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Long-term effects of metformin on offspring health: A review of current evidence and future directions

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Abstract

Metformin is widely prescribed for the management of type 2 diabetes mellitus, polycystic ovary syndrome, and gestational diabetes mellitus in pregnancy. Its use is driven by factors including oral administration, lower patient and health system burden and cost, and benefits including lower risk of excess gestational weight gain and hypoglycemia compared with insulin. Metformin use appears safe in pregnancy; however, there remain concerns regarding long-term effects of intrauterine metformin exposure on offspring health. Randomized controlled trial follow-up studies suggest that metformin-exposed offspring may have altered postnatal growth trajectories and increased adiposity in childhood, although data are limited. Whether this is a transient adaptation or a precursor to long-term metabolic dysfunction is unclear, as data on cardiometabolic and neurodevelopmental parameters, including glucose homeostasis, lipid metabolism, and cognitive function, are sparse and inconsistent. Methodological challenges include heterogeneous study designs, high attrition rates, and inadequate control for confounding variables. Given these uncertainties, further well-powered, long-term prospective studies and individual patient data meta-analyses, harmonizing data and adjusting for confounders, are needed to clarify risks and benefits of metformin use in pregnancy. Until such data are available, clinicians must weigh the benefits and advantages of metformin use in pregnancy against the unknowns regarding potential long-term impact on offspring health.

Plain Language Summary

Metformin is a medicine often used during pregnancy to help manage conditions such as type 2 diabetes, gestational diabetes, and polycystic ovary syndrome (PCOS). It is commonly chosen because it is taken as a tablet rather than by injection, has a lower risk of causing low blood sugar, and is generally easier and less expensive to use than insulin.

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Research has shown that metformin is safe for use during pregnancy in the short term. However, there are still questions about whether it has any lasting effects on children who were exposed to it before birth. This review explores this topic in detail.

Some studies have found that children exposed to metformin during pregnancy may have slightly different growth patterns, such as having more body fat or being heavier in early childhood. However, these results are inconsistent and most studies show no clear differences in overall health outcomes, including in heart health, metabolism, or brain development. The results are mixed, and many studies are small or have design limitations, which makes it difficult to draw strong conclusions.

At this stage, there is no clear evidence that metformin causes harm to children in the long term. However, because some studies suggest there may be effects on childhood growth and development, researchers emphasize the need for further long-term research. These future studies should follow children into adolescence and adulthood to better understand any lasting impacts.

Until more is known, doctors and patients will need to carefully consider the known benefits of metformin in pregnancy alongside the current uncertainties about long-term effects on child health.

KEYWORDS
infant, long-term outcomes, metformin, offspring, pregnancy, review, safety

1 | INTRODUCTION

Metformin is a widely used biguanide and insulin sensitizer with complex physiological actions that are yet to be fully elucidated.[1] It is known that metformin enhances insulin sensitivity, facilitates receptor-mediated intestinal and peripheral glucose uptake, and reduces gluconeogenesis.[2] Collectively, these actions stabilize blood glucose levels and can limit ongoing weight gain with modest potential weight loss.[3,4] With prediabetes and type 2 diabetes (T2DM) as conditions driven by insulin resistance, impaired insulin secretion, or both, with resulting hyperglycemia,[5,6] metformin is recommended in the prevention and management.[7,8] Metformin is also recommended by International Evidence-based Guidelines for the general management of metabolic symptoms in polycystic ovary syndrome (PCOS), a highly prevalent endocrine disorder that affects approximately 10–13% of women of reproductive age.[9,10]

While metformin is a preferred pharmacotherapy for the management of T2DM and metabolic symptoms of PCOS,[11] its use in pregnancy is more controversial.[1] Here, indications include T2DM, PCOS, and gestational diabetes mellitus (GDM), the latter defined as hyperglycemia with first onset in pregnancy.[12] Pre-gestational diabetes and GDM currently affect 1–2% and 14% of pregnancies, respectively.[12,13] While a detailed discussion of the efficacy and role of metformin in these conditions is beyond the scope of this review, indications in T2DM,[14] PCOS,[15] and GDM[1] have recently been reviewed elsewhere.

In summary, during pregnancy, hyperglycemia can lead to a range of complications, including polyhydramnios, preterm delivery, respiratory distress, neonatal hypoglycemia, macrosomia, and an increased risk of miscarriage.[16,17] Treatment via lifestyle, metformin, and/or insulin therapy has been shown to ameliorate these risks and associated perinatal adverse outcomes.[18,19] According to prospective clinical studies, as an anti-diabetic agent, metformin could offer important benefits for pregnancies complicated by hyperglycemia, with potential advantages of less patient and health professional burden and cost, and a lower risk of hypoglycemia and excess gestational weight gain, compared with insulin.[20,21]

Yet, in T2DM, PCOS, and GDM, potential benefits need to be offset against the risks of metformin use in pregnancy, which continue to be controversial in the context that it traverses the placental barrier and enters the foetal circulation.[22] Current guidelines from the National Institute for Health and Care Excellence (NICE) recommend that women with GDM be offered metformin if glycemic targets are not met with diet and exercise within 1–2 weeks.[23] Guidelines in Scotland and Canada recommend that metformin or glibenclamide be considered as initial treatments in GDM[24] or as alternatives to insulin,[25] but that women be informed of its transplacental passage, the lack of evidence on long-term safety, and the likelihood of metformin failure necessitating insulin initiation. Conversely, the American[26] and Australian[27] Diabetes Associations recommend insulin as the first-line treatment for GDM if lifestyle management is unsuccessful, classifying metformin as a Category B and C drug, respectively, noting a lack of evidence on long-term safety data in offspring. Some evidence suggests that maternal metformin use may be associated with adverse effects on foetal, neonatal, and long-term offspring health outcomes. Reported effects include restricted foetal growth and reduced birth weight, increased risk of prematurity, and a higher susceptibility to metabolic disorders, such as childhood obesity.[22,28,29]

However, other studies report no effects of metformin on foetal growth or the duration of gestation,[30] with some suggesting reduced miscarriage and prolonged gestation with metformin compared with placebo.[31] Overall, there remain notable discrepancies between studies and guidelines regarding the impacts of metformin use during pregnancy, and a comprehensive understanding of its long-term effects on offspring health is lacking.

This review summarizes the primary molecular mechanisms by which metformin regulates metabolism and crosses the placenta, providing a foundation for understanding foetal metformin exposure. We then explore and synthesize existing human studies, with a critical evaluation of evidence from observational studies, randomized controlled trials (RCTs) and systematic reviews and meta-analyses on potential long-term effects on offspring health. Finally, key limitations in existing research are identified, and priorities for future research are outlined to advance understanding in this important area of study.

