OBSTETRICS

Metformin use in obese mothers is associated with improved cardiovascular profile in the offspring

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BACKGROUND: Maternal obesity increases the risk for pregnancy complications and adverse neonatal outcome and has been associated with long-lasting adverse effects in the offspring, including increased body fat mass, insulin resistance, and increased risk for premature cardiovascular disease. Lifestyle interventions in pregnancy have produced no or modest effects in the reduction of adverse pregnancy outcomes in obese mothers. The Metformin in Obese Pregnant Women trial was associated with reduced adverse pregnancy outcomes and had no effect on birthweight. However, the long-term implications of metformin on the health of offspring remain unknown.

OBJECTIVE: The purpose of this study was to assess whether prenatal exposure to metformin can improve the cardiovascular profile and body composition in the offspring of obese mothers.

STUDY DESIGN: In 151 children from the Metformin in Obese Pregnant Women trial, body composition, peripheral blood pressure, and arterial pulse wave velocity were measured. Central hemodynamics (central blood pressure and augmentation index) were estimated with the use of an oscillometric device. Left ventricular cardiac function and structure were assessed by echocardiography.

RESULTS: Children were 3.9±1.0 years old, and 77 of them had been exposed to metformin prenatally. There was no significant difference in peripheral blood pressure, arterial stiffness, and body composition apart from gluteal and tricep circumferences, which were lower in the metformin group ($P<.05$). The metformin group, compared with the placebo group, had lower central hemodynamics (mean adjusted decrease, −0.707 mm Hg for aortic systolic blood pressure, −1.65 mm Hg for aortic pulse pressure, and −2.68% for augmentation index; $P<.05$ for all) and lower left ventricular diastolic function (adjusted difference in left atrial area, −0.525 cm^2, in isovolumic relaxation time, −0.324 msec, and in pulmonary venous systolic wave, 2.97 cm/s; $P<.05$ for all). There were no significant differences in metabolic profile between the groups.

CONCLUSION: Children of obese mothers who were exposed prenatally to metformin, compared with those who were exposed to placebo, had lower central hemodynamic and cardiac diastolic indices. These results suggest that the administration of metformin in obese pregnant women potentially may have a beneficial cardiovascular effect for their offspring.

Key words: children, exposure, metformin, obesity, offspring, outcome, placebo, pregnancy

Maternal obesity increases the risk for pregnancy complications[1−3] and adverse neonatal outcomes[4] and may have long-lasting adverse effects in the offspring, such as increased body fat mass and systolic blood pressure (SBP) in childhood, increased insulin resistance and dyslipidemia both in childhood and young adulthood, and increased risk for premature all-cause death and hospital admissions for cardiovascular events.[5−7]

Randomized controlled trials on overweight and obese women during pregnancy have investigated the effect of interventions in the reduction of adverse pregnancy outcomes; however, very few trials have reported the influences of these interventions on the health of the offspring.[8−10] Following dietary and lifestyle interventions in obese mothers, pregnancy outcomes have been largely unaffected, and changes in body fat distribution of the offspring have been none or only modest.[10] Pharmacologic interventions might produce a greater response; to date, few trials have examined the effect of metformin in obese nondiabetic women in the reduction of adverse pregnancy outcomes.[11−14] Although the primary outcome (birthweight) was similar between groups in both studies, experimental and clinical data suggest that in utero exposure to metformin use can have long-term effects in the offspring by modifying processes that regulate fat accumulation and cardiovascular health.[15]

To investigate this hypothesis, we followed children from the Metformin in Obese Pregnant Women trial to assess whether in utero exposure to metformin can improve the cardiometabolic profile and body fat distribution in the offspring of obese mothers.

Methods

Study population and study design

Our study population consisted of the offspring from the Metformin in Obese Pregnant Women trial; in this trial, obese (body mass index, >35 kg/m^2) nondiabetic pregnant women were assigned randomly to receive metformin or placebo from 12−18 weeks gestation until delivery in 3 National Health Service maternity hospitals in the United Kingdom.[11] In this study, we aimed to invite the mothers of the 393 cases with live births to bring their child to the Harris Birthright Research Centre for detailed cardiometabolic phenotyping. The examinations were conducted by 1 trained clinical research fellow (O.P.) who was blinded to all maternal

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AJOG at a Glance

Why was this study conducted?

Maternal obesity is associated with an adverse cardiometabolic outcome in the offspring. The purpose of this study was to assess whether in utero exposure to metformin can impact on cardiometabolic profile and body fat distribution in the offspring of obese mothers who participated in the Metformin in Obese Pregnant Women randomized controlled trial.

Key findings

Children of obese mothers who were exposed to metformin in utero had improved central hemodynamics and left ventricular diastolic functional indices. No harmful effect on body composition was noted.

What does this add to what is known?

