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Author

Zhen, Xi May, Li, Xue, Chen, Chen

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Review

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Xi May Zhen, Xue Li, Chen Chen

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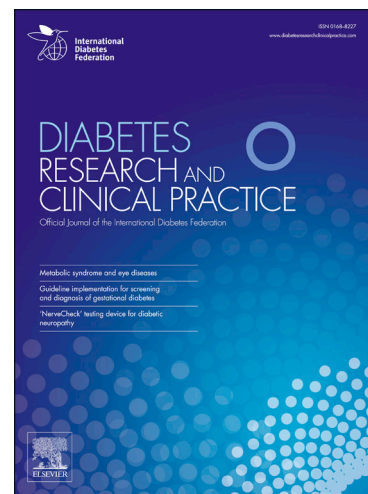
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Longer-term Outcomes in Offspring of GDM Mothers Treated with Metformin versus Insulin

Dr Zhen, Xi May^{1,2}
Professor Li, Xue³
Professor Chen, Chen⁴

- 1) School of Medicine, The University of Queensland, Brisbane, Australia 4072
- 2) Royal Prince Alfred Hospital, Sydney, Australia 2050
- 3) School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, Queensland, Australia 4072
- 4) School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland, Australia 4072

Correspondence to:

Dr Xi May Zhen

Email (preferred route of contact): xi.zhen@uqconnect.edu.au

Address: Physician Training Unit, Royal Prince Alfred Hospital, Post Office Box M30; Missenden Road, Camperdown, NSW 2050

or

Professor Chen Chen

Email: chen.chen@uq.edu.au

Address: School of Biomedical Science, The University of Queensland, St Lucia, QLD 4072, Australia

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Abstract

Insulin has traditionally been the gold standard pharmacological treatment for gestational diabetes mellitus (GDM). Insulin requires multiple injections a day, can cause frequent hypoglycaemia, requires careful handling, and is generally more expensive compared to oral agents. Metformin has been increasingly popular in recent years. Based on the short-term data available, metformin appears to be safe and effective for the treatment of GDM but existing studies have all stressed the lack of longer-term offspring data. This article will analyse the evidence available on the longer-term outcomes in the offspring of women with GDM treated with metformin versus insulin. Pubmed, EMBASE, CENTRAL, and CNKI were searched for follow-up studies of randomised controlled trials that compared metformin with insulin for the treatment of GDM. Existing follow-up studies did not find any significant increase in the risk of adverse effects in terms of growth and development in the offspring of GDM mothers managed with metformin versus insulin.

Keywords: offspring; growth; development; metformin; insulin; gestational diabetes

Contribution statement

Xi May Zhen

designed the study, collected data, and analysed/interpreted data
wrote the draft and revised the draft critically for important intellectual content
approved the final version to be published

Xue Li

collected data, and analysed/interpreted data
revised the draft critically for important intellectual content
approved the final version to be published

Chen Chen

collected data, and analysed/interpreted data
revised the draft critically for important intellectual content
approved the final version to be published

Longer-term Outcomes in Offspring of GDM mothers treated with metformin versus insulin

1. Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing rapidly over the past two decades, with figures ranging widely between regions and countries.¹⁻³ Insulin has traditionally been the gold standard treatment for GDM when diet and lifestyle modifications fail to provide satisfactory blood glucose control.⁴⁻⁶ Figures vary according to the population studied, but around 15-30% of women with GDM require pharmacological therapy.^{5,7} Oral anti-hyperglycaemic agents such as metformin and glyburide have been increasingly popular in recent years as they are cheaper, do not require injections; and are easier to use and store when compared with insulin. The American Diabetes Association (ADA) considers glyburide to be inferior to both insulin and metformin, and emphasised that women must be counselled on the lack of long-term safety data for both metformin and glyburide.⁸

In the offspring of women with GDM, neonatal complications include most commonly macrosomia and its complications, as well as prematurity, hyperinsulinaemia, hypoglycaemia, hypoxaemia, respiratory distress syndrome, asphyxia, polycythaemia, and postpartum hyperbilirubinaemia.⁹⁻²¹ Currently, the available evidence suggests that metformin use in women with GDM is relatively safe and effective when compared to insulin with respect to short-term maternal and offspring outcomes.^{10,11,22-31} However, data is sorely lacking regarding the longer-term outcomes in offspring born to women with GDM treated with metformin versus insulin.

