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ORIGINAL RESEARCH ARTICLE

Comparison of glucose metabolism and anthropometry in women with previous gestational diabetes treated with metformin vs. insulin: 9-year follow-up of two randomized trials

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Abstract

Introduction: The main aim was to study whether the long-term incidences of type 2 diabetes, pre-diabetes and metabolic syndrome differed between women who were treated with metformin or insulin for gestational diabetes.

Material and methods: This 9-year follow-up study of two open-label randomized trials compares metformin and insulin treatments of gestational diabetes. In all, 165 women, 88 previously treated with insulin and 77 treated with metformin in the index pregnancy, were included in the analyses. An oral glucose tolerance test was performed, and measures of anthropometry, glucose metabolism, serum lipids and inflammatory markers were compared between the treatment groups. Disorders of glucose metabolism (pre-diabetes and type 2 diabetes) at the 9-year follow-up was the primary outcome of this study. This study was registered at ClinicalTrials.gov: NCT02417090.

Results: The incidences of pre-diabetes and type 2 diabetes (40.3% vs. 46.6%, odds ratio [OR] 0.77, 95% CI 0.40–1.50, $p = 0.51$), type 2 diabetes (14.3% vs. 15.9%, OR 0.88, 95% CI 0.34–2.26, $p = 0.94$), pre-diabetes (26.0% vs. 30.7%, OR 0.79, 95% CI 0.38–1.65, $p = 0.62$), and metabolic syndrome (45.9% vs. 55.2%, OR 0.69, 95% CI 0.35–1.35, $p = 0.31$) were comparable between the metformin and insulin groups. Moreover, there were no evident differences in the individual measures of anthropometry, glucose metabolism including HOMA-insulin resistance, serum lipids or inflammatory markers between the two treatment groups.

Conclusions: Treatment of gestational diabetes with metformin vs. insulin during pregnancy is unlikely to have diverging long-term effects on maternal anthropometry,

Abbreviations: ALT, alanine aminotransferase; ApoB, apolipoprotein B; BMI, body mass index; GDM, gestational diabetes; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; OR, odds ratio; T2DM, type 2 diabetes.

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glucose metabolism or serum lipids. From this perspective, both treatments may be considered in gestational diabetes.

KEYWORDS
gestational diabetes, insulin, metabolic syndrome, metformin, type 2 diabetes

1 | INTRODUCTION

Gestational diabetes (GDM) is a common disorder in pregnancy[1] that increases the risk of adverse pregnancy outcomes such as macrosomia, preeclampsia, cesarean delivery, neonatal hypoglycemia, hyperbilirubinemia and need for neonatal intensive care.[2,3] In addition, prior GDM is a major risk factor for the development of type 2 diabetes (T2DM)[4] and metabolic syndrome (MetS)[5] later in life.

Impaired beta-cell function and increased insulin resistance have been observed in women already prior to GDM diagnosis,[6] as well as after delivery.[7] Therefore, it has been questioned whether the treatment of GDM could modify the risk of long-term metabolic morbidity. A follow-up study 7 years after a randomized trial comparing treatment vs. no treatment of mild GDM found no differences in rates of T2DM, MetS, homeostasis model assessment of insulin resistance (HOMA-IR) or body mass index (BMI) between the groups.[8] However, in that study the GDM was mild and only about 5% of the participants required pharmacological treatment.[9]

Metformin, an alternative to insulin for GDM patients requiring pharmacological intervention, has been proven to be comparable regarding short-term perinatal outcomes.[10] However, during pregnancy, metformin treatment has been associated with higher triglycerides, very-low-density lipoprotein lipids, low-density lipoprotein (LDL) lipids, total fatty acids, saturated fatty acids and monounsaturated fatty acids in pregnancy.[11,12] One follow-up study found similar maternal anthropometry, amount of body fat, and rates of self-reported diabetes 7–9 years after the pregnancy in mothers randomized to metformin or insulin during the pregnancy;[13] however, the maternal glucose metabolism, lipids and inflammatory markers were not assessed.

The aim of the present study was to evaluate whether the rates of T2DM, pre-diabetes and MetS differ between the metformin- and insulin-treated GDM patients 9 years after delivery. Furthermore, we compared anthropometry, serum lipids and inflammatory markers between these two groups, as these parameters are known to predict subsequent T2DM.[14–16] We hypothesized that there would be no large differences between the groups.

Key message

Gestational diabetes is a risk factor for future abnormal glucose metabolism. Treatment with metformin compared with insulin during pregnancy does not appear to modify this risk.

