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Clinical Research Article

Postnatal Cardiometabolic Health After Metformin Use in Gestational Diabetes: A Secondary Analysis of the EMERGE Trial

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Abstract

Aim: Women with gestational diabetes mellitus (GDM) display adverse lifetime cardiometabolic health. We examined whether early metformin in GDM could impact cardiometabolic risk factors postpartum.

Methods: EMERGE, a double-blind, placebo-controlled trial, randomized pregnancies 1:1 to placebo or metformin at GDM diagnosis and followed participants from randomization until 12 ± 4 weeks postpartum. In total, 478 pregnancies were available for postpartum maternal assessment, 237 and 241 assigned to metformin and placebo respectively. Weight (kg), body mass index (BMI) (kg/m^2), waist circumference (cm), and blood pressure (mmHg) were measured, infant feeding method documented, and blood specimens drawn for a 75-gram oral glucose tolerance test, fasting insulin, C-peptide, and lipid analysis.

Results: Despite similar weight and BMI at trial randomization, participants receiving metformin had significantly lower weight (79.5 ± 15.9 vs 82.6 ± 16.9 kg; $P = .04$) and BMI (29.3 [5.6] vs 30.5 [5.4]; $P = .018$) at the postpartum visit. However, no difference in weight change from randomization to 12 weeks postpartum was observed between metformin and placebo groups. Overall, 29% (n = 139) of the cohort met criteria for prediabetes or diabetes, with no positive impact with metformin. There were also no differences in measurements of insulin resistance, blood pressure, or lipids between groups.

Conclusion: Early metformin use in GDM did not impact important cardiometabolic parameters in the early postpartum period despite significant benefits in weight gain and insulin use in pregnancy.

Key Words: metformin, gestational diabetes, postpartum health

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-%B, homeostatic model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA2-IR, updated version of homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance IQR, interquartile range; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Gestational diabetes mellitus (GDM), defined as hyperglycemia that develops during pregnancy (1), is a global health problem and impacts almost 3 million pregnancies/year worldwide. There is convincing evidence that improved glycemic control improves maternal and fetal outcomes in pregnancies impacted by GDM (2, 3). In the EMERGE trial (4), metformin reduced the requirement for insulin, reduced maternal weight gain, improved maternal glycemic control, and reduced rates of infants born large for gestational age or with macrosomia, without any increase in preterm birth or perinatal morbidities (5).

Women with GDM have an increased lifetime risk of developing type 2 diabetes mellitus (DM) (6-8) and/or premature cardiovascular disease (CVD) (6, 8, 9). Underlying B-cell dysfunction is characteristic of both GDM and type 2 DM, which may persist in women with GDM outside of pregnancy (10). Interventions during pregnancy that reduce insulin resistance (including gestational weight management and use of metformin) may improve B-cell function and have potential to reduce future risk (11). However, interventions after delivery are also likely needed to further reduce risk. While screening practices and diagnostic thresholds for GDM differ internationally (12), a diagnosis of GDM offers an opportunity for enhanced subsequent screening and risk factor modification (13). Ideally, the management of GDM should target not only imminent obstetric and neonatal outcomes, but also consider the potential for long-term cardiometabolic risk reduction. Here, we report early maternal cardiometabolic risk factors

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Table 1. Baseline characteristics of included participants

