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SHORT COMMUNICATION

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Long-term follow-up of children with in utero exposure to sulfonylurea medications

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Abstract

Background: Offspring born to mothers with gestational diabetes mellitus (GDM) are more likely to have negative neurodevelopmental health outcomes, early obesity, type 2 diabetes, and metabolic syndrome in childhood, adolescence, and adulthood. Standard of care management for GDM and type 2 diabetes mellitus during pregnancy is insulin, but oral sulfonylurea use is increasing, and these medications cross the placenta. Literature on treatment with sulfonylureas for maternal GDM has focused on maternal glycemic control and neonatal outcomes. Studies that have evaluated the long-term outcomes of children exposed to sulfonylureas in utero are limited.

Objective: This study evaluated anthropometric and neurodevelopmental outcomes of 55 children (ages 5–10) born to mothers with diabetes during pregnancy treated with sulfonylurea or insulin.

Methods and Results: A group of 25 sulfonylurea-exposed and 30 insulin-exposed participants were age- and sex-matched between groups. No significant differences were identified in z-scores for body mass index (BMI), waist circumference, skinfold measurements, and body fat or rates of overweight/obese BMI between groups. On performance-based cognitive assessment, the sulfonylurea-exposed group had significantly lower scores on inhibition ($p = 0.043$).

Conclusion: In summary, children with in utero sulfonylurea exposure had similar physical measurements compared to children with insulin exposure and lower performance on a measure of executive function (inhibition), which is associated with adverse health outcomes.

KEYWORDS
child body composition, child neurodevelopmental outcomes, gestational diabetes mellitus, sulfonylurea exposure

All research was conducted at Ann & Robert H. Lurie Children's Hospital and Northwestern University, Chicago, Illinois, USA.

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1 | INTRODUCTION

Maternal gestational diabetes mellitus (GDM) and type 2 diabetes mellitus (T2DM) during pregnancy are associated with adverse neonatal and childhood outcomes. GDM is defined as new-onset diabetes diagnosed during pregnancy, and the risk of GDM is significantly increased in women with obesity, with almost 50% attributable to elevated body mass index (BMI).[1,2] The prevalence of GDM, estimated in the United States to range from 3% to 14% of pregnancies,[3] continues to increase worldwide, mirroring the increasing rates of obesity in women of childbearing age, with significant costs to society and need for treatment to avoid adverse maternal and neonatal outcomes.[4–6] Most data arise from mothers with GDM as it is the leading cause of diabetes during pregnancy, and prevalence data of pre-existing T2DM in pregnancy is not available. GDM, and even hyperglycemia below the diagnostic threshold for GDM, has been shown to have long-term consequences on the offspring.[7–12] Children of mothers with GDM are more likely to develop early obesity, elevated adiposity (as measured by body fat percentage, waist circumference, and skinfold measurements), impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in childhood, adolescence, and adulthood.[10,13,14] Though maternal obesity also constitutes a risk factor for these outcomes, GDM seems to have an additive effect on many outcomes, specifically the risk for obesity, elevated adiposity, and disorders of glucose metabolism.[10,14] These adverse outcomes may be the result of fetal programming in the setting of maternal hyperglycemia, leading to an intergenerational cycle of diabetes and associated obesity.[15]

Negative effects of GDM exposure on children's neurodevelopmental health (NDH) outcomes have been demonstrated, with worse mental and psychomotor development in infants of mothers with diabetes compared to controls.[16] A reduction in intelligent quotient of school-aged children with diabetes exposure was demonstrated by meta-analysis, though significant heterogeneity was noted, potentially related to differences in socioeconomic status.[16] Studies have shown increased inattention in children exposed to in utero diabetes, and together, lower socioeconomic status and GDM are correlated with Attention Deficit Hyperactivity Disorder (ADHD) symptoms and diagnosis.[17]

While first-line treatment for GDM and T2DM is diet and lifestyle modifications, continued hyperglycemia warrants initiation of medical treatment. Though insulin is the only United States Food and Drug Administration-approved treatment for diabetes in pregnancy, sulfonylurea use has increased worldwide after data supporting adequate control in some women and absence of complications in their neonates.[13,18,19] Sulfonylurea use improves maternal satisfaction and adherence but has risks of maternal hypoglycemia, and the medications are known to cross the placenta and alter placental GLUT1 expression.[20–22] In utero exposure to sulfonylureas has been associated with increased incidence of neonatal hypoglycemia and large-for-gestational age (LGA) neonates as compared to insulin exposed. However, newer data indicate less concern for LGA, yet consistent higher rates of neonatal hypoglycemia among newborns exposed to sulfonylureas.[13,20,23,24] In addition to effects of GDM on NDH, neonatal hypoglycemia is associated with impaired neurological development in children, including delayed cognitive development as compared to normoglycemic neonates.[25] Importantly, poor NDH has been associated with adverse health outcomes, including obesity, perhaps due to impact on self-regulatory behavior.[26–28]

The objective of this pilot study was to evaluate long-term effects of in utero sulfonylurea exposure by investigating the anthropometric and neurodevelopmental outcomes of 5- to 10-year-old children whose mothers were treated with sulfonylurea as compared to insulin.

