Sex-Specific Associations of Gestational Glucose Tolerance With Childhood Body Composition

Nolwenn Regnault, phd, mph
Matthew W. Gillman, md, sm
Sheryl L. Rifas-Shiman, mph

Emma Eggleston, md, mph
Emily Oken, md, mph

OBJECTIVE—To examine the associations of maternal gestational glucose tolerance with offspring body composition in late childhood.

RESEARCH DESIGN AND METHODS—Among 958 women in the prebirth cohort Project Viva, glucose tolerance was assessed in the second trimester by nonfasting 50-g 1-h glucose challenge test (GCT), followed if abnormal by fasting 100-g 3-h oral glucose tolerance test (OGTT). We categorized women as normoglycemic (83.3%) if GCT was ≤140 mg/dL, isolated hyperglycemia (9.1%) if GCT was abnormal but OGTT normal, intermediate glucose intolerance (IGI) (3.3%) if there was one abnormal value on OGTT, or gestational diabetes mellitus (GDM) (4.5%) if there were two or more abnormal OGTT values. Using multivariable linear regression, we examined adjusted associations of glucose tolerance with offspring overall (N = 958) and central (N = 760) adiposity and body composition using dual X-ray absorptiometry (DXA) measured at the school-age visit (95 ± 10 months).

RESULTS—Compared with that in the male offspring of normoglycemic mothers, DXA fat mass was higher in male offspring of GDM mothers (1.89 kg [95% CI 0.33–3.45]) but not in male offspring of mothers with IGI (0.06 kg [−1.45 to 1.57]). DXA trunk-to-peripheral fat mass, a measure of central adiposity, was also somewhat higher in male offspring of GDM mothers (0.04 [−0.01 to 0.09]). In girls, DXA fat mass was higher in offspring of mothers with IGI (2.23 kg [0.12–4.34]) but not GDM (−1.25 kg [−3.13 to 0.63]). We showed no association of gestational glucose tolerance with DXA lean mass.

CONCLUSIONS—In this study, only male offspring of GDM mothers manifested increased adiposity, whereas only female offspring of mothers with IGI did so. Sex differences in glycemic sensitivity may explain these findings.

Diabetes Care 36:3045–3053, 2013

The prevalence of gestational diabetes mellitus (GDM) has increased during the past 20 years, alongside obesity and type 2 diabetes (1). Heavier mothers are more likely to exhibit hyperglycemia during pregnancy than are normal-weight mothers. Because GDM is associated with both higher birth weight and increased fetal adiposity (2) and because birth weight is directly associated with later obesity, it has been postulated that hyperglycemic intrauterine environment may program the fetus via metabolic changes in the child (3,4).

Two recent meta-analyses concluded that the evidence for an association between preexisting diabetes or GDM and offspring overweight and obesity in childhood is inconsistent (5,6). One reason is that many studies did not adjust for maternal prepregnancy adiposity, which itself is a major determinant of both GDM and offspring adiposity. In their review, Philipps et al. (5) reported that in offspring of mothers with diabetes (all types of diabetes combined vs. no diabetes), the unadjusted mean BMI z score was 0.28 higher (95% CI 0.09–0.47) but that the z score was only 0.07 higher (−0.15 to 0.28) after adjustment for maternal prepregnancy BMI.

Another reason for inconsistency is that many studies used BMI or other weight and height measures for the childhood outcome instead of more direct and accurate measures of adiposity or fat distribution. Indeed, we previously reported that 3-year-old children of mothers with GDM had greater adiposity than normoglycemic mothers when it was assessed by the sum of skinfold thicknesses but not by BMI (7). Two studies reported results of the association of GDM exposure with body composition measured by dual X-ray absorptiometry (DXA) or magnetic resonance imaging in school-aged children. Chandler-Laney et al. (8) showed that maternal glucose concentration during pregnancy was positively associated with both fat and lean mass as measured by DXA in children aged 5–10 years (8). However, these results were not adjusted for maternal BMI. Crume et al. (9) reported that exposure to maternal GDM was associated with more subcutaneous abdominal fat (+ 34.7 cm², P = 0.01) as measured by magnetic resonance imaging in children aged 6–13 years, but adjustment for maternal prepregnancy BMI substantially attenuated the association (+ 22.4 cm², P = 0.10).

Another important consideration is that the association of GDM exposure with offspring adiposity or weight seems to be transient (10,11). For example, Silverman et al. (12) showed that offspring of mothers with diabetes were larger than a reference population at birth and again at school age but not as toddlers. Discrepancies in the literature could to some extent be explained by differences in the age at which the outcome was measured.

Finally, while an increasing number of studies suggest that intrauterine programming may differ by sex (13), few studies have explored sex differences in

the associations of GDM with offspring adiposity in childhood (14,15).

Our aim was to fill these research gaps by examining associations of maternal gestational glucose tolerance with several measures of childhood adiposity at the school-age visit, before and after adjustment for maternal prepregnancy BMI, and according to sex of the child.

RESEARCH DESIGN AND METHODS—Project Viva is an ongoing prospective prebirth cohort study in which we recruited pregnant women at their initial prenatal visit from Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts, between April 1999 and July 2002. All mothers gave informed consent, and institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethics standards established by the Declaration of Helsinki (16).

Of the 2,128 mothers with a live birth in Project Viva, excluded were those with missing or incomplete records on glucose tolerance testing (n = 47), those with a history of previous type 1 (n = 9) or type 2 (n = 7) diabetes and polycystic ovarian syndrome with glucose intolerance (n = 2), and 29 pregnancies with gestation <34 weeks. We followed the children with in-person visits just after delivery and at 6 months, 3 years, and 7 years of age and with annual mailed questionnaires at other ages. Of the 1,709 eligible for the school-age visit, 1,116 agreed to participate in an in-person visit. Anthropometry could be measured in 1,070, but not all participants accepted to undergo DXA. Our final sample included 958 children with data on maternal glucose tolerance during pregnancy, anthropometry measured at the school-age visit, and relevant covariates. A subsample of 760 of these 958 children had body composition measures with DXA.

