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Sex-specific associations of maternal gestational glycemia with hormones in umbilical cord blood at delivery

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Abstract

Background—Few studies have examined sex-specific associations of maternal gestational glycemia with cord blood hormones, which might predict later health.

Methods—In 976 women without pre-existing diabetes in the Project Viva cohort, we used linear regression to examine associations of maternal gestational glycemia with cord hormone concentrations, adjusted for maternal characteristics and stratified by infant sex.

Results—6.1% of women had gestational diabetes mellitus (GDM), 8.8% isolated hyperglycemia, 3.2% gestational impaired glucose tolerance, and 81.9% were normoglycemic. In boys, compared with infants of normoglycemic mothers, infants of GDM mothers had higher cord levels of IGF-2 (β 35.55 ng/mL; 95% CI: 2.60, 68.50), IGFBP-3 (111.2 ng/mL; 5.53, 216.8), insulin (4.66 uU/mL; 2.38, 6.95), C-peptide (0.46 ng/mL; 0.25, 0.67) and leptin (3.51 ng/mL; 1.37, 5.64) but lower IGF-1 (−6.71 ng/mL; −12.7, −0.76, adjusted for IGFBP-3). In girls, GDM offspring had higher cord blood levels of IGF-1 adjusted for IGFBP-3 (12.45 ng/mL; 4.85, 20.04). Boys, but not girls, of mothers with abnormal glucose tolerance but not GDM also had higher levels of some hormones.

Conclusion—GDM was associated with growth factors and adipokines in cord blood from boys, but only IGF-1 in girls. These findings suggests sex differences in responses to fetal overnutrition.

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Keywords

gestational diabetes mellitus; pregnancy; umbilical cord blood; hormones; insulin-like growth factor (IGF); leptin; c-peptide

Background

Over 60 years ago, Pedersen suggested that infants exposed to maternal hyperglycemia during pregnancy were more likely to be macrosomic as a result of excess maternal glucose crossing the placenta, stimulating fetal overproduction of insulin.¹ This hypothesis has since been refined to reflect the understanding that excess circulating levels of other fuels in addition to glucose, especially fatty acids, likely contribute to the fetal overgrowth.² This “fetal overnutrition” influences not only infant size, but also body composition.² Women with gestational diabetes mellitus (GDM), even those with excellent glucose control, have neonates with substantially greater fat mass, but not lean mass, at birth.³

One of the pathways by which maternal GDM might influence offspring growth and development is through changes in the regulation of mitogenic hormones and adipokines, including insulin, the insulin-like growth factor (IGF) axis, adiponectin, and leptin. Several studies have examined differences in IGF-axis and adipokine hormone concentrations in maternal plasma among pregnant women who will or have developed GDM (e.g.^{4,5}), while only a few^{6–8} have looked at cord blood, a more proximal marker of fetal *in utero* environment and hormone production. However there is a paucity of data on differences in these cord blood hormones by fetal sex, itself a driver of fetal growth and metabolism. We have previously found that associations of gestational glycemia with child adiposity in mid-childhood differed by sex,⁹ and a more general literature is emerging that developmental exposures may have sex-specific effects,^{10–12} including differences in fetal growth.^{13,14} In addition, few studies have examined cord blood hormones from women with more moderate gestational glucose intolerance that does not meet criteria for GDM diagnosis, although evidence suggests graded increases in the likelihood of adverse pregnancy outcomes across the range of maternal glycemia.¹⁵ Therefore, we conducted the present analysis to investigate umbilical blood hormone profiles by fetal sex according to maternal gestational glycemia.

Methods

Between 1999 and 2002 we recruited pregnant women at 8 obstetric offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts.¹⁶ Exclusion criteria included multiple gestation, inability to answer questions in English, gestational age < 22 weeks at recruitment, and plans to move away from the study area before delivery. All participating women provided written informed consent, and institutional review boards reviewed and approved the project in line with ethical standards established by the Declaration of Helsinki.