2 | RESEARCH DESIGN AND METHODS

Children, ages 5–10 years old, who were born full-term to mothers with a diagnosis of GDM or T2DM treated with the oral sulfonylurea glyburide or glipizide for at least 4 weeks during gestation or insulin injections were recruited. Eligible participants were identified by the Northwestern Medicine Enterprise Data Warehouse of labor and delivery records, using search terms of: GDM, T2DM, insulin, sulfonylurea, glyburide, and glipizide. Children born to mothers treated with diabetes medications other than sulfonylurea or insulin, such as metformin, beyond the first prenatal visit were excluded. During the study visit, mothers provided written informed consent for review of their pregnancy medical record and for their child to participate and completed questionnaires. The study protocol was approved by the institutional review boards at Northwestern University and Lurie Children's Hospital of Chicago.

Children underwent anthropometric data collection, including height, blood pressure, skinfolds: triceps, subscapular, and suprailiac (Harpenden calipers), and air displacement plethysmography (BOD POD; Cosmed) for weight and body fat percentage. In children older than 9 years, a pubertal assessment was performed by a pediatric endocrinologist.

The child's BMI percentile for age, as well as weight category, was determined using the CDC database. Blood pressure percentiles were determined,[29] waist circumference z-scores were calculated using NHANES III LMS tables calculator,[30] and triceps and subscapular skinfold z-scores were calculated based on CDC data.[31]

Children completed age-appropriate NEPSY-II (Developmental NEuroPSYchological Assessment) and Wechsler Intelligence Scale for Children Fifth Edition (WISC-5) subtests administered with Q-interactive to evaluate executive functions (inhibition, shifting, updating of working memory, reasoning, and cognitive flexibility). Mothers completed questionnaires, including Behavior Rating Inventory of Executive Function (BRIEF-2)[32] that assess executive function and emotion regulation in daily life settings.

Analysis included paired *t*-tests, chi-square test, and Analysis of variance (ANOVA) to identify differences in demographics, physical outcomes, and neuropsychological outcomes between groups.

TABLE 1 Maternal and child demographics

	Cohort	Sulfonylurea group	Insulin group	
	N (%) or mean (s.d.)			*p*-value
Number of children	55	25 (45.5%)	30 (54.5%)	-
Female child participants	25 (45.5%)	11 (44.0%)	14 (46.7%)	0.884
Age of children	7 years 8 months (19.6 months)	7 years 8 months (18.8 months)	7 years 8 months (20.7 months)	0.947
Maternal demographics				
Race/Ethnicity:				
Hispanic/Latinx	33 (60.0%)	20 (80.0%)	13 (43.3%)	0.080
Black/African American	3 (5.5%)	3 (12.0%)	0 (0.0%)	0.058
White	13 (23.6%)	1 (4.0%)	12 (40.0%)	**0.006**
Asian	4 (7.3%)	0 (0.0%)	4 (13.3%)	0.068
Other	2 (3.6%)	1 (4.0%)	1 (3.3%)	0.897
Number with type 2 diabetes mellitus during pregnancy	13 (23.6%)	7 (28.0%)	6 (20.0%)	0.543
Cesarean section delivery	21 (38.1%)	9 (36.0%)	12 (40.0%)	0.811
Age at delivery (years)	31.4 (5.5)	28.2 (5.0)	33.6 (4.9)	**0.0002**
Maternal BMI at delivery (kg/m^2)	35.4 (6.8)	35.7 (7.6)	35.1 (6.1)	0.765
Maternal education past high school	41 (74.5%)	13 (52.0%)	28 (93.3%)	0.077
Employed full or part-time	42 (76.4%)	16 (64.0%)	26 (86.7%)	0.338
Current diabetes treatment	24 (43.6%)	12 (48%)	12 (40%)	0.655
Current median family income by address (US$)	83,000 (49,900)	58,100 (21,300)	104,000 (57,200)	**0.0004**
Neonatal data				
Birthweight (kg)	3.45 (0.53)	3.65 (0.53)	3.29 (0.46)	**0.009**
Large for gestational age	11 (20.0%)	10 (40%)	1 (3.3%)	**0.003**
Hypoglycemia	20 (36.3%)	13 (52.0%)	7 (23.3%)	0.079

Note: Bold values indicate significant of p<0.05p.