2 | METHODS

A search was performed using PubMed and Google Scholar databases through a combination of keywords related to metformin, pregnancy, offspring health, and long-term effects. The review was limited to published studies in the English language with data from the earliest record date up to December 2024. We included all study designs provided that long-term outcomes were reported following maternal metformin use. Studies which either did not report relevant outcomes or focused only on short-term effects were excluded. As this is a narrative review, the search was not conducted systematically and is intended to provide an extensive overview of the literature, rather than generate new data or conclusions.

3 | MECHANISMS OF METFORMIN IN CELLULAR METABOLISM

Metformin is a synthetic biguanide which is chemically related to compounds in the plant *Galega officinalis*, with similar physiological actions.[32] It was not synthesized to bind specific molecular targets, and some of its actions, particularly its secondary effects including on mitochondrial function and epigenetic changes, remain unclear.[33,34] However, the glucoregulatory actions of metformin are well-documented, with mechanisms including inhibiting hepatic gluconeogenesis, reducing intestinal glucose absorption, and increasing peripheral glucose uptake – actions that collectively improve insulin sensitivity and stabilize glucose levels.[2] While glycemic control is considered its primary function, metformin has also been shown to impact on weight regulation, lipid metabolism, mitochondrial function, cellular energy homeostasis, and vascular health,[34] effects that could have lasting consequences when exposure occurs *in utero*.

As a hydrophilic molecule, metformin is transported by organic cation transporters (OCTs) expressed in key metabolic organs including the intestine, liver, and kidneys. In the intestinal environment, plasma membrane monoamine transporter (PMAT), localized on the luminal side, facilitates the uptake of metformin from the intestinal lumen into enterocytes.[5,35] Additionally, OCT1 is expressed in the basolateral membrane and cytoplasm of enterocytes and may contribute to the transport of metformin from enterocytes into interstitial fluid.[5,36] In the liver, both OCT1 and OCT3 are expressed in the basolateral membrane of hepatocytes, with evidence suggesting that OCT1 primarily mediates the hepatic uptake of metformin, while OCT3 plays a supplementary role.[36,37] In the kidneys, OCT2 transporters, predominantly expressed in renal epithelial cells in the basolateral membrane in renal tubules, facilitate the primary intake of metformin in kidneys,[37] while multidrug and toxin extrusion protein 1 and 2-K (MATE1 and MATE2-K), expressed in the apical membrane of the renal proximal tubule cells, promote the renal excretion of metformin.[37,38] The reabsorption of metformin may also be facilitated by OCT1 expressed on the apical and subapical domain side of both proximal and distal tubules in the kidneys,[39] and by PMAT, expressed in the apical membrane of renal epithelial cells.[5,40]

Among these tissues, the intestine has emerged as a primary site of action for metformin, rather than the liver, where concentrations can be 30 to 300 times higher than those observed in the blood or liver.[41] This high intestinal concentration plays an important role in initiating the metabolic effects of metformin, beginning with the inhibition of mitochondrial complex I in the respiratory chain. This inhibition disrupts the conversion of NADH to NAD+ leading to a relative deficiency of NAD+, which in turn promotes the conversion of pyruvate to lactate in enterocytes, enhancing glucose utilization and contributing to a reduction in systemic glucose levels.[42,43] The increase in intestinal lactate production contributes to a form of metabolic gut–liver cross-talk. Lactate produced in the intestine is transported to the liver, where it can be used as a substrate for gluconeogenesis—a process that forms part of a splanchnic glucose–lactate–glucose cycle which, although energetically costly, may play a regulatory role in glucose homeostasis.[42,43]

Inhibition of complex 1 by metformin also leads to an increase in cellular AMP to ATP ratio, and subsequent activation of 5' adenosine monophosphate-activated protein kinase (AMPK). AMPK is a master regulator of cellular energy homeostasis, playing a key role in glucose and fatty acid uptake and oxidation.[44–46] The AMPK activation and downstream metabolic effects described herein have been specifically observed in the context of metformin exposure. However, AMPK activation is not unique to metformin, and the mitochondrial effects of metformin are multifactorial, involving both AMPK-dependent and -independent pathways.[47]

Activated AMPK influences metabolic regulation by inhibiting several key enzymes and proteins involved in lipogenesis, cholesterol synthesis, and hepatic gluconeogenesis, including 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, mammalian target of rapamycin (mTOR), acetyl-CoA carboxylase (ACC), acetyl-CoA carboxylase 2 (ACC-2), glycerol-3-phosphate acyltransferase, and carbohydrate response element-binding protein (ChREBP).[5,48,49] Additionally, AMPK activation suppresses the expression of sterol regulatory element-binding protein-1 (SREBP1), a key transcription factor involved in lipid and cholesterol biosynthesis.[5,50] In an AMPK-

independent manner, metformin has also been shown to directly interfere with the coactivation of pregnane X receptor (PXR) with steroid receptor coactivator 1 (SRC1), leading to the downregulation of the cytochrome P450 3A4 (*CYP3A4*) gene and a reduction in the CYP3A4 enzyme involved in lipogenesis.[5,51]

Beyond suppressing lipid and glucose production, AMPK activation also enhances glucose utilization and metabolic efficiency in skeletal muscle, adipocytes, and cardiomyocytes. Here, AMPK promotes glucose uptake by facilitating the translocation of glucose transporter type 4 (GLUT4) to the cell membrane. This enables ATP-independent facilitated diffusion of glucose into the cell, supporting glycolytic flux and, under certain conditions, intracellular glucose storage as glycogen.[5,45,46] Furthermore, AMPK activation shifts metabolic balance towards energy conservation by simultaneously inhibiting fatty acid and triglyceride synthesis in the liver while promoting fatty acid oxidation in skeletal muscle and adipose tissue. This dual role enhances systemic insulin sensitivity and promotes metabolic flexibility.[5,45] Activated AMPK also upregulates peroxisome proliferator-activated receptor-γ coactivator 1α (Pgc-1α) expression via silent mating type information regulation 2 homologue 1 (SIRT1), facilitating downstream mitochondrial biogenesis. In maternal tissues, these effects improve insulin sensitivity and metabolic efficiency, yet AMPK activation in placental and foetal tissues may have distinct effects on nutrient metabolism, growth regulation, and energy storage that persist beyond gestation.