2 | MATERIAL AND METHODS

This study is a follow-up of two Finnish randomized trials conducted between 2005 and 2009 at Oulu University Hospital (patients were also recruited and treated at Kainuu Central Hospital),[17] and between 2006 and 2010 at Turku University Hospital.[18] The original recruitment, randomization and perinatal outcomes have been reported previously in detail.[17,18] Briefly, women with a singleton pregnancy and need for medical treatment for GDM were randomized to receive either metformin or insulin. Originally, 97 women were included in the study in Oulu and 217 in Turku. Randomization was performed in 1:1 ratio using sealed envelopes at the study hospital when medical treatment was indicated. In the original trials, the sample sizes were calculated to demonstrate 30% difference in the rates of macrosomia (birthweight >4000 g) in Oulu[17] and non-inferiority in birthweights in Turku.[18]

GDM was diagnosed by a 75-g 2-h oral glucose tolerance test (OGTT). In Oulu, one elevated value was required for diagnosis; the thresholds for fasting, 1-h, and 2-h glucose values in capillary plasma were 5.3, 11.0 and 9.6 mmol/L. In Turku, two elevated values were required; the corresponding threshold values in venous plasma were 4.8, 10.0 and 8.7 mmol/L until December 2008, when the Finnish national guidelines were published, and 5.3, 10.0 and 8.6 mmol/L thereafter. The maximum metformin doses were 2250 mg/day in Oulu and 2000 mg/day in Turku. Insulin therapy was performed using neutral protamine Hagedorn insulin and/or rapid-acting insulin analogues insulin lispro or insulin aspart. In the metformin groups, 32% and 21% of women required additional insulin to achieve glycemic goals in Oulu and Turku, respectively. In our follow-up study, these women are included in the metformin group. There were no differences between the treatment groups in the primary outcomes; birthweight[18] and rates of macrosomia and large-for-gestational-age neonates,[17] respectively. For this analysis, birthweight was adjusted for gestational weeks and fetal sex according to new Finnish population-based references, and represented as SD units and centiles.[19]

At the follow-up study visit, weight, height, abdominal circumference and waist circumference were measured three times, and the mean values of the three measurements were used in the analyses. Three blood pressure measurements were also taken, and the mean values of the second and third measurements were used. Weight categories were defined as normal weight (BMI <25 kg/m^2), overweight (BMI ≥25 and <30 kg/m^2) and obese (BMI ≥30 kg/m^2).

A 75-g OGTT was performed, and glucose values were measured at fasting and at 30 and 120 min. Glycated hemoglobin (HbA1c), C-peptide, insulin, alanine aminotransferase (ALT), apolipoprotein A-1 (ApoA1), apolipoprotein B (ApoB), total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, high sensitivity C-reactive protein (hs-CRP), ferritin and adiponectin were measured from fasting samples. Analysis details are described in Appendix S1. HOMA-IR was calculated as *fasting glucose (mmol/L) x fasting insulin (mU/L)/22.5*, and non-HDL cholesterol as *total cholesterol – HDL cholesterol*.

Pre-diabetes was defined as impaired fasting glucose (fasting glucose 6.1–6.9 mmol/L), impaired glucose tolerance (OGTT 2-h glucose 7.8–11.0 mmol/L) or HbA1c 6.0–6.4% (42–47 mmol/mol). T2DM was defined as fasting glucose ≥7.0 mmol/L, OGTT 2-h glucose >11.0, or HbA1c ≥6.5% (48 mmol/mol). MetS was defined according to International Diabetes Federation as waist circumference ≥80 cm plus at least two of the following four criteria: (1) raised triglyceride concentration (≥1.7 mmol/L), (2) reduced HDL cholesterol concentration (<1.29 mmol/L) or treatment for dyslipidemia, (3) raised blood pressure (systolic ≥130 or diastolic ≥85 mmHg) or treatment for previously diagnosed hypertension, and (4) raised fasting plasma glucose concentration (≥5.6 mmol/L) or previously diagnosed T2DM.[20]

Parity and educational level of the participants were recorded. Breastfeeding duration was recorded only in the participants recruited at Turku.[21] The women were also asked to describe their well-being as "extremely poor", "poor", "average", "good" or "excellent", and physical activity was assessed by asking the women on how many days per week exercises were done. Data regarding the offspring anthropometry, glucose and lipid metabolism have been published in a separate report.[22]

Primary outcome of the study was the rate of disorder of glucose metabolism, ie composite outcome of pre-diabetes and T2DM. Main secondary outcomes were incidences of pre-diabetes, T2DM and MetS—long-term consequences of GDM[4,5] with clinical significance. Exploratory secondary outcomes were measures of maternal anthropometry, components of MetS according to IDF,[20] individual measures of glucose metabolism, insulin resistance, low-grade inflammation and lipid homeostasis, and adiponectin (detailed in Appendix S1).

2.1 | Statistical analyses

Baseline characteristics of both cohorts during pregnancy were compared between the participants and non-participants of the follow-up study and between the metformin and insulin groups. Additional comparisons between the participants and non-participants were performed in the metformin and insulin groups separately. Outcome variables were compared between the metformin and insulin groups in the whole population. Between-group comparisons were performed using the *t*-test, the Mann–Whitney *U*-test, the chi-square test or Fisher's exact test depending on the data. In cases of slightly skewed data, the *P*-values were calculated after log-transformation.

