongst women of childbearing age, there have been few randomized controlled trials investigating the safety and efficacy of metformin as a treatment for T2DM during pregnancy.[103,106–110]

TABLE 3 Systematic reviews and meta-analyses of metformin use in GDM pregnancies, published in the last 3 years (extension of a previously published table by Newman et al.[84]).

Lead author, year	Comparator	Studies Included	Outcomes associated with metformin use
Zhang,[85] 2024	Insulin	10 RCTs, 1 retrospective cohort study	Reduced risk: GWG, neonatal hypoglycaemia No difference in: maternal fasting plasma glucose, maternal HbA1c, preterm birth, neonatal jaundice, macrosomia, neonatal respiratory distress syndrome *Neonatal birthweight not included in meta-analysis*
Wu,[86] 2024	Insulin	24 RCTs	Reduced risk: pre-eclampsia, induction of labour, Caesarean delivery, macrosomia, NICU admission, neonatal hypoglycaemia, LGA No difference in: gestational hypertension, spontaneous vaginal delivery, emergency Caesarean delivery, shoulder dystocia, preterm birth, polyhydramnios, birth trauma, 5-min Apgar score <7, SGA, RDS, jaundice, birth defects *Neonatal birthweight not included in meta-analysis*
Sheng,[87] 2023	Insulin	24 RCTs (focusing on short-term neonatal outcomes only)	Lower neonatal birthweight Reduced risk: macrosomia, NICU admission, neonatal hypoglycaemia No difference in: LGA, SGA, neonatal height, RDS, abnormal 5-min Apgar score, hyperbilirubinemia, congenital anomalies, preterm birth, abnormal umbilical cord pH, neonatal death, neonatal sepsis, birth trauma
Shah,[88] 2022 *Bayesian Network Meta-analysis*	Insulin	18 RCTs	Lower neonatal birthweight Reduced risk: maternal postprandial hyperglycaemia, LGA, NICU admission No difference in: maternal fasting blood glucose, HbA1c, rate of Caesarean delivery, neonatal hypoglycaemia, mean gestational age at delivery, RDS, macrosomia
	Glyburide	5 RCTs	Lower neonatal birthweight Reduced risk: LGA, maternal postprandial hyperglycaemia No difference in: maternal fasting blood glucose, HbA1c, rate of Caesarean delivery, neonatal hypoglycaemia, mean gestational age at delivery, RDS, macrosomia, NICU admission
de Oliveira,[89] 2022	Glyburide	5 RCTs	Reduced risk: GWG No difference in: maternal fasting blood glucose, maternal postprandial hyperglycaemia, neonatal birthweight
Li,[90] 2022	Insulin	17 RCTs	Lower neonatal birthweight, lower gestational age at delivery Reduced risk: maternal hypoglycaemia, GWG, pre-eclampsia, gestational hypertension, NICU admission, neonatal hypoglycaemia, LGA, macrosomia No difference in: maternal glycaemic control, mode of delivery, hyperbilirubinemia, neonatal anthropometrics, preterm birth, SGA, shoulder dystocia, 5-min Apgar score <7, RDS, birth defects
	Glyburide	4 RCTs	Lower neonatal birthweight Reduced risk: GWG No difference in: maternal glycaemic control, gestational age at delivery, pre-eclampsia, mode of delivery, NICU admission, macrosomia, neonatal hypoglycaemia, LGA, preterm birth
Li,[91] 2022	Insulin	50 RCTs conducted in China	Reduced risk: maternal dysglycaemia, neonatal hypoglycaemia, RDS, preterm birth *Neonatal birthweight not included in meta-analysis*

Abbreviations: GDM, gestational diabetes; GWG, gestational weight gain; LGA, large for gestational age; NICU, neonatal intensive care unit; RCT, randomized controlled trial; RDS, respiratory distress syndrome; SGA, small for gestational age.