4 | PLACENTAL TRANSFER AND PHARMACOKINETICS OF METFORMIN IN PREGNANCY

During pregnancy, the placenta plays a critical role in metabolic regulation, serving as the interface between maternal and foetal circulations and facilitating the transport of essential nutrients, such as glucose and fatty acids. It is well established that metformin, when administered during pregnancy, readily crosses the placenta and is detectable in foetal circulation.[52] Although the effects of metformin on placental development are not fully understood, some studies suggest that it may help normalize placental morphology in women with hyperglycemia. Specifically, placentas from metformin-treated GDM pregnancies appear similar to those of normoglycemic controls, whereas those from GDM pregnancies managed with diet alone exhibit pathological features such as villous immaturity, infarction, chorangiosis, and increased syncytial knots.[53] However, other studies suggest that metformin may reduce placental ATP production and mitochondrial respiration.[54] This raises potential concerns about whether mitochondrial suppression could impair placental capacity for efficient nutrient transfer to the foetus, with possible implications for foetal growth, development, and future metabolic programming.[54]

Maternal-to-foetal transfer of metformin appears to be mediated primarily by OCT3, which is localized at the foetal-facing basal membrane of the placenta. Notably, OCT3 expression in the placenta increases with gestational age, leading to higher foetal exposure in late pregnancy. In a murine study, mOCT3 expression was gestational age-dependent, with mRNA levels increasing up to 128-fold between gestational days 10 and 19.[55] In humans, OCT3 expression is relatively high even in early pregnancy and moderately increases in the second trimester and term placentas.[55,56] However, as reported by Meyer et al.,[57] there are notable differences in the affinity of metformin for OCTs between humans and mice, and metformin concentrations in the liver are significantly higher in mice than in humans. These findings highlight limitations of murine models for predicting OCT-mediated placental pharmacokinetics in humans. Other transporters, including the norepinephrine transporter (NET), serotonin transporter (SERT), and organic cation transporter novel type 2 (OCTN2), located at the maternal interface, may also contribute to metformin transfer to the foetus.[58] In 15 pregnant women with PCOS receiving 850 mg of metformin twice a day, metformin concentrations were significantly higher, but corresponding to therapeutic levels in adults, in the umbilical vein ($\mu = 2.81$ μmol/L) and umbilical artery ($\mu = 3.16$ μmol/L) compared to levels detected in maternal venous blood ($\mu = 1.50$ μmol/L), confirming foetal exposure.[52] Other studies have shown similar results.[52,55,56,58] One study also demonstrated that the net secretion clearance of metformin during mid and late pregnancy is significantly higher, reported at 480 ± 190 mL/min and 419 ± 78 mL/min, respectively, when compared to a clearance rate of 313 ± 98 mL/min observed postpartum. These findings suggest that maternal plasma concentrations of metformin are lower during pregnancy than in non-pregnant women.[59]

The mechanisms underlying metformin transfer back to maternal circulation (i.e. foetal-to-maternal efflux) are less well-defined but likely involve both placental transporters and physiological factors such as pH gradients. In the rat placenta, coordinated activity of OCT3 on the foetal-facing membrane and the apical efflux transporter MATE1 on the maternal-facing membrane enable foetal-to-maternal metformin clearance via a proton-coupled antiport mechanism.[60] This dynamic bidirectional transfer of metformin may explain why metformin generally does not appear to accumulate in foetal tissues in human studies. However, recent evidence from a non-human primate model (rhesus macaques) demonstrated foetal bioaccumulation of metformin, particularly in the kidney, and associated this with foetal growth restriction and renal dysmorphology.[61] These findings challenge earlier assumptions and underscore the importance of species-specific investigations into foetal exposure and potential developmental consequences.

Beyond transporter-mediated transfer mechanisms, pregnancy-related physiological changes can also impact metformin pharmacokinetics and foetal exposure at different gestational stages. As a hydrophilic cation with a five-hour half-life, metformin is not metabolized in humans, and its bioavailability, volume of distribution, and clearance vary throughout pregnancy. These variations occur due to increased renal clearance, expanded plasma volume, altered gastric absorption, and changes in drug transport mechanisms, all of which influence maternal plasma concentrations and foetal exposure. However, the effects of these factors on placental metabolism and potential genetic impacts on the foetus remain poorly understood.[59]

Upon reaching the developing foetus, metformin has been shown to activate AMPK and modulate mTOR signalling, leading to reduced

TABLE 1 Characteristics of studies examining the effects of metformin on long-term offspring health.

First author, Year, Country	Design/Population	Children age	Metformin group (n), dose (mg)	Comparator group (n)	Outcomes measures	Summary results
Retrospective and prospective observational studies						
Martine-Edith et al., 2023, UK[68]	Prospective longitudinal cohort; women with GDM, $n = 10\,024$	0 to 5 years	***n* = 76;** 1700 mg/day metformin + lifestyle changes from first trimester to delivery	***n* = 420;** insulin + lifestyle ***n* = 234;** lifestyle alone ***n* = 9171;** offspring not exposed to GDM (No-GDM)	Height and BMI z-score trajectories	Metformin treatment was not associated with differences in offspring growth trajectories compared to insulin treatment
Brand et al., 2022, Finland[69]	Population register-based retrospective cohort; children with maternal exposure to metformin or insulin regardless of the indication (GDM, pre-gestational T2DM, and PCOS) (metformin cohort), $n = 10\,129$	1 week to 11 years (median time 3.5 years)	***n* = 3967;** metformin (556–1667 mg/d) exposed offspring of mothers with T2DM ($n = 154$), PCOS ($n = 464$), obesity ($n = 1897$), GDM ($n = 2897$), toxaemia ($n = 557$)	***n* = 889;** combination treatment (metformin + insulin) ***n* = 5273;** insulin treatment (only include children born to mothers with GDM and T2DM)	Childhood obesity, hypoglycemia, hyperglycemia, hypertension, diabetes, PCOS, and challenges in motor-social development	No increased long-term risk associated with pregnancy exposure to metformin (alone or in combination with insulin), compared with insulin only
Fornes et al., 2022, Sweden[70]	Retrospective nationwide population-based cohort; singleton births ($n = 1\,016\,805$) from 686 847 women with/without PCOS	Before 11.5 years of age	***n* = 347;** offspring of pregnant women with PCOS who received metformin (received at least one dispensed prescription) from the last menstrual period until delivery ***n* = 864;** offspring of pregnant women without PCOS who received metformin (having received at least one dispensed prescription)	***n* = 21 385;** offspring of pregnant women with PCOS who did not receive metformin ***n* = 991 019;** offspring of pregnant women without PCOS who did not receive metformin	Childhood obesity	Metformin use during pregnancy in women without PCOS was associated with an increased risk of childhood obesity; metformin use in women with PCOS was not linked to any adverse outcomes in offspring
Landi et al., 2019, New Zealand[71]	Retrospective population-based cohort; women with GDM, $n = 3928$	4 years	***n* = 3818;** 1700 mg/day metformin from first trimester to delivery	***n* = 3450;** insulin-treated group	Body composition measurements	No meaningful difference in weight, BMI, or weight for height between children exposed to metformin compared with insulin
Glueck et al., 2004, USA[72]	Prospective cohort; infants of women with PCOS who conceived on metformin and continued until delivery vs. infants from healthy women not treated with metformin, $n = 388$	18 months	***n* = 126;** offspring of women who conceived on, and continued metformin (1500–2500 mg/d) until delivery	***n* = 262;** infants born to healthy women	Major birth defects, infant birth weight and height, and growth and motor-social development	No adverse effects were observed in birth length and weight, growth or motor-social development
Randomized controlled trial follow-up studies						
Paavilainen et al., 2023, Finland[73]	RCT; women with GDM, $n = 172$	9 years	***n* = 82;** metformin	***n* = 90;** insulin	Anthropometrics, adipocytokines,	No effects of metformin exposure