While the longer-term outcomes of offspring with in-utero metformin exposure has mainly been studied in the offspring of women with GDM, metformin is also used in mothers with polycystic ovary disease (PCOS) and we will briefly summarise the evidence here. Mothers with PCOS are often prescribed metformin but again, there is very limited data regarding the longer-term effects of metformin use on the offspring in this cohort.^{32,33} A recent follow-up study that assessed the offspring of women with PCOS managed with metformin versus placebo reported higher BMI and increased prevalence of overweight/obesity in the children exposed to metformin in-utero when followed up at 4 years of age.³³ A nonrandomized study reported no significant differences in birth length, birth weight, growth or motor-social development in the first 18 months of life when comparing gender-specific Centers for Disease Control and Prevention (CDC) infant data with 126 offspring born to PCOS mothers treated using metformin.³⁴ A follow-up study of a randomised controlled trial (RCT) that randomised pregnant women with PCOS to metformin versus placebo reported that infants exposed to metformin in-utero were heavier than those in the placebo group at 1 year of age (10.2 ± 1.2 kg vs 9.7 ± 1.1 kg, $P = 0.003$).³⁵

Here, we will analyse the emerging evidence on the longer-term outcomes of offspring born to women with GDM treated with metformin versus insulin (longer-term outcomes are defined as outcomes beyond the first four weeks after birth). The effects of GDM on offspring growth and development will also be discussed.

1.1 The effects of GDM on offspring metabolic disease and future diabetes

GDM has epigenetic effects at genes that are preferentially involved in diabetes and other metabolic diseases, as well as foetal growth and development (which may play a part in the association between GDM and macrosomia).^{36,37} Compared to the offspring of normoglycaemic mothers, offspring of mothers with GDM are more likely to be overweight or obese in childhood and adolescence, are more likely to have reduced insulin sensitivity and impaired pancreatic beta-cell function as adults, and are at greater risk of progressing to type 2 diabetes and metabolic syndrome.³⁸⁻⁴⁴

A Finnish longitudinal cohort study found that, in comparison to adolescents born to non-diabetic mothers, adolescents born to mothers with GDM had a higher median BMI (20.8 vs 20.2 kg/m²), greater median waist circumference (73.3 vs 71.5 cm), higher fasting insulin levels (10.2 vs 9.3 milliunits/L), and were at increased risk of being overweight (18.8% vs 8.4%).⁴² Similarly, a study of Mexican-American mothers and their offspring found that, after adjusting for confounding variables, the group of children born to mothers with GDM had higher BMI measurements compared with the offspring of normoglycaemic mothers (the two groups were matched by age, BMI, and parity).⁴⁰ A large German cohort study again showed a significant association between GDM and the risk of overweight, obesity, and abdominal adiposity in the offspring, after adjusting for potential confounders.⁴³

A recent study followed up 970 mothers from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO)⁴⁵ study and found that, at 7 years of age, offspring born to GDM mothers were more likely to be overweight or obese, have greater body-mass index (BMI) and higher blood pressure, have lower oral disposition indexes, have higher rates of abnormal glucose tolerance, and also demonstrated a trend toward reduced β -cell function, when compared to the offspring of mothers without GDM. Additionally, with each SD increase in maternal fasting, 1-h, and 2-h glucose levels on oral glucose tolerance tests (performed at 24-32 weeks of the index pregnancy), the risk of abnormal glucose tolerance in the offspring showed a corresponding increase. These associations were found to be independent of BMI before pregnancy, childhood obesity, or being born large for gestational age.⁴⁶