We hypothesized that there would be no differences between the treatment groups and therefore no adjustments for the *P*-values were done. For odds ratios (OR), 95% confidence intervals (CI) were calculated with Fisher's exact test. All analyses were performed using R statistical software (version 4.0.3).

2.2 | Power analyses

This being a follow-up study, we performed post-hoc power analysis regarding the primary outcome (composite of pre-diabetes and T2DM). To demonstrate a clinically significant 30% difference in the rate of outcome between 47.0% (observed rate in the insulin group) and 32.6% with power of 80%, 192 participants would have been needed per group.

2.3 | Ethical approval

This study was approved by the ethics committee of The Hospital District of Southwest Finland (ETMK 31/2015) on April 27, 2015 and registered at ClinicalTrials.gov (NCT02417090). All study participants provided an informed consent.

3 | RESULTS

A flowchart of the study is presented in Figure 1. Three mother–child dyads were excluded from the original data due to the child's trisomy-21, valproate syndrome and stillbirth. Between August 2015 and November 2019, 311 dyads were contacted and 173 (55.6%) were willing to participate. Thirty-seven mothers were not reached, 65 were not willing to participate, 12 canceled their participation, three did not participate due to undisclosed disease of the child, and for 21 the reason was not recorded. The reasons not to participate were similar between the metformin and insulin groups. Finally, 82 and 91 mother–child dyads participated in the 9-year follow-up in the metformin and insulin groups, respectively. In two cases, only the child participated in the follow-up study. Two mothers were diagnosed with autoimmune diabetes after the index pregnancy, one was pregnant at the time of follow-up, and three had undergone a bariatric surgery; these women were excluded from the analyses. Fifteen patients with previously diagnosed T2DM were excluded from the comparison of glucose metabolism, insulin resistance, inflammation and ALT. Eleven patients with medications affecting lipids (ie antihyperglycemic drugs, antihyperlipidemic drugs, systemic hormonal contraceptives) were also excluded from the analysis of serum lipids.

3.1 | Baseline characteristics

Following randomization, the participants of the follow-up study were older (32.6 vs. 31.3 years, $p = 0.046$) and weighted less (80.4 vs. 84.3 kg, $p = 0.043$) compared with the non-participating women (Table 1). They

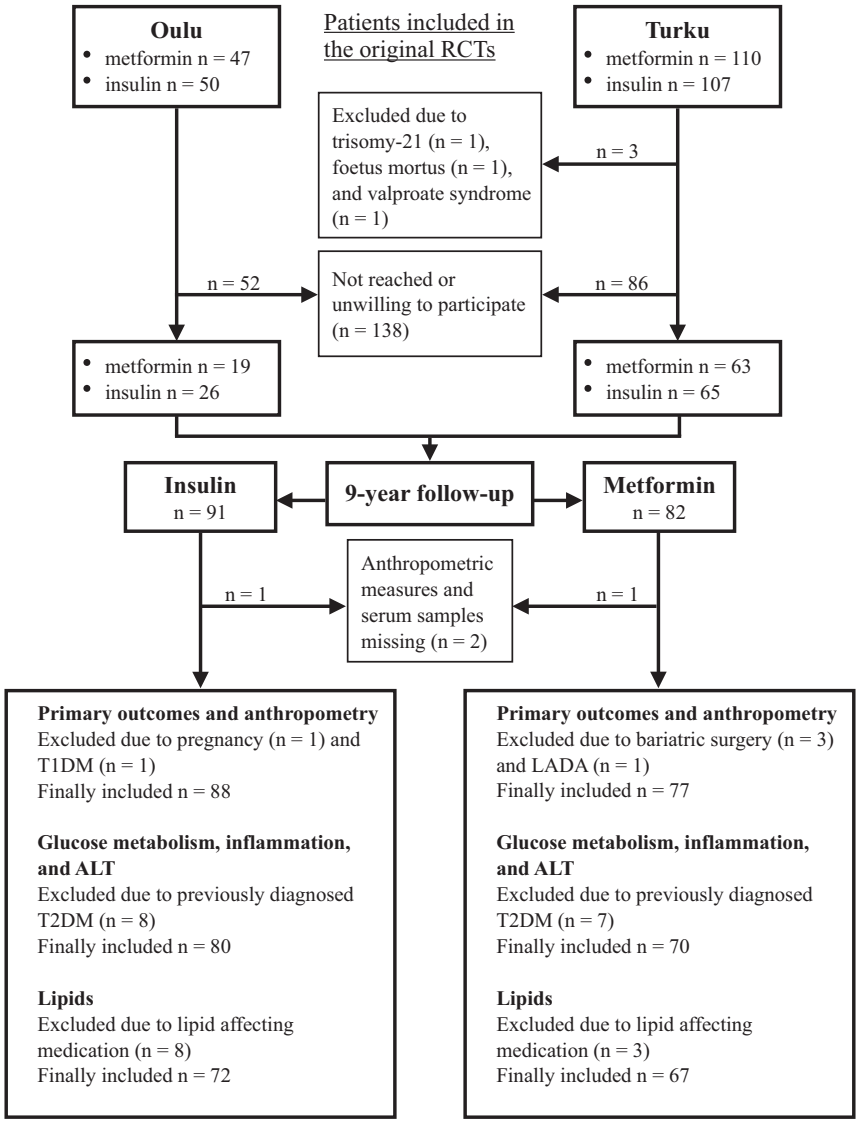

FIGURE 1 Study flow chart. ALT, alanine aminotransferase; LADA, latent autoimmune diabetes in adults; RCT, randomized controlled trial; T1DM, type 1 diabetes; T2DM, type 2 diabetes