We followed women throughout their pregnancies and obtained clinical data on obstetric and delivery outcomes on 2,128 live singleton births. We collected umbilical cord blood from

infants delivered at only one of the two main delivery hospitals that accounted for approximately three-quarters of the births. The midwife or obstetrician obtained umbilical cord blood via syringe and needle from the umbilical vein. We obtained cord blood from about two-thirds of those births, or about one-half of the whole cohort. Collection of cord blood was challenging given the varied timing of deliveries attended by different clinicians whose primary focus was on clinical care, not research. For this analysis, we excluded 16 mothers with type 1 or type 2 diabetes, 1097 with no cord blood collected, and 39 with missing exposures or outcomes. Thus the final analysis sample included 976 mother-child pairs with information on prenatal glycemic status and cord blood hormone levels. Among these 976 vs. the 1152 excluded participants, we found similar mean maternal age (32 years in both groups), pre-pregnancy BMI (24.9 vs. 24.8 kg/m²), total gestational weight gain (15.6 vs. 15.5 kg) and rates of smoking during pregnancy (13% in both groups). Women included were less likely to have completed a college degree (63 vs. 66%), more likely to be white (70% vs. 63%) and nulliparous (55% vs. 50%), and had lower annual household income (60 vs. 62% reported \$70,000/year) and had slightly longer gestation length (39.7 vs. 39.2 weeks).

Measures

Exposure - gestational glucose tolerance—We defined gestational glucose tolerance in categories according to the results of routine prenatal screening. Atrius clinicians screened all pregnant women at 26–28 weeks of gestation with a non-fasting oral glucose challenge test, 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 fasting, >180 mg/dl at 1 h, >155 mg/dl at 2 h, or > 140 mg/dl at 3 h.¹⁷ Women with two or more abnormal values on the OGTT were diagnosed with GDM.¹⁷ We further classified those with one abnormal value on the OGTT as having gestational impaired glucose tolerance (GIGT), those with an abnormal glucose challenge test but a normal OGTT as having isolated hyperglycemia (IH) and the remaining women as having normal glucose tolerance.⁹ Women diagnosed with GDM were typically followed by an endocrinologist and nutritionist, instructed to check their finger stick blood sugars daily, treated with dietary modifications, and in some cases received insulin.¹⁸ Mothers with GIGT or IH did not have any further screening and were generally clinically managed in the same way as women with normal glucose challenge test results. We additionally searched the clinical prescription database derived from the electronic medical record system used by all study obstetric practices to identify women treated with insulin during pregnancy and in a sensitivity analysis excluded them from the GDM group.

Outcomes – umbilical cord hormone levels—We included as outcomes umbilical cord plasma concentrations of IGF-1, IGF-2, IGFBP-3, insulin, C-peptide, leptin, and adiponectin. We collected cord blood samples from the umbilical vein after delivery of the infant, refrigerated whole blood for <24 hours, then spun and aliquotted plasma samples for storage in liquid nitrogen.¹⁹ We measured hormones using the following commercial assays: adiponectin and leptin (radioimmunoassay, Linco Research Inc., St. Charles, MO);²⁰ C-peptide and insulin (competitive electrochemiluminescence immunoassay, Roche

Diagnostics, Indianapolis, IN), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein 3 (IGF-BP3; ELISA, R&D Systems, Minneapolis, MN); and insulin-like growth factor-2 (IGF-2; ELISA, Alpco Diagnostics, Salem, NH). Day to day variabilities for each of these assays were below 10%.

Other variables—At the initial prenatal visit (median 9.9 weeks gestation), we collected self-reported maternal pre-pregnancy weight, height, education, smoking history, race/ethnicity, and parity.¹⁶ All data collection instruments used in Project Viva are publicly available at <https://www.hms.harvard.edu/viva/>. We calculated pre-pregnancy body mass index (BMI) in kg/m². Among 343 Project Viva women who had weight recorded in the medical record in the 3 months before their last menstrual period, the association between self-reported and clinically measured pre-pregnancy weight was linear ($r = 0.997$).²¹ We extracted serial prenatal weights from medical records and gestational weight gain to 26 weeks of gestation.^{22,23} We did not include total gestational weight gain as a covariate in this analysis, because diagnosis of and treatment for GDM can influence subsequent weight gain. We obtained infant birth date, weight, and sex from the hospital medical record. We calculated gestational age at birth using the date of the last menstrual period, or from a mid-pregnancy ultrasound if the two estimates differed by >10 days. We determined sex-specific birth weight for-gestational-age z scores using US reference data.²⁴