Compared with the mothers who were not included in this analysis (n = 1,170), included mothers (n = 958) were more likely to be older (32.3 vs. 31.4 years at enrollment), white (69.7 vs. 62.5%), college graduates (70.0 vs. 60.1%), and nonsmokers (90.3 vs. 84.3%) and have household income >$70,000/year (74.6 vs. 65.3%). However, they did not differ substantially in terms of mean maternal prepregnancy BMI (24.9 vs. 25.2 kg/m^2), gestational weight gain (15.4 vs. 15.6 kg) or gestational glucose tolerance status (normoglycemic: 83.1 vs. 82.2%).

Father's BMI was similar in the included and excluded groups (26.4 kg/m^2). Children included in the analysis had slightly higher birth weight for gestational age z score than those who were not included (0.21 vs. 0.14).

Measures
Exposures: gestational glucose tolerance. Obstetric clinicians routinely screened all women for GDM at 26–28 weeks of gestation with a nonfasting oral glucose challenge test (GCT), in which venous blood was sampled 1 h after a 50-g oral glucose load. If the blood glucose exceeded 140 mg/dL, the clinician referred the woman for a fasting 3-h 100-g oral glucose tolerance test (OGTT). Abnormal OGTT results were a blood glucose >95 mg/dL at baseline, >180 mg/dL at 1 h, >155 mg/dL at 2 h, or >140 mg/dL at 3 h (17). We categorized women with two or more abnormal values on the OGTT as having GDM; those with one abnormal value on the OGTT as having an intermediate glucose intolerance (IGI) previously called impaired glucose tolerance (7); those with an abnormal GCT but a normal OGTT as having isolated hyperglycemia (IH); and the remaining women as having normal glucose tolerance. Those who were diagnosed with GDM were typically followed by a nutritionist, instructed to check their fasting blood glucose daily, and treated with diet and in some cases insulin (7). Mothers with IGI or IH did not have any further screening and were managed in the same way as women with normal GCT results.
Outcomes: child overall adiposity, fat, and lean mass. During the in-person school-age visit, trained research assistants measured children's weights (TBF-300A; Tanita, Arlington Heights, IL) and heights (calibrated stadiometer; Shorr Productions, Olney, MD). We calculated age- and sex-specific BMI percentiles and z scores using U.S. national reference data (18). The research staff measured subscapular (SS) and triceps (TR) skinfold thicknesses using Holtain calipers (Holtain, Crosswell, U.K.) and calculated the sum (SS+TR) and the ratio (SS/TR) of skinfolds. BMI z score and SS+TR represent overall adiposity, whereas SS/TR is a measure of central or truncal adiposity (19). To measure waist circumference, we used the method used in the National Health and Nutrition Examination Survey (NHANES) (20). For each measurement, the measuring tape was positioned

parallel to the floor with the participant standing—abdomen relaxed, arms at the sides, and feet together—and facing the observer with the waist exposed (21). We measured waist circumference just above the right iliac crest at the midaxillary line to the nearest 0.1 cm using a Hoechstmass measuring tape (Hoechstmass Balzer, Sulzbach, Germany). Research assistants followed standardized techniques and participated in biannual in-service training to ensure measurement validity (IJ Shorr; Shorr Productions) (22). Inter- and intrarater errors for skinfold measurements were within published reference ranges for all measurements (23).

Trained research assistants administered whole-body DXA scans with Hologic model Discovery A (Hologic, Bedford, MA) that they checked for quality control on visit days. We used Hologic software version 12.6 for scan analysis. A single trained research assistant checked all scans for positioning, movement, and artifacts and defined body regions for analysis. Intrarater reliability was high (r = 0.99). We calculated the DXA fat mass and fat-free mass indexes using the following formula: [total DXA fat mass (or fat free mass) in kg]/(height in meters)^2 (24). We also calculated the DXA trunk to peripheral fat mass ratio, a measure of central adiposity (25,26).
Covariates. During pregnancy and in late childhood, using a combination of questionnaires and interviews, we obtained information about maternal age, race/ethnicity, education, parity, smoking during pregnancy, marital status, and household income. We collected information from prenatal medical records on serial pregnancy weights and blood pressure readings and infant birth weight and delivery date. Mothers reported their prepregnancy weight and height and the paternal weight and height. We calculated gestational weight gain as the difference between prepregnancy weight and the last clinically recorded weight before delivery. We derived gestational age from the last menstrual period or from the second trimester ultrasound if the two estimates differed by >10 days. Based on U.S. national natality data, we determined sex-specific birth weight for gestational age z scores (27).

At the school-age visit, mothers reported—separately for weekdays and weekend days—the number of hours per day that the children participated in light, moderate, and vigorous physical

activities; watched television or other electronic screen media; and slept. Mothers also reported the frequency of children's consumption of sugar-sweetened beverages, fast food, and fried foods.

Statistical analysis

We report age-, race/ethnicity, and sex-adjusted means for child body composition and behaviors reported at the school-age visit. Using multivariable linear regression, we built models based on bivariate associations and on our expectation of which variables would independently predict the outcomes as demonstrated by prior studies (8,9,28,29). Our basic model was adjusted for child age at examination (model 1) and subsequently adjusted for maternal prepregnancy BMI (model 2), gestational weight gain and paternal BMI (model 3), and maternal race/ethnicity, age, education, and parity and smoking during pregnancy, marital status, and household income (model 4: final model). When the outcome was a measurement of central adiposity, we additionally adjusted for child BMI because we were interested in fat distribution after controlling for overall body size. We further adjusted for birth weight for gestational age z score to assess whether it might be in the pathway linking gestational glucose tolerance with child adiposity (model 5).

Within the multivariable modeling context, we tested the interaction of gestational glucose tolerance and child sex on child body composition. Because we found evidence of an interaction of maternal gestational glucose tolerance with child sex on overall adiposity measured by DXA total fat mass, DXA fat mass index, and SS+TR (all P for interaction ≤0.04) and with BMI, albeit less so (P for interaction = 0.14), we present all the adiposity results separately according to child sex. We did not detect an interaction of gestational glucose tolerance and child sex on DXA fat-free mass (P for interaction = 0.85) or fat-free mass index (P for interaction = 0.48), so we present sex-adjusted results for fat-free mass with boys and girls combined (Supplementary Table 1). We performed all the analyses using SAS version 9.3 (Cary, NC).