also had a GDM diagnosis later in gestation (27 vs. 26 weeks, $p = 0.015$) and a slightly lower fasting glucose (5.42 vs. 5.55 mmol/L, $p = 0.051$) and HbA1c (37.4 vs. 38.3 mmol/mol, $p = 0.074$). When the metformin and the insulin groups were analyzed separately, these differences between the participants and non-participants were in the same direction, although with reduced statistical power (*P*-values 0.052–0.36; data not shown). Among the follow-up participants, the only difference was the higher rate of labor inductions in the insulin (58.2%) than in the metformin group (39.0%, $p = 0.018$) (Table 2).

3.2 | Maternal characteristics at follow-up

At the follow-up visit 9 years after the index pregnancy, there were no differences between the groups in the number of pregnancies after the index pregnancy, rates of smoking, educational level or physical activity (Table 3). The perception of one's own health was "poor" in only 7.9% and 6.8% of the women in the metformin and insulin groups, respectively, and none considered their health "extremely poor".

3.3 | Primary and main secondary outcomes

Nine years after the index pregnancy, the observed rate of composite outcome of pre-diabetes and T2DM was comparable between the metformin and insulin groups (40.3 vs. 46.6%, OR 0.77, 95% CI 0.40–1.50, $p = 0.51$) (Table 4). The rates of pre-diabetes (26.0 vs. 30.7%, OR 0.79, 95% CI 0.38–1.65, $p = 0.62$), T2DM (14.3 vs. 15.9%, OR 0.88, 95% CI 0.34–2.26, $p = 0.94$) and MetS (45.9 vs. 55.2%, OR 0.69, 95% CI 0.35–1.35, $p = 0.31$) were also comparable between the groups. Seven (9.1%) and eight (9.1%) women had previously diagnosed T2DM, and four (5.2%) and six (6.8%) had an incident, ie newly diagnosed, T2DM (based on OGTT and/or HbA1c at 9-year study visit) in the metformin and insulin groups, respectively.

TABLE 1 Baseline characteristics at index pregnancy: comparison of follow-up participants and non-participants

	Participants	Non-participants	*p*-value
Age (years)	32.6 ± 5.2 (173)	31.3 ± 5.6 (141)	0.046
Parity (*n*)	1 [0–2] (173)	1 [0–2] (141)	0.93
Nulliparous (*n*/total)	68/173 (39.3)	57/141 (40.4)	0.92
Smoking (*n*/total)	21/171 (12.3)	25/137 (18.2)	0.19
Weight (kg)	80.4 ± 15.2 (169)	84.3 ± 18.0 (130)	0.043
BMI (kg/m^2)	29.2 ± 5.4 (173)	30.5 ± 5.8 (141)	0.057
Glucose metabolism			
OGTT fasting glucose (mmol/L)	5.42 ± 0.55 (172)	5.55 ± 0.64 (140)	0.051
OGTT 60-min glucose (mmol/L)	11.2 [10.5–12.0] (171)	11.2 [10.5–12.3] (141)	0.93
OGTT 120-min glucose (mmol/L)	8.22 ± 1.85 (172)	8.02 ± 1.74 (140)	0.35
HbA1c at OGTT (mmol/mol)	37.4 ± 4.3 (173)	38.3 ± 4.5 (140)	0.074
HbA1c at OGTT (%)	5.57 ± 0.40 (173)	5.65 ± 0.41 (140)	
Gw at OGTT (weeks)	27 [26–28] (172)	26 [25–28] (140)	0.015
HbA1c at 36 gw (mmol/mol)	38.3 ± 3.9 (155)	39.1 ± 4.2 (127)	0.084
HbA1c at 36 gw (%)	5.65 ± 0.36 (155)	5.73 ± 0.39 (127)	
Treatment			
Gw at randomization (weeks)	31 [29–32] (173)	31 [29–32] (141)	0.46
Treatment			0.36
Insulin (*n*/total)	91/173 (52.6)	66/141 (46.8)	
Metformin (*n*/total)	82/173 (47.4)	75/141 (53.2)	
Additional insulin (*n*/total, of metformin-treated patients)	22/82 (26.8)	16/75 (21.3)	0.54
Obstetric outcomes			
Weight gain in pregnancy (kg)	8.5 ± 4.9 (173)	7.9 ± 5.2 (140)	0.33
Hypertensive disorders (*n*/total)	13/173 (7.5)	16/141 (11.3)	0.33
Induction of labor (*n*/total)	85/173 (49.1)	64/141 (45.4)	0.58
Operative vaginal delivery (n/total)	20/173 (11.6)	8/141 (5.7)	0.10
Cesarean delivery (*n*/total)	36/173 (20.8)	25/141 (17.7)	0.59
Gestational weeks at delivery (n/total)	39.1 [38.4–40.1] (173)	39.1 [38.1–40.0] (141)	0.34
Birthweight (g)	3590 ± 500 (173)	3630 ± 460 (141)	0.55
Adjusted birthweight (SD)	0.11 ± 1.11 (173)	0.27 ± 1.17 (141)	0.23
Adjusted birthweight (centiles)	50 [27–79] (173)	58 [34–84] (141)	0.19
SGA (*n*/total)	19/173 (11.0)	13/141 (9.2)	0.74
LGA (*n*/total)	30/173 (17.3)	26/141 (18.4)	0.92
Breastfeeding[a] (months)	3.5 [2–6] (115)	3 [2–6] (66)	0.33

