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MATERNAL-FETAL MEDICINE

Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis

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Abstract

Purpose Oral antidiabetic medication of metformin is increasingly used in pregnant women with gestational diabetes mellitus (GDM), polycystic ovary syndrome (PCOS) and obesity. The drug passes through the placenta and can potentially influence the fetus. The aim of the study is to investigate the possible long-term effects of prenatal exposure to metformin on growth and development of the offspring.

Methods A systematic review and meta-analysis was conducted to examine the longer term outcomes by the follow-up studies of the already published RCTs focusing on the body composition, metabolic parameters and neurophysiological development of the children prenatally exposed to metformin. The primary sources of the reviewed studies through August 2018, with restriction on the language of English, were Pubmed and Embase.

Results 11 follow-up studies were included, with a maximal age of children being 13 years, comprising 823 children of mothers with GDM or PCOS who were randomized to either metformin or insulin/placebo during pregnancy. From the pooled meta-analysis we found that children prenatal exposure to metformin were associated with a significantly heavier weight (MD = 0.48 kg, 95% CI 0.24 kg, 0.73 kg; $P = 0.0001$, $I^2 = 0$). As for other parameters of body composition, metabolic parameters and neurophysiological development, the results were similar between metformin and placebo/insulin use.

Conclusion Increased offspring weight was more observed in children prenatal exposure to metformin. Heathcare providers and patients should be aware that metformin is increasingly prescribed in pregnancy based on the relatively limited evidences but nonetheless encouraging long-term offspring data are available.

Keywords Metformin · Gestational diabetes mellitus · Polycystic ovary syndrome · Offspring

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, which mainly refers to the decline of glucose tolerance during pregnancy, leading to the continuous improvement of blood glucose level of pregnant women, and has a certain impact on their health and fetal development. Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in women of reproductive age, characterized by chronic anovulation and hyperandrogenism. Fetal exposure to maternal hyperglycemia increases the risk of metabolic disorders (such as obesity and type 2 diabetes) in offspring during childhood [1, 2]. At present, more and more patients with GDM and PCOS are given oral insulin sensitizers (such as metformin) to improve the sensitivity of insulin receptors [3]. Classical treatments for hyperglycemia of GDM and PCOS include dietary intervention, lifestyle modification, and the use of insulin when necessary. Studies have shown that insulin is relatively safe for fetuses because it does not cross the placenta. On the contrary, metformin can pass through the placenta and can be found in the fetal circulation with therapeutic concentration. Metformin has been proved to be safe during pregnancy and can be used as an effective substitute for insulin [4]. Recent RCT studies have shown that metformin is not associated with the

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incidence of poor pregnancy or perinatal outcomes in GDM and PCOS patients compared with insulin alone [5–8]. Evidence suggests that intrauterine exposure to metformin may improve insulin action in the fetus, leaving the fetus in a healthier metabolic state, with more subcutaneous fat storage, and less heterotopic fat [9, 10].

Although recent meta-analyses suggest that large amounts of prenatal metformin exposure do not appear to have adverse effects on the short-term prognosis of newborns [11, 12], the long-term effects on newborns are not conclusive [13]. Thus the present systematic review and meta-analysis was conducted to examine the longer term outcomes by the follow-up studies of the already published randomized controlled trials (RCTs) focusing on the body composition, metabolic parameters and neurophysiological development of the children prenatally exposed to metformin.

Methods

The methods of literature search, inclusion and exclusion criteria, outcome measures, and methods of statistical analysis were following the *Cochrane Handbook for Systematic Reviews of Interventions*, and defined in a protocol according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement* [14]. Patient consent and ethical approval and were not mandatory, as all data available were based on previously published studies.

