Associations of Gestational Glucose Tolerance With Offspring Body Composition and Estimated Insulin Resistance in Early Adolescence

Véronique Gingras,[1] *Sheryl L. Rifas-Shiman,*[1] *Ivonne P.M. Derks,*[1,2] *Izzuddin M. Aris,*[1,3,4] *Emily Oken,*[1,5] *and Marie-France Hivert*[1,6]

Diabetes Care 2018;41:e164–e166 | https://doi.org/10.2337/dc18-1490

Although studies suggest that hyperglycemia during pregnancy is associated with offspring adiposity (1) and an increased risk of type 2 diabetes (2), the latter outcome has been investigated in a small number of studies and in atypical populations. Furthermore, it remains unclear whether the association between gestational diabetes mellitus (GDM) and child's adiposity is independent of parental weight status (1). We aimed to examine the associations of maternal gestational glucose tolerance with adiposity and estimated insulin resistance (IR) in early adolescence. We hypothesized that previously reported sex-specific associations of gestational glucose tolerance with mid-childhood adiposity would persist in early adolescence.

We studied participants from the Project Viva cohort (initial cohort $N = 2{,}128$ mother-child pairs; NCT02820402; www.hms.harvard.edu/viva/) (3). The study was approved by the institutional review board of Harvard Pilgrim Health Care, and participants provided written informed consent. We included in this analysis 880 mother-child pairs, without pregestational diabetes, with available exposure and covariates, and with at least one outcome in early adolescence.

We assessed gestational glucose tolerance using a nonfasting 50-g 1-h glucose challenge test (GCT) followed, if abnormal, by a 100-g 3-h oral glucose tolerance test (OGTT) (4). Glucose tolerance categories included normal glucose tolerance (NGT) (normal GCT: 83%), isolated hyperglycemia (IH) (abnormal GCT, normal OGTT: 9%), gestational impaired glucose tolerance (GIGT) (one abnormal OGTT value: 3%), and GDM (≥2 abnormal OGTT values: 5%).

We measured each child's height and weight (from which we derived age- and sex-specific BMI *z* scores), waist circumference, and subscapular and triceps skinfold thicknesses using standardized techniques (3,4). We estimated fat mass with whole-body dual X-ray absorptiometry (DXA) scans. We used fasting insulin and glucose measurements to estimate IR with HOMA-IR (5).

We used sex-stratified multivariable linear regression models to examine associations of gestational glucose tolerance with outcomes in early adolescence, adjusting for maternal and child sociodemographic characteristics (as listed in Table 1, model 1), and subsequently for prepregnancy BMI and paternal BMI (model 2). We decided a priori to conduct analyses separately for boys and girls because of our previous observations showing sex-specific associations in mid-childhood in this cohort (4).

Mothers included in this study were 32.8 ± 4.6 years old (mean ± SD), 73% were white, 65% had annual household income >70,000 USD, 75% were college graduates, 91% did not smoke during pregnancy, and prepregnancy BMI was 24.7 ± 5.1 kg/m^2. In early adolescence (13.2 ± 0.9 years old), children (50% male) had a BMI *z* score of 0.37 ± 1.0 and whole-body fat percentage of 28.7 ± 7.4%.

Compared with NGT, female offspring of mothers with IH had higher sum of skinfolds, DXA whole-body fat percentage, fat mass index, and truncal fat mass (Table 1, model 1). Additional adjustments for parental BMI attenuated the effect estimates by 38–54% with all CIs overlapping the null (model 2). We did not find significant associations for HOMA-IR. In male offspring, we did not observe significant associations with adiposity or glycemic indices before or after adjustments for sociodemographic characteristics and parental BMI (Table 1). We performed sensitivity analyses additionally adjusting for first trimester or total

[1]*Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*
[2]*Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, the Netherlands*
[3]*Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore*
[4]*Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore, Singapore*
[5]*Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA*
[6]*Diabetes Unit, Massachusetts General Hospital, Boston, MA*

Corresponding author: Véronique Gingras, veronique_gingras@harvardpilgrim.org.

Received 11 July 2018 and accepted 24 September 2018.