The results of the study suggest that metformin has a beneficial effect on the cardiovascular system of the offspring of obese mothers. The clinical implications of this finding require further exploration.

information, including arm of randomization.

Ethical approval for the study was obtained from the London-Surrey Borders Research Ethics Committee (REC no 08/H0806/80). Signed informed consent was obtained from the parents and assent from the child when possible.

Adiposity measures

The following measurements were recorded while children were standing with arms hanging down to the side: (1) weight and height, (2) arm relaxed, arm flexed and tense, waist, gluteal, mid-thigh and calf circumferences with the use of a flexible tape with 0.5 cm width and 0.5 mm precision, and (3) skinfold thickness at the biceps, triceps, subscapular, suprapinal, and medial calf with the use of a calibrated Harpenden caliper (Baty International, West Sussex, UK) according to the International Society for Advancement of Kinanthropometry. All anthropometric measurements were performed in duplicate, and the mean of the measurements is provided.

Body fat distribution was determined as previously reported with the BIA-ACC device (BioTekna, Inc, Venice, Italy),[16,17] with the children dressed in light clothing without wearing any shoes. Information about weight gain since birth was obtained by measurements recorded by health visitors in the Child's Health Record (Red book).

Hemodynamic measurements and vascular measurements

Peripheral SBP and diastolic blood pressure were measured as the average of the last 2 seated readings with an automated oscillometric device (Welch Allyn spot vital signs; Welch Allyn, Skaneateles Falls, NY) in the right arm with the use of the appropriate sized-cuff after a 5-minute rest. Carotid-to-femoral pulse wave velocity was measured with the Vicorder device (software version 4.0; Skidmore Medical Limited, Bristol, United Kingdom). The method has been previously described and has excellent intra- and interobserver repeatability and ease of use in childhood.[18] The device also determines brachial oscillometric blood pressure with the use of a cuff that is placed around the upper arm. Central blood pressure parameters (aortic SBP and pulse pressure and augmentation index) are then derived from brachial blood pressure waveforms by the application of a previously described brachial to aortic transfer function.[19]

Measures of cardiovascular function and structure

Conventional and tissue Doppler echocardiography was performed with the use of a Philips CX50 system (Philips Healthcare, Netherlands) according to American Society of Echocardiography guidelines.[20] Measures which were assessed included left ventricular mass (LVM) and relative wall thickness, measures of systolic and diastolic function:peak systolic mitral annular tissue velocity, and midwall fractional shortening and peak mitral annular velocities in early diastole (e'), a measure of diastolic relaxation. The ratio of early diastolic transmitral flow velocity E/e' was calculated. Left atrial area was measured in the apical 4 chamber view at the ventricular end systole. LVM measurements were normalized to height$^{2.7}$, as indexed LVM. LVM Z-scores were calculated for all children.[21] Global strain analysis included the average of all 16 segments, and the peak systolic strain values were reported by the use of 2-dimensional speckle-tracking software (QLAB, version 9.0, Philips Healthcare, Andover, MA). Right ventricle systolic function was also assessed by tricuspid annular plane systolic excursion. All measurements were performed by the same clinical Fellow who was trained in pediatric echocardiography.

Biomarker analysis

A 5-mL nonfasting venous blood sample was taken according to standard procedures for children whose parents have agreed to venipuncture. A numbing cream was applied 30 minutes before venipuncture to minimize discomfort. Serum lipids (total cholesterol, triglycerides, and high-density lipoprotein cholesterol and low-density cholesterol) were measured by modification of the standard Lipid Research Clinics Protocol with the use of enzymatic reagents for lipid determination. All assay coefficients of variation were $<5\%$. High sensitivity C-reactive protein and leptin and adiponectin were measured with enzyme-linked immunosorbent assay methods. All samples were separated and frozen at $-80^{\circ}C$ within 1 hour of collection.

Statistical analysis

Continuous variables are expressed as mean$\pm$standard deviation (SD) or median and interquartile range (IQR) if not following the normal distribution. Numeric variables are presented as number (percentage). Normality of

distribution was evaluated graphically by histograms and Q-Q plots. Inverse rank normalization was used to allow for unbiased estimates of effect sizes in regression analysis of dependent cardiometabolic parameters that deviated from Gaussian distribution.