Data sources and searches

The primary data sources of Pubmed, Embase, Web of science, EBSCO, and the Cochrane library were searched until August 2018. Only those with English abstracts were considered in order to confirm the quality of included studies. We combined the database-specific search terms of metformin and offspring respectively as well as truncated search terms utilizing the wildcard ("*") character for the long-term follow-up studies of blinded and open-label RCTs on the pregnant women with GDM or PCOS. Additionally, the "related articles" function was also used to broaden the search, and the reference lists of retrieved studies and relevant reviews, primary studies, and abstracts from meetings were also hand-searched until no further article was identified (the process was performed repeatedly). All enrolled studies were imported into the bibliographic citation management software of EndNote (Version X6, Thomson Corporation, Toronto, Canada). Authors of relevant abstracts were contacted to obtain any unpublished data (if available). When the results of a single study were reported in more than one publication, only the most recent and complete data were included.

Study selection

Long-term follow-up studies comparing the body composition, metabolic parameters and neurophysiological development of children who were prenatally exposed metformin versus insulin/placebo were selected. In addition, all of the studies included in the meta-analysis met the following criteria:

(1) Follow-up studies regarding the post-neonatal health effects of the offspring of the mothers with GDM or PCOS, who had participated in the previously published RCTs.

(2) Corresponding original RCTs investigating the efficacy of metformin in the prevention of fetal macrosomy and its influence on neonatal morbidity in women with GDM or PCOS in comparison with no treatment, placebo or insulin therapy.

(3) Long-term follow-up contents should contain at least one of the following items: body composition, metabolic parameters or neurophysiological development.

(4) Women with singleton pregnancies diagnosed with GDM or PCOS between 12 and 34 weeks of gestation were asked to participate in the study.

Outcome measures

Growth, body composition of height, weight and BMI, and metabolic parameters, by the methods of anthropometry, bioimpedance analysis, dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and fasting bloods. Neurodevelopment was examined with the Bayley Scales of Infant Development V.2 mental development index (MDI) and psychomotor development index (PDI). The systolic and diastolic blood pressure was measured by oscillometric. As animal studies have raised a concern that metformin may have harmful effects on developing testes [15], we also assess the testicular size and development by orchidometer and ultrasonography. Also, the risk of neurodevelopmental difficulties was measured by cortical excitability, long-term depression (LTD)-like neuroplasticity.

Data extraction and synthesis

The literature was independently screened and cross-checked by two researchers according to the inclusion and exclusion criteria set beforehand. In case of disagreement, the literature was discussed and resolved and submitted to a third researcher for decision if necessary. Data were extracted and entered by one researcher and checked by another according to a pre-designed data extraction table.

Mean difference (MD) and risk ratio (RR) were used as a summary statistics for the pooled outcomes. Heterogeneity

among the results was analyzed by Q test, the test level was alpha = 0.1, and I^2 was used to measure the heterogeneity. If there were no statistical and clinical heterogeneity between the results of each study ($P > 0.1$, $I^2 < 50\%$), the fixed-effect model was used for meta-analysis; if there were moderate or higher statistical heterogeneity among the results but no clinical heterogeneity ($P < 0.1$, $I^2 < 50\%$), subgroup analysis or sensitivity analysis could be performed, if there were no obvious heterogeneity sources [16]. A random effect model was used for meta-analysis. Sensitivity analysis was performed by eliminating the impact of individual studies on the overall analysis results. Using funnel plots to analyze whether publication bias exists in inclusion studies meta-analysis was conducted by Review Manager 5.3 software (Cochrane collaboration, Copenhagen, Denmark) [17]. The Quality in Prognostic Studies (QUIPS) tool was used for study reliability assessment.

Results

Literature retrievals

Figure 1 illustrates the study screening and selection process. A total of 405 papers were found, 168 were excluded from duplicate and unrelated papers, 237 were preliminarily screened, 195 were excluded from retrospective case analysis and non-contrast group after reading the title and abstract, and incomplete data, other interventions and low quality were excluded after reading the full text. A total of 42 publications were reviewed and 31 publications were excluded. Finally, a total of 11 studies qualified for inclusion in this systematic review with a total of 823 children of mothers with GDM or PCOS [18–28].