	Metformin N = 237	Placebo N = 241	*P* value
Age (years), mean ± SD	34.3 ± 4.9	34.3 ± 4.7	.4
Weight (kg), mean ± SD	85.7 ± 16.5	87.7 ± 16.8	.182
Ethnicity, % (n)			
European or White	83% (n = 197)	79% (n = 190)	.234
Asian	7% (n = 17)	12% (n = 28)	
African/Black	3% (n = 6)	2% (n = 4)	
Irish Traveller	3% (n = 6)	0.4% (n = 1)	
Other	5% (n = 11)	8% (n = 18)	
BMI (kg/m^2), mean ± SD	29.8 ± 6.2	30.8 ± 5.7	.084
BMI category, % (n)			
Obese	56.5% (n = 134)	62.2% (n = 150)	.198
Overweight	34.2% (n = 81)	32.4% (n = 78)	
Normal	9.3% (n = 22)	5.4% (n = 13)	
Baseline OGTT results (mmol/L), mean ± SD			
Fasting glucose	5.19 ± .46	5.20 ± .48	.906
1 hour PP glucose	9.30 ± 1.89	9.75 ± 1.85	.008
2 hour PP glucose	7.15 ± 1.59	7.16 ± 1.56	.934
Gestation (weeks), mean ± SD	25.4 ± 4.3	25.5 ± 4.1	.777
Medical card, % (n)	23.5% (n = 63)	23.7% (n = 63)	1.0
Unemployed, % (n)	7.1% (n = 19)	10.2% (n = 27)	.27
Smoking in pregnancy, % (n)	6.3% (n = 17)	6.4% (n = 17)	1.0
Nulliparous, % (n)	31.3% (n = 84)	31.5% (n = 84)	1.0
SBP (mmHg), mean ± SD	114.5 ± 9.3	114.3 ± 9.1	.811
DBP (mmHg), mean ± SD	68.8 ± 7.8	68.5 ± 8.6	.729
Prior macrosomia, % (n)	31.5% (n = 57)	25.6% (n = 44)	.27
Preeclampsia in a previous pregnancy, % (n)	13.3% (n = 24)	13.4% (n = 23)	1.0
Prepregnancy hypertension, % (n)	4.5% (n = 12)	1.5% (n = 4)	.077

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; OGTT, oral glucose tolerance test; PP, postprandial; SBP, systolic blood pressure.

(12 weeks postpartum) and explore whether the early use of metformin during pregnancy was associated with a more favorable cardiometabolic profile, even after the discontinuation of metformin.

Methods

Study Design

The EMERGE trial was a phase 3, parallel-group, 2-site, superiority, randomized, double-blind, placebo-controlled trial of metformin (in addition to usual care) prescribed following women with a diagnosis of GDM and continuing until delivery. The design and primary outcome of EMERGE were published previously (4, 5). In brief, women with GDM (diagnosed by World Health Organization [WHO] 2013 criteria (1)) and a singleton fetus up to 28 + 6 weeks gestation were included. A minimization strategy was used to balance proportion of women with a body mass index (BMI) ≤ 30 kg/m^2 and a history of GDM between groups. The trial reported no significant difference between metformin and placebo for the composite primary outcome (insulin initiation or fasting glucose ≥ 5.1 mmol/L at week 32 or 38 gestation). Here, we include all randomized pregnancies with available data from the postpartum follow-up visit, conducted at 12 ± 4 weeks. Data included blood pressure (BP), anthropometrics, 75-g oral glucose tolerance test (OGTT) (fasting glucose, insulin and C-peptide, and 2-hour post-glucose load glucose), fasting lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides) and glycated hemoglobin (HbA1c). Lipid levels were assessed using the Roche Modular Analytics system and reported in mmol/L, HbA1c was measured using reverse phase cation exchange chromatography, calibrated with IFCC standardization and reported in mmol/mol. Insulin and C-peptide were measured using the Roche modular analytics immunoassay system. Ethical approval was granted by the ethics committee and all participants provided written consent.

Outcomes

We report maternal weight (kg), BMI (kg/m^2), gestational weight gain (kg) (randomization—postpartum visit), waist circumference (cm) and BP (mmHg). Glycemic status was categorized as: (i) impaired fasting glucose (IFG; fasting glucose ≥ 5.6 and < 7 mmol/L); (ii) impaired glucose tolerance (IGT; 2-hour glucose ≥7.8 and <11.1 mmol/L); and (iii) diabetes (fasting glucose ≥ 7 mmol/L or 2-hour glucose ≥ 11.1 mmol/L or HbA1c ≥ 6.5% [≥ 48 mmol/mol]). Insulin resistance was measured using homeostatic model assessment