Comparison of anthropometric, hemodynamic, and cardiometabolic parameters in offspring of mothers who were exposed to metformin or placebo in pregnancy was performed with the use of independent samples t-test or the nonparametric Mann-Whitney test and chi-squared test. Subsequently, we used multivariable linear regression analysis to identify independent determinants of the cardiometabolic profile of the offspring. Adiposity measures and cardiovascular measures with a signal of difference ($P<.1$) in unadjusted comparisons among groups were used as outcome variables. Independent variables in regression models were prespecified on the basis of biologic plausibility and observed differences between the total randomized population of the Metformin in Obese Pregnant Women trial and the current sample, and no selection procedure was followed. The use of metformin in pregnancy was inserted in all models as a factor variable, and its effect size was adjusted for available exposure variables. In detail, multivariable regression models for hemodynamic and cardiac outcomes included offspring age, mother's age at conception, sex, weight, height, race, blood pressure indices, and heart rate. For adiposity outcomes, we used the same set of confounders. Possible collinearity among covariates in regression analysis was explored through assessment of the variance inflation factor. We compared nested multivariable models with and without appropriate terms (likelihood ratio tests) to assess potential effect modification of metformin by sex. In certain analyses of dichotomous outcomes (ie, highest vs lower tertiles of transmitral flow ratio), adjusted logistic regression analysis was used.

Multilevel linear mixed model analysis was used to examine the impact of metformin exposure during pregnancy on longitudinal measurements of weight gain of the offspring across a range of approximately 7 years. The linear mixed model analysis included 2 random effects (random slope and random intercept) with unstructured variance-covariance and was adjusted for time intervals between sequential measurements, exposure to placebo or metformin, gender, race, changes in height, and mother's conception age as fixed effects.

Statistical analysis was performed with the Stata software package(version 13.1; StataCorp, College Station, TX). All tests were 2-sided, and statistical significance was $P<.05$.

Our sample size of 151 subjects, allocated in 2 unequal groups of 77 and 74 participants, provided power of 80% to detect a clinically significant difference of 0.5×IQR in weight and/or 0.5×SD in SBP between children who were exposed to metformin and placebo, respectively. The dispersion parameters of SD and IQR for power calculations were retrieved from previous published data. Power analysis for the nonparametric Mann-Whitney test was based on 2000 simulations with resampling.

TABLE 1
Characteristics and history of the population as allocated in the 2 groups

Characteristic	Placebo (N=74)	Metformin (N=77)	*P* value[a]
Gender of offspring (male), %	50	49.4	.94
Age at follow up, y[b]	37±5.2	37.5±5.8	.60
Race, n (%)			.86
White	44 (59.5)	49 (63.6)	
Afro-Caribbean	25 (33.8)	23 (29.9)	
Asian	5 (6.8)	5 (5.5)	
Weight at 12 weeks gestation, kg[c]	106 (97-121)	104 (93 -114)	.17
Body mass index at 12 weeks gestation (kg/m^2)[b]	40±4.8	39.6±5.1	.67
Gestational weight gain, kg[c]	7.1 (4.2-9.6)	3.7 (1.2-7)	<.001
Smoking, n (%)	4 (5.4)	5 (6.5)	.78
Preeclampsia, n (%)	6 (8.1)	1 (1.3)	<.05
Gestational diabetes mellitus, n (%)	12 (16.2)	13 (16.9)	.91

[a] Derived from independent samples t-test or Mann-Whitney test and chi-squared test; [b] Data are presented as mean±standard deviation; [c] Data are presented as median (interquartile range).

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Results

Study population

In the Metformin in Obese Pregnant Women trial cohort, there were 393 live births; 86 live births (11.8%) were not contactable. Of the 307 women (78.2%) who were invited to participate in this study, 156 women (50.8%) refused. In total, 151 children (38.5%) were assessed, including 77 from the metformin and 74 from the placebo groups. Compared with the total Metformin in Obese Pregnant Women trial cohort, mothers in the current study were older (32.8 ±5.2 years vs 31.4 ±5.8; P<.01); however, no other differences in the risk factor profile and in the incidence of pregnancy complications were noted (Supplemental Table). The characteristics of the current study population are described in Table 1. As previously shown, obese mothers who were treated with metformin during pregnancy had reduced gestational weight gain and incidence of preeclampsia, compared with women who received placebo.[11]

Adiposity phenotype

Children in the metformin group, compared with the placebo group, had no significant difference in weight,

TABLE 2
Comparison of metabolic and body composition parameters of offspring of obese mothers