Notes: Continuous data are expressed as mean ± SD (total *n*) or median [interquartile range] (total *n*) and binary data as *n*/total *n* (%). Adjusted birthweight was adjusted for gestational age at delivery and neonate sex according to Finnish population reference charts. *p*-values are given for the *t*-test, the Mann–Whitney *U*-test, the chi-square test or Fisher's exact test where appropriate.

Abbreviations: BMI, body mass index; Gw and gw, gestational week; HbA1c, glycated hemoglobin; LGA, large-for-gestational-age (adjusted birthweight >90th centile); OGTT, oral glucose tolerance test; SD, standard deviation; SGA, small-for-gestational age (adjusted birthweight <10th centile).

[a]Data available only from Turku.

3.4 | Exploratory secondary outcomes at follow-up

At the 9-year follow-up, over half of the women were obese and only 13.4% normal weight; there were no differences between the metformin and insulin groups. There were no evident differences between the groups in maternal anthropometry, glucose metabolism, insulin resistance, ALT, inflammation, serum lipids and adiponectin (details in Table 5). Lipid profile was, however, marginally better in the metformin group, with lower ApoB, LDL and non-HDL cholesterol, and higher HDL cholesterol (*p*-values 0.057–0.099).

TABLE 2 Baseline characteristics at index pregnancy of the follow-up study participants

	Insulin	Metformin	*p*-value
Age (years)	32.5 ± 5.5 (91)	32.7 ± 4.9 (82)	0.83
Parity (*n*)	1 [0–2] (91)	1 [0–2] (82)	0.56
Nulliparous (*n*/total)	40/91 (44.0)	28/82 (34.1)	0.24
Smoking (*n*/total)	15/90 (16.7)	6/81 (7.4)	0.11
Weight (kg)	79.3 ± 14.9 (90)	81.5 ± 15.6 (79)	0.36
BMI (kg/m^2)	28.9 ± 4.9 (91)	29.6 ± 5.9 (82)	0.41
Glucose metabolism			
OGTT fasting glucose (mmol/L)	5.45 ± 0.46 (91)	5.38 ± 0.63 (81)	0.37
OGTT 60-min glucose (mmol/L)	11.2 [10.3–11.8] (90)	11.3 [10.6–12.3] (81)	0.11
OGTT 120-min glucose (mmol/L)	8.10 ± 1.78 (90)	8.35 ± 1.93 (80)	0.38
HbA1c at OGTT (mmol/mol)	37.5 ± 4.1 (91)	37.2 ± 4.6 (82)	0.64
HbA1c at OGTT (%)	5.59 ± 0.38 (91)	5.56 ± 0.42 (82)	
Gw at OGTT (weeks)	27 [26–28] (91)	27 [26–28] (81)	0.96
HbA1c at 36 gw (mmol/mol)	38.5 ± 4.1 (80)	38.1 ± 3.7 (75)	0.54
HbA1c at 36 gw (%)	5.67 ± 0.38 (80)	5.64 ± 0.34 (75)	
Treatment			
Gw at randomization (weeks)	31 [29–32] (91)	31 [29–32] (82)	0.56
Additional insulin (*n*/total, of metformin treated patients)		22/82 (26.8)	
Obstetric outcomes			
Weight gain in pregnancy (kg)	8.6 ± 5.2 (91)	8.4 ± 4.6 (82)	0.85
Hypertensive disorders (*n*/total)	9/91 (9.9)	4/82 (4.9)	0.26
Induction of labor (*n*/total)	53/91 (58.2)	32/82 (39.0)	0.018
Operative vaginal delivery (*n*/total)	10/91 (11.0)	10/82 (12.2)	0.99
Cesarean delivery (*n*/total)	19/91 (20.9)	17/82 (20.7)	0.99
Gestational weeks at delivery (*n*/total)	39.1 [38.5–40.3] (91)	39.0 [38.4–40.1] (82)	0.61
Birthweight (g)	3570 ± 520 (91)	3610 ± 480 (82)	0.60
Adjusted birthweight (SD)	0.08 ± 1.16 (91)	0.15 ± 1.08 (82)	0.67
Adjusted birthweight (centiles)	50 [21–80] (91)	52 [31–79] (82)	0.46
SGA (*n*/total)	12/91 (13.2)	7/82 (8.5)	0.46
LGA (*n*/total)	17/91 (18.7)	13/82 (15.9)	0.77
Breastfeeding[a] (months)	3 [2–6] (58)	4 [1.5–7] (57)	0.42