3 | RESULTS

Table 1 displays the demographic data, as well as neonatal data, for the two study groups. Fifty-five children, 25 with in utero sulfonylurea exposure and 30 with mothers treated with insulin, participated in the study with a mean age of 7 years 8 months. There were five sets of siblings; children were from 49 unique mothers, 23 in the sulfonylurea group and 26 in the insulin group. There were similar numbers of mothers with GDM and T2DM in each group. The children in the sulfonylurea group had in utero exposure to sulfonylurea for a mean of 14.8 weeks (SD 9.5 weeks), with a range of 3–30.3 weeks and a median of 10.5 weeks (excluding missing data from two prenatal records). Race and age of the mothers were different between groups. The insulin group was 40% white as compared to the sulfonylurea group with 4% ($p = 0.006$), and the mean age at delivery was 33.6 years (SD 4.9) in the insulin group as compared to 28.2 years (SD 5.0) in the sulfonylurea group ($p < 0.001$). Children in the sulfonylurea group had lower median family income of $58,100 (SD $21,300) based on residential zip code as compared to the insulin group (mean $104,000, SD $57,200) ($p < 0.001$). More mothers in insulin group had education beyond high school (93.3%) compared to mothers in the sulfonylurea group (52%), yet this difference did not reach statistical significance ($p = 0.077$). Other demographic characteristics were similar.

Physical and neurodevelopmental outcomes of the two study groups are displayed in Table 2. Across the two groups, childhood characteristics were similar except more children of mothers treated with insulin required learning services, evaluated by survey where mothers reported whether their child at any time received school-based learning services (speech, occupational, and/or physical therapy). Learning services were received by 60% of children with insulin exposure as compared to 20.8% with sulfonylurea exposure ($p = 0.018$). With regard to physical outcomes, the groups did not differ in BMI, percentages of overweight or obese category, blood pressure, skinfold measurements, waist circumference, and body fat percent.

TABLE 2 Physical outcomes and neurodevelopmental outcomes by performance-based cognitive assessment and parent reports

	Cohort	Sulfonylurea group	Insulin group	
	N (%) or mean (s.d.)			*p*-value
Number of children	55	25 (45.5%)	30 (54.5%)	
Age of children	7 years 8 months (19.6 months)	7 years 8 months (18.8 months)	7 years 8 months (20.7 months)	0.947
Weight (kg)	30.2 (12.1)	31.2 (13.4)	29.3 (11.1)	0.566
Height (cm)	126.0 (11.2)	127.0 (11.3)	125.1 (11.2)	0.534
BMI (kg/m^2)	18.5 (5.0)	18.8 (5.3)	18.3 (4.7)	0.723
BMI z-score	0.64 (1.40)	0.75 (1.26)	0.55 (1.53)	0.60
Blood pressure (mmHg)	101.0 (9.9)/62.9 (8.0)	98.9 (9.7)/61.6 (8.2)	102.7 (9.9)/63.9 (7.8)	0.16/0.30
Blood pressure percentile	62.3 (26.3)/65.4(22.1)	56.2 (27.5)/61.3 (23.1)	67.4 (24.6)/68.9 (21.1)	0.12/0.21
Waist circumference (cm)	64.1 (13.6)	64.7 (15.0)	63.5 (12.5)	0.75
Waist circumference z-score	0.5 (1.1)	0.6 (1.0)	0.5 (1.2)	0.75
Triceps skinfold (mm)	14.2 (7.7)	13.9 (6.3)	14.4 (8.9)	0.80
Triceps skinfold z-score	0.8 (1.1)	0.8 (1.0)	0.7 (1.3)	0.80
Subscapular skinfold (mm)	11.2 (8.9)	12.1 (9.8)	10.4 (8.1)	0.48
Subscapular skinfold z-score	1.0 (1.1)	1.2 (0.8)	0.9 (1.2)	0.26
Iliac crest skinfold (mm), *N* = 54	12.8 (10.1)	12.2 (9.4)	13.3 (10.9)	0.68
Sum of 3 skinfolds (mm), *N* = 54	38.2 (25.5)	38.2 (24.8)	38.1 (26.4)	0.98
Body fat percent	21.2% (11.5)	21.9% (12.2)	20.7% (11.1)	0.70
Overweight BMI	9 (16.4%)	5 (20.0%)	4 (13.3%)	0.543
Obese BMI	12 (21.8%)	6 (24.0%)	6 (20.0%)	0.752
Normal blood pressure	43 (78.2%)	22 (88.0%)	21 (70.0%)	0.452
Elevated blood pressure	5 (9.1%)	3 (12.0%)	2 (6.7%)	0.514
Stage 1 hypertension	6 (10.9%)	0 (0%)	6 (20.0%)	**0.025**
Stage 2 hypertension	1 (1.8%)	0 (0%)	1 (3.3%)	0.361
Children requiring learning services or therapy, *N* = 54	23 (42.6%)	5 (20.8%)	18 (60.0%)	**0.018**
Performance-based cognitive measures[a]				
Matrix Reasoning (MR)	10.1 (2.8)	9.6 (2.4) *N* = 25	10.5 (3.2) *N* = 26	0.263
Picture Completion (PC)	9.8 (3.3)	9.8 (3.5) *N* = 23	9.7 (3.3) *N* = 26	0.958
Inhibition (IN)	9.2 (4.1)	8.1 (3.6) *N* = 24	10.6 (4.2) *N* = 19	**0.043**
Word Generation (WG)	8.2 (3.0)	8.3 (2.5) *N* = 14	8.1 (3.4) *N* = 14	0.852
Spatial Working Memory (SWM)	10.0 (3.4)	9.2 (2.3) *N* = 25	10.7 (3.2) *N* = 26	0.063
Parent-report cognitive measures (BRIEF)[b]				
Inhibition	51.00 (12.69)	52.30 (13.29)	49.44 (12.01)	0.410
Self-monitor	49.07 (10.00)	48.50 (10.30)	49.76 (9.78)	0.646
Shift	51.05 (11.63)	51.63 (12.34)	50.36 (10.88)	0.690
Emotion control	52.42 (11.69)	54.30 (12.75)	50.16 (10.06)	0.194
Initiate	49.11 (11.13)	47.92 (11.50)	50.10 (10.90)	0.475
Working memory	50.98 (11.75)	48.76 (10.98)	52.83 (12.22)	0.203
Plan/organize	48.73 (10.93)	49.24 (11.36)	48.30 (10.73)	0.754