RESULTS—Our sample included 43 (4.5%) mothers with GDM, 32 (3.3%) with IGI, 87 (9.1%) with IH, and 796 (83.1%) with normal glucose tolerance in mid-pregnancy (Table 1). Compared with normoglycemic mothers, those with an abnormal gestational glucose tolerance (GDM, IGI, or IH) were older and had higher prepregnancy BMI and lower pregnancy weight gain (Table 1). Mothers with GDM or IGI were more frequently black or Hispanic and more frequently smokers during pregnancy. Offspring of mothers with GDM, IGI, or IH all tended to have a higher birth weight and birth weight for gestational age z score and a lower gestational age compared with the offspring of normoglycemic mothers (Table 1).

At the school-age visit, mean (SD) age was 95 (10) months and mean BMI was 17.1 (2.8) kg/m^2 in boys and 17.2 (3) kg/m^2 in girls ($P = 0.56$). DXA fat mass and percentage fat mass were 6.6 (3.5) kg and 22.2% (5.7), respectively, in boys and 8.0 (3.7) kg and 26.8% (5.8) in girls ($P < 0.0001$). DXA trunk-to-peripheral fat mass ratio was lower in boys than in girls (0.57 [0.10] vs. 0.59 [0.10], $P = 0.04$) In boys and girls combined, mean weight or BMI, adjusted for age at examination, sex, and maternal race/ethnicity, did not greatly differ across the categories of gestational glucose tolerance (Table 1). However, offspring of mothers with IGI or GDM had a higher overall adiposity as measured by SS+TR and DXA (DXA percent fat mass: norm, 24.3%; IGI, 26.3%; and GDM, 26.4%). They also had a larger waist circumference (norm, 59.8 cm; IGI, 61.4 cm; and GDM, 61.9 cm) and more trunk fat (norm, 2.5 kg; IGI, 2.9 kg; and GDM, 3.2 kg). Other indicators of overall and central adiposity showed similar trends. Offspring of normoglycemic, IGI, and GDM mothers had similar fat-free mass. Child physical activity and intake of sugar-sweetened beverages and fried food did not materially differ according to maternal gestational glucose tolerance status (Table 1).

Table 2 presents the associations of gestational glucose tolerance with overall and central adiposity measured by DXA, according to child sex. Among boys, unadjusted analyses (model 1) showed that offspring of GDM mothers had a higher total fat mass (2.57 kg [95% CI 0.95–4.2]) and trunk-to-peripheral fat mass ratio (0.05 [0.003–0.09]) than offspring of normoglycemic mothers. Among girls, compared with offspring of normoglycemic mothers, fat mass was higher in female offspring of IGI mothers (2.57 kg [0.22–4.91]) but not among offspring of GDM mothers (−0.31 kg [−2.35 to 1.72]). In contrast to the boys, trunk-to-peripheral fat mass ratio in girls was not different for IGI or GDM (IGI 0.01 kg [−0.05 to 0.07] and GDM 0.00 kg [−0.05 to 0.05]; both vs. normoglycemic), although there was a suggestion of higher DXA trunk-to-peripheral fat mass ratio in offspring of IH mothers (0.03 [0.00–0.06]).

Additional adjustment for maternal prepregnancy BMI (Table 2 [model 2]) and other covariates (models 3 and 4) partially attenuated the associations of GDM (in boys) and IGI (in girls) with total fat mass (1.89 kg [95% CI 0.33–3.45] for GDM in boys and 2.23 [0.12–4.34] for IGI in girls) and, in boys, with trunk-to-peripheral fat mass ratio (0.04 [−0.01 to 0.09]) (Fig. 1).

Table 3 presents the adjusted estimates (model 4) of the association of gestational glucose tolerance with other measures of overall and central adiposity. Consistent with the results shown in Table 2 for the DXA trunk-to-peripheral fat mass ratio, SS/TR was higher in male offspring of GDM mothers (β = 0.34 kg/m^2 [95% CI 0.04–0.63]) (Table 3). However, we did not detect similar increases with waist circumference or DXA trunk fat mass adjusted for child BMI. In fact, it was the offspring of IGI, not GDM, mothers who showed a greater waist circumference (1.38 [0.20–2.56]).

Associations of gestational glucose tolerance with other measures of overall adiposity (SS+TR, DXA fat mass index, and BMI z score) were similar to those described for DXA total fat mass, although we did not detect an association of gestational glucose tolerance with BMI z score in boys (Table 3).

To assess potential mediation, we additionally adjusted the final model (Table 2 [model 4]) for birth weight for gestational age z score (model 5) and found no attenuation of the association of GDM with fat mass in boys (1.85 vs. 1.89 kg) or the association of IGI with fat mass in girls (2.24 vs. 2.23 kg) (Table 3).

For DXA fat-free mass, the other categories of gestational glucose tolerance did not significantly differ from offspring of normoglycemic mothers (model 1, IH 0.09 kg [95% CI −0.22 to 0.40], IGI 0.86 kg [−0.50 to 2.23], and GDM 1.0 kg [−0.31 to 2.31]). Results were similarly null for fat-free mass index (Supplementary Table 1).