Notes: Continuous data are expressed as mean ± SD (total *n*) or median [interquartile range] (total *n*) and binary data as *n*/total *n* (%). Adjusted birthweight was adjusted for gestational age at delivery and neonate sex according to Finnish population reference charts. *p*-values are given for the *t*-test, the Mann–Whitney *U*-test, the χ^2 test or the Fisher's exact test where appropriate.

Abbreviations: BMI, body mass index; Gw and gw, gestational week; HbA1c, glycated hemoglobin; LGA, large for gestational age (adjusted birthweight >90th centile); OGTT, oral glucose tolerance test; SD, standard deviation; SGA, small for gestational age (adjusted birthweight <10th centile).

[a]Data available only from Turku.

4 | DISCUSSION

In this 9-year follow-up of two randomized trials, we found comparable rates of pre-diabetes, T2DM and MetS between women who were treated with metformin or insulin for GDM. Additionally, individual measures of glucose metabolism, insulin resistance, lipids, blood pressure and anthropometry were comparable. In this respect, choosing either metformin or insulin treatment for GDM probably has only small effects, if any, on the long-term maternal health. Furthermore, the differences between metformin and insulin groups in maternal circulating triglycerides in late pregnancy[11,12] disappear during the first decade after pregnancy.

Approximately half of the original study population participated in the 9-year follow-up, which is close to the drop-out rate reported in similar studies.[8,13] The participating women were older, weighted less at baseline and tended to have lower fasting glucose and HbA1c compared with those not participating in the follow-up study. Our findings at 9 years are, however, in line with a previous report from

TABLE 3 Maternal characteristics at follow-up

	Insulin	Metformin	*p*-value
Age (years)	42.1 ± 5.4 (88)	42.3 ± 4.8 (77)	0.86
Parity (*n*)	2 [2–3] (88)	3 [2–3] (77)	0.69
ΔParity from the study recruitment (*n*)	1 [1–2] (64)	1 [1–2] (60)	0.95
Smoking (*n*/total)	11/88 (12.5)	9/77 (11.7)	0.99
Education post-secondary or higher (*n*/total)	32/84 (38.1)	22/71 (30.1)	0.45
Exercise (days/week)	2.75 [1.0–4.0] (88)	3.0 [1.5–5.0] (77)	0.17

Notes: Continuous data is expressed as mean ± SD (total *n*) or median [interquartile range] (total *n*), and binary data as *n*/total *n* (%). *p*-values are given for the *t*-test, the Mann–Whitney *U* test or the chi-square test where appropriate.

TABLE 4 Primary and main secondary outcomes at 9-year follow-up

	Insulin	Metformin	*P*-value	Odds ratio [95% CI]	Risk difference [95% CI]
Primary outcome					
Pre-diabetes and type 2 diabetes	41/88 (46.6)	31/77 (40.3)	0.51	0.77 [0.40–1.50]	−6.3% [−21.5–8.8]
Main secondary outcomes					
Pre-diabetes	27/88 (30.7)	20/77 (26.0)	0.62	0.79 [0.38–1.65]	−4.7% [−18.4–9.0]
Type 2 diabetes	14/88 (15.9)	11/77 (14.3)	0.94	0.88 [0.34–2.26]	−1.6% [−12.6–9.3]
Metabolic syndrome	48/87 (55.2)	34/74 (45.9)	0.31	0.70 [0.35–1.35]	−9.2% [−24.7–6.2]

Note: Data are expressed as *n*/total *n* (%), *p*-values are given for the chi-square test.
Abbreviation: CI, confidence intervals.

the Turku study population at 1 year postpartum where the participation rate was 83% and the rates of impaired fasting glucose and impaired glucose tolerance were similar between the insulin and metformin groups.[21]

It is currently not known whether GDM treatment improves long-term outcomes,[8] or whether differences between metformin and insulin treatments exist. Dietary interventions and increased physical activity in pregnancy may have long-lasting positive effects on metabolism, and treatment allocation to metformin or insulin could affect differently on maternal adherence to lifestyle treatment. Metformin not only alleviates hyperglycemia but also affects low-grade inflammation and the gastrointestinal tract,[23] which may have long-term effects. In our study, 26.8% of the participants in the metformin group also received insulin, which might have attenuated the differences in the outcome measures. Exclusion of these women from the metformin group, however, would have introduced bias.