Variable	Placebo	Metformin	*P* value[a]
Metabolic profile[b]			
Cholesterol, mmol/L[c]	3.7±0.64	3.8±0.66	.32
Low-density lipoprotein, mmol/L[c]	1.5±0.33	1.5±0.33	.43
High-density lipoprotein, mmol/L[c]	2.3±0.54	2.4±0.60	.41
Triglycerides, mmol/L[d]	0.91 (0.69–1.38)	0.94 (0.74–1.73)	.74
Non high density lipoprotein, mmol/L[d]	2.47 (2.13–2.93)	2.70 (2.25–2.96)	.31
C-reactive protein, mg/L[d]	0.39 (0.22–1.25)	0.62 (0.27–2.22)	.50
Adiponectin, mg/L[d]	13.30 (9.81–15.48)	13.10 (11.60–14.82)	.60
Leptin, μg/L[d]	2.50 (1.70 –5.78)	2.07 (1.53–2.93)	.18
Body composition[e]			
Birthweight, kg[d]	3.5 (3.1–3.7)	3.32 (3.0–3.68)	.28
Weight, kg[d]	18.7 (15.6–21.2)	17.3 (15.7–20.1)	.15
Height, m[d]	1.04 (0.99–1.09)	1.02 (0.97–1.07)	.25
Body mass index, kg/m^2[c]	17.4±2.1	17.0±2.0	.27
Waist circumference, cm[d]	52.3 (50.0–55.2)	51.3 (49.4–53.8)	.12
Gluteal circumference, cm[d]	58.3 (54.5–62.0)	56.5 (53.5–59.5)	.02
Triceps circumference, cm[d]	31.4 (29.0–34.7)	30.2 (27.8–32.7)	.04
Calf circumference, cm[d]	22.5 (21.1–24.2)	21.9 (20.4–23.3)	.18
Triceps skinfold, mm[d]	11.3 (9.2–13)	10.8 (9.0–12.6)	.44
Biceps skinfold, mm[d]	5.6 (4.9–6.8)	5.2 (4.4–6.2)	.10
Subscapularis skinfold, mm[d]	6.7 (5.8–8.7)	6.7 (5.7–8.7)	.77
Supraspinal skinfold, mm[d]	5.8 (4.8–7.3)	5.8 (4.4–7.0)	.24
Medial calf skinfold, mm[d]	11.1 (9.1–13.7)	11.1 (9.5–12.7)	.80
Free fat mass, kg[d]	16.2 (14.1–18.2)	15.6 (14.0–17.2)	.17
Fat mass, kg[d]	2 (1.1–3.3)	2.2 (1.2–2.8)	.92
Maximum oxygen uptake[d]	48.1 (44.2–53.4)	48.6 (45.4–51.6)	.75
Total body water, L[d]	14.1 (12.2–16.1)	14.0 (12.0–15.7)	.27
Extracellular water, L[d]	7.6 (7.2– 7.9)	7.4 (7.1–7.8)	.11
Intracellular water, L[d]	6.4 (4.8–8.2)	7.0 (4.7–8.1)	.47

[a] Derived from independent samples t-test or Mann-Whitney test and chi-squared test; [b] Placebo, 30; metformin, 39; [c] Data are presented as mean±standard deviation; [d] Data are given as median (interquartile range); [e] Placebo, 74; metformin, 77.

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height, body mass index, skinfold, and body fat distribution measurements but had lower gluteal circumference (56.5 vs 58.3 cm; $P<.05$) and tricep circumference (30.2 vs 31.4 cm; $P<.05$; Table 2). After adjustment for age, sex, race, weight, and height, metformin exposure was associated independently with decreased gluteal circumference (mean difference after inverse rank normalization, −0.183; 95% confidence interval, −0.344 to −0.022; $P<.03$) and tricep circumference (mean difference, −0.189; 95% confidence interval, −0.376 to −0.001; $P<.05$). The rate of weight gain from birth to early childhood was also comparable between the 2 groups ($P=.579$ for interaction of time×group classification; ie, metformin or placebo; Supplemental Figure).

Cardiac and metabolic measurements

Children in the metformin group, compared with the placebo group, had shorter isovolumic relaxation time and smaller left atrial area and higher pulmonary vein peak systolic Doppler velocity value (Table 3). These associations remained after multivariable adjustment (mean adjusted difference,

TABLE 3
Comparison of cardiovascular indices between offspring of obese mothers according to randomization status