It has also been suggested that the exposure of a female foetus to maternal hyperglycaemia in-utero may increase the offspring's own risk of subsequently developing GDM in future pregnancies.^{47,48}

1.2 Neurodevelopment

Ornoy et al. compared the neuropsychological function of 32 school age children born to GDM mothers and 57 children born to non-diabetic mothers matched by parental socioeconomic status, age, and birth order.⁴⁹ The children born to GDM mothers were found to have lower gross and fine motor performance, lower cognitive scores, and a higher rate of attention deficit when compared to children born to non-GDM mothers.⁴⁹ Another case control study (including 1835 singletons from the Quebec Longitudinal Study of Child Development and 998 twins from the Quebec Newborn Twin Study) concluded that GDM was associated with lower expressive language performance in offspring until middle childhood.⁵⁰ The authors commented that genes

and maternal education both moderated the effect of gestational diabetes on expressive language during this period.⁵⁰

There is also some evidence to suggest that foetal postprandial brain responses may be slower in the offspring of mothers with GDM, and this finding raises the possibility that GDM may affect brain development and central nervous system insulin resistance in the foetus.⁵¹

1.3 Blood pressure

A systematic review and meta-analysis published in 2012 found that the offspring of mothers with GDM had higher systolic blood pressures compared to the offspring of non-diabetic mothers, but there was no difference in diastolic blood pressure between offspring of GDM and non-diabetic mothers.⁵²

1.4 Testicular size

Tartarin et al. published a study in 2012 which found that, in human and mouse organotypic cultures in vitro, metformin reduced testosterone secretion and mRNA expression of the principal factors involved in steroid production.⁵³ In vivo administration of metformin to pregnant mice resulted in decreased testicular size of the foetal and neonatal testes.⁵³ While metformin treatment did not reduce the germ cell number, the number of Sertoli cells was slightly but significantly reduced in both foetal and neonatal periods.⁵³

2. Methods

The aim of this article was to assess the longer-term outcomes in the offspring of women with GDM treated with metformin versus insulin. Literature searches were performed in (from inception to 27/05/2018):

Pubmed

EMBASE

CENTRAL

CNKI (China National Knowledge Infrastructure)

We included all offspring follow-up studies of blinded and open-label RCTs comparing metformin versus insulin for the treatment of GDM.

The search strategies for Pubmed, EMBASE, and CENTRAL are included in Appendices 1-3. The search strategy for CNKI was adapted from the search strategy for Pubmed. Two reviewers independently performed study selection. For any disagreements that could not be resolved by consensus, a third reviewer was asked to participate.

3. Results

Please see the search flow diagram in **Figure 1**. The search identified 4068 results from Pubmed, 343 results from Embase, and 387 results from CENTRAL (4798 results in total). Seven offspring follow-up studies based on four RCTs were included

for review.⁵⁴⁻⁶⁰ The search identified 142 results from CNKI and no offspring follow-up studies were identified.

3.1 Body composition

Rowan et al. published the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study in 2011.⁵⁶ This follow-up study assessed offspring at 2 years of age and included a smaller proportion of children of Polynesian ethnicity when compared with the original MiG RCT population (14 vs. 20%, $P = 0.02$). Baseline maternal characteristics and pregnancy outcomes did not differ between the follow-up groups. Children included in this follow-up study had a shorter crown-rump length at birth (33.0 vs. 33.5 cm, $P = 0.005$) and smaller triceps skinfolds (4.80 vs. 5.15 mm, $P = 0.0002$) and subscapular skinfolds (4.95 vs. 5.20 mm, $P = 0.07$) at birth when compared with the original MiG RCT population. Otherwise, the maternal and offspring baseline characteristics were not different between the follow-up group and the original MiG RCT population. When compared with the children of mothers treated with insulin, the offspring of metformin-treated mothers had slightly larger mid-upper arm circumferences (17.2 +/- 1.5 vs. 16.7 +/- 1.5 cm; $P = 0.002$) and subscapular (6.3 +/- 1.9 vs. 6.0 +/- 1.7 mm; $P = 0.02$) and biceps skinfolds (6.03 +/- 1.9 vs. 5.6 +/- 1.7 mm; $P = 0.04$).⁵⁶ After adjusting for age, ethnicity, sex, and maternal glucose control during pregnancy, the P values were $P = 0.005$, $P = 0.01$, and $P = 0.02$ for upper-arm circumference, sub-scapular skinfold, and biceps skinfold respectively. Total fat mass and percentage body fat evaluated using bioimpedance ($n = 221$) and dual-energy x-ray absorptiometry (DEXA) ($n = 114$) were not significantly different between groups. There were no significant differences between groups in terms of abdominal circumference, total fat mass, central fat measures, percentage body fat, or central-to-peripheral fat as measured by waist-to-hip ratio and DEXA-calculated abdominal-to-thigh fat ratios.