TABLE 1 (Continued)

First author, Year, Country	Design/Population	Children age	Metformin group (n), dose (mg)	Comparator group (n)	Outcomes measures	Summary results
					markers of the low-grade inflammation	on adiposity, body composition, liver fat, or inflammation markers in prepubertal offspring compared to insulin but higher adiponectin concentration and lower leptin/adiponectin-ratio in boys
Rowan et al., 2023, New Zealand[74]	RCT, hospital-based; women with GDM, *n* = 98	9 years	n/a	Insulin	Size and adiposity (using BIA and DXA)	In boys, BMI and lean mass were positively associated with metformin treatment
Deussen et al., 2023, New Zealand and Australia (GRoW trial)[75]	RCT; women with GDM, *n* = 524	6 months to 5 years	***n* = 228;** metformin 500–2000 mg/day	***n* = 220;** placebo	Child weight, height, anthropometry, diet, physical activity and neurodevelopment	At 18 months and 3–5 years of age, more than half of the children had a BMI z-score > 85th centile, indicating a high risk of childhood obesity
Feig et al., 2022, Canada and Australia (MiTy trial)[76]	RCT, hospital-based; women with T2DM, *n* = 283	0 to 2 years	***n* = 135;** metformin 2000 mg/day	***n* = 148;** placebo	Anthropometric measurements, including weight, height, and skinfold thicknesses	Similar anthropometrics overall. In males, metformin led to higher BMI growth trajectory between 8 and 24 months
Yang et al., 2022, UK[77]	RCT; DM = 115, obese pregnant women	4 to 7 years	***n* = 19;** metformin, 500–2500 mg/day	***n* = 21;** placebo	Body composition, peripheral blood pressure, arterial pulse wave velocity and central hemodynamics	Metformin or placebo during pregnancy had no effects on body composition or vascular measures
Paavilainen et al., 2022, Finland[78]	RCT; women with GDM, *n* = 172	9 years	***n* = 82;** metformin	***n* = 90;** insulin	Measurements included anthropometrics, blood pressure, lipoproteins, and oral glucose tolerance tests.	No differences between groups in anthropometric measures, including BMI and waist-to-height ratio. Higher HDL-C but lower LDL-C and apolipoprotein B in metformin-exposed offspring compared with insulin. Difference in HDL-C was only significant in boys
Hanem et al., 2021, Norway[79]	RCT; women with PCOS, *n* = 117	5 to 10 years	***n* = 63;** metformin 2000 mg/d	***n* = 54;** placebo	Steroid hormone levels.	No difference in hormone levels between metformin- and placebo-exposed girls, but higher 11-deoxycortisol z-score in boys (not significant after Holm-Bonferroni correction)

(Continues)

TABLE 1 (Continued)

First author, Year, Country	Design/Population	Children age	Metformin group (n), dose (mg)	Comparator group (n)	Outcomes measures	Summary results
Paul et al. 2021, India[80]	RCT; women with GDM, *n* = 78	9 years	***n* = 41;** metformin	***n* = 37;** glibenclamide	Anthropometric measurements, lipid profile, and blood pressure	No difference in anthropometric measures, blood pressure, and lipid profile except for triglyceride which was higher in the offspring of mothers treated with metformin
Panagiotopoulou O et al., 2020, UK[81]	RCT; GDM = 151 children from obese pregnant women	3 to 5 years	***n* = 77;** metformin	***n* = 74;** placebo	Cardiovascular profile and body composition	No significant difference in peripheral blood pressure, arterial stiffness but lower central hemodynamic and cardiac diastolic indices in metformin versus placebo-exposed group
Greger et al., 2020, Norway[82]	RCT; PCOS, *n* = 93	5 to 10 years	**n = 52;** metformin 1700 and 2000 mg/d	**n = 41;** placebo	Cognitive function	No evidence of long-term effects of metformin on average child cognitive function
Hanem et al., 2019, Norway (PregMet study)[83]	RCT, Cohort; women with PCOS, *n* = 141	5 to 10 years	***n* = 71;** metformin 1700 and 2000 mg/d	***n* = 70;** placebo	Body composition measurements	Higher BMI z-score in metformin versus placebo group
Hanem et al., 2018, Norway[84]	RCT, double-centre, hospital-based; women with PCOS, *n* = 182	4 years	***n* = 92;** metformin 1700 and 2000 mg/d	***n* = 90;** placebo	Height, weight, BMI, and overweight/obesity converted to z scores.	Higher weight z-score and BMI z-score in metformin versus placebo group
Rowan et al., 2018, New Zealand and Australia[85]	RCT, hospital-based; women with GDM, *n* = 200	7 to 9 years	***n* = 103;** metformin	***n* = 105;** insulin	Anthropometry, BIA, DXA, MRI and fasting bloods	No differences in offspring measures at 7 years. At 9 years, metformin-exposed children were larger by measures of weight, arm and waist circumferences, waist: height ratio; BMI, triceps skinfold; DXA fat mass and lean mass; MRI abdominal fat volume, but similar offspring total and abdominal body fat percent and metabolic measures
Tertti K et al., 2016, Finland[86]	RCT, hospital-based; GDM, *n* = 52	3 to 7 years	***n* = 25;** metformin 1700 mg/day	***n* = 27;** insulin	Body composition measurements	No differences in height, weight, BMI, BMI z-score, or waist-to-hip ratio in boys or in prepubertal testicular size between groups
Wouldes et al., 2016, New	RCT; women with GDM, *n* = 211	2 years	n/a	Insulin	Neurodevelopment	No difference between the

TABLE 1 (Continued)