One of the largest studies of metformin in T2DM pregnancies was the MiTy (Metformin in Women With Type 2 Diabetes in Pregnancy) trial, published in 2020 by Feig et al.[109] During MiTy, 502 pregnant women with T2DM (diagnosed pre-pregnancy or before 20 weeks' gestation) were randomized in a 1:1 ratio to receive either metformin (1000 mg twice daily) or placebo, in addition to insulin. The primary outcome measure was a composite fetal and neonatal safety outcome comprising pregnancy loss, preterm birth, birth injury, neonatal respiratory distress, neonatal hypoglycaemia or NICU admission lasting longer than 24 h. The study did not demonstrate a significant difference in the primary outcome between the metformin and the placebo groups. However, the authors did find significant benefits in the secondary maternal outcomes, including reduced maternal weight gain with metformin compared with placebo (7.2 vs. 9.0 kg; difference −1.8 kg; 95% CI −2.7 to −0.9; $p < 0.0001$), lower third trimester HbA1c (41.0 vs. 43.2 mmol/mol; difference −2.0 mmol/mol; 95% CI −3.6 to −0.3; $p = 0.015$), lower third trimester insulin dose (1.1 vs. 1.5 units/kg/day; difference −0.4 units/kg/day; 95% CI −0.5 to

−0.2; $p < 0.0001$), and lower rates of Caesarean delivery (53% vs. 63%; RR 0.85; 95% CI 0.73 to 0.99; $p = 0.031$). Analysis of secondary neonatal outcomes revealed lower birthweights in the metformin group compared with placebo (3.156 vs. 3.375 kg; difference −0.44 kg; 95% CI −0.7 to −0.18; $p = 0.0016$), fewer extreme LGA (>97th centile for weight) babies (9% vs. 15%; RR 0.58; 95% CI 0.34 to 0.97; $p = 0.041$), fewer babies with macrosomia at birth (12% vs. 19%; RR 0.65; 95% CI 0.43 to 0.99; $p = 0.046$), and less neonatal body fat mass (13.2 vs. 14.6 g; difference −1.5 g; 95% CI −2.7 to −0.3; $p = 0.017$). Of important note from the MiTy trial, there was a higher proportion of SGA babies in the metformin group, and this is discussed in more detail in Section 4.6 below.

The largest trial to date in this area was published in 2023 by Boggess et al.[110] MOMPOD (Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy) recruited 831 women living in the United States either with pre-existing type 2 diabetes (79%) or with diabetes diagnosed prior to 23 weeks' gestation that required insulin (21%). Participants were randomized in a 1:1 ratio to receive either metformin (1000 mg twice daily) or placebo, in addition to insulin. The primary outcome was a composite fetal and neonatal safety outcome. Trial recruitment was stopped early at 75% due to futility in detecting a significant difference in the primary outcome. Secondary analyses demonstrated a reduction in mean birth weight in the metformin group compared with the placebo group (3.089 vs. 3.244 kg; difference −0.155 kg; 95% CI −0.265 to −0.045) and a reduction in the proportion of babies born LGA (26% vs. 36%; adjusted OR 0.63; 95% CI 0.46 to 0.86). There was no difference in the proportion of babies born SGA in the metformin group compared with the placebo group (8% vs. 7%; adjusted OR 1.17; 95% CI 0.68 to 2.02), though the authors note that MOMPOD was not powered to determine a difference for this outcome. Exploratory outcomes such as total daily insulin dose, excessive maternal weight gain and pre-eclampsia did not differ between the intervention arm and the placebo arm. Diarrhoea was reported more frequently as an adverse outcome by women taking metformin compared with those taking placebo (28% vs. 12%; $p < 0.01$). However, in MOMPOD, drug adherence was self-reported (no pill count) at approximately 60%. In addition, 269/831 (32%) of those randomized discontinued or did not take the study drug, which may have affected outcomes.