TABLE 2 (Continued)

	Cohort	Sulfonylurea group	Insulin group	
	N (%) or mean (s.d.)			*p*-value
Task monitor	49.89 (10.98)	49.68 (10.21)	50.07 (11.75)	0.898
Organization of materials	49.36 (9.28)	47.44 (8.90)	50.97 (9.43)	0.162

Note: Bold values indicate significant of p<0.05.

Abbreviations: IN, inhibition; MR, matrix reasoning; PC, picture completion; SWM, spatial working memory; WG, word generation.

[a]MR and PC measures were from the WISC-5; IN, WG, and SWM measures were from the NEPSY. Scaled scores were used in analyses, and scores between 8 and 12 are described as average with a corresponding percentile rank of 25–75. Higher scores indicate greater ability on a specific test.

[b]T-scores were used for analyses ($M = 50$, SD = 10). T-scores at or above 65 are considered clinically significant and scores between 60 and 64 are interpreted as "mildly elevated."

BMI, evaluated by z-score, was not different, with mean z-score of 0.75 (SD 1.26) for sulfonylurea-exposed as compared to mean of 0.55 (SD 1.53) for insulin group. Comparison of children with overweight and obese BMI between groups demonstrated 20.0% overweight and 24.0% obese BMI among children with sulfonylurea exposure, compared to 13.3% overweight and 20.0% obese BMI in children of mothers treated with insulin. Statistical significance was found for Stage 1 hypertension range blood pressure with more cases in the insulin group (20.0% insulin group compared to 0% sulfonylurea group, $p = 0.025$). However, the average blood pressure and percentile did not differ between groups, with average blood pressures of 99/61 in sulfonylurea-exposed children as compared to 103/64 in the insulin-exposed group. Mean body fat percentage was similar in sulfonylurea-exposed children 21.9% (SD = 12.2) as compared to 20.7% (SD = 11.1) in children in the insulin group.

From review of delivery records, it was determined that the children with in utero sulfonylurea exposure had larger birth weight. The mean neonatal weight in the sulfonylurea group was 3.65 kg (SD 0.53), with 40% categorized as LGA, as compared to mean of 3.29 kg (SD 0.46) and 3.3% LGA in the insulin group ($p = 0.009$ and $p = 0.003$, respectively). Notably, there were more small-for-gestational age neonates in the insulin-exposed group ($N = 6$ vs. $N = 1$ in sulfonylurea-exposed group), though this difference was not statistically significant.