Table 2. Anthropometric measurements at the 12-week postpartum visit

	Metformin N = 237	Placebo N = 241	Mean difference (95% CI)	*P* value
Time since delivery (days), mean ± SD	96.1 ± 16	98.3 ± 17.6	−2.2 (−5.2 to 0.8)	.155
Randomization weight (kg), mean ± SD	85.7 ± 16.5	87.7 ± 16.8	−2.0 (−5.0 to 1.0)	.182
Follow-up weight (kg), mean ± SD	79.5 ± 15.9	82.6 ± 16.9	−3.1 (−6.1 to −0.1)	.04
Weight change (kg, randomization to follow-up), mean ± SD	−5.9 ± 4.4	−5.1 ± 4.9	0.8 (−1.6 to 0.1)	.068
Postpartum BMI (kg/m^2), mean ± SD	29.3 (5.6)	30.5 (5.4)	−1.1(−2.2 to −0.21)	.018
BMI category, % (n)				
Obese	39.9% (n = 91)	47.9% (n = 113)	n/a	.11
Overweight	36.4% (n = 83)	35.6% (n = 84)		
Normal	22.8% (n = 52)	16.1% (n = 38)		
Waist circumference (cm), mean ± SD	92.9 ± 13	95.2 ± 12.2	−2.2 (−4.6 to 0.1)	.056
Waist circumference > 88 cm, % (n)	64.9% (n = 148)	72.8% (n = 171)	n/a	.06

Abbreviation: BMI, body mass index.

Table 3. Maternal characteristics between those who attended the postpartum visit and those who did not

	Attenders n = 478	Non-attenders n = 57	*P* value
Treatment group			.585
Placebo	241 (50.4%)	26 (45.6%)	
Metformin	237 (49.6%)	31 (54.4%)	
Age, mean ± SD	34.6(4.6)	31.5 (5.4)	<.001
BMI, mean ± SD	30.3 (6)	32.5 (6.8)	.021
European n (%)	387 (81%)	41 (71.9%)	<.001
Medical card n (%)	100 (20.9%)	26 (46.4%)	<.001
Tertiary education	400 (83.7%)	34 (60.7%)	<.001

of insulin resistance (HOMA-IR) calculated as [fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5] (14). Insulin resistance was defined as HOMA-IR > 1.8 (15). Beta-cell function was calculated using the homeostasis model assessment of beta-cell function (HOMA-%B), as [20 × fasting insulin (μIU/mL)/(fasting glucose [mmol/L] − 3.5)] (14). In addition, we also measured an updated version of HOMA-IR (HOMA2-IR) which also includes insulin (HOMA2-ins) and C-peptide (HOMA2-Cpep), using an online calculator (16-18). Metabolic syndrome was defined by the presence of 3 or more of the items from the Adult Treatment Panel III (ATPIII) criteria (19): (i) abdominal obesity (waist circumference > 88 cm); (ii) hypertriglyceridemia (triglycerides > 1.69 mmol/L); (iii) low HDL (< 1.29 mmol/L); (iv) BP > 130/85 mmHg; and (v) fasting glucose > 6.1 mmol/L. Exclusive breastfeeding was defined as no formula use from birth to the time of assessment.

Statistical Analysis

Analyses were performed according to the intention-to-treat principle. Categorical data were summarized using percentages and counts; continuous data were summarized using mean and SD or median and interquartile range (IQR), as appropriate. Differences between groups were assessed using *t* test and ANOVA (or a nonparametric alternative, Mann-Whitney or Kruskal-Wallis, in the case of non-normality). Linear regression models were used to adjust for covariates and for the search of interactions. Our original sample size calculation showed that even with a 50% loss to follow-up we would still maintain 80% power at .05 significance to detect a minimum difference in mean weight change of 1.36 kg between treatment arms. Statistical significance was set at $\alpha = .05$. No imputations were used for missing data. All analyses were completed using R-software 2023.12.1 (20).

Results

Participants

From June 2017, to September 2022, 535 pregnancies were randomized in EMERGE. Enrollment ended once the target of participants had been reached. Data were available on 478 (89.3%) of participants (237 metformin and 241 placebo).