CONCLUSIONS—In this cohort study of pregnant women and their children, male offspring of mothers who had

Table 1—Parental and child characteristics according to categories of gestational glucose tolerance

	N	Normoglycemic, N = 796 (83.1%)	IH, N = 87 (9.1%)	IGI, N = 32 (3.3%)	GDM, N = 43 (4.5%)	P*
Maternal and family characteristics, N (%)						
Maternal race/ethnicity (% white)	958	553 (69.5)	69 (79.3)	19 (59.4)	27 (62.8)	0.14
% black		115 (14.5)	6 (6.9)	7 (21.9)	8 (18.6)	
% Hispanic		47 (5.9)	8 (9.2)	2 (6.3)	5 (11.6)	
% other		81 (10.2)	4 (4.6)	4 (12.5)	3 (7.0)	
Mother married or cohabitating**	958	697 (87.6)	77 (88.5)	27 (84.4)	38 (88.4)	0.94
Annual household income >$70,000**	958	593 (74.5)	66 (75.9)	24 (75.0)	32 (74.4)	0.99
Mother's education ≥ college graduate	958	556 (69.9)	67 (77.0)	19 (59.4)	29 (67.4)	0.27
Smoking during pregnancy	958	76 (9.6)	4 (4.6)	5 (15.6)	8 (18.6)	0.05
Multiparity	958	410 (51.5)	45 (51.7)	19 (59.4)	22 (51.2)	0.86
Child sex (% girls)	958	403 (54.0)	51 (62.1)	10 (31.3)	20 (46.5)	0.02
Parental anthropometry						
Maternal age at enrollment (years)	958	32.1 (0.2)	33.8 (0.6)	32.8 (0.9)	33.5 (0.8)	0.009
Maternal prepregnancy BMI (kg/m^2)	958	24.7 (0.2)	25.2 (0.6)	26.0 (0.9)	28.1 (0.8)	0.0002
Gestational weight gain (kg)	958	15.7 (0.2)	14.6 (0.6)	15.3 (0.9)	12.5 (0.8)	0.0004
Paternal BMI (kg/m^2)	958	26.3 (0.1)	27.3 (0.4)	26.9 (0.7)	27.0 (0.6)	0.08
Child characteristics at birth and in infancy						
Gestational age (weeks)	958	39.7 (0.1)	39.9 (0.2)	39.8 (0.3)	39.1 (0.2)	0.03
Birth weight (kg)	955	3.5 (0.0)	3.6 (0.1)	3.7 (0.1)	3.6 (0.1)	0.08
Birth weight for gestational age (z score)	957	0.18 (0.03)	0.39 (0.10)	0.42 (0.17)	0.38 (0.15)	0.08
Weight gain between birth and 6 months (kg)	703	4.65 (0.04)	4.44 (0.12)	4.40 (0.20)	4.60 (0.18)	0.26
Child anthropometrics at the school-age visit†						
Age (months)	958	95.1 (0.4)	93.7 (1.1)	93.2 (1.8)	97.0 (1.5)	0.23
Weight (kg)	958	29.3 (0.3)	30.4 (0.7)	30.3 (1.1)	30.8 (1.0)	0.22
Weight-, age-, sex-specific z score	958	0.5 (0.0)	0.7 (0.1)	0.8 (0.2)	0.6 (0.2)	0.13
Height (cm)	958	128.8 (0.3)	129.1 (0.6)	130.8 (1.0)	130.0 (0.9)	0.15
BMI (kg/m^2)	958	17.4 (0.1)	18.0 (0.3)	17.5 (0.5)	17.9 (0.4)	0.21
BMI z score	958	0.4 (0.0)	0.7 (0.1)	0.6 (0.2)	0.5 (0.2)	0.18
Waist circumference (cm)	958	59.8 (0.4)	62.0 (0.9)	61.4 (1.3)	61.9 (1.2)	0.02
SS+TR (mm)	958	20.3 (0.4)	22.1 (1.0)	22.4 (1.6)	23.1 (1.4)	0.04
SS/TR	958	0.73 (0.01)	0.76 (0.02)	0.74 (0.03)	0.76 (0.03)	0.38
DXA total fat mass (kg)	760	7.5 (0.2)	8.2 (0.4)	8.5 (0.7)	8.8 (0.7)	0.05
DXA fat mass index (kg/m^2)	760	4.4 (0.1)	4.8 (0.2)	4.9 (0.3)	5.0 (0.3)	0.06
DXA % fat	760	24.3 (0.3)	25.6 (0.7)	26.3 (1.1)	26.4 (1.1)	0.03
DXA trunk fat mass (kg)	760	2.5 (0.1)	2.8 (0.2)	2.9 (0.3)	3.2 (0.3)	0.03
DXA peripheral fat mass (kg)	760	4.2 (0.1)	4.6 (0.2)	4.9 (0.4)	4.9 (0.4)	0.08
DXA trunk-to-peripheral fat ratio	760	0.58 (0.01)	0.60 (0.01)	0.57 (0.02)	0.62 (0.02)	0.06
DXA total fat-free mass (kg)	760	21.9 (0.2)	22.2 (0.4)	22.6 (0.7)	22.8 (0.6)	0.38
DXA fat-free mass index (kg/m^2)	760	13.1 (0.1)	13.3 (0.2)	13.1 (0.2)	13.2 (0.2)	0.84
Child behaviors at the school-age visit						
Physical activity (h/day)‡	927	1.8 (0.0)	1.7 (0.1)	1.6 (0.2)	1.8 (0.2)	0.94
Sugar-sweetened beverages (servings/day)	923	2.3 (0.1)	2.5 (0.2)	2.2 (0.3)	2.0 (0.2)	0.45
Fast food (times/week)	928	0.7 (0.0)	0.7 (0.1)	0.8 (0.1)	0.6 (0.1)	0.86
Fried food (times/week)	927	0.9 (0.0)	0.8 (0.1)	1.1 (0.2)	1.3 (0.2)	0.19
Total screen time (h/day)	912	3.4 (0.1)	3.3 (0.2)	3.6 (0.4)	3.6 (0.3)	0.88
Sleep duration (h/day)	924	9.8 (0.0)	10.0 (0.1)	10.2 (0.2)	9.7 (0.1)	0.04

Data are means (SE) unless otherwise indicated. Data from 958 mother-child pairs in Project Viva. *Global P value. **Reported at the school-age visit. †All the means that describe child anthropometrics at the school-age visit are adjusted for age at examination, race/ethnicity, and sex. ‡Physical activity includes walking, as well as light and vigorous physical activity.

GDM, but not IGI, exhibited higher overall adiposity at the school-age visit than offspring of normoglycemic mothers. However, girls of IGI, but not GDM mothers, had higher adiposity.