First author, Year, Country	Design/Population	Children age	Metformin group (n), dose (mg)	Comparator group (n)	Outcomes measures	Summary results
Zealand and Australia[87]						neurodevelopment of children at 2 years
Ijäs H et al., 2015, Finland[88]	RCT, hospital-based cohort; women with GDM, *n* = 97	12 and 18 months	***n* = 47;** metformin 1700 mg/day	***n* = 50;** insulin	Body measurement	Metformin-exposed group was heavier at 12 months and taller and heavier at 18 months
Battin et al., 2015, New Zealand[89]	RCT; GDM, *n* = 222	2 years	***n* = 83;** metformin 1700 mg/day	***n* = 87;** insulin	Blood pressure measurement	No difference in blood pressure between the metformin and insulin treatment arms
Carlsen et al., 2012, Norway[90]	RCT, multicentre; women with PCOS, *n* = 256	1 year	***n* = NR;** metformin 2000 mg/day	***n* = NR;** placebo	Body composition and metabolic measurements	Women who used metformin in pregnancy lost less weight and their infants were heavier than those in the placebo group at 1 year
Rø et al., 2012, Norway[91]	RCT, hospital-based; PCOS, *n* = 550	8 years	***n* = 11;** metformin 1700 mg/d	***n* = 12;** placebo	Body composition and metabolic measurements	No difference in growth and body composition but higher fasting glucose and systolic blood pressure and lower LDL-C in the metformin-exposed group, thought to be coincidental
Rowan et al., 2011, New Zealand (MiG trial)[92]	RCT, hospital based; women with GDM, *n* = 154	2 years	***n* = 154;** metformin	***n* = 164;** insulin	Body composition measurements	Larger mid-upper arm circumferences and subscapular and biceps skinfolds but no difference in total fat mass and percentage body fat by bioimpedance and DXA
Systematic reviews and meta-analyses						
Dutta et al., 2024[93]	Meta-analysis; T2DM/GDM; *n* = 7 studies (participant n NR)	5 to 9 years	Metformin	Insulin	BMI, obesity, changes in lipids and adipocytokines	No long-term adverse effects
Gordon et al., 2024[94]	Meta-Analysis; women using metformin at any gestation for any indication with neurodevelopmental follow-up results for offspring, *n* = 14 042	0 to 14 years	Metformin	Insulin/placebo	Neurodevelopmental	In utero exposure to metformin was not associated with adverse neurodevelopmental outcomes in children up to the age of 14 years
Fu et al., 2024[95]	Meta-Analysis; *n* = 7975 children with metformin exposure in utero and over 1 million children without metformin exposure	1 to 11.5 years	Metformin	Insulin/glibenclamide/placebo/no treatment	Anthropometric and childhood obesity	Metformin exposure in pregnancy showed no significant difference in long-term offspring BMI, overweight, or waist circumference compared to non-exposed children;

(Continues)

TABLE 1 (Continued)

First author, Year, Country	Design/Population	Children age	Metformin group (n), dose (mg)	Comparator group (n)	Outcomes measures	Summary results
						Slightly higher BMI was observed in metformin-exposed children aged 1–3 years (SMD 0.15), but no difference was seen at older ages (3–6 and 6–11 years).
Tarry-Adkins et al., 2019[29]	Meta-Analysis; women with GDM, $n = 3976$	0 to 9 years	Metformin	Insulin	Foetal, infant, and childhood growth, including weight, height, BMI, and body composition	Lower average birth weight and accelerated postnatal growth, resulting in heavier infants and higher BMI by mid-childhood in metformin compared to insulin-exposed groups
Xu et al., 2019[96]	Meta-Analysis; GDM/PCOS, $n = 823$	0 to 13 years	Metformin	Insulin/ placebo	Weight, body composition, metabolic parameters and neurological development	Prenatal exposure to metformin was associated with significantly heavier weight. Other parameters showed no difference between groups
Van Weelden W et al., 2018[97]	Meta-Analysis; GDM/PCOS, $n = 778$	0 to 9 years	Metformin	Insulin/ placebo	Weight, height, BMI	Increased offspring weight, but not height or BMI in metformin-exposed groups

Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; GDM, gestational diabetes mellitus;HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LGA, large for gestational age (birth weight > 90% centile); MiG, Metformin in Gestational Diabetes; MiTy, Metformin in Women with Type 2 Diabetes in Pregnancy; MRI, magnetic resonance imaging; n, sample size; NR, not reported; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; SD, standard deviation; SGA, small for gestational age (birth weight < 10% centile); T2DM, type 2 diabetes mellitus.

glucose production and oxygen consumption.[62] Indeed, foetal metformin exposure has been associated with an increased risk of small-for-gestational age (SGA) infants, as well as obesity later in life.[58] However, in pooled RCT data from 800 pregnant women with PCOS, metformin exposure did not affect birthweight or birth length but resulted in larger head circumference.[63] Swenson et al.[62] also reported that metformin influences signalling and metabolism in foetal hepatocytes, increasing stress pathway activation and modifying hepatokine secretion.[62] It should be noted, however, that this study involved direct foetal infusion of supratherapeutic metformin concentrations (5–120 mmol/L), which exceed levels typically observed in human foetal plasma (<2 mg/L), and may limit the clinical relevance of these findings. Nevertheless, these effects suggest possible long-term implications for metabolic health that have, as yet, not been established, but are thought to involve AMPK-driven metabolic adaptations, epigenetic modifications influencing energy metabolism, alterations in placental nutrient transport, or a combination of these.[62]

In addition to its metabolic effects, metformin exposure has been linked to maternal vitamin B12 deficiency[64,65] and antifolate activity, raising concerns regarding other potential long-term consequences. Metformin may contribute to B12 deficiency by reducing intestinal absorption through altered gut motility and by impairing the calcium-dependent absorption of the intrinsic factor-B12 complex. Its antifolate-like activity can disrupt one-carbon metabolism, which is essential for DNA methylation and nucleic acid synthesis. Metformin-induced mitochondrial dysfunction may also impair B12 utilization, potentially affecting foetal growth and increasing the risk of metabolic diseases in offspring.[58] A major concern of vitamin B12 deficiency is its association with irreversible neurological impairments, including an increased risk of peripheral neuropathy.[66] An imbalance between folate and B12 can also disrupt one-carbon metabolism, DNA methylation, and nucleic acid synthesis, which are essential for proper foetal growth and development. These disruptions may contribute to genomic instability and dysregulated gene expression, potentially altering foetal programming in a manner that increases susceptibility to metabolic disorders later in life.[58] However, a study by Estrella et al.[67] found no evidence of vitamin B12 deficiency in neonates exposed to metformin *in utero*. Although subtle elevations in several

acylcarnitines were observed, these changes were consistent with known cellular actions of metformin and were not considered harmful.[67] Based on the available evidence, the full extent of the impact of metformin on vitamin B12 metabolism and its long-term implications on foetal development remain unclear, warranting further study.

While metformin use in pregnancy has been suggested to influence long-term offspring health, the nature, magnitude, and clinical significance of these effects remain uncertain. Methodological limitations, inconsistent findings, and a lack of longitudinal data present challenges in this field, impacting on patient and clinician decision-making. This uncertainty underscores the need for a comprehensive synthesis of available research to assess the strength of existing evidence, identify consistent patterns, and clarify unresolved questions that must be addressed to inform future research and refine clinical recommendations.