Statistical analysis—We used linear regression models adjusted for maternal race/ethnicity, pre-pregnancy BMI, parity, education, and pregnancy smoking status. *A priori*, given our prior finding of a difference in childhood anthropometric outcomes according to maternal GDM status,⁹ we stratified analyses by child sex. Additional adjustment for maternal gestational weight gain before glycemic screening and length of gestation did not appreciably alter findings, so we did not include these measures in our final models. We did not adjust for birth weight, fetal growth, or gestation length because these factors might be on the causal pathway, and conditioning on factors present at birth is likely to introduce collider bias.^{25,26}

All models met standard assumptions for linear regression. Distributions of insulin and C-peptide were somewhat right-skewed, but when we re-ran our analyses using log-transformed results, the directions and significance of estimates were very similar, and therefore we present the untransformed values for ease of interpretation and for comparability across outcomes. We additionally adjusted models with IGF-1 or IGF-2 as the outcome for levels of IGFBP-3, to get an estimate of the effect of IGF-1 or IGF-2 independent of the level of the binding protein. We performed all analyses using SAS version 9.3 (SAS Institute, Cary NC).

Results

Of the 976 women included in this analysis, 799 (81.9%) were normoglycemic, 86 (8.8%) had isolated hyperglycemia, 31 (3.2%) had gestational impaired glucose tolerance, and the remaining 60 (6.1%) had GDM. Compared with normoglycemic mothers, mothers with GDM were older and a higher proportion were obese (BMI ≥ 30.0 kg/m²), non-white, and parous (Table 1). Overall 52.5% of infants were male, but among mothers with GDM, 60%

were male. Infant birth weight and birth weight for gestational age were higher among the infants born to women in any category of abnormal glucose tolerance compared with normal glucose tolerance. Gestation length was about 0.5 week shorter among those with GDM (Table 1). Cesarean delivery was more common among women with impaired glucose tolerance or GDM.

Umbilical cord blood hormone concentrations were correlated with each other to varying degrees (Table 2), with the strongest correlations between C-peptide and insulin (Spearman $r=0.80$), IGFBP-3 and IGF-1 ($r=0.65$), and between IGFBP-3 and IGF-2 ($r=0.65$). IGF-1 was modestly correlated with IGF-2 ($r=0.26$) and also with insulin ($r=0.38$), c-peptide ($r=0.33$), and leptin ($r=0.23$). Concentrations of all hormones were highest in the cord blood from women with GDM, with the exception of adiponectin (Table 3). Cord blood hormone concentrations also differed substantially by infant sex (Table 4), with lower levels of all hormones except C-peptide among boys.

We observed associations of maternal prenatal glycemic status with cord blood hormones that differed by infant sex for many outcomes. Interaction p values indicated significant differences by sex for IGF-1 ($p=0.03$), insulin ($p=0.01$), and C-peptide ($p=0.004$), but not for the other hormones. For consistency we report all associations separately among boys and girls. Estimates of association were only minimally different unadjusted vs. adjusted for pre-pregnancy BMI, education, smoking, race/ethnicity, and parity, and so we report only the adjusted estimates (Table 4).

Among boys, infants of mothers with GDM (vs. normoglycemia) had higher cord blood levels of IGF-2 (β 35.55 ng/mL; 95% CI: 2.60, 68.50), IGFBP-3 (111.2 ng/mL; 95% CI: 5.53, 216.8), insulin (4.66 uU/mL; 95% CI: 2.38, 6.95), C-peptide (0.46 ng/mL; 95% CI: 0.25, 0.67) and leptin (3.51 ng/mL; 95% CI: 1.37, 5.64). When we additionally adjusted for IGFBP-3, maternal GDM was now significantly associated with lower IGF-1 (-6.71 ng/mL; 95% CI: -12.7 , -0.76), but the association with IGF-2 was attenuated (11.51 ng/mL, 95% CI: -12.4 , 35.4). In boys, leptin concentrations were also higher among offspring of mothers with GDM (vs. normoglycemia), whereas insulin and c-peptide levels were higher among mothers with IH (Table 4).