The differences in results between MiTy and MOMPOD may be partially attributable to differences in the ethnicities, ages and BMIs of the participants, which may have led to MOMPOD having a more insulin-resistant cohort, notwithstanding the inclusion of women with early GDM in the sample. Systematic review and meta-analysis of the limited literature in this area are lacking, though an individual participant data meta-analysis using MiTy and MOMPOD data is planned.[111] Whilst metformin may be beneficial to reduce rates of LGA, insulin requirements and maternal weight gain in pregnancies complicated by T2DM, further large, randomized, placebo-controlled trials may be required to ascertain its efficacy and safety in specific subgroups, with adequate power to detect differences in SGA as a primary safety outcome.

4.6 | Concerns regarding SGA babies

In the MiTy trial of metformin for the treatment of T2DM during pregnancy, a higher proportion of SGA babies was reported in the metformin group compared with the placebo group (12.5% vs. 6.6%; RR 1.96; 95% CI 1.10 to 3.64; $p = 0.026$).[109] A similar SGA finding had previously been reported by a smaller, open-label trial carried out by Ainuddin et al. in Pakistan.[103] These findings deserve further consideration, as SGA infants are at increased risk of hypoglycaemia, hypothermia and death in the perinatal period; persistent short stature, increased fat mass and insulin resistance during childhood; and higher cardiometabolic risk in adulthood.[112] As noted by the authors of the MiTy trial, it is unclear whether this finding represented an increase in pathological growth restriction or an overall downward shift in birthweight with an increase in smaller but healthy infants.[109]

Mouse models have suggested that maternal caloric intake may play an important role in determining the birthweight of metformin-exposed offspring, with metformin preventing excessive fetal weight gain in nutrient-rich intrauterine environments but producing lower birthweights in less nutrient-rich intrauterine environments.[15] However, secondary analysis of the MiTy trial found that maternal weight gain below the IOM (Institute of Medicine) recommendations was not a predictor of SGA in their cohort.[113] This analysis included 460 neonates, 45 of whom had been born SGA, of which 30 had been exposed to metformin and 15 to placebo. A maternal comorbidity variable comprising chronic hypertension or diabetic nephropathy was found to be predictive of SGA in a multivariate logistic regression model (OR 3.05; 95% CI 1.58 to 5.81; $p < 0.001$). The use of metformin appeared to amplify this effect. Though numbers in this post-hoc analysis were small, the authors concluded by advising caution around the use of metformin in T2DM pregnancies where chronic hypertension or diabetic nephropathy exist as comorbidities.

To date, trials of metformin in GDM have demonstrated lower birthweights but not an increase in babies born SGA. Secondary analysis of the EMERGE trial showed that metformin-exposed SGA infants did not display a more severe SGA phenotype than placebo-exposed SGA infants.[114] A recent population-based cohort study from the United Kingdom did not find a statistically significant risk of SGA in metformin-treated compared with insulin-treated GDM pregnancies (hazard ratio 1.33; 95% CI 0.67 to 2.00).[115] Nevertheless, the interactions between metformin and the maternal comorbidities of diabetes, hypertension and nephropathy will require further investigation in future clinical trials to fully elucidate the impact of metformin on fetal growth in different clinical scenarios.

4.7 | Metformin for the management of other conditions during pregnancy

There has been significant interest in the potential for metformin to be of benefit in conditions other than overweight, obesity, PCOS or diabetes.[3,4] These emerging investigational indications for metformin are discussed briefly below.

4.7.1 | Metformin to reduce the risk of hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) include gestational hypertension and pre-eclampsia and are leading causes of maternal and perinatal morbidity and mortality worldwide.[116] Maternal risk factors for HDP include obesity, PCOS, PGDM, GDM, age >40, chronic hypertension and chronic kidney disease (CKD). Pre-clinical studies using primary human tissues have shown that metformin can reduce placental secretion of anti-angiogenic molecules and improve vascular endothelial dysfunction, suggesting a role for metformin as a potential preventative or therapeutic treatment for pre-eclampsia.[117] In a small, randomized trial of 40 pregnant women with PCOS, metformin therapy reduced uterine artery impedance between 12 and 19 weeks gestation, and this was associated with a reduced composite pregnancy complication rate versus placebo, which included preterm delivery, severe pre-eclampsia or serious postpartum event (0/18 vs. 7/22, $p = 0.01$).[118]