Although chance is one plausible explanation for this sex difference given the relatively small number of children in each stratum of exposure and outcome, another potential explanation relies on

the observation that male and female fetuses seem to have different strategies in utero. Eriksson et al. (30) hypothesized that "boys live dangerously in the womb." Indeed, male fetuses grow faster in all

Table 2—*Crude and adjusted regression coefficients (95% CI) for associations of maternal glucose tolerance with total fat mass and trunk-to-peripheral fat ratio, measured by DXA, according to child sex*

	Model 1 β	Model 1 95% CI	Model 1 P	Model 2 β	Model 2 95% CI	Model 2 P	Model 3 β	Model 3 95% CI	Model 3 P	Model 4 β	Model 4 95% CI	Model 4 P	Model 5 β	Model 5 95% CI	Model 5 P
Boys															
Overall adiposity: DXA total fat mass (kg)															
GDM	2.57	0.95–4.20	0.002	2.01	0.43–3.59	0.01	2.09	0.54–3.63	0.01	1.89	0.33–3.45	0.02	1.85	0.27–3.42	0.02
IGI	0.38	−1.21 to 1.96	0.64	0.15	−1.38 to 1.68	0.85	−0.02	−1.52 to 1.47	0.98	0.06	−1.45 to 1.57	0.94	0.04	−1.47 to 1.55	0.96
IH	−0.1	−1.40 to 1.19	0.87	0.00	−1.25 to 1.25	0.99	0.02	−1.21 to 1.24	0.98	0.01	−1.22 to 1.25	0.98	−0.01	−1.25 to 1.23	0.99
Norm	0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.	
Central adiposity: DXA trunk-to-peripheral fat ratio															
GDM	0.05	0.00–0.09	0.04	0.05	0.00–0.09	0.03	0.05	0.00–0.09	0.04	0.04	−0.01 to 0.09	0.09	0.05	0.00–0.09	0.05
IGI	−0.03	−0.08 to 0.01	0.14	−0.03	−0.08 to 0.01	0.15	−0.03	−0.07 to 0.01	0.17	−0.02	−0.07 to 0.02	0.27	−0.02	−0.07 to 0.02	0.34
IH	−0.01	−0.05 to 0.02	0.54	−0.01	−0.05 to 0.02	0.53	−0.01	−0.05 to 0.02	0.51	−0.01	−0.05 to 0.02	0.52	−0.01	−0.04 to 0.03	0.65
Norm	0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.	
Girls															
Overall adiposity: DXA total fat mass (kg)															
GDM	−0.31	−2.35 to 1.72	0.76	−1.92	−3.85 to 0.001	0.05	−1.35	−3.24 to 0.54	0.16	−1.25	−3.13 to 0.63	0.19	−1.25	−3.13 to 0.64	0.19
IGI	2.57	0.22–4.91	0.03	2.07	−0.10 to 4.24	0.06	2.23	0.12–4.21	0.05	2.23	0.12–4.34	0.04	2.24	0.13–4.34	0.04
IH	1.06	−0.03 to 2.14	0.06	0.69	−0.31 to 1.70	0.18	0.64	−0.34 to 1.62	0.20	0.64	−0.34 to 1.61	0.20	0.64	−0.33 to 1.62	0.20
Norm	0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.	
Central adiposity: DXA trunk-to-peripheral fat ratio															
GDM	0.00	−0.05 to 0.05	0.98	0.01	−0.04 to 0.07	0.60	0.02	−0.04 to 0.07	0.58	−0.01	−0.06 to 0.05	0.84	−0.01	−0.06 to 0.05	0.84
IGI	0.01	−0.05 to 0.07	0.78	0.01	−0.05 to 0.07	0.75	0.01	−0.05 to 0.07	0.73	−0.01	−0.07 to 0.05	0.65	−0.01	−0.07 to 0.05	0.66
IH	0.03	0.00–0.06	0.03	0.03	0.00–0.06	0.02	0.03	0.01–0.06	0.02	0.03	0.00–0.06	0.05	0.03	0.00–0.06	0.04
Norm	0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.		0.0	ref.	