The MiG TOFU study followed up offspring from the Adelaide ($n=109/181$) and Auckland ($n=99/396$) subgroups at 7-9 years of age to assess body composition and metabolic outcomes using anthropometry, bioimpedance analysis (BIA), DEXA, magnetic resonance imaging (MRI), and fasting bloods.⁶⁰ In the Adelaide subgroup, the population was predominantly European/Caucasian (89.7% and 84.3% in the metformin and insulin groups). Baseline maternal characteristics were generally similar between groups though women randomized to metformin versus insulin had higher glycaemia during treatment ($p=0.002$) and had more neonates with birth weight >90th percentile as assessed using customised birth weight charts (20.7% vs 5.9%; $p=0.029$). In comparison to the insulin group, offspring from the metformin group were younger by 5 months ($p=0.02$). At 7 years of age, no significant difference was found between groups in the Adelaide subgroup for all measures of body composition as well as fasting plasma glucose (nil other blood tests were performed in the Adelaide subgroup). The Auckland subgroup was ethnically heterogeneous, with 55.6% and 38.9% of participants identifying as Caucasian/European in the metformin and insulin groups, respectively (ethnicity was not significantly different between groups, $p=0.17$). In the Auckland subgroup, mothers randomised to metformin had a trend towards higher body mass index (BMI) ($p=0.08$) and less weight gain during treatment ($p=0.07$). When assessed at 9 years of age, the metformin-exposed offspring were heavier ($37.0\pm 12.6\text{kg}$ vs $32.7\pm 7.7\text{kg}$; $p=0.049$), and larger in terms of waist circumference ($69.1\pm 12.2\text{cm}$ vs $64.2\pm 8.4\text{cm}$; $p=0.04$) and waist to height ratio

(0.51 ± 0.08 vs 0.47 ± 0.05 ; $p=0.02$). Metformin-exposed children had significantly larger mid-upper arm circumferences ($23.0\pm 4.3\text{cm}$ vs $21.2\pm 2.9\text{cm}$; $p=0.02$) as well as upper arm fat mass as measured by DEXA (1568 ± 801 vs $1285\pm 534\text{g}$; $p=0.047$). Note that when the 6 children (3 each in the metformin and insulin groups) with signs of early puberty were excluded, body weight and DEXA arm fat mass were no longer significantly different between groups ($p=0.07$ for both measures). Percentage of body fat (as measured using DEXA and BIA) was similar between groups. Compared to the insulin group, children in the metformin group demonstrated a trend towards larger subcutaneous fat ($3231\pm 2412\text{cm}^3$ vs $2398\pm 1566\text{cm}^3$; $p=0.059$) and visceral fat ($941\pm 629\text{cm}^3$ vs $722\pm 365\text{cm}^3$; $p=0.051$) volumes as measured using abdominal MRI. Fasting glucose, triglyceride, insulin, insulin resistance, haemoglobin, glycosylated hemoglobin (HbA1c), cholesterol, liver transaminases, leptin and adiponectin were similar between metformin and insulin groups. Adjusting for age, ethnicity and gender did not change findings for the Adelaide and Auckland subgroups.

