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

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/m². 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 adjustment for sociodemographic characteristics and parental BMI (Table 1). We performed sensitivity analyses additionally adjusting for first trimester or total...
### 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     |                |          |                  |          |
| NGT              | 0.20 (0.18, 0.57) | Ref     | 0.09 (0.25, 0.44) | Ref     |
| GIGT             | -0.17 (-0.67, 0.32) | Ref     | -0.26 (-0.72, 0.20) | Ref     |
| GDM              | 0.08 (-0.37, 0.53) |          | 0.12 (-0.54, 0.30) |          |
| Sum of skinfolds, mm | Ref          |          | 4.84 (1.06, 8.63) | Ref     |
| NGT              | 0.49 (-4.42, 5.40) | Ref     | -0.88 (-5.42, 3.66) | Ref     |
| GIGT             | -0.93 (-7.41, 5.55) |          | -2.17 (-8.15, 3.80) |          |
| GDM              | 2.71 (-3.20, 8.61) |          | -0.11 (-5.63, 5.41) |          |
| DXA whole-body fat, % | Ref          |          | 3.39 (1.27, 5.51) | Ref     |
| NGT              | 0.29 (-3.32, 3.89) | Ref     | -0.28 (-3.08, 3.65) | Ref     |
| GIGT             | 0.26 (-4.17, 4.70) |          | -0.56 (-4.71, 3.58) |          |
| GDM              | 2.39 (-1.87, 6.66) |          | 0.14 (-3.95, 4.22) |          |
| DXA fat mass index, kg/m² | Ref          |          | 1.37 (-2.11, 4.85) | Ref     |
| NGT              | -0.19 (-1.60, 1.21) | Ref     | -0.19 (-1.48, 1.09) | Ref     |
| GIGT             | -0.07 (-1.80, 1.66) |          | -0.43 (-2.01, 1.16) |          |
| GDM              | 1.27 (-0.39, 2.94) |          | 0.27 (-1.29, 1.84) |          |
| Central adiposity|                |          |                  |          |
| Waist circumference, cm | Ref         |          | 1.70 (0.53, 2.88) | Ref     |
| NGT              | 1.58 (-2.75, 5.91) | Ref     | 0.39 (-3.64, 4.42) | Ref     |
| GIGT             | 0.24 (-5.48, 5.95) |          | -0.81 (-6.11, 4.50) |          |
| GDM              | 2.71 (-2.50, 7.91) |          | 0.43 (-4.47, 5.33) |          |
| DXA truncal fat mass, kg | Ref         |          | 2.38 (-2.41, 7.18) | Ref     |
| NGT              | -0.22 (-1.99, 1.55) | Ref     | -0.22 (-1.85, 1.40) | Ref     |
| GIGT             | 0.06 (-2.11, 2.24) |          | -0.37 (-2.38, 1.63) |          |
| GDM              | 1.20 (-0.89, 3.30) |          | -0.07 (-2.04, 1.90) |          |
| DXA truncal to peripheral fat ratio | Ref       |          | 1.01 (-0.93, 2.94) | Ref     |
| NGT              | 0.00 (-0.04, 0.05) | Ref     | 0.00 (-0.04, 0.05) | Ref     |
| GIGT             | -0.02 (-0.08, 0.04) |          | -0.03 (-0.08, 0.03) |          |
| GDM              | 0.02 (-0.03, 0.08) |          | 0.00 (-0.06, 0.05) |          |
| Skinfold ratio (SS:TR) | Ref        |          | 0.04 (-0.02, 0.11) | Ref     |
| NGT              | -0.05 (-0.13, 0.04) | Ref     | -0.06 (-0.14, 0.02) | Ref     |
| GIGT             | 0.01 (-0.10, 0.12) |          | -0.00 (-0.11, 0.11) |          |
| GDM              | 0.01 (-0.09, 0.11) |          | -0.03 (-0.13, 0.07) |          |
| Glycemic indices |                |          |                  |          |
| Fasting glucose, mg/dL | Ref       |          | 1.5 (-2.8, 5.8) | Ref     |
| NGT              | -3.8 (-12.3, 4.8) | Ref     | -3.9 (-12.5, 4.7) | Ref     |
| GIGT             | -4.6 (-17.4, 8.2) |          | -4.6 (-17.5, 8.2) |          |
| GDM              | -0.2 (-11.5, 11.1) |          | -0.7 (-12.3, 10.9) |          |
| Fasting insulin, μU/mL | Ref       |          | 9.5 (-11.6, 35.6) | Ref     |
| NGT              | 14.9 (-13.5, 52.7) | Ref     | 12.6 (-14.8, 48.8) | Ref     |
| GIGT             | 1.9 (-33.4, 56.1) |          | 2.0 (-32.8, 54.8) |          |
| GDM              | 23.9 (-14.9, 80.4) |          | 13.1 (-22.4, 65.0) |          |
| HOMA-IR           |               |          | 7.2 (-36.4, 35.5) |          |
| NGT              | 11.5 (-16.1, 48.2) | Ref     | 9.2 (-17.3, 44.2) | Ref     |
| GIGT             | 0.0 (-34.7, 53.3) |          | 0.0 (-34.1, 51.7) |          |
| GDM              | 26.2 (-13.4, 83.9) |          | 14.9 (-21.2, 67.6) |          |

Data are β (95% CI) except for fasting insulin and HOMA-IR, which are expressed as % difference (95% CI). SS, subcapsular; 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 pre-birth 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 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.

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