We found neither of the treatments to be superior in affecting the burden of adverse metabolic traits in the long term, although we observed numerically marginally lower hs-CRP, lower ApoB and higher HDL cholesterol in the metformin group. We cannot exclude small differences in glucose and lipid metabolism between the treatment groups, but metformin treatment seems very unlikely to be inferior to insulin, to a clinically significant extent.

Possible small long-term effects of treatment may have been obscured by modifying factors such as weight gain, breastfeeding and changes in diet. Therefore, a larger study would be needed to compare the possible long-term outcomes with more certainty. Given that follow-up of the largest randomized trial comparing metformin and insulin in GDM included 208 subjects (109 at 7 and 99 at 9 years postpartum),[13] sufficiently powered long-term follow-up studies are unlikely to emerge and perhaps meta-analyses will provide more conclusive data in the future.

Rowan et al similarly compared metformin- and insulin-treated GDM from two separate study centers at 7 or 9 years after the index pregnancy, respectively.[13] They found no differences in maternal anthropometrics or rate of self-reported diabetes between the treatment groups. Maternal glucose metabolism was not, however, assessed in that study. Our results strengthen the findings of similar maternal anthropometry and rates of diabetes[13] and provide a more detailed insight into maternal metabolism 9 years after the index pregnancy. Moreover, as approximately half of the T2DM cases in our study represented incident T2DM, the self-reported diagnosis in the study by Rowan et al may be an underestimation.

Maternal serum triglycerides in late pregnancy are higher in metformin- than in insulin-treated woman with GDM.[11,12] This difference disappeared in our data during the first decade after pregnancy. Our results suggest that the shift towards a more atherogenic lipid profile in the metformin- compared with the insulin-treated patients in late pregnancy is unlikely to lead to inferior metabolic health by 9 years postpartum.

Markers of low-grade inflammation such as CRP and interleukin 6[14] have been associated with increased risk of developing T2DM,

TABLE 5 Exploratory secondary outcomes

	Insulin	Metformin	*p*-value
Maternal anthropometry			
Weight (kg)	83.4 ± 16 (88)	85.5 ± 16.8 (76)	0.43
BMI (kg/m^2)	30.8 ± 5.34 (88)	31.4 ± 6.1 (76)	0.50
BMI category (*n*/total)			0.60
Normal, <25 kg/m^2	11/88 (12.6)	11/76 (14.5)	
Overweight, 25–30 kg/m^2	32/88 (36.4)	22/76 (28.9)	
Obese, ≥30 kg/m^2	45/88 (51.1)	43/76 (56.6)	
Waist circumference (cm)	95 ± 12 (88)	96 ± 14 (76)	0.71
Hip circumference (cm)	105 ± 13 (88)	106 ± 14 (76)	0.83
ΔWeight from 1st antenatal visit in the index pregnancy (kg)	3.6 ± 6.6 (87)	4.2 ± 8.0 (73)	0.59
Systolic blood pressure (mmHg)	124 ± 13.9 (87)	122 ± 14.8 (75)	0.40
Diastolic blood pressure (mmHg)	74.9 ± 8.49 (87)	74.6 ± 9.17 (74)	0.86
Metabolic syndrome (individual components)			
Elevated fasting glucose[b] (*n*/total)	52/88 (59.1)	45/77 (58.4)	0.99
Elevated blood pressure[c] (*n*/total)	31/87 (35.6)	25/74 (33.8)	0.94
Dyslipidemia[d] (*n*/total)	48/88 (54.5)	36/77 (46.8)	0.40
Waist circumference ≥80 cm (*n*/total)	80/88 (90.9)	66/76 (86.8)	0.56
Glucose metabolism			
IFG (*n*/total)	21/80 (26.2)	19/70 (27.1)	0.99
IGT (*n*/total)	17/80 (21.2)	11/70 (15.7)	0.51
Elevated HbA1c (*n*/total)	14/79 (17.7)	11/70 (15.7)	0.91
OGTT fasting glucose (mmol/L)	5.70 ± 0.79 (80)	5.69 ± 0.60 (70)	0.92[a]
OGTT 30-min glucose (mmol/L)	9.09 ± 1.74 (80)	8.92 ± 1.29 (70)	0.66[a]
OGTT 120-min glucose (mmol/L)	6.51 ± 1.96 (80)	6.19 ± 1.92 (70)	0.24[a]
HbA1c (mmol/mol)	38.6 [36.7–40.5] (79)	38.6 [36.7–40.5] (70)	0.94
HbA1c (%)	5.60 [5.40–5.79] (79)	5.60 [5.40–5.79] (70)	0.96
Fasting insulin (mU/L)	13.8 ± 8.6 (80)	13.1 ± 8.4 (70)	0.56[a]
Fasting C-peptide (μg/L)	2.46 [1.94–3.22] (80)	2.35 [1.85–2.96] (70)	0.37
HOMA-IR	3.55 ± 2.21 (80)	3.42 ± 2.46 (70)	0.61[a]
ALT and inflammation			
ALT (U/L)	23.6 ± 15.8 (80)	24.2 ± 16 (70)	0.76[a]
Ferritin (μg/L)	39.0 [22.5–76.1] (78)	40.8 [18.9–66.2] (70)	0.51
hs-CRP (mg/L)	1.67 [0.60–4.43] (77)	1.0 [0.35–3.6] (67)	0.086
Lipids and adiponectin			
ApoA1 (g/L)	1.43 ± 0.22 (72)	1.46 ± 0.25 (67)	0.46
ApoB (g/L)	0.97 ± 0.25 (72)	0.90 ± 0.20 (67)	0.068
Total cholesterol (mmol/L)	5.40 ± 1.09 (72)	5.24 ± 0.84 (67)	0.34
HDL cholesterol (mmol/L)	1.34 ± 0.39 (72)	1.46 ± 0.39 (67)	0.057
LDL cholesterol (mmol/L)	3.44 ± 0.92 (72)	3.21 ± 0.72 (67)	0.099
Non-HDL cholesterol (mmol/L)	4.06 ± 1.09 (72)	3.78 ± 0.88 (67)	0.096
Triglycerides (mmol/L)	1.23 ± 0.58 (72)	1.18 ± 0.66 (67)	0.55[a]
Adiponectin (μg/L)	7.38 ± 4.72 (72)	7.69 ± 3.98 (67)	0.39[a]