Tertti et al. compared the offspring of metformin-treated and insulin-treated GDM mothers at the age of 33 to 85 months.⁵⁸ This follow-up study (designed to assess offspring testicular size) included 25 (42.4% of invited) and 27 (52.9% of invited) male offspring born to mothers with GDM treated with metformin or insulin respectively. There were no statistically significant differences between the two groups of boys in terms of waist-to-hip ratio ($p=0.32$), BMI ($p=0.11$), BMI z-score ($p=0.16$), height ($p=0.95$), or weight ($p=0.61$). The lack of female offspring is a major but expected limitation given that this follow-up study focused on testicular size.

3.2 Growth and development

Ijas et al. followed up offspring (at the ages of 6, 12, and 18 months) from their original RCT comparing metformin vs insulin in the treatment of GDM.⁵⁵ Baseline maternal characteristics upon enrolment in the follow-up study were similar between groups for the Adelaide subgroup. While there was no significant difference between groups in terms of gestational age ($p=0.355$) and mean birth weight ($p=0.119$), neonates from the metformin group were significantly longer at birth ($p=0.047$). Information including weight and height measurements, and assessment of motor, social, and linguistic development was recorded during routine visits to child welfare clinics from 47/50 of offspring in the metformin group and 50/50 of offspring in the insulin group. This follow-up study found that offspring with intrauterine exposure to metformin were heavier at 12 months (10.47 vs 9.85 kg, 95% CI 0.04–1.20) and taller and heavier at 18 months (83.9 vs 82.2 cm, 95% CI 0.23–3.03, 12.05 vs 11.32 kg, 95% CI 0.04–1.43) when compared to the offspring of GDM mothers treated with insulin. There was no statistically significant difference in body composition (as defined using the mean Ponderal Index) between the two groups of children ($p=0.827$). There was no statistically significant difference between groups in terms of motor development (assessed using measures including capability of standing and walking without support, normal pinch grip, and coordination of upper limbs) when the offspring were assessed at 18 months. Social, emotional, and language development was assessed by evaluating the response to spoken commands, and the ability to make understandable spoken words and reciprocal contact. Again, there was no statistically significant difference between groups in terms of social, emotional and language development. Ijas et al. concluded that in-utero exposure to metformin did

not appear to adversely affect early motor, linguistic, or social development. A limitation of this study was the small sample size, which did not allow detection of differences in infrequent or rare conditions (e.g. developmental delays) between the two groups of children.

Terti et al. followed up the 2-year-old children of GDM mothers treated with metformin vs insulin.⁵⁷ Maternal and neonatal baseline characteristics were similar between groups. From the original RCT, 151 (74.4%) children participated in this follow-up study. Cognitive, language, and motor skills as well as neurological examination findings were evaluated using the Bayley Scales of Infant and Toddler Development (Bayley-III) and the Hammersmith Infant Neurological Examination. There was no statistically significant difference between the offspring of metformin- and insulin-treated mothers in terms of receptive communication ($p=0.14$), expressive communication ($p=0.75$), fine motor performance ($p=0.10$), gross motor performance ($p=0.13$), global scores of the Hammersmith Infant Neurological Examination ($p=0.14$), or results when tested using the Bayley-III scales ($p=0.12$). None of the children followed up had a clinically significant developmental problem that required further assessment by a psychologist or paediatric neurologist. Terti et al. reported weaker language performance in the offspring of GDM mothers (treated with both metformin and insulin) when compared with age-adjusted Finnish normative data.⁵⁷

Wouldes et al. followed up (at 2 years of age) 211 children from New Zealand and Australia out of the 577 eligible offspring that were born to mothers from the MiG trial.⁵⁹ At follow-up, no significant differences were found between groups for most family environment and socio-economic status measures. While the New Zealand cohort birth length in the insulin group was longer than that in the metformin group ($p=0.03$), perinatal outcomes were similar between the offspring from the metformin and insulin groups. Neurodevelopment was evaluated with the Bayley Scales of Infant Development V.2 mental development index (MDI) and psychomotor development index (PDI). A paediatrician performed a structured physical examination on the 95 children from New Zealand but a formal physical examination was performed on only 10 of the Australian children. At follow-up, no statistically significant differences were detected between groups in terms of global cognitive and motor development. However, Wouldes et al. reported significantly lower scores for both cognitive and motor development in the offspring from New Zealand compared with Australian offspring.