Data from 366 boys and 394 girls and their mothers in Project Viva. Model 1: adjusted for child age at examination. Model 2: model 1 adjustments plus maternal prepregnancy BMI. Model 3: model 2 adjustments plus maternal gestational weight gain and paternal BMI. Model 4: model 3 adjustments plus maternal race/ethnicity, age, education, parity, smoking during pregnancy, marital status, and household income. Model 5: model 4 adjustments plus birth weight for gestational age z score. All of the models with trunk-to-peripheral fat ratio were additionally adjusted for child BMI, but adjustment for other measures of overall adiposity yielded the same results. Norm, normoglycemic.
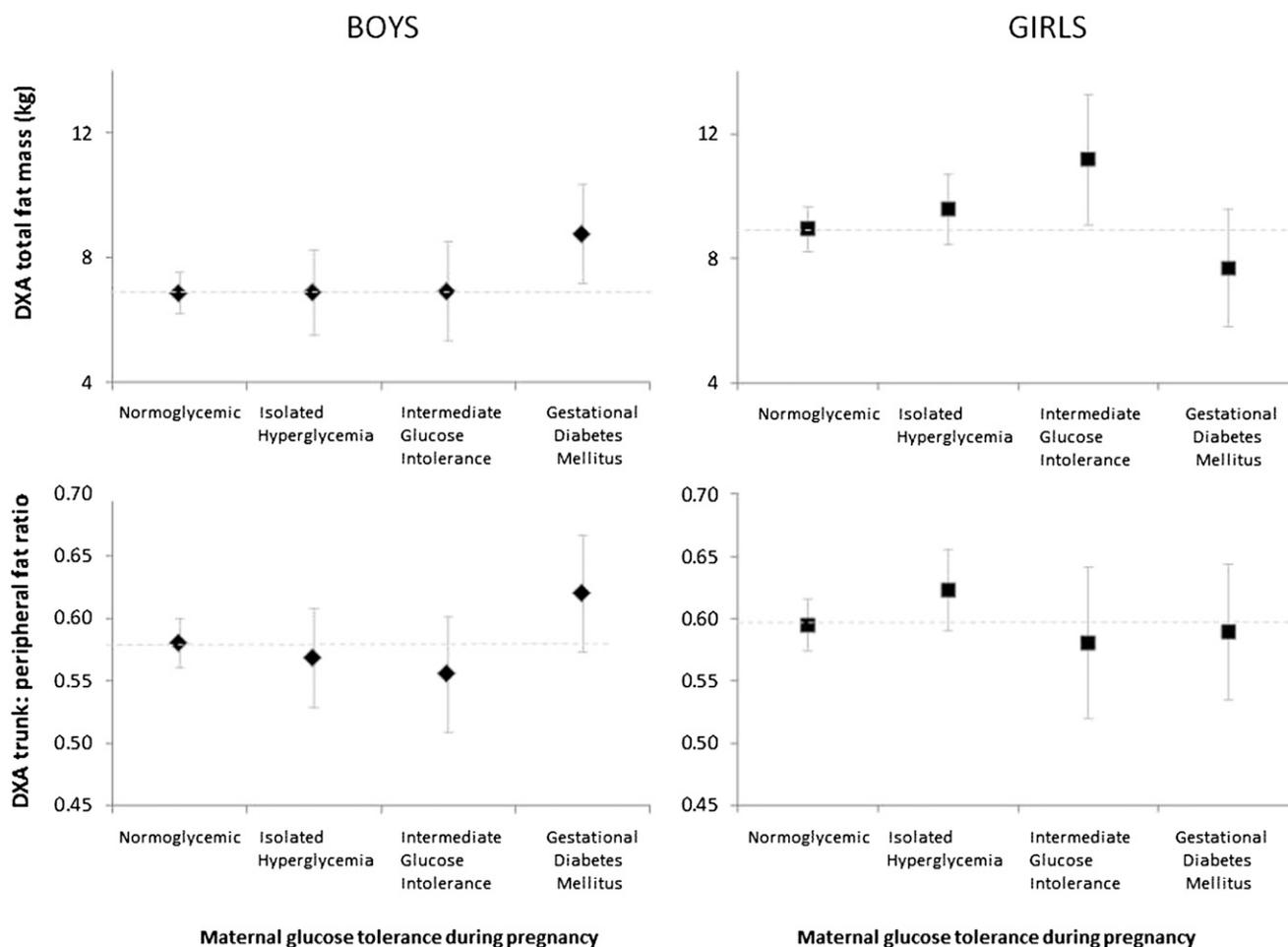
Figure 1—*Adjusted means (95% CI) of total fat and trunk-to-peripheral fat ratio, by DXA, according to maternal glucose tolerance and child sex. Data from 366 boys and 394 girls and their mothers in Project Viva. Adjusted for child age at examination, maternal prepregnancy BMI, gestational weight gain, race/ethnicity, age at enrollment, education, parity, maternal smoking during pregnancy, household income, marital status, paternal BMI, and (for DXA trunk-to-peripheral fat ratio) child BMI (model 4 [Table 2]). The dotted lines are drawn to facilitate the comparison between the normoglycemic group (reference) and the other groups.*

dimensions than female fetuses (31) as early as the preimplantation stage (32), but they seem to invest less in placental growth. Male placentas are smaller than those of female fetuses at any given birth weight (30). Male placentas are also more efficient; at any placental weight, male fetuses tend to be heavier. This can result in less reserve capacity in the male fetus in the presence of a stressful event (33). In case of shortage of key nutrients, male fetuses attempt to compensate, more or less successfully, by expanding their placental surface in late gestation (30). In utero, boys seem more responsive to the mother's current diet and metabolism than girls, who appear more influenced by their mother's lifetime nutrition and metabolism (30,34). As a consequence, male fetuses may be more vulnerable to variations in nutrient intake or transfer during pregnancy. In contrast, female fetuses

seem to take a more cautious route that favors survival. They grow more slowly in weight and length and they have a larger placenta for a given birth weight than boys (30). Female neonates also have higher insulin concentrations at birth and higher adiposity for a given birth weight, indicating that they allocate more resources toward fat mass than do male fetuses (35).

These characteristics may result in differential sensitivity to hyperglycemia in pregnancy and in differential long-term programming in male and female fetuses. Ricart et al. (36) showed at birth in >9,000 newborns that GDM was a predictor of macrosomia only in males. In 84 newborns born to GDM mothers, maternal fasting blood glucose was the major predictor of adiposity measured by air displacement plethysmography in male newborns but had little effect on adiposity

in females. Conversely, maternal BMI was the primary predictor in female newborns but not in males (37). A recent report from a large randomized controlled trial of treatment for mild GDM by the U.S. Maternal-Fetal Medicine Network reported a greater reduction of birth weight and fat mass in male than in female neonates (38). Studies also reported sex-specific associations with measures of adiposity in childhood. A study of >600 French children born to GDM mothers paired with children born to non-GDM mothers (i.e., normoglycemic, IH, and IGI combined) showed that only the male offspring of GDM mothers had a higher BMI at 5–7 years after adjustment for prepregnancy BMI, gestational weight gain, caloric intake, physical activity, screen time, and a range of sociodemographic variables (14). In contrast to our findings, Krishnaveni et al. (15) showed

Table 3—Adjusted* regression coefficients (95% CI) for the associations of maternal glucose tolerance with overall and central adiposity according to child sex