5 | EVIDENCE OF THE EFFECTS OF METFORMIN ON LONG-TERM OFFSPRING HEALTH

5.1 | Observational studies

Few observational studies have examined the long-term effects of intrauterine metformin exposure on offspring health (Table 1), with the majority examining weight-related and cognitive outcomes and most reporting no significant associations. A recent population-based retrospective cohort study conducted in New Zealand[71] investigated 3928 children aged 4 years who had been exposed to either metformin or insulin for the treatment of GDM. The study assessed various health outcomes, including growth parameters (weight and height) and behavioural development. The findings indicated no significant differences between children exposed to metformin and those exposed to insulin.[71] Similarly, a population-based retrospective cohort study in Finland examined 10,129 children with a mean age of 3.5 years who had been exposed to metformin, insulin, or a combination of both for the treatment of GDM, PCOS, obesity, or T2DM in pregnancy.[69] This study evaluated multiple health outcomes, including obesity, hypoglycaemia, hyperglycaemia, diabetes, hypertension, PCOS, and motor-social development. The results showed no significant differences in these parameters between children exposed to metformin and those exposed to insulin or combination therapy.[69] A large Swedish retrospective cohort study including 686,847 women ($n = 1\,016\,805$ singleton births) reported a higher risk of childhood obesity before 11.5 years of age among offspring of women with PCOS who did not use metformin and those without PCOS who did use metformin during pregnancy.[70] These findings suggest that the variable effects of metformin depend on maternal PCOS status, although potential confounders such as maternal obesity and medication adherence may have influenced these results.[70]

In an earlier prospective cohort study in 2004, Glueck et al.[72] reported that metformin exposure did not adversely affect growth or motor-social development in the first 18 months of life in offspring born to mothers with PCOS ($n = 126$) compared to unexposed children born to healthy mothers ($n = 262$).[72] More recently, a prospective cohort study from the Born in Bradford (BiB) cohort examined the weight, height, and body mass index (BMI) z-score trajectories from birth to 5 years of age in metformin-exposed offspring of mothers with GDM who also adopted lifestyle interventions ($n = 76$) compared to insulin-treated GDM offspring with lifestyle interventions ($n = 420$).[68] The findings showed no significant differences in growth trajectories between the two groups.[68]

Despite these reassuring findings, methodological limitations, variability in study populations and underlying maternal conditions constrain interpretation of retrospective and prospective observational data. Many studies lack diverse representation, which limits generalizability, and rely on routine health records, which may lack detailed metabolic and developmental assessments and are subject to misclassification and incomplete follow-up. Most importantly, observational studies are inherently prone to confounding, as treatment allocation is not randomized, and residual biases are likely to influence results. Given these limitations, the absence of harm cannot be confirmed from these studies, and well-designed RCTs with long-term follow-up remain essential to accurately assess the long-term implications of intrauterine metformin exposure.

5.2 | Randomized controlled trial follow-up studies

A series of RCTs have investigated the impact of metformin in pregnancy, with long-term health follow-up of offspring outcomes, focusing primarily on weight-related and cognitive measures (Table 1). Offspring follow-up studies were conducted on participants from the landmark 'Metformin in Gestational Diabetes' (MiG) RCT by Rowan et al. in New Zealand and Australia to evaluate outcomes of children whose mothers had GDM and received treatment with either metformin or insulin between 20 and 33 weeks of gestation.[98] At 2 years of age, comprehensive assessments of anthropometry including bioimpedance and dual-energy X-ray absorptiometry (DXA) showed that children exposed to metformin *in utero* ($n = 154$) had larger mid-upper arm circumferences, as well as increased subscapular and biceps skinfolds, compared to the insulin group ($n = 164$). However, total fat mass and percentage body fat evaluated by bioimpedance ($n = 221$) and DXA ($n = 114$) showed no significant differences between the two groups, leading researchers to conclude that while metformin-exposed children had greater subcutaneous fat, their overall body fat levels were comparable to insulin-exposed children at 2 years of age.[92] Other follow-up studies of the MiG trial at 2 years of age found no differences in blood pressure measurements in 170 children[89] and no differences in neurodevelopment measures in 211 children using the Bayley Scales of Infant Development V.2 mental development index and psychomotor development index.[87]

Further follow-up of MiG trial participants located in Adelaide ($n = 109$) demonstrated comparable anthropometric measurements at the age of 7; while follow-up of participants in Auckland ($n = 99$) showed significantly higher weight, arm and waist circumferences,

and waist: height ratio in children at age 9 exposed to metformin *in utero*, with no differences in body fat percentage by DXA or bioimpedance.[85] While metformin-exposed groups also had higher BMI, triceps skinfold, DXA-measured fat mass and lean mass, and abdominal fat volume on magnetic resonance imaging (MRI), these differences were not statistically significant. Fasting glucose, triglycerides, insulin, insulin resistance, glycosylated haemoglobin A1c (HbA1c), cholesterol, liver transaminases, leptin, and adiponectin were also similar between the two groups.[85] Additional analysis of the MiG 9-year follow-up data among metformin-exposed boys ($n = 56$) found a positive association between fat-free mass indexed to height squared and maternal weight, BMI, maternal glycemia, and metformin treatment.[74] It should be noted that the MiG follow-up studies had a high attrition rate, leading to poorly matched groups at follow-up assessments. Moreover, maternal characteristics, including higher baseline BMI and less gestational weight gain in the metformin-treated group– potentially influenced by reduced caloric intake– may confound the observed differences in offspring outcomes, independent of any direct effects of metformin. There were also no adjustments made for gender, ethnicity, and other important factors which influence body size; thus, results should be interpreted with caution.

Beyond the MiG trial, a Finnish study examined infants born to mothers with GDM receiving metformin ($n = 47$) or insulin ($n = 50$) between 12 and 34 weeks of gestation. Measurements done at 6, 12, and 18 months showed that *in utero* metformin-exposed infants had significantly higher weights at 12 months and were taller and heavier at 18 months compared to those exposed to insulin.[88] However, there were no differences in the mean ponderal index (a measure of leanness assessed as weight/length^3) between the metformin and insulin groups, and motor, social, and linguistic development outcomes were comparable between groups.[88] Conversely, another Finnish study ($n = 52$) of mothers with GDM treated with metformin at 22–34 weeks of gestation reported that, at a mean age of 60 months (5 years), the height, weight, BMI, and waist-to-hip ratio were comparable between boys whose mothers were treated with metformin or insulin.[86] Combined analysis of these two Finnish studies by Paavilainen et al.[73] showed no significant differences between metformin- and insulin-treated mothers in levels of adiposity, body composition, liver fat, or inflammation markers of children at 9 years of age ($n = 172$). Notably, however, boys in the metformin group exhibited higher adiponectin levels and a lower leptin/adiponectin ratio.[73] Further analysis of the same combined cohort of offspring of women with GDM,[78] also at 9 years of age, showed higher levels of high-density lipoprotein cholesterol and lower levels of low-density lipoprotein cholesterol and apolipoprotein B in the metformin group compared with insulin. In sex-stratified analysis, these differences were statistically significant only among boys.[78] Authors concluded that metformin treatment for GDM was associated with comparable growth and glucose metabolism in offspring, while presenting a more favourable lipid and adipocytokine profile at the age of 9 years, compared with insulin.[78] In another follow-up of a RCT of mothers with GDM in India treated with metformin or glibenclamide at 20–33 weeks of gestation,[80] there were no differences in anthropometric measures, blood pressure, and lipid profiles in offspring at 9 years old ($n = 78$), except for triglyceride levels, which were higher in the metformin-exposed group.