Characteristics of the included studies

Table 1 listed the baseline clinicopathological characteristics of the original metformin-based RCTs in gestational diabetes. Table 2 listed the characteristics of the included long-term offspring follow-up studies. Cognitive, language, and motor skills and results of neurological examination in 2-year-old children were analyzed by standardized developmental and neurological measures in Tertti et al. follow-up study [25] of their own RCT [29]. Furthermore, they also observed the metformin effects on the testicular size in offspring born to mothers with GDM [21]. Ijäs et al. [24] conducted a follow-up study of the growth and development of the children at the age of 18 months. The risk of offspring

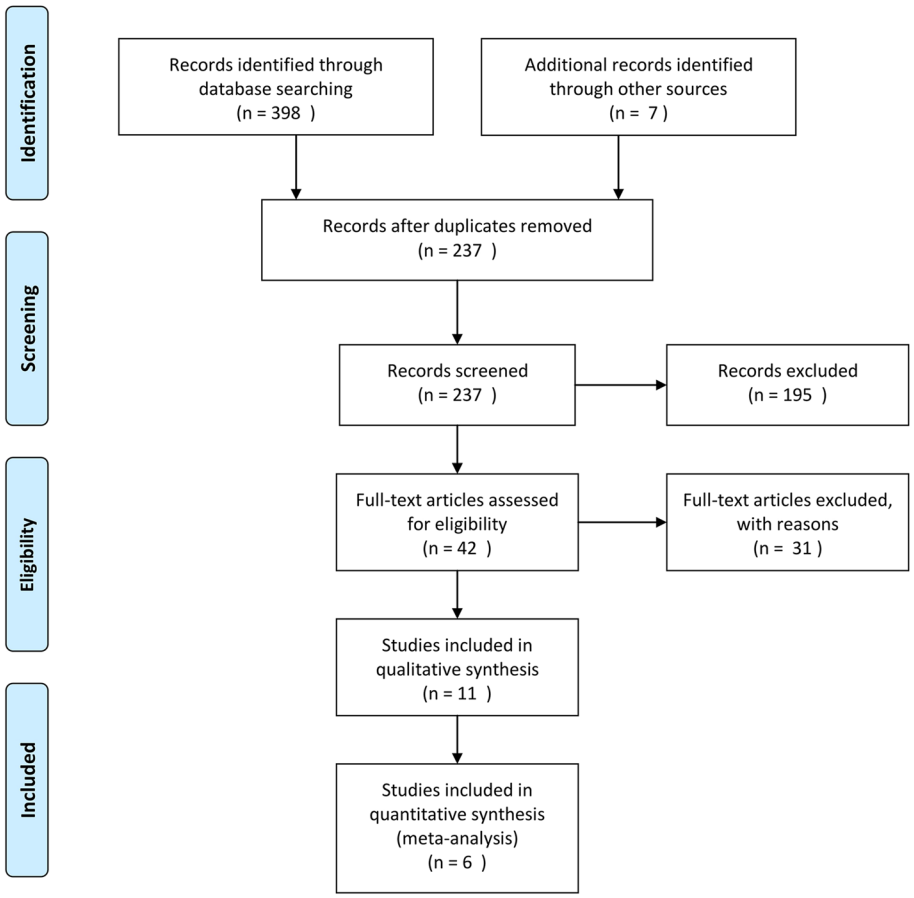

Fig. 1 Flowchart of publication search and selection

Table 1 Characteristics of the original metformin-based RCTs in gestational diabetes