Variables	Placebo (N=74)	Metformin (N=77)	*P* value[a]
Systolic blood pressure, mm Hg[b]	98.3±7.0	96.8±5.7	.16
Diastolic blood pressure, mm Hg[b]	60.7±5.0	60.8±5.2	.93
Pulse pressure, mm Hg[b]	37.5±5.13	36.0±4.2	<.05
Aortic systolic blood pressure, mm Hg[b]	96.2±6.4	94.2±5.8	<.05
Aortic pulse pressure, mm Hg[b]	35.5±4.8	33.4±4.7	<.01
Augmentation index, %	22 (18–30)	18 (15–29)	.09
Pulse wave velocity, m/sec	5.1 (4.7–5.5)	5.0 (4.7–5.5)	.93
Heart rate, bpm	97 (91–105)	99 (92–106)	.21
Cardiac measurements			
Left ventricular mass indexed, g	29.8 (25.0–34.0)	30.1 (25.3–33.5)	.98
FS, %	1.8 (29.5–34.1)	31.8 (29.3–34.4)	.95
IVSD, mm	0.45 (0.4–0.51)	0.44 (0.40–0.49)	.44
IVSD z-score	−0.77 (−1.20– −0.23)	−0.76 (−1.19– −0.39)	.83
TAPSE, cm	1.80 (1.7–1.9)	1.8 (1.7–1.9)	.75
TAPSE z-score	0.46 (−0.31–1.23)	0.46 (−0.31–1.23)	.64
Isovolumic relaxation time, mm	50 (40–60)	50 (40–50)	.03
Left atrium, cm^2	6.1 (5.3–6.9)	5.5 (4.9–6.2)	.001
E, cm/sec	89.4 (83.3–95.0)	88.2 (80.7–95.5)	.59
A, cm/sec	53.4 (47.5–61.0)	57.1 (50.5–61.8)	.22
Ratio of E–A	1.64 (1.45–1.89)	1.55 (1.43–1.71)	.17
A duration, msec	80 (80–90)	80 (80–90)	.81
Deceleration time, msec	90 (80–100)	90 (80–100)	.84
Isovolumic contraction time, msec	50 (40–60)	50 (40–50)	.92
e' lateral, cm/sec	18.0 (16.4–20.3)	17.9 (16.4–19.4)	.56
e' septal, cm/sec	12.4 (11.8–13)	12.5 (11.6–13.3)	.86
e'avgerage, cm/sec	15.4 (13.9–16.2)	15.2 (14.1–15.9)	.57
a' lateral, cm/sec	7.22 (6.40–8.37)	7.07 (6.19–8.14)	.53
a' septal, cm/sec	5.6 (5.0–6.5)	5.5 (4.9–6.2)	.32
a' avg, cm/sec	6.48 (5.78–7.44)	6.45 (5.58–7.10)	.44
E/e' avg	5.86 (5.36–6.44)	5.88 (5.30–6.59)	.82
E/e'	4.96 (4.35–5.58)	4.93 (4.46–5.76)	.77
Pulmonary vein systolic wave, cm/sec	53 (51–56)	56 (52–61)	<.01
Pulmonary vein diastolic wave, cm/sec	56 (51–61)	57 (53–60)	.50
Global longitudinal strain overall, %	−19 (−21– −18)	−19.6 (−21– −17.75)	.86

Data are given as median (interquartile range).

A, peak velocity of late transmitral flow; *a'*, peak velocity of diastolic mitral annular motion as determined by pulsed wave Doppler; *E*, peak velocity of early diastolic transmitral flow; *e'*, peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; *FS*, fraction shortening; *IVSD*, interventricular septum thickness at end of diastole; *TAPSE*, tricuspid annular plane systolic excursion.

[a] Derived from independent samples t-test or Mann-Whitney test and chi-squared test; [b] Data are presented as mean±standard deviation

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TABLE 4
Multivariable regression analysis for main cardiometabolic outcomes of the study

Variable	Adjusted mean decrease (95% confidence interval) Untransformed	*P* value	Inverse rank transformation	*P* value
Central hemodynamics				
Aortic systolic blood pressure	−0.71 (−1.21 to −0.20)	<.01	—	
Aortic pulse pressure	−1.65 (−2.98 to −0.31)	.02	—	
Augmentation index	−2.68 (−5.35 to −0.01)	<.05	−0.32 (−0.633 to −0.007)	<.05
Diastolic indices				
Isovolumic relaxation time	−3.2 (−5.78 to −0.70)	.01	−0.34 (−0.61 to −0.07)	.02
Left atrial area	−0.53 (−0.84 to −0.201)	<.01	−0.43 (−0.68 to −0.17)	<.01
Pulmonary veins: systolic wave	2.97 (0.94 to 5.0)	<.01	0.41 (0.08 to 0.73)	.01

All models are adjusted for age and mother's age, sex, race, weight, height, systolic blood pressure, and heart rate.
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−0.324 msec, −0.525 cm^2, and 2.97 cm/sec for isovolumic relaxation time, left atrial area. and pulmonary venous systolic wave, respectively; $P<.05$ for all; Table 4; Figure). In addition, exposure to metformin was associated with decreased odds ratio (OR) for increased early to late transmitral blood flow ratio (OR, 0.48 for increased tertile of peak Doppler blood flow mitral valve velocity in early diastole [E wave] to peak velocity flow during atrial contraction [A wave] metformin vs placebo; $P<.05$) after adjustment for the age of the mother and child, sex, weight, height, race, and SBP. However, this association was further attenuated when heart rate was also included in the analysis. No difference in tissue Doppler measurements was noted between groups. Measures of cardiac systolic function, which included strain measurements, and measurement of LVM were similar in the 2 groups. No association was found between maternal pregnancy body mass index and offspring cardiovascular parameters in the placebo- and metformin-exposed group.

The metabolic profile was assessed in 39 infants from each group, and there were no significant differences between the metformin and placebo groups (Table 2).