There were no significant differences in baseline characteristics of participants when stratified by study allocation, except a small difference in 1-hour glucose that likely occurred by chance (Table 1). Overall, the mean and median weeks from enrollment to delivery did not differ by study allocation, study drug was well tolerated (4.9% [n = 13] discontinued due to gastrointestinal side effects), and 92% of participants were adherent to study drug (> 80% of drug taken) across trial visits. No participant used any glucose-lowering agents at the time of postpartum assessment. The mean interval from delivery (and discontinuation of study drug) to the postpartum visit was similar by study allocation ($P = .155$) (Table 2).

Compared with participants in the total EMERGE cohort, the women excluded from this analysis were younger, had a higher BMI, were less well educated, and were of lower socioeconomic status (Table 3).

Anthropometric Outcomes

Although at 12 weeks postpartum the metformin-exposed women weighed on average 3.1 kg (95% CI −6.1 to −0.1 kg), $P = .04$) less than those in the placebo group, there was no significant difference in weight change or BMI change from randomization (mean 25 weeks gestation) to 12 weeks

Table 4. Glucometabolic status at follow-up visit

Parameter	Metformin N = 237	Placebo N = 241	Mean difference (95% CI)	*P* value
Fasting glucose (mmol/L), median (IQR)	5.2 (0.7)	5.2 (0.6)	0 (−0.1 to 0)	.348
2-hour glucose (mmol/L), median (IQR)	5.5 (1.8)	5.6 (1.7)	−0.1 (−0.3 to 0.1)	.38
Fasting insulin (muIU/mL), median(IQR)	9.6 (6.8)	10.3 (7.9)	0.5 (−1.5 to 0.5)	.323
Fasting C-peptide (nmol/L), mean ± SD	0.78 ± 0.36	0.8 ± 0.35	−0.03 (−0.08 to 0.02)	.305
IFG, n (%)	51 (22.1%)	52 (22.1%)	0% (−7.6% to 7.5%)	1
IGT, n (%)	15 (6.5%)	16 (6.8%)	−0.3% (−5.1% to 4.5%)	1
Type 2 DM, n (%)	1 (0.4%)	4 (1.7%)	−1.3% (−3.6% to 1%)	.381
IFG and IGT, n (%)	6 (2.6%)	8 (3.4%)	−0.8% (−4.3% to 2.7%)	.818
IFG and IGT and type 2 DM; n (%)	61 (26.4%)	63 (26.8%)	−0.4% (−8.8% to 8%)	1
HbA1c (mmol/mol), mean ± SD	35.1 ± 2.9	35.2 ± 3.4	−0.1 (−0.7 to 0.5)	.701
HbA1c (%), mean ± SD	(5.4 ± 2.4)	(5.4 ± 2.5)		
HOMA-IR insulin, median (IQR)	2.2 (1.6)	2.5 (2)	−0.2 (−0.4 to 0.1)	.218
Insulin resistance, n (%)	153 (68.9%)	159 (69.4%)	−0.5% (−9.5% to 8.5%)	.987
HOMA-%B insulin, median (IQR)	123.2 (89.7)	122.5 (89.7)	−2.5 (−14.3 to 9.3)	.679
HOMA2-IR insulin, median (IQR)	1.2 (0.9)	1.3 (1)	−0.1 (−0.2 to 0.1)	.282
HOMA2-IR C-peptide, median (IQR)	1.7 (0.9)	1.8 (0.8)	−0.1 (−0.2 to 0.1)	.318

Abbreviations: HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-%B, homeostasis model assessment of beta-cell function; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

postpartum (Table 2). Mean total weight loss was 5.9 kg in the metformin group vs 5.1 kg in the placebo group. The lower average postpartum weight in the metformin arm in the absence of a significant absolute difference in weight loss may be explained by a lower and statistically nonsignificant difference in baseline weight between the 2 groups at randomization (metformin-exposed participants were on average 2 kg lighter than those in the placebo arm). There was no difference in waist circumference by study allocation.

Multivariable adjustment (feeding method, allocation, age, enrollment BMI, and baseline 1-hour OGTT glucose) revealed that postpartum weight was significantly associated with enrollment BMI ($P < .001$) and 1-hour OGTT glucose only ($P = .009$) (supplemental table S1) (21) (https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi%3A10.7910%2FDVN%2F507MVA&version=DRAFT). Additional adjustment for socioeconomic status (medical insurance and employment) did not impact results (supplemental table S2) (21).