Large RCTs have not consistently shown a benefit from metformin in at-risk groups. During the MOP study,[34] in women with BMI >35 kg/m^2, those receiving metformin 3000 mg daily had a pre-eclampsia incidence of 3.0%, compared with 11.3% with placebo (OR, 0.24; 95% CI, 0.10 to 0.61; $p = 0.001$). Similarly, Nascimento et al.[44] demonstrated that for non-diabetic pregnant women with an average BMI of 37.4 kg/m^2, women randomized to metformin 1000 mg daily had a pre-eclampsia incidence of 3.5%, compared with 17.7% with standard care (OR. 0.17; 95% CI, 0.10 to 0.41; $p < 0.01$). However, these positive findings were not replicated in the EMPOWaR[38] or GRoW[36] trials, although those trials had lower BMI cut-offs for entry and included women of different ethnicities. For pregnant women with PCOS, the PregMet studies did not demonstrate a benefit of metformin on the incidence of HDP.[49,50,119] In women with GDM or T2DM, none of the aforementioned large RCTs showed that metformin reduced the incidence of HDP compared with insulin.[21,73,109,110,120] However, with the exception of the first PregMet trial,[49] the incidence of HDP was not listed as a primary outcome in any of these large RCTs, and they may all have been under-powered to detect a true therapeutic effect.

Systematic reviews and meta-analyses in this area have provided conflicting results, with some finding that metformin reduces the risk of HDP in at-risk women,[90,121,122] and others finding no effect.[43,123] The meta-analyses of both Tarry-Adkins et al.[58] and Wu et al.[86] found that metformin reduced the risk of pre-eclampsia but had no effect on the risk of gestational hypertension. These differences may arise from substantial heterogeneity in the studies included in these analyses, where multiple groups of at-risk patients are combined and varying definitions for pre-eclampsia may have been used. Indeed, when Nascimento et al. performed a systematic review and meta-analysis confined to non-diabetic pregnant women with obesity only,[124] they found a significantly reduced risk of pre-eclampsia in metformin-treated women (RR 0.34; 95% CI 0.20 to 0.56; $p = 0.000$), albeit with high heterogeneity.

In summary, there is currently insufficient evidence to support the use of metformin for the prevention of HDP. Further RCT evidence will be required to evaluate the effectiveness of metformin in women with obesity, particularly BMI >35 kg/m^2. As a clinical practice point, it should be noted that the ADA does not recommend the use of metformin in pregnant people with hypertension or those with pre-eclampsia due to the potential for growth restriction or acidosis in the setting of placental insufficiency.[11]

4.7.2 | Metformin for the treatment of pre-eclampsia

Separately, metformin also has been investigated as a treatment for those with established pre-eclampsia. PI 2 (Pre-eclampsia Intervention 2) was a proof-of-concept RCT,[125] in which 180 women with preterm pre-eclampsia between 26 + 0 and 31 + 6 weeks' gestation (and undergoing expectant management) were randomized in a 1:1 ratio to extended-release metformin (3000 mg daily in divided doses) or placebo. The median time from randomisation to delivery was 17.7 days in the metformin group versus 10.1 days in the placebo group, a median difference of 7.6 days, which did not reach statistical significance (geometric mean ratio 1.39, 95% CI 0.99 to 1.95; $p = 0.057$). PI 3 (Pre-eclampsia Intervention 3) is a larger follow-on phase III trial that aims to recruit 500 participants, and will further assess metformin's role in the management of pre-eclampsia.[126]