Hemodynamic parameters and vascular phenotype

In the metformin group, compared with the placebo group, there was no significant difference in peripheral SBP and diastolic blood pressure; pulse pressure was lower (36.1±4.2 vs 37.5±5.1 mm Hg; $P<.05$), but this difference was attenuated after adjustment for current adiposity. After multivariable adjustment, children who were exposed to metformin during pregnancy had lower aortic pulse pressure (mean adjusted difference, −1.65 mm Hg; 95% confidence interval, −2.98 to −0.314; $P<.02$), aortic SBP (mean adjusted difference, −0.707 mm Hg; 95% confidence interval, −1.21 to −0.201; $P=.007$), and augmentation index (−2.68%; 95% confidence interval, −5.35 to −0.01; $P=.049$; Table 4; Figure 1). Carotid-to-femoral pulse wave velocity was similar in the 2 groups.

Comment

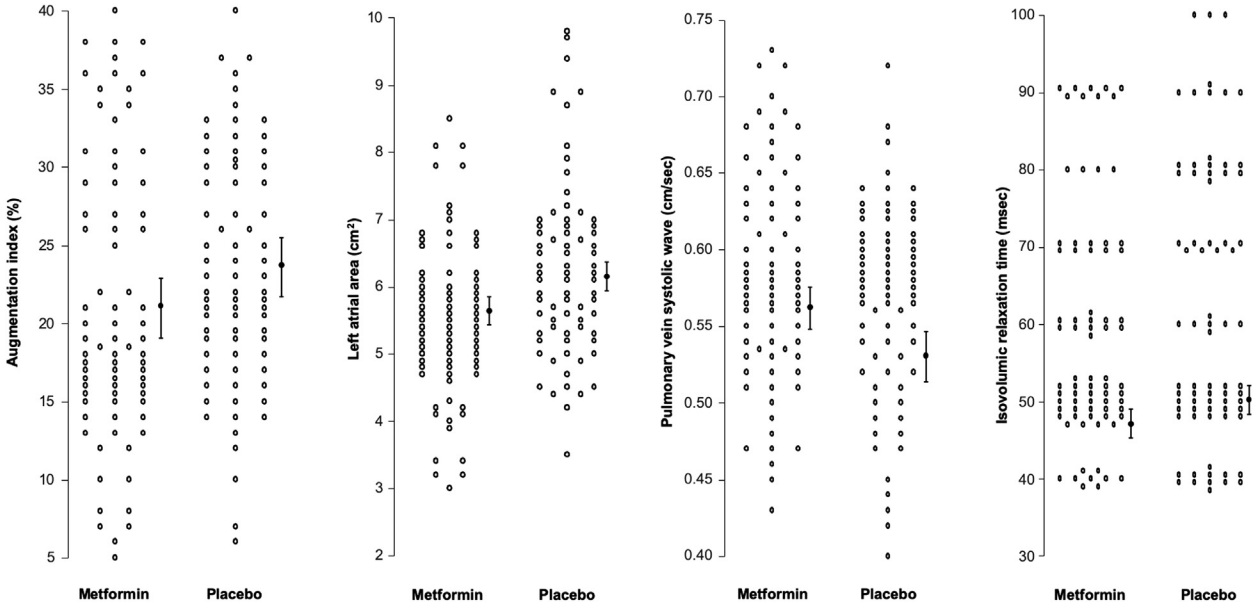
Main findings of the study

This study has demonstrated that in utero exposure to metformin, compared with placebo, is associated with reduced central blood pressure and augmentation index and lower cardiac diastolic indices at the age of 4 years and has no harmful effect on body composition and metabolic profile. These results suggest a putative beneficial effect of metformin to the cardiovascular system of the offspring and, if replicated and ideally supported by longer term data, can have important clinical implications that include a rationale for the clinical use of metformin in obese mothers during pregnancy to protect the cardiovascular health of the offspring.

Interpretation of results and comparison with existing literature

A number of different studies have suggested that maternal obesity can have adverse cardiometabolic implications for the offspring.[5,8,9] However, it remains unknown whether interventions during pregnancy can modify this link. In the current study, offspring of obese mothers were exposed in utero to metformin or placebo as part of the Metformin in Obese Pregnant Women trial. To assess cardiovascular profile in offspring, we used a variety of methods to define early arterial and cardiac changes. We used an oscillometric device, Vicorder, to estimate central hemodynamics and assess arterial stiffness between carotid to femoral segment. This technique has been used widely in childhood and is reproducible and operator independent; and its measurements have been validated to invasive measurements in both children and adults.[19,22] We

FIGURE
Comparison of measurements of infant cardiovascular function in the metformin and placebo groups



The *open circles* show the observed values; the *closed circles with vertical lines* represent adjusted mean estimates along with 95% confidence intervals after the data have been controlled for baby's and mother's age, race, weight, height, systolic blood pressure, and heart rate. The adjusted probability values were .049 for augmentation index, .001 for left atrial area, .004 for pulmonary veins systolic wave, and .013 for isovolumic relaxation time.