Similar multivariable adjustment revealed that postpartum BMI was significantly associated with enrollment BMI ($P < .001$) (supplemental table S3) (21) (https://doi.org/10.7910/DVN/507MVA). Additional adjustment for socioeconomic status (medical insurance and employment) revealed that postpartum BMI was significantly associated with enrollment BMI ($P < .001$) and employment ($P = .033$) only (supplemental table S4) (21) (https://doi.org/10.7910/DVN/507MVA). There was no significant interaction between study allocation and postpartum feeding method for any of these models.

Glucometabolic Status

At follow-up, there were no differences between metformin and placebo groups for fasting glucose, 2-hour glucose, insulin, and C-peptide (Table 4). Overall, 21.5% (n = 103) had IFG, 6.5% (n = 31) had IGT, and 1.0% (n = 5) had type 2 DM (Table 4), with no significant differences by study allocation ($P = 1$ for IFG; $P = 1$ for IGT; and $P = .381$ for type 2 DM). In addition, there were no differences in HbA1c or measures of insulin resistance by study allocation. Breastfeeding was not associated with rates of IFG ($P = .07$), IGT ($P = .33$), or IFG and IGT ($P = .85$). There were no difference in rates of glucose intolerances between participants who exceeded the Institute of Medicine guidelines for gestational weight gain and those who did not. There were no differences between the metformin and placebo groups for systolic and diastolic BP, fasting total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and non-HDL-cholesterol (supplemental table S5) (21) (https://doi.org/10.7910/DVN/507MVA). The ratio of total cholesterol to HDL was also similar. There was no difference in rate of metabolic syndrome by study allocation.

Discussion

We report that the early introduction of metformin for GDM was associated with lower weight and BMI than placebo at 12 weeks postpartum. However, there was no difference in absolute weight loss from randomization to 12 weeks postpartum or any significant differences in glucometabolic status. The lower postpartum weight in the metformin group weight likely reflects the small, statistically insignificant baseline differences between groups (baseline weight was 85.7 kg in the metformin group vs 87.7 kg in the placebo group), as no difference in weight change from randomization to 12 weeks postpartum was observed. Importantly half of the women in EMERGE had a baseline BMI ≥ 30 kg/m^2, where minimization of excess weight gain is desirable (22, 23).

Increases in both pre- and post-pregnancy BMI are strong predictors of long-term diabetes risk in women with GDM (24, 25). Meta-analysis of 129 studies reported significant increase in risk of type 2 DM up to 15 years after a GDM

pregnancy (18% per unit of BMI) (26). In EMERGE, 44% of women had a postpartum BMI in the obesity range. However, those treated with metformin during pregnancy gained significantly less weight during pregnancy. Excessive gestational weight gain increases the risk of weight retention at 6 months onward; furthermore, reduced inter-pregnancy weight gain reduces the risk of infants born large for gestational age, GDM, and hypertensive disorders in subsequent pregnancies, highlighting the importance of weight management as part of optimizing health in pregnancy.

The prevalence of ongoing prediabetes and diabetes in this cohort emphasizes the need for ongoing surveillance and lifestyle and pharmacological interventions post-GDM to prevent dysglycemia. Our results fit within the range of postpartum prediabetes or diabetes reported in the literature, where 28.9% to 42.2% of women with GDM have some degree of glucose intolerance at short interval testing (27-30). While our findings for IGT (6.5%) and type 2 DM (1%) are similar to a longitudinal cohort (31), we observed a much higher rate of IFG (20%). This is potentially due to the interval introduction of citrate buffer specimen tubes, which better preserves glucose from degradation (32, 33). In addition, we did not have follow-up data for 57 participants who had a higher BMI on study entry, and these women may be more likely to have adverse glucometabolic outcomes. Our results also show that despite treating to a target of fasting glucose < 5.1 mmol/L during pregnancy (lower than the 5.5 mmol/L target used in other large randomized controlled trials of metformin in GDM (23) and the target of 5.3 mmol/L set by many guidelines (34)), women with GDM have unfavorable postpartum metabolic profiles as more than two-thirds had central obesity and 69.2% met the criteria for insulin resistance. While the initial EMERGE study discontinued metformin after delivery, a large follow-up study of women with GDM (The Diabetes Prevention Programme) found that the use of metformin reduced the risk of developing type 2 DM in the future (hazard ratio 0.59).