Authors/country	Treatment indications	Comparisons	No. of patients	Ages (years)	Pre- or early pregnancy BMI (kg/m^2)	Medication (mg/day)
Tertti et al. [29]/Finland (2013)	GDM	Metformin	110	31.9 ± 5.0	29.4 ± 5.9	500–2000
		Insulin	107	32.1 ± 5.4	28.9 ± 4.7	Usual practice
Ijäs et al. [33]/Finland (2011)	GDM	Metformin	47	32.3 ± 5.6	31.5 ± 6.5	750–2250
		Insulin	50	31.7 ± 6.1	30.8 ± 5.4	Usual practice
Vanky et al. [30]/Norway (2010)	PCOS	Metformin	135	29.6 ± 4.4	29.5 ± 7.0	1000–2000
		Placebo	138	29.2 ± 4.4	28.5 ± 7.2	1000–2000
Rowan et al. [32]/New Zealand (2008)[a]	GDM	Metformin	363	33.5 ± 5.4	32.2 ± 8.2	500–2500
		Insulin	370	33.0 ± 5.1	31.9 ± 7.6	Usual practice
Vanky et al. [31]/Norway (2004)[b]	PCOS	Metformin	18	28.9 ± 4.8	32.1 ± 6.1	850–1700
		Placebo	22	28.3 ± 3.7	29.3 ± 8.0	850–1700

GDM gestational diabetes mellitus, *PCOS* polycystic ovary syndrome, *BMI* body mass index, *RCT* randomized controlled trial

[a]10 New Zealand and Australian urban obstetrical hospitals were included for the RCT

[b]This is a pilot study of 40 women with PCOS included at St Olav's Hospital in Trondheim, Norway

overweight at 4 years of age was explored by Hanem et al. combined follow-up study [18] of two RCTs [30, 31] in 2018. Offspring anthropometry at birth and weight 1 year postpartum were registered in Carlsen et al. [26]. Five follow-up studies [19, 20, 22, 23, 28] of the original RCT conducted by Rowan et al. [32] in 2008 were included. Two studies [19, 28] focused on the body composition and metabolic outcomes. Specifically, using transcranial magnetic stimulation, Van Dam et al. assessed cortical excitability, long-term depression (LTD)-like neuroplasticity in 45 GDM-exposed and 12 control children aged 11–13 years [20]. Wouldes et al. study seeks to examine the neurodevelopment of offspring of women treated with metformin or insulin for GDM [22]. The systolic and diastolic blood pressure at 2 years of age in a cohort of children exposed to GDM were determined by Battin et al. [23]. Rø et al. investigated the possible long-term effects of metformin exposure on growth and development of the offspring in their follow-up study of an RCT on PCOS women [27].

Growth, body composition of height, weight and BMI

Five follow-up studies reported the height data for the use of metformin on offspring [21, 24, 26–28]. In Fig. 2, from the pooled meta-analysis, we found that children prenatal exposure to metformin was associated with a significantly heavier weight (MD = 0.48 kg, 95% CI 0.24 kg, 0.73 kg; $P = 0.0001$, $I^2 = 0$). As for height and BMI, non-significant differences were observed, and the pooled MDs were − 0.45 cm (95% CI − 0.55 cm, 1.45 cm; $P = 0.38$, $I^2 = 42\%$) and 0.30 kg/m^2 (95% CI − 0.01 kg/m^2, 0.61 kg/m^2; $P = 0.06$, $I^2 = 27\%$), respectively. In Rowan et al. study, metformin offspring at 9 years were larger by measures of weight, arm and waist circumferences, waist:height ($P < 0.05$); BMI, triceps skinfold ($P = 0.05$).

Metabolic parameters

As for the metabolic parameters of glycosylated hemoglobin (HbA1c), fasting glucose, insulin, insulin resistance, triglyceride, cholesterol, leptin and adiponectin, liver transaminases, they were similar between metformin and placebo/insulin exposed. However, a higher fasting glucose level (4.93 mmol/L vs. 4.60 mmol/L, $P = 0.04$) and a possible higher systolic blood pressure and lower LDL cholesterol level in the metformin group in Rø et al. follow-up study of an RCT on PCOS women was noted, which may be coincidental and should be further explored [27].