For the neuropsychological assessment, children underwent performance-based cognitive testing. Not all participants were able to complete all tasks, thus group numbers differed for each measure as indicated in Table 2. Sulfonylurea-exposed children had lower scores on an assessment of inhibition (NEPSY-II) with mean score of 8.1 (SD 3.6) compared to the insulin-exposed group with mean 10.6 (SD 4.2) ($p = 0.043$). The sulfonylurea-exposed group performed in the low average range and the insulin-exposed group performed in the average range on inhibition. No clinically or statistically significant differences were observed on the BRIEF-2,[32] a parent-report measure of executive function. Results from the BRIEF-2 indicated that both groups had average scores that fell in a normal (nonelevated) range.

4 | DISCUSSION

This study of children with in utero exposure to sulfonylureas as compared to insulin demonstrated differences in the neurodevelopmental outcome of executive function (inhibition), but no significant differences in anthropometric outcomes. To our knowledge, this is the first report of long-term outcomes in children with in utero sulfonylurea exposure. These findings are preliminary, yet important to consider when treating diabetes during pregnancy with sulfonylurea medication. Poor childhood NDH, especially poor inhibition, is associated with excess weight gain and other lifestyle risk behaviors, including medication adherence and risky behaviors.[27]

In the present study, in which all children were exposed to mothers with diabetes, similar rates of overweight/obesity and adiposity in the children exposed to either sulfonylurea or insulin were documented. Sulfonylurea exposure has been associated with increased birthweight and LGA incidence, although rigorous glucose control has been demonstrated to reduce these outcomes.[13,20,23,24] While the increased LGA incidence in this cohort may represent inferior glucose control of mothers treated with sulfonylurea, there was no sufficient data on maternal glucose control to study this association. A number of studies have documented increased incidence of neonatal hypoglycemia among children exposed to sulfonylurea,[13,20] and while more children with sulfonylurea exposure in this study experienced neonatal hypoglycemia, the difference was not statistically significant.

Performance on an inhibition task was lower for the sulfonylurea-exposed group compared to the insulin-exposed group. While inhibition was reduced on a performance-based measurement, the BRIEF-2 parent-report questionnaire did not indicate executive function impairments in daily life activities. These questionnaires were completed from maternal perspective, without input from a variety of sources, particularly school. Moreover, the study was not powered to analyze neonatal hypoglycemia as an etiology of differences in the NDH outcomes.

This study is limited by retrospective design, demographic differences, and sample size. The retrospective design of the study increases confounding prenatal variables, including blood glucose control throughout pregnancy. Another limitation was the variable length of sulfonylurea treatment in the mothers, ranging from 3 to 30 weeks, with a median of 10.5 weeks. Most mothers who were treated with sulfonylurea received prenatal care at a Federally Qualified Health Center, lived in poorer neighborhoods, and many speak exclusively Spanish. These factors may affect cognitive development and outcomes on neurodevelopmental testing.[33] Whether

the women or her provider chose the oral agent sulfonylurea over insulin for diabetes in pregnancy treatment is not known. However, we can hypothesize that these health centers may not have the resources to provide education on glucose monitoring and insulin injections as one factor leading to the choice of oral agents for treatment of diabetes in pregnancy. This health disparity requires further evaluation in a future study.

Due to the limited sample size, this study was not adequately powered to include covariates in the statistical analyses of the anthropometric measurements and performance-based tests; however, this is an important consideration for future research. Ultimately, more data are needed regarding the long-term physical and neurodevelopmental outcomes in a larger study to understand the effects of in utero sulfonylurea exposure on growth and development. This information may guide medical decision-making in the use of oral sulfonylurea medication as an alternative to insulin injections for the treatment of diabetes in pregnancy.

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CONFLICTS OF INTEREST

All authors report no potential conflicts of interest relevant to this article.

AUTHOR CONTRIBUTIONS

Marissa S. Rodenstein contributed to study design and implementation, drafting of the IRB protocol, data acquisition, analysis, and interpretation, and drafting of the manuscript. Monica E. Bianco contributed to study design, drafting of the IRB protocol, data collection, and editing of manuscript. Maegan U. Ramchal performed the NDH data collection. Michael Murias conducted the NDH assessment. Rebecca L. Silton contributed to the study design, NDH data collection, analysis and interpretation of NDH data, and drafting of the manuscript. Jami L. Josefson designed the study, obtained funding, directed the study, and contributed to data acquisition, analysis, interpretation, and drafting of the manuscript. All authors gave final approval for submission.

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