We report a high prevalence of postpartum insulin resistance (mean HOMA-IR 2.35), which has potentially serious long-term consequences, including type 2 DM, greater beta-cell deterioration in the early postpartum period (35), lower insulin sensitivity, and lower beta-cell compensation for insulin resistance. While there was no difference between HOMA-IR levels in the metformin arm, insulin use is an independent risk factor for the development of type 2 DM after GDM. The relatively few published reports regarding the long-term impact of metformin use during pregnancy on insulin resistance have recorded no difference in patients exposed to metformin (36, 37). In these studies, participants were recruited later in pregnancy and were only offered treatment with metformin after failure of lifestyle interventions (while the EMERGE trial offered early treatment), and the results of long-term follow-up of these participants will be highly informative.

Although metformin did not impact lipid parameters in EMERGE, the overall mean total cholesterol and LDL-cholesterol values were higher than recommended levels for low-risk adults (< 5 mmol/L and < 3 mmol/L respectively) (38). Non-HDL-cholesterol and the total cholesterol to HDL-C ratio were as expected in health (< 4 mmol/L and < 4 respectively) (39). HDL-cholesterol was >1.2 mmol/L, the target for healthy women (40). Metabolic syndrome, which is associated with a 3- to 4-fold increased risk of cardiovascular disease and all-cause mortality (41), occurred in 9.9% of EMERGE participants, with no difference by metformin exposure. This is similar to our previous report of 10.8% prevalence at 12 weeks postpartum in women with GDM treated with insulin and lifestyle modification (15), and lower than other reports where prevalence was 17% (35).

The main strength of our study is that these analyses were planned a priori and are based on a robust randomized controlled trial with high rates of adherence and high rates of follow-up. EMERGE is also the first trial to measure postpartum cardiometabolic parameters in women with GDM diagnosed using the WHO criteria, treated to a lower fasting glucose of 5.1 mmol/L (rather than the higher target of 5.3 mmol/L favored by other international guidelines) (33) and offered early treatment following a GDM diagnosis alongside lifestyle interventions. The main limitation of our study is the early assessment of postpartum glucometabolic status at 12 weeks. Second, EMERGE was completed in one geographical region, which may limit the generalizability of our findings. Those excluded from this analysis had higher baseline BMI, lower levels of tertiary level education, and higher levels of social deprivation and therefore are likely to display higher rates of type 2 DM, insulin resistance, and adiposity. This suggests that our estimates may be under-reporting true prevalence within our population. Lastly, we had no information regarding family history of type 2 DM and this may have impacted the likelihood of developing postpartum dysglycemia.

Conclusion

Obesity, prediabetes, and diabetes are ongoing significant clinical issues following GDM, which require ongoing surveillance and targeted interventions. Despite significant improvements in gestational weight gain and insulin use in pregnancy, use of metformin in pregnancy did not impact postpartum dysglycemia, insulin resistance, serum lipids, weight change, or post-adjustment. In cases where limitation of insulin usage and gestational weight gain are desirable, consideration should be given to the use of early metformin even if benefits do not extend to the postpartum period.

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Author Contributions

F.D., A.E., A.S., D.D., and M.O.D. devised the concept for this trial and F.D., A.E., C.N., A.S., D.D., and M.O.D. wrote the protocol. A.A.I. performed statistical analysis and P.G. is responsible for the planned economic analyses. P.O.S. oversaw biochemical analysis of laboratory samples. All authors drafted and revised the manuscript. All authors approved the final version of the manuscript and are accountable for the integrity of the work.

Disclosures

The authors have no conflicts of interest to declare.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Role of the Funder

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Clinical Trial Information

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