Neurodevelopment and risk of neurodevelopmental difficulties

Treatment of GDM improves pregnancy and birth outcomes; however, very little evidence exists regarding the effects of treatment on later neurodevelopment of the offspring. In Wouldes et al. follow-up study, the mental development index and psychomotor development index composite scores were tested with general linear models, without significant differences were found between metformin and insulin, respectively [22]. Similarly, in Tertti et al. standardized developmental and neurological measures, there were no significant differences between the metformin and insulin groups in the Bayley Scales of Infant and Toddler Development (Bayley-III) test of cognitive scale, receptive communication or expressive

Table 2 Characteristics of the included long-term offspring follow-up studies

Original RCTs	Corresponding follow-up studies	Period of follow-up	Outcomes measured	Comparisons	Gestational age at randomization (weeks)	No. of offspring (male%)	Offspring follow-up age (months)
Tertti et al. [29]	Tertti et al. [21]	2013–2014	Testicular size and development by orchidometer, and by ultrasonography	Metformin	22–34	25 (100)	60.4 ± 17.0
				Insulin	22–34	27 (100)	60.7 ± 15.4
	Tertti et al. [25]	2008–2012	Standardized developmental and neurological measures	Metformin	30.3 ± 2.0	75 (47)	24 (23–24)
				Insulin	30.4 ± 1.8	71 (46)	24 (23–24)
Ijäs et al. [33]	Ijäs et al. [24]	2007–2011	Weight and height measurements, and motor, social, and linguistic development	Metformin	30.0 ± 4.5	45 (47)	6, 12, and 18
				Insulin	30.4 ± 4.1	48 (46)	6, 12, and 18
Vanky et al. [30]	Hanem et al. [18][e]	2014–2016	Height, weight, BMI and overweight/obesity	Metformin	5–12	81 (NA)	4 years
				Placebo	5–12	79 (NA)	4 years
	Carlsen et al. [26]	2006–2010	Weight gain	Metformin	10.6 (5–12)	102 (49)	1 year
				Placebo	10.7 (5–12)	94 (47)	1 year
Rowan et al. [32]	Van Dam et al. [20]	2004–2008	Risk of neurodevelopmental difficulties, by cortical excitability, LTD-like neuroplasticity	Metformin	30 ± 2.6	23 (NA)	11–13 years
				Insulin	30 ± 2.6	22 (NA)	11–13 years
	Rowan et al. [19][a]	2009–2011	Body composition and metabolic outcomes, by the methods of anthropometry, bioimpedance analysis, DEXA, MRI and fasting bloods	Metformin[b]	31.3 ± 2.8	58 (60)	7.0 ± 1.0 (years)
				Insulin[b]	31.6 ± 2	51 (45)	7.4 ± 1.1 (years)
				Metformin[c]	29.9 ± 3.6	45 (62)	8.9 ± 0.5 (years)
				Insulin[c]	29.5 ± 3.4	54 (52)	8.9 ± 0.4 (years)
	Wouldes et al. [22][d]	2004–2008	Neurodevelopment was examined with the Bayley Scales of Infant Development V.2 mental development index (MDI) and psychomotor development index (PDI)	Metformin[b]	20–33	39 (56)	33.2 ± 1.9
				Insulin[b]	20–33	44 (46)	33.6 ± 1.4
				Metformin[c]	20–33	64 (52)	27.4 ± 2.5
				Insulin[c]	20–33	64 (45)	27.3 ± 2.4
	Battin et al. [23]	2004–2008	Oscillometric measurement of the systolic and diastolic blood pressure	Metformin	20–33	83 (48)	29 (22–38)
				Insulin	20–33	87 (47)	29 (22–38)
	Rowan et al. [28]	2004–2008	Body composition, assessed with anthropometry, bioimpedance, and DEXA	Metformin	30.4 ± 3.3	154 (56)	28.7 ± 3.6
				Insulin	30.0 ± 3.3	164 (48)	29.4 ± 3.8
Vanky et al. [31]	Rø et al. [27]	2008–2011	Growth, body composition and metabolic parameters	Metformin	5–12	12 (67)	8.2 ± 0.6 (years)
				Placebo	5–12	13 (23)	8.1 ± 0.8 (years)