Model	N	Boys β	Boys 95% CI	Boys P	Girls β	Girls 95% CI	Girls P
Overall adiposity							
BMI (kg/m^2)	958						
GDM		0.67	−0.37 to 1.72	0.21	−0.68	−1.82 to 0.46	0.24
IGI		−0.60	−1.65 to 0.46	0.27	1.49	−0.07 to 3.06	0.06
IH		0.43	−0.45 to 1.31	0.34	0.27	−0.44 to 0.98	0.45
Norm		0.0	ref.		0.0	ref.	
BMI *z* score	958						
GDM		0.06	−0.33 to 0.44	0.77	−0.11	−0.52 to 0.29	0.58
IGI		−0.17	−0.56 to 0.22	0.38	0.69	0.14–1.25	0.01
IH		0.24	−0.08 to 0.56	0.14	0.09	−0.16 to 0.34	0.47
Norm		0.0	ref.		0.0	ref.	
SS+TR (mm)	958						
GDM		3.36	0.01–6.72	0.05	−0.57	−4.55 to 3.40	0.78
IGI		−0.60	−3.99 to 2.78	0.73	7.00	1.54–12.5	0.01
IH		0.10	−2.71 to 2.91	0.94	1.68	−0.79 to 4.15	0.18
Norm		0.0	ref.		0.0	ref.	
DXA fat mass index (kg/m^2)	760						
GDM		0.95	0.14–1.77	0.02	−0.79	−1.78 to 0.21	0.12
IGI		−0.10	−0.89 to 0.69	0.80	1.30	0.18–2.41	0.02
IH		−0.03	−0.67 to 0.62	0.93	0.43	−0.09 to 0.94	0.10
Norm		0.0	ref.		0.0	ref.	
Central adiposity							
Waist circumference (cm)	958						
GDM		0.37	−0.80 to 1.54	0.53	1.23	−0.16 to 2.61	0.08
IGI		1.38	0.20–2.56	0.02	1.34	−0.56 to 3.25	0.17
IH		0.48	−0.50 to 1.46	0.34	0.68	−0.18 to 1.54	0.12
Norm		0.0	ref.		0.0	ref.	
DXA trunk fat mass (kg)	760						
GDM		0.04	−0.03 to 0.11	0.29	0.05	−0.29 to 0.39	0.76
IGI		0.02	−0.06 to 0.09	0.65	0.06	−0.32 to 0.44	0.76
IH		0.00	−0.06 to 0.06	0.97	0.15	−0.03 to 0.32	0.10
Norm		0.0	ref.		0.0	ref.	
SS/TR	958						
GDM		0.34	0.04–0.63	0.02	−0.01	−0.09 to 0.07	0.77
IGI		0.15	−0.13 to 0.43	0.28	−0.05	−0.15 to 0.06	0.38
IH		−0.16	−0.39 to 0.07	0.16	0.02	−0.03 to 0.07	0.37
Norm		0.0	ref.		0.0	ref.	

Data from 471 boys and 487 girls (366 and 394 for DXA outcomes) and their mothers in Project Viva. Norm, normoglycemic. *Adjusted for child age at examination, maternal prepregnancy BMI, gestational weight gain, race/ethnicity, age at enrollment, education, parity, maternal smoking during pregnancy, household income, marital status, paternal BMI, and (for central adiposity outcomes only) child BMI (corresponds to model 4 in Table 2).

that female offspring of Indian mothers with GDM had higher adiposity at age 5 and 9.5 years than offspring of mothers without GDM. They did not find an increased adiposity in male offspring of GDM mothers, although they noted some signs of metabolic dysfunction at age 9.5 years. These dissimilar findings could be explained by genetic, cultural, or environmental differences in the two populations. In particular, body composition differs in Indian and white populations (39).

Our results also suggest that the offspring of IGI and IH women in this study are noticeably different from the offspring of normoglycemic mothers. Unfortunately, many earlier studies did not separately examine offspring of IGI mothers, but this group has recently received enhanced attention after results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study that showed a continuous association of maternal glycemia during pregnancy with offspring adiposity at birth (2). In a sample of

>9,000 mother-child pairs, Hillier et al. (40) showed that offspring of IGI mothers, but not IH, had a higher risk of childhood overweight than offspring of normoglycemic mothers, but they did not mention any sex-specific associations. The female-only associations that we show in offspring of IGI mothers have never been reported before. While we did not have data on degree of control or adherence to treatment in women with GDM in this study, a possible explanation for the observed difference is that

exposure of the fetuses to excess glycemia may differ in intensity and timing among those whose mothers have IGI versus GDM. In addition, sensitivity may also differ in males and females, which may result in differential long-term programming. However, our results should be tempered by the fact that if we could have used the recent criteria recommended by the International Association of the Diabetes and Pregnancy Study Groups, a large proportion of the women diagnosed with IGI in our study would have been diagnosed with GDM (41).

We did not find an effect of gestational glucose tolerance on fat-free mass in boys or girls.

Similarly, Catalano et al. (42) did not show a significant difference in lean mass measured by DXA in 9-year olds between the offspring of GDM (mean [SD] 25.0 [6.7] kg) and of normoglycemic mothers (24.5 [4.9] kg, $P = 0.72$). Chandler-Laney et al. (8) showed a positive, albeit modest, correlation of maternal glucose measured during pregnancy with children's lean mass at 5–10 years of age after adjustment for height and sex ($r = 0.37$, $P = 0.07$). It will be important to reevaluate these associations during and after puberty, since muscle mass acquisition takes place largely at puberty in a sex-specific manner.

Previous studies have suggested that the association of exposure to the hyperglycemic environment with later child obesity is only in part explained by its influence on birth weight (3,7,8,29). Our finding that adjustment for birth size did not markedly attenuate associations with increased childhood adiposity confirms these reports.

Strengths of this study include prospectively collected longitudinal data beginning in early pregnancy; detailed assessment of demographic, socioeconomic, and biological family and child characteristics; and research standard measurements of child body composition. We assessed overall and central adiposity using DXA as well as other anthropometric measures.

One limitation of this study is the lack of information on glycemic control in the GDM group. The sample size also prevented us from assessing whether women being categorized as IGI because of an abnormal fasting glucose value or an abnormal 1-h, 2-h, or 3-h postglucose value modifies the association with child adiposity. Indeed, it has been shown that the metabolic implications of impaired

glucose tolerance in pregnancy vary in relation to the timing of the abnormal glucose value from the diagnostic OGTT (43). Another limitation is attrition. It is possible that loss to follow-up could have introduced bias, but many baseline variables were similar in the study sample and in those excluded. Generalizability may be limited given the relatively higher socioeconomic status of the study participants.

In conclusion, maternal hyperglycemia in pregnancy was associated with excess adiposity but not greater lean body mass in offspring. In girls, IGI but not GDM was associated with greater offspring adiposity, whereas in boys we found the opposite. A different sensitivity of male and female fetuses in utero may result in differential programming and metabolic consequences in the long run.