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showed that children of obese mothers who were exposed to metformin in utero had improved central hemodynamics as assessed by central SBP, central pulse pressure, and augmentation index, whereas no difference in peripheral blood pressure or arterial stiffness could be detected when current adiposity was accounted for in the analysis. These results are novel and are in keeping with data that suggest that changes in aorta and central blood pressure may precede any alterations in the peripheral circulation.[23,24] They are also in agreement with a previous study where in utero exposure to metformin did not modify peripheral blood pressure in 2-year-old children compared with those children who were exposed to insulin treatment in the context of gestational diabetes mellitus.[25]

Considering that central aortic blood pressure and augmentation index reflect the pressure that the heart and the brain are directly exposed to these results may have important clinical implications.[26] In adults, central SBP has been shown to be better at the prediction of future cardiovascular events; however, such a link remains to be established in children because central hemodynamics are not measured routinely in clinical practice.[27] The results from the current study address a conclusion of the 2016 European Society of Hypertension guidelines that highlighted the need to increase knowledge in pediatrics and assess central blood pressure, especially in children who are at increased risk for hypertension, as a means to better stratify their cardiovascular risk.[27]

Functional alterations in the heart usually precede structural changes; in this study, we used a variety of echocardiographic parameters to characterize systolic and diastolic left ventricular functional changes. We found that, in the metformin group compared with the placebo group, isovolumic relaxation time was shorter, left atrial area was smaller, and pulmonary venous systolic waveform was increased; these associations remained after adjustment for a number of hemodynamic and anthropometric parameters. Although values remained within normal range for age, these findings suggest that in utero exposure to metformin is associated with better early diastolic myocardial relaxation; however, it remains uncertain whether these changes will translate in long-term cardiovascular benefit. We found no significant differences between the metformin and placebo groups in left ventricular systolic function or LVM. Data derived from animal studies suggest that diastolic dysfunction that leads to increased diastolic filling pressures are present early in the development of obesity and contribute to the reduction of cardiac reserve and exercise intolerance in obese population.[28] The mechanism by which in utero exposure to metformin may affect diastolic function in postnatal life remains speculative. It is possible that changes in myocardial architecture or myocyte metabolism occur in utero as a

consequence of exposure to a hyperglycemic environment and that metformin may modify these processes.[29] It is also possible that metformin may be involved in epigenetic alterations, which potentially affect arterial and cardiac growth later in life.[30]

Prenatal metformin crosses the placenta and exposes the fetus to a dose that would not be used in a newborn or child, and concerns were raised that this may also have long-term programming effects on fetal metabolism and bodyweight and composition. In relation to metabolism, in a small subgroup of children, we measured a series of parameters, including lipid profile, inflammatory markers and leptin and adiponectin and found similar blood levels in the placebo and metformin groups. Although the lack of association between prenatal metformin exposure and metabolic abnormalities is consistent with data from the PregMed and MiG trial,[31,32] the limited sample size of our study population does not allow firm conclusions to be drawn about late metabolic consequences of in utero exposure to metformin. In relation to bodyweight, we used a variety of anthropometric measurements to assess fat content and its distribution and found no significant difference between the metformin and placebo groups in fat content, distribution, or weight gain since birth. These results contradict data from the PregMet trial and from 2 recent meta-analyses that indicated that prenatal exposure to metformin is associated with increased offspring weight.[32–35] There are 2 possible explanations for such inconsistency in results: First, in our study we intentionally aimed to recruit children before the adiposity rebound period to minimize the confounding effect of additional risk factors that accumulate with increasing age,[36] whereas previous studies revealed associations between prenatal exposure to metformin and increased weight approximately at the age of 9 years.[32,37] Second, our study was confined to obese women, whereas previous studies examined women with either polycystic ovary syndrome or gestational diabetes mellitus that may be associated with different in utero environments.

Strengths and limitations

The main strengths of our study are (1) recruitment from a randomized controlled trial with high compliance rate where metformin or placebo was given from the early second trimester until the end of pregnancy and (2) recording of measurements by a research fellow who was blinded to randomization. The main limitation is that only 38.5% of children from the original cohort had body composition assessment and that 19.8% had blood sample for metabolic measurements. Although there were no statistically significant differences in maternal or fetal characteristics between our study population and the original cohort, we cannot exclude that this is due to type II error because there was a trend towards a higher frequency of risk factors, such as Afro-Caribbean race and gestational diabetes mellitus, in the studied population compared with the original cohort.