RCT randomized controlled study, *BMI* body mass index, *DEXA* dual-energy X-ray absorptiometry, *MRI* magnetic resonance imaging, *LTD* long-term depression

[a]Children were assessed at 7 years in Adelaide ($n = 109/181$) and 9 years in Auckland ($n = 99/396$)

[b]Offspring were from the origin population in Adelaide of Australia

[c]Offspring were from the origin population in Auckland of New Zealand

[d]Of the 211 children followed up at 2 years, 128 were from Auckland, New Zealand (64 metformin vs 64 insulin), and 83 from Adelaide, Australia (39 metformin vs 49 insulin)

[e]This study is a follow-up of two double-blinded RCTs, eligible to participate in the follow-up study were children of mothers who participated in "The Metformin Treatment of Pregnant Women with Polycystic Ovary Syndrome study" (the pilot study) [11] from 2000 to 2003 or "The Metformin in Pregnant PCOS Women study" (the PregMet study) [11] from 2005 to 2009

communication, fine motor scale or gross motor scale, or the global scores of Hammersmith Infant Neurological Examination [25]. None of the children had a clinically significant developmental problem, supporting the safety of metformin in the treatment of GDM. Additionally, GDM-exposed children had reduced cortical excitability ($P = 0.003$), long-term depression-like neuroplasticity ($P = 0.005$), and salivary cortisol ($P < 0.001$) when

compared with control children by Van Dam et al. [20], and metformin seems to be safe for these aspects of nerve development, and the result is similar to insulin.

Other outcomes

Tertti et al. performed a follow-up study in male offspring (mean age at 60) of GDM patients to determine the effect of metformin on testicular size and insulin therapy during pregnancy [21]. There was no difference in prepubertal testicular size between offspring of metformin-treated mothers and offspring of insulin-treated mothers. Blood pressure data were obtained at approximately 2 years of age in a substantial cohort of children whose mothers received treatment for GDM [23], and no difference was found between the metformin and insulin treatment arms. Moreover, the motor, social, or linguistic development evaluated at the age of 18 months did not differ between the metformin and insulin groups [24].

Discussion

This systematic review and meta-analysis provides strong evidence that there is no difference between the body composition, metabolic parameters and neurophysiological development of children whose mothers had received metformin during pregnancy compared with those whose mothers received insulin or placebo to treat their GDM. Only the pooled outcome of the weight was significantly heavier in offspring prenatally exposed to metformin as compared with controlled group. What's more, prenatal exposure to metformin did not seem to affect the child's motor, linguistic, or social development, neither the testicular size nor blood pressure. At present, metformin, as an oral preparation, is increasingly used by medical institutions in addition to insulin in pregnant women with GDM or PCOS. Among them, insulin treatment has been confirmed by several RCT and reached a unified conclusion [29–33]. Furthermore, of note is the observation that metformin crosses the placenta. Thus possible long-term effects are undetermined and