References
1. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care 2007;30(Suppl. 2): S141–S146
2. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009; 58:453–459
3. Pettitt DJ, Knowler WC, Bennett PH, Aleck KA, Baird HR. Obesity in offspring of diabetic Pima Indian women despite normal birth weight. Diabetes Care 1987; 10:76–80
4. Bush NC, Chandler-Laney PC, Rouse DJ, Granger WM, Oster RA, Gower BA. Higher maternal gestational glucose concentration is associated with lower offspring insulin sensitivity and altered β-cell function. J Clin Endocrinol Metab 2011;96:E803–E809
5. 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
6. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. Exp Diabetes Res 2011;2011:541308
7. Wright CS, Rifas-Shiman SL, Rich-Edwards JW, Taveras EM, Gillman MW, Oken E. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. Am J Hypertens 2009;22:215–220
8. Chandler-Laney PC, Bush NC, Rouse DJ, Mancuso MS, Gower BA. Maternal glucose concentration during pregnancy predicts fat and lean mass of prepubertal offspring. Diabetes Care 2011;34:741–745
9. Crume TL, Ogden L, West NA, et al. Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. Diabetologia 2011;54:87–92
10. Pettitt DJ, McKenna S, McLaughlin C, Patterson CC, Hadden DR, McCance DR. Maternal glucose at 28 weeks of gestation is not associated with obesity in 2-year-old offspring: the Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) family study. Diabetes Care 2010;33: 1219–1223
11. Knight B, Shields BM, Hill A, Powell RJ, Wright D, Hattersley AT. The impact of maternal glycemia and obesity on early postnatal growth in a nondiabetic Caucasian population. Diabetes Care 2007;30:777–783
12. Silverman BL, Rizzo TA, Cho NH, Metzger BE; The Northwestern University Diabetes in Pregnancy Center. Long-term effects of the intrauterine environment. Diabetes Care 1998;21(Suppl. 2):B142–B149
13. Gabory A, Attig L, Junien C. Sexual dimorphism in environmental epigenetic programming. Mol Cell Endocrinol 2009; 304:8–18

14. Le Moullec N, Fianu A, Chazelle E, et al. Diabète gestationnel et risque de surpoids chez l'enfant de 5-7 ans à la Réunion (étude Obegest): Des différences selon le sexe de l'enfant? Diabetes Metab 2012;38:(Suppl. 2):A46

15. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. Diabetes Care 2010;33:402–404

16. World Medical Association. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925–926

17. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2004;27(Suppl. 1):S88–S90

18. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002;2002:1–190

19. Goran MI, Kaskoun M, Shuman WP. Intra-abdominal adipose tissue in young children. Int J Obes Relat Metab Disord 1995;19:279–283

20. Centers for Disease Control and Prevention. *NHANES Anthropometry Procedures Manual*. 2000, p. 3–30 and 33–31

21. Pettitt DJ, Talton JW, Liese AD, et al.; SEARCH for Diabetes in Youth Study Group. Comparison of two waist circumference measurement protocols: the SEARCH for diabetes in youth study. Pediatr Obes 2012;7:e81–e85

22. Shorr I. *How to Weigh and Measure Children*. New York, NY, United Nations, 1986

23. Mueller W, Martorell R. Reliability and accuracy of measurement. In *Anthropometric Standardization Reference Manual*. Lohman T, Roche A, Eds. Champaign, IL, Home Kinetics Books, 1988:83–86

24. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. Am J Clin Nutr 1990;52:953–959

25. Ketel IJG, Volman MNM, Seidell JC, Stehouwer CD, Twisk JW, Lambalk CB. Superiority of skinfold measurements and waist over waist-to-hip ratio for determination of body fat distribution in a population-based cohort of Caucasian Dutch adults. Eur J Endocrinol 2007;156:655–661

26. Morimoto Y, Maskarinec G, Conroy SM, Lim U, Shepherd J, Novotny R. Asian ethnicity is associated with a higher trunk/peripheral fat ratio in women and adolescent girls. J Epidemiol 2012;22:130–135

27. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr 2003;3:6

28. Lawlor DA, Fraser A, Lindsay RS, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia 2010;53:89–97

29. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 2003;111:e221–e226

30. Eriksson JG, Kajantie E, Osmond C, Thornburg K, Barker DJ. Boys live dangerously in the womb. Am J Hum Biol 2010;22:330–335

31. de Zegher F, Devlieger H, Eeckels R. Fetal growth: boys before girls. Horm Res 1999;51:258–259

32. Mittwoch U. Blastocysts prepare for the race to be male. Hum Reprod 1993;8:1550–1555

33. Forsén T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. BMJ 1999;319:1403–1407

34. van Abeelen AF, de Rooij SR, Osmond C, et al. The sex-specific effects of famine on the association between placental size and later hypertension. Placenta 2011;32:694–698

35. Hawkes CP, Hourihane JO, Kenny LC, Irvine AD, Kiely M, Murray DM. Gender- and gestational age-specific body fat percentage at birth. Pediatrics 2011;128:e645–e651

36. Ricart W, López J, Mozas J, et al.; Spanish Group for the study of the impact of Carpenter and Coustan GDM thresholds. Maternal glucose tolerance status influences the risk of macrosomia in male but not in female fetuses. J Epidemiol Community Health 2009;63:64–68

37. Lingwood BE, Henry AM, d'Emden MC, et al. Determinants of body fat in infants of women with gestational diabetes mellitus differ with fetal sex. Diabetes Care 2011;34:2581–2585

38. Bahado-Singh RO, Mele L, Landon MB, et al. Fetal male gender and the benefits of treatment of mild gestational diabetes mellitus. Am J Obstet Gynecol 2012;206:422.e1–422.e5

39. Lakshmi S, Metcalf B, Joglekar C, Yajnik CS, Fall CH, Wilkin TJ. Differences in body composition and metabolic status between white U.K. and Asian Indian children (EarlyBird 24 and the Pune Maternal Nutrition Study). Pediatr Obes 2012;7:347–354

40. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007;30:2287–2292

41. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682

42. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr 2009;90:1303–1313

43. Retnakaran R, Zinman B, Connelly PW, Sermer M, Hanley AJ. Impaired glucose tolerance of pregnancy is a heterogeneous metabolic disorder as defined by the glycemic response to the oral glucose tolerance test. Diabetes Care 2006;29:57–62