Table 1—Adjusted* linear regression coefficients for associations of glucose tolerance status during pregnancy and offspring's overall and central adiposity as well as glycemic indices at early adolescence

	Male offspring		Female offspring	
	Model 1	Model 2	Model 1	Model 2
Overall adiposity				
BMI, *z* score	(*N* = 439)		(*N* = 441)	
NGT	Ref	Ref	Ref	Ref
IH	0.20 (−0.18, 0.57)	0.09 (−0.25, 0.44)	0.30 (−0.00, 0.60)	0.14 (−0.13, 0.41)
GIGT	−0.17 (−0.67, 0.32)	−0.26 (−0.72, 0.20)	0.26 (−0.37, 0.90)	0.25 (−0.32, 0.81)
GDM	0.08 (−0.37, 0.53)	−0.12 (−0.54, 0.30)	0.50 (0.04, 0.96)	0.12 (−0.29, 0.54)
Sum of skinfolds, mm	(*N* = 438)		(*N* = 440)	
NGT	Ref	Ref	Ref	Ref
IH	0.49 (−4.42, 5.40)	−0.88 (−5.42, 3.66)	4.84 (1.06, 8.63)	3.00 (−0.38, 6.39)
GIGT	−0.93 (−7.41, 5.55)	−2.17 (−8.15, 3.80)	1.98 (−5.96, 9.91)	1.96 (−5.12, 9.04)
GDM	2.71 (−3.20, 8.61)	−0.11 (−5.63, 5.41)	0.59 (−5.12, 6.31)	−3.74 (−8.93, 1.45)
DXA whole-body fat, %	(*N* = 301)		(*N* = 322)	
NGT	Ref	Ref	Ref	Ref
IH	0.29 (−3.32, 3.89)	0.28 (−3.08, 3.65)	3.39 (1.27, 5.51)	1.92 (−0.01, 3.83)
GIGT	0.26 (−4.17, 4.70)	−0.56 (−4.71, 3.58)	1.65 (−3.80, 7.09)	1.92 (−2.94, 6.78)
GDM	2.39 (−1.87, 6.66)	0.14 (−3.95, 4.22)	1.37 (−2.11, 4.85)	−1.10 (−4.29, 2.09)
DXA fat mass index, kg/m^2	(*N* = 301)		(*N* = 322)	
NGT	Ref	Ref	Ref	Ref
IH	−0.19 (−1.60, 1.21)	−0.19 (−1.48, 1.09)	1.38 (0.44, 2.31)	0.63 (−0.17, 1.44)
GIGT	−0.07 (−1.80, 1.66)	−0.43 (−2.01, 1.16)	0.26 (−2.13, 2.66)	0.37 (−1.67, 2.41)
GDM	1.27 (−0.39, 2.94)	0.27 (−1.29, 1.84)	0.61 (−0.92, 2.14)	−0.76 (−2.09, 0.58)
Central adiposity				
Waist circumference, cm	(*N* = 439)		(*N* = 441)	
NGT	Ref	Ref	Ref	Ref
IH	1.58 (−2.75, 5.91)	0.39 (−3.64, 4.42)	3.02 (−0.15, 6.20)	1.35 (−1.42, 4.12)
GIGT	0.24 (−5.48, 5.95)	−0.81 (−6.11, 4.50)	1.76 (−4.89, 8.41)	1.58 (−4.21, 7.37)
GDM	2.71 (−2.50, 7.91)	0.43 (−4.47, 5.33)	2.38 (−2.41, 7.18)	−1.77 (−6.01, 2.48)
DXA truncal fat mass, kg	(*N* = 301)		(*N* = 322)	
NGT	Ref	Ref	Ref	Ref
IH	−0.22 (−1.99, 1.55)	−0.22 (−1.85, 1.40)	1.70 (0.53, 2.88)	0.78 (−0.24, 1.80)
GIGT	0.06 (−2.11, 2.24)	−0.37 (−2.38, 1.63)	0.32 (−2.70, 3.34)	0.45 (−2.13, 3.03)
GDM	1.20 (−0.89, 3.30)	−0.07 (−2.04, 1.90)	1.01 (−0.93, 2.94)	−0.72 (−2.41, 0.97)
DXA truncal to peripheral fat ratio	(*N* = 301)		(*N* = 322)	
NGT	Ref	Ref	Ref	Ref
IH	0.00 (−0.04, 0.05)	0.00 (−0.04, 0.05)	0.05 (0.01, 0.09)	0.03 (−0.01, 0.07)
GIGT	−0.02 (−0.08, 0.04)	−0.03 (−0.08, 0.03)	0.00 (−0.10, 0.10)	0.00 (−0.09, 0.10)
GDM	0.02 (−0.03, 0.08)	0.00 (−0.06, 0.05)	0.04 (−0.02, 0.11)	0.00 (−0.06, 0.07)
Skinfold ratio (SS:TR)	(*N* = 438)		(*N* = 440)	
NGT	Ref	Ref	Ref	Ref
IH	−0.05 (−0.13, 0.04)	−0.06 (−0.14, 0.02)	0.04 (−0.02, 0.11)	0.03 (−0.04, 0.09)
GIGT	0.01 (−0.10, 0.12)	−0.00 (−0.11, 0.11)	0.02 (−0.11, 0.15)	0.02 (−0.11, 0.15)
GDM	0.01 (−0.09, 0.11)	−0.03 (−0.13, 0.07)	−0.00 (−0.10, 0.09)	−0.04 (−0.13, 0.06)
Glycemic indices				
Fasting glucose, mg/dL	(*N* = 263)		(*N* = 240)	
NGT	Ref	Ref	Ref	Ref
IH	−3.8 (−12.3, 4.8)	−3.9 (−12.5, 4.7)	1.5 (−2.8, 5.8)	0.7 (−3.6, 5.0)
GIGT	−4.6 (−17.4, 8.2)	−4.6 (−17.5, 8.2)	−5.9 (−14.1, 3.3)	−5.9 (−15.0, 3.2)
GDM	−0.2 (−11.5, 11.1)	−0.7 (−12.3, 10.9)	−7.2 (−14.8, 0.5)	−9.6 (−17.3, −1.9)
Fasting insulin, μU/mL	(*N* = 263)		(*N* = 240)	
NGT	Ref	Ref	Ref	Ref
IH	14.9 (−13.5, 52.7)	12.6 (−14.8, 48.8)	9.5 (−11.6, 35.6)	7.0 (−13.4, 32.3)
GIGT	1.9 (−33.4, 56.1)	2.0 (−32.8, 54.8)	15.4 (−27.0, 82.4)	16.9 (−25.5, 83.3)
GDM	23.9 (−14.9, 80.4)	13.1 (−22.4, 65.0)	−7.2 (−36.4, 35.5)	−17.9 (−43.9, 20.2)
HOMA-IR	(*N* = 263)		(*N* = 240)	
NGT	Ref	Ref	Ref	Ref
IH	11.5 (−16.1, 48.2)	9.2 (−17.3, 44.2)	11.7 (−10.2, 38.9)	8.4 (−12.5, 34.3)
GIGT	0.0 (−34.7, 53.2)	0.0 (−34.1, 51.7)	8.8 (−31.8, 73.7)	10.3 (−30.1, 74.1)
GDM	26.2 (−13.4, 83.9)	14.9 (−21.2, 67.6)	−13.5 (−41.2, 27.2)	−25.3 (−49.2, 10.0)