4.7.3 | Metformin to slow the progression of CKD

Women with established CKD are at increased risk of adverse outcomes during pregnancy, including progression of CKD, pre-eclampsia, preterm birth and SGA infants.[127] In non-pregnant adults with CKD, metformin may have renoprotective benefits. The REMOVAL trial (in which non-pregnant individuals with T1DM and other cardiovascular risk factors were randomized to receive metformin or placebo) demonstrated that those who received metformin had an average eGFR of 4.0 mL/min/1.73 m^2 (95% CI 2.19 to 5.81; $p < 0.0001$) higher than the placebo group after 3 years of follow-up, with no significant difference in HbA1c.[99] A 2024 Cochrane review concluded with low certainty that in individuals with CKD, metformin may result in a slightly smaller decline in kidney function compared with placebo (3 RCTs, 505 participants: mean difference 1.92 mL/min, 95% CI 0.33 to 3.51; $I^2 = 0\%$).[128]

Regardless of pregnancy status, metformin is currently not recommended for use in the presence of CKD stages 4 and 5 (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), due to an increased potential for lactic acidosis during severe inter-current illness.

4.7.4 | Metformin for the treatment of metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with and is often considered the hepatic manifestation of the metabolic syndrome, sharing common pathophysiological

features of obesity, dyslipidaemia and insulin resistance.[129] The hallmark of MASLD is fat accumulation in the liver, which can progress to MASH (metabolic dysfunction-associated steatohepatitis) and cirrhosis. Population-based studies have shown that pregnant women with MASLD are at increased risk of adverse outcomes such as GDM, hypertensive disorders, Caesarean delivery, preterm birth, postpartum haemorrhage and low birthweight babies.[130,131] There is currently insufficient evidence to support metformin monotherapy for the treatment of MASLD or MASH, and metformin is not currently recommended by international guidelines for this purpose.[132] Forthcoming RCTs may reveal therapeutic benefit for MASLD when metformin is used in combination with other therapies such as GLP-1 agonists, SGLT2 inhibitors or pioglitazone[133]; however, these studies are unlikely to be applicable to pregnant women with MASLD, in whom these agents are contraindicated due to insufficient safety data.

5 | CONCLUSION

Metformin use has been studied in diverse cohorts of pregnant women. The off-label use of metformin to treat GDM in clinical practice is increasing,[20] but there is widespread variability internationally, reflecting the current heterogeneity of the evidence regarding its use.

To date, most trials have demonstrated maternal benefits for those with GDM or T2DM, particularly for limiting GWG and improving glycaemic control. However, uncertainty remains regarding potential adverse effects of metformin on fetal and neonatal outcomes, particularly SGA. Currently, it would seem prudent to avoid the use of metformin in pregnant women with chronic hypertension, nephropathy, or those whose fetal growth scans are suggestive of growth restriction.

To progress our knowledge in this field, future randomized clinical trials will need to control for all relevant maternal baseline characteristics and conditions that could influence the efficacy and safety of metformin.[134] Furthermore, all trials should report on core maternal, fetal and neonatal outcome measures to enhance comparison in systematic reviews and meta-analyses.[135,136] Finally, trial investigators should plan for long-term follow-up of all mother–child research participant pairs exposed to metformin in pregnancy.

AUTHOR CONTRIBUTIONS

RPM and CN performed the literature review. RPM, CN, AME and FPD drafted and critically reviewed the work.

ACKNOWLEDGMENT

This article was commissioned by the Editor as part of a Themed Issue on Women's health made possible by funding from Merck. Sponsor identity was not disclosed to the authors prior to publication.

CONFLICT OF INTEREST STATEMENT

FPD is the principal investigator, and CN is a sub-investigator on the EMERGE trial and the ongoing EMERGE follow-up trial. RPM is a sub-investigator on the EMERGE follow-up trial.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16361.

DATA AVAILABILITY STATEMENT

All data was taken from publicly available sources.

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How to cite this article: McEvoy RP, Newman C, Egan AM, Dunne FP. A narrative review of metformin in pregnancy: Navigating benefit and uncertainty. *Diabetes Obes Metab*. 2025;27(Suppl. 3):16-30. doi:10.1111/dom.16361