Clinical perspective

Metformin crosses the placenta; although the safety of the medication has been demonstrated during pregnancy, a number of studies have provided conflicting results regarding its long-term effects on the health of the offspring. Our study is the first to report on the impact of in utero exposure to metformin in the offspring of obese nondiabetic mothers. By performing a detailed cardiometabolic phenotype, we were able to show improved cardiac and vascular indices in children who were exposed prenatally to metformin compared with those who were exposed to placebo. In addition, no difference in body composition and metabolic profile were noted between groups. Although the differences between groups are small and their long-term clinical significance remains unknown, the current findings are important because they suggest that metformin use in obese pregnant mothers is not only associated with reduced weight gain during pregnancy and incidence of preeclampsia for the mother[11] but also with potential cardiovascular benefit for their offspring. Further studies, however, will be needed to confirm the long-term absence of any harmful effects of in utero exposure to metformin in the different systems of the offspring before clinical use of this medication in obese mothers is advocated.

Conclusion

Our study suggests that in utero metformin exposure in the context of maternal obesity is associated with hemodynamic and echocardiographic changes that might have a direct cardioprotective effect on the offspring. Differences between groups were small, and their clinical significance remains questionable; therefore, further long-term studies are needed to determine whether these changes translate in long-term cardiovascular benefit and provide a rationale for the use of metformin in obese mothers to protect the cardiovascular system of the offspring. ■

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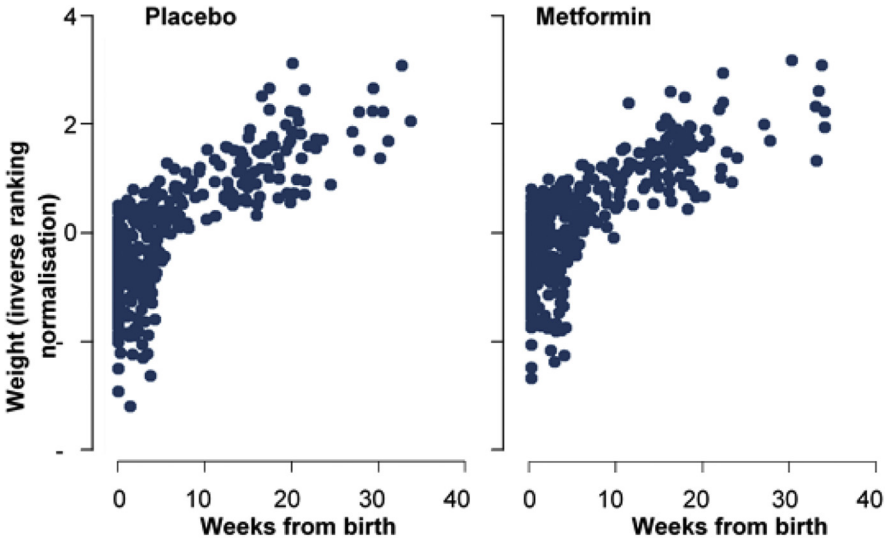
SUPPLEMENTAL FIGURE
Longitudinal measurements of weight from birth to early childhood



The longitudinal measurements of weight from birth to early childhood did not differ between children who were exposed to placebo or metformin (*P* for interaction=.579). The probability value was derived from linear mixed model analysis (interaction term between time and group classification) after adjustment for child sex, race, elapsed time between follow-up visits, and changes in height.

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SUPPLEMENTAL TABLE
Comparison of the original Metformin in Obese Pregnant Women trial population with the subcohort of the offspring with available cardiometabolic data

Characteristic	Total trial population (N=393)	Offspring follow up population (N=151)	*P* value[a]
Age, y[b]	35.5±6.01	37.3±5.47	<.01
Weight, kg[c]	105 (96–115)	104 (95.6–117)	.98
Height, cm[c]	165 (160–168)	164 (159–169)	.66
Body mass index, kg/m^2[b]	39.6±4.6	39.7±5.0	.84
Race, n (%)			
White	273 (69.2)	93 (61.6)	
Afro-Caribbean	103 (26.2)	48 (31.8)	
Asian	18 (4.58)	10 (6.62)	.22
Smoking, n (%)	34 (8.7)	9 (6.0)	.30
In vitro fertilization, n (%)	4 (1.0)	3 (2.0)	.56
Gestational diabetes mellitus, n (%)	47 (11.96)	25 (16.56)	.16
Preeclampsia, n (%)	29 (7.38)	7 (4.64)	.25
Gestational age at delivery, wk[c]	39.6 (38.7–40.6)	39.9 (39-40.6)	.43
Birthweight[c]	3.4 (3.02–3.73)	3.4 (3.01-3.70)	.63
Birthweight percentile[c]	54.3 (25.3–82)	50.6 (21.6–75)	.28
Male fetuses, n (%)	204 (51.9)	74 (49.0)	.54

[a] Derived from independent samples t-test or Mann-Whitney test and chi-squared test; [b] Data are presented as mean±standard deviation; [c] Data are presented as median (interquartile range).

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