Wouldes et al. reported that children with a birth weight >4000 g were found to be at greater risk of poorer cognitive development.⁵⁹ Additionally, children with two or more episodes of neonatal hypoglycaemia (blood glucose <2.6 mmol/L) and those born to mothers with higher glucose levels were more likely to have poorer motor development regardless of whether the mothers were treated with metformin or insulin. Wouldes et al. concluded that, at the age of 2 years, the neurodevelopment of children born to women with GDM did not differ according to treatment with metformin or insulin. However, this study was limited by the large lost to follow-up rate.

3.3 Blood pressure

Battin et al. published a study in 2015 which followed up offspring of the MiG⁶¹ trial at 2 years of age to assess systolic and diastolic blood pressure.⁵⁴ Blood pressure measurements were obtained in 170 children (median age of 29 months corrected gestational age). No significant differences were found in the distribution of metformin vs insulin treatment by ethnicity. There was no evidence of any statistically significant difference in blood pressure at 2 years of age when comparing offspring from the metformin and insulin treatment groups, with height and weight being the only two factors associated with the blood pressure measurements.⁵⁴ This study was quite limited given that blood pressure measurements were obtained from just less than 30 percent of the 577 children potentially available from the original MiG RCT. Further follow-up down the track would be required as monitoring at 2 years of age is probably too early to capture differences in blood pressure and/or cardiovascular health.

3.4 Testicular size

Terti et al. compared testicular size (by a ruler, an orchidometer, and by ultrasonography) in the offspring of metformin-treated and insulin-treated GDM mothers at the age of 33 to 85 months.⁵⁸ A total of 52 boys (42.4% of offspring from the metformin group and 52.9 % of offspring from the insulin group) were included, with 25 born to metformin-treated mothers and 27 born to insulin-treated mothers. The mean age of offspring did not differ significantly between groups ($p = 0.88$). There were no significant differences between the two groups of boys in terms of testicular size (p always ≥ 0.40).

4. Discussion

The MiG TOFU study found that the offspring of metformin-treated mothers had a slight but statistically significant increase in biceps skinfolds, mid-upper arm circumferences, and subscapular skin folds.⁵⁶ Subsequently, Rowan et al. suggested that in-utero exposure to metformin resulted in a favourable increase in fat deposition at subcutaneous sites and likely less visceral fat in the offspring.⁵⁶ The MiG TOFU study found no significant difference between groups for abdominal circumference and crude measures of central fat.⁵⁶ While abdominal circumference has been suggested as a good surrogate measure of visceral fat in adults and children⁶²⁻⁶⁴, other studies have reported that waist circumference may in fact be more predictive of abdominal subcutaneous fat in children⁶⁵. It has also been suggested that waist circumference in children may be more highly correlated with the accumulation of whole body fat rather than abdominal visceral fat.^{5,66} In the context of excessive nutritional intake in adults, healthy subcutaneous adipocytes grow and become dysfunctional.^{56,67,68} Excess fat then deposits in visceral adipocyte depots which release fatty acids and inflammatory adipocytokines that are associated with insulin resistance.^{56,65,67-71} Contrastingly, insulin-sensitive obesity is associated with a higher proportion of healthy subcutaneous adipocytes and smaller amounts of visceral fat.^{56,65,67-71} It is unclear whether the same pattern is seen in children. However, there is some evidence to suggest that, unlike in adults, subcutaneous adiposity instead of visceral adiposity may in fact be the strongest predictor of insulin resistance and hypertriglyceridemia in children.⁷²⁻⁷⁵ Therefore, the clinical significance of the