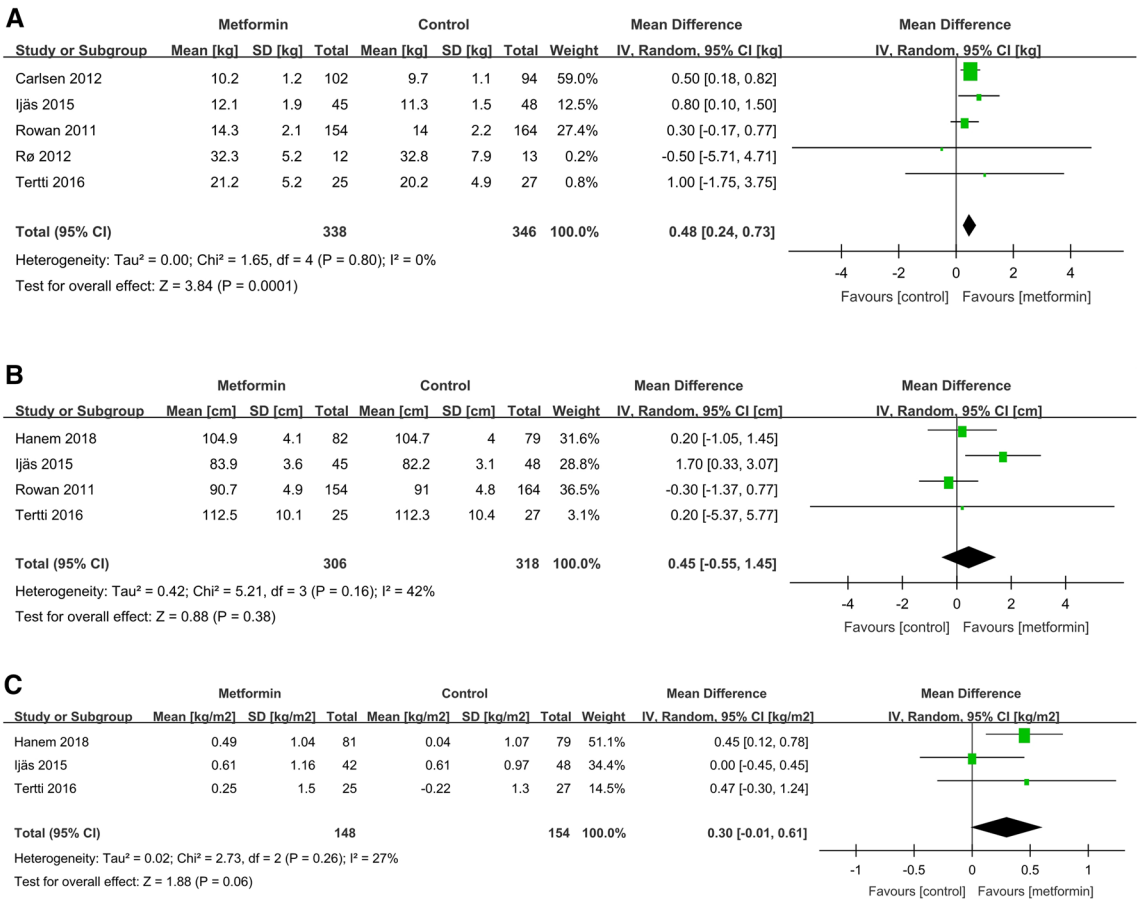

Fig. 2 Forest plots depicting the pooled outcomes of **a** weight, **b** height and **c** BMI of long-term follow-up studies of metformin versus control group (placebo/insulin)

comprehensive assessment is needed for the follow-up studies of the offspring.

Body composition is the main follow-up outcome in Rowan et al. study [19]. The offspring of women enrolled in the MiG trial have been followed at two centers: Auckland and Adelaide. In the former population from New Zealand, a higher BMI was observed for the women randomized to metformin group, however they gained less weight during treatment period, and offspring birth measures were similar. At 9 years, metformin offspring were larger by measures of weight, arm and waist circumferences, waist:height, BMI, and triceps skinfold. In the latter population from Australia, mothers were similar at enrollment. Women randomized to metformin versus insulin had higher treatment glycemia and more infants with birth weight > 90th percentile. However, there were no differences in offspring measures at 7 years of follow-up. It is thus suggested that metformin might interact with other intrauterine environmental nutritional factors to influence long-term outcomes for offspring of women with GDM [19].