The important pilot and PregMet trials by Vanky et al. and Lovvik et al.[30,31,99] assessed metformin use from the first trimester (5–12 weeks gestation) until delivery in women with PCOS, with long-term follow-up studies in offspring. In 2012, the impact of intrauterine metformin exposure on weight gain was assessed during the first year of life among 199 participants from the PregMet trial,[90] suggesting higher weight in the metformin-exposed offspring at 1 year compared to placebo-exposed offspring. When the anthropometric measurements were assessed in 4-year-old children ($n = 182$) from combined pilot and PregMet data, those who were exposed to metformin *in utero* had higher BMI and an increased prevalence of overweight/obesity at this age compared with placebo.[84] However, analysis of a subset of pilot data ($n = 25$) showed no differences in height, weight, or body composition between children exposed to metformin *in utero* and those exposed to placebo when assessed between the ages of 7 and 9.[91] Follow-up of the PregMet study evaluating children aged –10 years ($n = 141$) found that *in utero* metformin-exposed children exhibited a higher BMI z-score ($p = 0.03$) compared to placebo-exposed children. The authors suggested that the increased BMI observed in metformin-exposed children may be associated with a potential risk of compromised cardiometabolic health outcomes.[83] Another follow-up study, CogMet, assessed follow-up data from the pilot and PregMet trials of offspring of women with PCOS at a mean age of 7.7 years and found that intrauterine metformin exposure did not affect cognitive function, measured as mean IQ score.[82] However, an increase in borderline intellectual function was observed in metformin-exposed children, noting the small sample size.[82]

Follow-up of RCTs on metformin use in overweight or obese women in pregnancy has also been conducted.[75–77,81] In the GRoW trial, 524 pregnant women with obesity were randomly assigned to receive either metformin or placebo at 10–20 weeks gestation until delivery.[100] Despite those on metformin having lower average weekly gestational weight gain (adjusted mean difference [MD]: −0·08 kg, 95% CI −0·14 to −0·02),[100] the proportion of infants or children with BMI > 85th centile for age and sex, assessed at six months ($n = 426$), 18 months ($n = 382$), or 3– 5 years of age ($n = 304$) was comparable between groups at all time points, as were other lifestyle and neurodevelopmental outcomes.[75] Similar results were found in a follow-up study of 51 children from the 'Metformin in Obese Pregnant women' (MOP) trial, where pregnant women with obesity received metformin treatment from 12 to 18 weeks of gestation until delivery.[81,101] Here, no significant differences were found in metabolic profiles, peripheral blood pressure, arterial stiffness, or overall body composition, with the exception of gluteal and triceps circumference, which were lower in the metformin group compared with placebo.[81] The metformin group also exhibited lower central hemodynamic measures and reduced left ventricular diastolic function compared with placebo.[81] These findings suggest that children born to obese mothers receiving metformin had improved central hemodynamic measures and cardiac diastolic indices compared with placebo, with potentially beneficial

long-term cardiovascular effects on the offspring.[81] Conversely, the 'Effect of metformin on maternal and foetal outcomes in obese pregnant women' (EMPOWAR) trial[102] examined pregnant women with obesity who received metformin or placebo from 12 to 16 weeks of gestation until delivery. Follow-up analysis of offspring at age 5.8 ± 0.9 years showed no significant differences in cardiovascular risk, body fat mass, or the likelihood of premature cardiovascular disease in children exposed to metformin *in utero* compared with placebo.[77]

Only one follow-up study has examined offspring outcomes following metformin exposure in pregnant women with T2DM. The 'Metformin in women with T2DM in pregnancy' (MiTy) trial[103] randomized 502 women with T2DM to metformin or placebo, in addition to a standard regimen of insulin from 6 to 22 weeks of gestation until delivery. In a follow-up study called 'MiTy Kids', 283 offspring underwent measurements of weight, height, BMI z-score and skinfold thickness at 24 months of age, showing no significant differences between in-utero metformin-exposed and placebo groups overall.[76] However, growth trajectories differed significantly for males, with a higher BMI trajectory from 6 to 24 months of age in the metformin group compared with placebo, although this may be a chance finding due to the multiple tests conducted.

5.3 | Systematic reviews and meta-analyses

Systematic reviews and meta-analyses have investigated the effects of metformin use in pregnancy on long-term health outcomes in offspring (Table 1). In 2019, a meta-analysis[29] examining long-term outcomes included two trials of 411 infants at 18–24 months from the MiG[92] and Finnish[88] follow-up studies in GDM described earlier. Those exposed to metformin *in utero* were significantly heavier than those exposed to insulin (mean MD: 440 g, 95% CI: 50, 830). At 5–9 years of age, analysis of two follow-up studies ($n = 301$ children) using MiG data[85] and the second Finnish study[86] showed that BMI was significantly higher in the metformin-exposed group (MD: 0.78 kg/m^2, 95% CI: 0.23, 1.33), but there was no difference in absolute weight compared with the insulin-exposed group. Limited evidence suggested that adiposity indices including abdominal and visceral fat volumes were higher in children born to mothers exposed to metformin compared to insulin (MD: 0.44 and 0.41 cm^3, respectively), but this was derived from a single study (MiG follow-up data[85]) with 104 children and possible attrition bias.[29] Two other systematic reviews assessed 11 follow-up studies from five RCTs ($n = 823$ children)[96] and 10 follow-up studies from five RCTs ($n = 778$ children)[97] of women diagnosed with GDM or PCOS randomized to either metformin or insulin/placebo during pregnancy. Both included a meta-analysis of five follow-up studies ($n = 684$), in which children exposed to metformin *in utero* had significantly heavier weights at up to 9 years of age compared to those who were exposed to insulin (MD: 0.48 kg, 95%CI: 0.24, 0.73 kg), but there were no differences in height or BMI. There were also no differences in metabolic parameters and neurodevelopmental outcomes between groups, though these data were not pooled in either review.