Data are β (95% CI) except for fasting insulin and HOMA-IR, which are expressed as % difference (95% CI). SS, subscapular; TR, triceps. *Model 1: adjusted for age at early adolescence visit, maternal age, race/ethnicity, education, parity, smoking during pregnancy, marital status, household income, and paternal history of type 1 or type 2 diabetes (for glycemic indices only); model 2: model 1 additionally adjusted for paternal BMI and maternal prepregnancy BMI.

gestational weight gain and found similar results, whereas adjusting for puberty slightly strengthened the associations in female offspring from IH mothers.

Our study had the following limitations. We could not account for the level of glycemic control or the type of GDM treatment, and we did not assess whether some women without GDM received nutritional/lifestyle counseling during pregnancy. Despite the considerable number of participants included, we were limited by our relatively small sample in IH/GIGT/GDM groups and by the fact that our sample was mostly white, with a generally high socioeconomic status, limiting generalizability. Finally, variability in child glycemic indices was relatively low, possibly due to participant age at examination.

In this prospective longitudinal prebirth cohort, we did not observe independent associations of abnormal gestational glucose tolerance with adiposity and IR in early adolescence. Some of the effect estimates in early adolescence were similar in size and direction with respective outcomes measured in mid-childhood (4), but CIs of our associations with outcomes measured at early adolescence were larger and overlapping with the null. The large variability in adiposity and IR changes associated with the transition to adolescence and puberty could explain the lack of associations. GDM treatment may also have attenuated the associations. Longer follow-up will help reveal whether associations of abnormal glucose tolerance in pregnancy with offspring adiposity and IR are observable after the adolescent hormonal transition.

Acknowledgments. The authors are very grateful to the participants and staff of Project Viva.
Funding. This work was supported by grants from the U.S. National Institutes of Health (R01 HD034568, UG3 OD023286).
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. V.G. and M.-F.H. designed the analysis. V.G. analyzed and interpreted the data and drafted the manuscript. S.L.R.-S. provided guidance on statistical analysis. S.L.R.-S., I.P.M.D., I.M.A., E.O., and M.-F.H. provided critical intellectual contributions and read and approved the final manuscript. V.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Philipps LH, Santhakumaran S, Gale C, et al. The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. Diabetologia 2011;54:1957–1966
2. Tam WH, Ma RCW, Ozaki R, et al. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. Diabetes Care 2017;40:679–686
3. Oken E, Baccarelli AA, Gold DR, et al. Cohort profile: Project Viva. Int J Epidemiol 2015;44:37–48
4. Regnault N, Gillman MW, Rifas-Shiman SL, Eggleston E, Oken E. Sex-specific associations of gestational glucose tolerance with childhood body composition. Diabetes Care 2013;36:3045–3053
5. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419