Notes: Continuous data are expressed as mean ± SD (total *n*) or median [interquartile range] (total *n*) and binary data as *n*/total *n* (%). *p*-values are given for the *t*-test (where the data that were log-transformed prior to the test are marked with superscript letter a), the Mann–Whitney *U*-test, or the chi-square test where appropriate. The individual components of metabolic syndrome are based on the International Diabetes Federation criteria; [b]fasting glucose ≥5.6 mmol/L or previously diagnosed type 2 diabetes, [c]blood pressure ≥130 systolic or ≥85 diastolic mmHg or treatment for hypertension, [d]plasma triglycerides ≥1.7 mmol/L or HDL cholesterol <1.29 mmol/L or treatment for dyslipidemia.

Abbreviations: ALT, alanine aminotransferase; ApoA1, apolipoprotein A-1; ApoB, apolipoprotein B; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SD, standard deviation.

whereas adiponectin is protective.[24] We evaluated the markers of inflammation (hs-CRP and ferritin) and adiponectin 9 years after the index pregnancy and observed that metformin treatment may be related to lower hs-CRP. This observation was, however, among the exploratory secondary outcomes and hence there is a high risk of a false-positive finding.

The rate of T2DM (15.2%) was similar to that reported previously[4] and it is expected to increase further after 10 years postpartum.[25] Strikingly, we found roughly as many new cases of T2DM (incident T2DM) as preexisting ones in the study population. This result probably reflects insufficient regular assessment of glucose metabolism and cardiovascular risk factors postpartum.

To our knowledge this is the second-largest follow-up study of women randomized to metformin or insulin treatment of GDM, and the only one to include subsequent detailed evaluation of maternal glucose metabolism. Other strengths of this study are use of data from two study centers, longitudinal design and treatment allocation by randomization. The diagnostic criteria[17,18] and management protocols between the study centers were slightly different, thus improving the generalizability of the results.

There are some limitations in our study. First, our follow-up study population may not be fully representative of all women with previous medically treated GDM due to possible selection at the time of recruitment (more health-conscious individuals participate more often) and to loss to follow-up. The non-participating subjects differed at baseline slightly from those who participated the 9-year follow-up. Thus the participating and non-participating subjects may have responded differently to metformin or insulin, causing the observed results to differ from a real-life scenario. Therefore, observational studies are required to complement our data.

Secondly, our study was underpowered to demonstrate small differences in the rates of the primary composite outcome of pre-diabetes and T2DM, or the main secondary outcomes: pre-diabetes, T2DM and MetS.

Thirdly, the diagnostic criteria for GDM were slightly different in the two study centers and, in addition, actually changed in Turku during the recruitment period. However, due to limited numbers of participants it is not possible to judge whether these issues affected the results.

Finally, a core outcome set for follow-up studies comparing insulin and/or oral glucose-lowering agents in GDM was published after the initiation of this study;[26] therefore, the number of pregnancies complicated by GDM after the index pregnancy was not recorded in our study.

5 | CONCLUSION

The available data regarding long-term metabolic effects of the main pharmacological treatment options for GDM have been scarce. Based on our study, neither metformin nor insulin seems to be superior to the other regarding the long-term effects on maternal health. From this perspective, both treatments may be considered in GDM.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KT, TR, HiN and MV were the authors of the original randomized trials and provided the baseline data of the study participants. KT, TR and HaN designed the follow-up study. HiN and EP collected the follow-up data. BML planned and supervised the collection and analysis of blood samples. MH combined the datasets, performed the statistical analyses and wrote the first draft of the manuscript. All the authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

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