In girls, GDM offspring had higher cord blood levels of IGF-1 (16.83 ng/mL; 95% CI: 6.53, 27.14) but not any other hormones (Table 4). The association of GDM with IGF-1 in girls persisted after additional adjustment for IGFBP-3 (12.45 ng/mL; 95% CI: 4.85, 20.04). Cord blood concentrations of adiponectin did not differ by gestational glucose tolerance status in either boys or girls.

We were interested to see whether insulin treatment explained the associations we observed among the women with GDM. We identified 15 mothers who were treated with insulin during pregnancy – 14 with GDM, and an additional mother who had impaired glucose tolerance, but who was treated with insulin because of a prior pregnancy complicated by macrosomia. Excluding those treated with insulin resulted in somewhat different effect estimates but no difference in the directions or significance of findings. For example, compared with boys born to normoglycemic mothers, boys born to mothers with GDM who

were not treated with insulin had higher IGF-2 (47.95 ng/mL; 95% CI: 11.40, 84.50), insulin (2.74 uU/mL; 95% CI: 0.23, 5.25), c-peptide (0.33 ng/mL; 95% CI: 0.09, 0.56), and leptin (4.11 ng/mL; 95% CI: 1.70, 6.52) for leptin. With additional adjustment for IGFBP-3, the estimate for IGF-1 became inverse (−8.06, 95% CI: −14.7, −1.42), the estimate for IGF-2 remained in the positive direction but became null albeit with extremely wide confidence intervals (13.41, 95% CI: −13.2, 40.04), and the estimate for leptin remained significant (3.91, 95% CI: 1.42, 6.40).

Discussion

In this prospective study of almost 1000 mother-infant pairs, we found sex-specific differences in associations of maternal glycemia with umbilical cord blood hormones. Boys born to mothers with gestational diabetes mellitus had higher growth factors and leptin compared to boys born to normoglycemic mothers. Among girls, we observed differences only in IGF-1. We did not see evidence that the differences in cord hormone concentrations were solely the result of the treatment of gestational hyperglycemia – results were similar when we excluded women with GDM who were treated with insulin, and we also saw some differences in insulin, C-peptide, and leptin even among those who had IH or GIGT, for whom standard of care was not different from normoglycemic mothers.

A number of studies have examined hormone levels among pregnant women with GDM.^{4,5} It's been long established that maternal hyperglycemia is associated with fetal hyperinsulinemia¹ which has been linked to risk of obesity, abnormal glucose tolerance, and metabolic syndrome later in childhood and adolescence.^{27–29} There is significant biological crosstalk between IGF and insulin systems³⁰ and both IGF-2 and insulin (but not IGF-1) bind with high affinity the A isoform of insulin receptor,³¹ which has a key role in embryogenesis.³² Some evidence exists that women with diabetes demonstrate higher circulating IGF-1^{7,22,33} and IGF-2³³ as compared to women with normoglycemia, and higher IGF-1 is associated with greater fetal size.^{7,8,33} However, fewer studies have examined hormones in cord blood according to gestational glucose intolerance, as we did in the current project.

While there may be some placental contribution to cord blood hormones, they are thought to originate primarily from the fetus.^{34–36} The higher hormone concentrations in fetal circulation might not only reflect differences in fetal brain and organ development, but also might influence subsequent organ structure and function, leading to differences in phenotype. For example, animal studies have shown that exposures to glucocorticoids, insulin, and leptin have long-lasting effects when the organism is exposed in “critical” periods before and after birth but not later in life.^{37–40}