New studies have since become available. A 2024 systematic review focused on children aged 5 to 11 years of age born to mothers with GDM treated with metformin or insulin during pregnancy.[93] There were no significant differences in z-scores for height, weight, or BMI at 5 years of age ($n = 420$). At 9 years, there were no differences in waist circumference-to-height ratio; total fat mass, fat percent, or fat-free mass measured by DXA; visceral adipose tissue volume and liver fat percentage assessed by MRI; or biochemical measures including serum adiponectin, leptin, alanine aminotransferase, and ferritin. For children aged 9–11 years, incidence of obesity or diabetes and challenges in motor and social development were comparable between groups.[93] However, these results were derived from a very small number of studies (1 cohort study of 1443 children or 2 RCTs with 224–266 children) and should be interpreted in light of the limited available data. A 2024 meta-analysis of neurodevelopmental outcomes in observational and RCT data ($n = 7$ studies) found that metformin use in pregnancy for any indication was not associated with neurodevelopmental delays in infancy (3 studies; $n = 9668$ children) or at ages 3–5 years (2 studies; $n = 6118$ children).[94] When compared to unexposed groups (insulin/placebo), intrauterine metformin exposure did not correlate with altered neurodevelopment (motor or cognitive scores) in a meta-analysis of 2–3 studies with $n = 714$–734 children.[94] Finally, a 2025 systematic review and meta-analysis of 18 RCTs and observational studies ($n = 7975$ metformin-exposed children and >1 million non-exposed children) found a slightly higher BMI in metformin-exposed children aged 1–3 years, but no differences were seen by ages 3–6 or 6–11 years.[95] In the subgroup of women with PCOS, metformin-exposed children had a higher BMI compared to non-exposed peers.[95]

Findings from systematic reviews and meta-analysis are largely in line with primary RCT data, suggesting that intrauterine exposure to metformin may influence weight and post-natal catch-up growth. While metformin does not appear to impact long-term metabolic or neurodevelopmental outcomes in offspring, there are very limited data for these outcomes, and most studies have not followed offspring into adulthood, when developmental programming effects are most likely to manifest.[94] The clinical significance of these findings therefore remains uncertain, given the small numbers of studies, considerable variability between studies, as well as attrition challenges, raising concerns about the validity of pooled aggregate data. These meta-analyses also fail to account for key effect modifiers such as maternal BMI, ethnicity, diagnostic criteria, and the timing of treatment initiation, further limiting the reliability of conclusions.

6 | LIMITATIONS AND FUTURE DIRECTIONS

Despite the widespread use of metformin in pregnancy for common indications including T2DM, PCOS, and GDM, important gaps remain in our understanding of the long-term effects of intrauterine exposure on offspring health. Studies vary by metformin indication and population, trial methods, treatment regimens, and outcome measures and

timing. Additionally, the reliance on follow-up studies of RCTs is problematic, as these are susceptible to recall and attrition bias. This leaves smaller, potentially non-representative samples that may not reflect the original randomized population, with selective retention introducing bias, reducing generalizability, and undermining causal inference. Moreover, as the original RCTs were not designed to assess long-term outcomes, follow-up data often have limited statistical power and rely on exploratory post-hoc analyses, limiting reliability. Together, the variability in studies and follow-up difficulties preclude reliable cross-study comparisons and make interpretation challenging.

Moreover, meta-analyses which aggregate such heterogeneous data risk obscuring true effects, introducing confounding and bias, and generating potentially misleading conclusions. Inadequate adjustment for key confounders such as maternal BMI, diet, ethnicity, and postnatal environmental factors further limits the ability to isolate the direct effects of intrauterine metformin exposure from broader metabolic and lifestyle determinants that shape long-term offspring health. This is particularly evident in follow-up studies of RCTs and meta-analyses of these studies, where the absence of covariate data raises the possibility that anthropometric differences may be driven by postnatal influences, such as diet and lifestyle, rather than foetal metformin exposure alone. However, exposure to metabolic stress during gestation, whether via hypercaloric environments or malnutrition, may also prime offspring to be more susceptible to these postnatal factors, potentially compounding long-term metabolic risk.

Overall, the main concern regarding long-term offspring safety relates to limited and inconsistent evidence linking intrauterine metformin exposure with childhood adiposity. Hence, clinical significance and broader offspring metabolic implications of metformin use in pregnancy remain unclear, with a notable paucity of data on long-term metabolic, cardiovascular, and neurodevelopmental outcomes. Most studies to date have focused on anthropometric measures, such as weight and BMI, yet a key unresolved question is whether metformin-induced alterations in foetal growth trajectories translate into lasting metabolic consequences or whether they represent transient, compensatory adaptations. Potential epigenetic effects of metformin on foetal programming also remain largely unexplored, despite emerging evidence from animal studies suggesting that metformin influences DNA methylation and gene expression *in utero*.[28] This is compounded by the lack of follow-up studies in adulthood, which are needed to delineate whether intrauterine exposure translates into clinically meaningful outcomes across the life course. Finally, the majority of data are derived from high-income countries, with predominantly high-BMI cohorts. Women in developing countries may have different metabolic profiles, including lower baseline BMI, with variable effects of metformin on foetal metabolic health. The lack of data from these populations represents a key gap in the evidence.

To address these limitations, future research must prioritize large-scale prospective data with rigorous follow-up protocols and the inclusion of diverse population groups including from low- and middle-income countries. Individual patient data (IPD) meta-analyses, incorporating harmonized, individual-level stratification, can enhance statistical power while mitigating some of the inherent limitations of individual long-term follow-up studies. Initiatives such as the Metformin in Pregnancy Study (MiPS) IPD meta-analysis represent an important step forward.[104] By systematically examining postnatal catch-up growth while controlling for relevant effect modifiers, MiPS may help delineate the true impact of intrauterine metformin exposure on long-term offspring health. Additional primary studies, including well-designed prospective studies and RCTs with pre-specified longitudinal follow-up, are also needed to capture the full spectrum of metabolic, cardiovascular, and neurodevelopmental outcomes following intrauterine metformin exposure.

7 | CONCLUSIONS

Metformin is widely used in pregnancy for the management of GDM, PCOS, and pre-existing T2DM. While its short-term safety profile in pregnancy is well-documented, evidence regarding its long-term effects on offspring health remains inconclusive. Findings from observational studies as well as RCT follow-up data suggest that intrauterine metformin exposure may be associated with altered postnatal growth trajectories, including increased adiposity in childhood. However, variable populations, heterogeneity in study designs, high attrition rates in follow-up studies and potential confounding variables limit the reliability of current evidence. Metformin exposure may have anthropometric offspring implications; however, evidence regarding the risk of metabolic dysfunction is unclear, and there is no evidence for adverse cardiovascular outcomes or neurodevelopmental impairment in later life, though studies assessing these outcomes are sparse. Addressing these limitations using well-powered, harmonized long-term data in an individual patient data meta-analysis is likely to significantly progress the field on the long-term safety of metformin use in pregnancy. Until such data are available, clinicians must balance the potential benefits of metformin in pregnancy against the uncertainties surrounding the long-term impact on offspring health.

AUTHOR CONTRIBUTIONS

T.M., S.S., D.A., T.M., and A.M. contributed to researching data, discussing content, and drafting, reviewing, and editing the manuscript before submission. E.V. and H.T. made a substantial intellectual contribution to the content and reviewed the manuscript. All authors contributed to the manuscript in line with ICJME criteria and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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