There existed an interesting animal experiment indicating prenatal metformin exposure leads to divergent metabolic phenotypes in offspring [34]. In the male offspring, metformin exposure has an inhibitory effect on weight gain. In addition, the weight of white fat bank and serum insulin and lipid tended to decrease within 7 months. In contrast, in female offspring, metformin exposure at three months impaired glucose tolerance and subsequently increased weight gain, fat content and serum cholesterol. Combined with Rowan et al. follow-up data and animal studies, important interactions between fetal nutrition, sex and metformin may affect pregnancy and long-term outcomes. Rø et al. small follow-up study of women with PCOS reported outcomes in 8-year-old human offspring exposed to metformin in utero [27]. The fasting blood glucose of 12 cases in metformin group was significantly higher than that of the control group, and there was a trend towards lower LDL cholesterol in the metformin group. It would be of interest to know analysis of other factors, such as weight gain during pregnancy and dietary quality, will help to understand whether their data are consistent with animal studies. All in all, lifestyle factors, timing of intervention, fetal sex, blood glucose control, and medication can interact because improvements in pregnancy outcomes can translate into improvements in long-term outcomes.

Few data on the neurodevelopment of offspring born to mothers with GDM treated with insulin compared with those treated with metformin were reported. There was no difference in neurological development between 2-year-old children whose mothers took metformin during pregnancy and those whose mothers took insulin for GDM [22]. Furthermore, while global cognitive and motor development at the 2-year follow-up of the MiG trial offspring did not differ between treatment groups in either New Zealand or Australia, New Zealand offspring scored significantly lower in cognitive and motor development than Australian offspring. Maternal ethnicity may be the explanation for lower scores. In addition, Van Dam et al. performed the first study to provide neurophysiological evidence that Intrauterine GDM exposure was associated with decreased cortical excitability and neuroplasticity and decreased salivary basal cortisol levels in offspring aged 11–13 [20]. The neurophysiological outcomes of children exposed to metformin were comparable to those of mothers receiving insulin therapy.

Animal studies suggest that metformin may have a detrimental effect on testicular development [15]. It was reported that metformin decreased testosterone secretion and mRNA expression of the main factors involved in steroid production in human and mouse organotypic cultures in vitro. In vivo administration of metformin to pregnant mice, although the number of germ cells was not affected by the metformin treatment, the number of Sertoli cells, the nurse cells of germ cells, was slightly yet significantly reduced [15]. Tertti et al. conducted the first follow-up study to evaluate the influence of metformin exposure on testicular development of human infants [21]. Participation in this follow-up study was close to 50%, and considering the delicate nature of testicular examination, we thought it was acceptable. All three different methods applied to measure testicular size in this study is widely used, and the results were consistent; none of them detected any difference in testicular size between the two groups. Battin et al. reported data on blood pressure obtained at approximately 2 years of age in a substantial cohort of children whose mothers had received treatment during their pregnancy for GDM [23]. The method of the study was robust because blood pressure data were collected prospectively by professional researchers, who were clear-sighted before taking measurements of their children and were in good communication and cooperation with them. Although it is important to continue assessing the cardiovascular status of this group in childhood, current studies provide important new data that in the MiG trial, the systolic blood pressure of offspring from GDM women can be comparable to the reported normal value, with no significant difference from the treatment group.

In conclusion, on the basis of this systematic review and meta-analysis of the existing follow-up studies, only the increased offspring weight in childhood after maternal metformin use during gestation is detected. Heathcare providers and patients should be aware that metformin are increasingly prescribed in pregnancy based on the relatively limited evidences but nonetheless encouraging long-term offspring data are available. Future long-term offspring follow-up studies would benefit from discussing the effects of ethnicity and

lifestyle factors to firmly conclude on the safety of metformin use in pregnancy and its programming impacts.

Author contribution QX: designed the study, collected data, and analyzed/interpreted data wrote the draft critically for important intellectual content approved the final version to be published. QX: collected data, and analyzed/interpreted data critically for important intellectual content approved the final version to be published.

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Compliance with ethical standards

Conflict of interest There are none to declare.

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