increase in fat deposition at subcutaneous sites at 2 years of age in the MiG TOFU study⁵⁶ remains unclear. Rowan et al. subsequently made use of abdominal MRI when following up offspring at 7-9 years, and found a trend towards larger volumes of both subcutaneous fat ($p=0.059$) and visceral fat ($p=0.051$) in the metformin group compared to the insulin group among children from the Auckland subgroup.⁶⁰ Children in the metformin group were also significantly heavier though when the children with signs of early puberty were excluded, body weight was no longer significantly different between groups ($p=0.07$). While the increase in body weight may be a consequence of puberty, the literature also demonstrates a well-described positive relationship between weight/BMI and the onset and progression of puberty for both sexes.⁷⁶⁻⁷⁸ These findings need to be considered in the context of previous studies which found that metformin-exposed children of PCOS mothers were heavier than those born to PCOS mothers treated with placebo.^{35,33} Future studies could perhaps explore whether any increase in weight in children with metformin exposure in-utero may be associated with changes in metabolism (in particular any insulin-mediated pathways).

Woulides et al. reported significantly lower scores for both cognitive and motor development in the offspring from New Zealand compared with Australian offspring. Subsequent analyses indicated that lower scores were predominantly associated with maternal ethnicity (Pacific or Indian) or lifestyle factors, and with higher scores being associated with Caucasian ethnicity.⁵⁹ A greater proportion of offspring from the follow-up study were of European or white ethnicity when compared with the original MiG RCT population (metformin 68% vs 44%, $p<0.001$; insulin 58% vs 43%, $p<0.005$).⁵⁹ A smaller proportion of offspring of Pacific or Polynesian ethnicity were included in this follow-up study at 2 years when compared with the original MiG RCT population (metformin 7% vs 22%, $p<0.001$; insulin 13% vs 21%, $p<0.060$). It was noted that a similar proportion of Pacific Island families were available for follow-up in the metformin and insulin groups. Similarly, in the Adelaide subgroup from the MiG TOFU follow-up study that assessed offspring at 7-9 years of age, participants were predominantly Caucasian (though the authors noted that adjusting for ethnicity did not change their findings).⁶⁰ The results from these follow-up studies or subgroups may not be suitable for extrapolation to non-Caucasian populations. This highlights the importance of assessing ethnicity and lifestyle factors when examining offspring development. However, maternal ethnicity and socioeconomic measures were only reported by the follow-up studies of the MiG trial.^{54,56,59}

There was no evidence of any significant difference in neurodevelopmental outcome between the offspring of women with GDM treated with metformin versus insulin.^{57,55,59,60} Based on these findings, we believe that there is currently no strong indication for additional neurodevelopmental assessment in early childhood for the offspring of GDM mothers treated with metformin when compared to the offspring of GDM mothers treated with insulin.

Terti et al. reported weaker language performance in the offspring of GDM mothers when compared with age-adjusted Finnish normative data.⁵⁷ Further assessment is required to determine if this difference in language performance persists later on in childhood and/or adulthood, and to determine if extensive and systematic testing of language performance may be necessary in the offspring of women with GDM.

Given that offspring data remains relatively limited, further high-quality follow-up studies are necessary to determine the presence and significance of any differences in long-term outcomes observed in children born to metformin- or insulin-treated mothers with GDM. Evidence is also lacking on whether any differences between groups in early childhood persist later in life, and how postnatal factors can mask or influence the effects of metformin exposure in-utero.

5. Conclusions

While it may be premature to draw final conclusions at this point in time, the existing follow-up studies are encouraging and do not show an increased risk of adverse effects in terms of growth and development in the children of GDM mothers treated with metformin versus insulin. These findings are reassuring for women with GDM treated with metformin, as well as their families and clinicians. In practice, clinicians should continue to ensure that all mothers with GDM considering metformin therapy are counselled regarding the relatively limited but nonetheless encouraging offspring data available. Ethnicity and lifestyle factors may influence offspring outcomes in a complex fashion and we believe that future studies would benefit from discussing ethnicity and lifestyle factors when reporting baseline characteristics and results.

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Figure 1. Search Flow Diagram