In our prior work within this cohort, at 3 years of age offspring born to mothers with GDM had similar weights but greater adiposity, as well as higher systolic blood pressure, as compared to offspring of women with normal glycemia in pregnancy.¹⁸ We did not investigate sex-specific effects at age 3, but by 6–10 years of age, only male offspring of GDM mothers exhibited greater weight and adiposity compared with normoglycemic offspring, whereas only female offspring of mothers with GIGT did so.⁹ We hypothesized

that boys and girls have differential sensitivity to hyperglycemia in pregnancy or its treatment, and thus differential long-term programming.⁹ This finding is supported by the recent report that only female offspring of women randomized to treatment for mild GDM had lower fasting glucose and insulin resistance at 5–10 years compared to those not randomized to treatment.⁴¹ In our prior papers as in the current study, associations of maternal gestational glycemia with offspring outcomes were robust to adjustment for a number of social and maternal factors, including pre-pregnancy BMI.

There is growing evidence that males and females have different physiologies not only after puberty, but also well before. For example, the growth hormone-IGF axis exhibits sexual dimorphism even at birth,^{42–44} and some evidence suggests that female fetuses are more insulin resistant than males.⁴⁵ What is also becoming increasingly evident is that there are sex-specific responses to a range of intrauterine exposures,^{10–12} including maternal diabetes and overnutrition more broadly. For example, in a population-based study in Sweden, boys born to mothers with GDM vs. normal glucose tolerance were found to be more likely to have birth defects, whereas the risk of major malformations was not higher in girls.⁴⁶ Boys born to mothers with GDM also are particularly likely to be macrosomic at birth.^{13,14} Additional evidence beyond our work in this cohort, including results from animal studies, suggests that sex differences in response to maternal glycemia may persist into later life.^{13,14,47,48} For example, one observational human study reported that boys born to mothers with obesity had higher body fat from ages 2–6 years compared to boys born to normal-weight and overweight mothers, whereas body composition of girls was not different across maternal weight groups.¹¹ Our findings of differences in the relationship between cord blood hormones and maternal glycemia by fetal sex are consistent with the observation that male fetuses may be more sensitive, and female fetuses more resilient, to the intrauterine metabolic environment,^{14,49} particularly prenatal glycemic status.^{13,50}

IGF-2 appears to have an important role in embryogenesis, especially in muscle and bone development,³⁰ whereas IGF-1 is a central mediator of growth and metabolism in mid to late pregnancy.⁵¹ IGFBP3 is the primary circulating IGF binding protein in humans, with approximately 80% of IGFI and II bound to IGFBP3 and 1% free.⁵² Cord blood IGF-2 has not been shown to correlate as strongly with fetal size at birth as IGF-1 in either normal pregnancies⁵³ or those complicated by diabetes,³³ however it has been shown to correlate with placental size.^{33,53,54} DNA methylation of IGF-2 on the fetal side of placenta was associated with placental weight and newborn height, but not with birth weight.⁵⁵ While the etiology of the higher IGF-2 that we observed in male fetuses is unclear, male infants typically have a higher fetal:placental weight ratio, and this difference is postulated to contribute the higher rates of perinatal morbidity observed in males.⁵⁶ Taken together with the increased sensitivity to hyperglycemia observed in male fetuses, the increased IGF-2 levels in the present study may represent an adaptive in response to a hyperglycemic uterine environment. Similarly, the observed decrease in IGF-1 in cord blood of male infants may reflect down-regulation of IGF-1 to slow excessive growth driven by hyperglycemia. Differences in sensitivity to hyperglycemia by fetal sex may also explain the increase in IGF-1 alone, and lack of observed increase in insulin, c-peptide, or leptin in female infants of GDM pregnancies, as females appear to be less sensitive to the uterine glycemic environment.^{13,50}

This study has many strengths, including analyses stratified by offspring sex, and prospective assessment of gestational glycemia. However, as we did not perform fasting glycemic screening on all women, we do not have a measure of fasting glucose on all women. Nevertheless, we saw some evidence of dose-response effects across the 4 categories of glycemia included. Although the overall sample size was large, numbers in each of the abnormal glucose tolerance groups were not. Women were generally well educated and all recruited from a single health system in Massachusetts; results may not be generalizable to more disadvantaged populations or to women elsewhere.

In summary, we found that mothers with abnormal gestational glucose tolerance status had infants with different cord blood hormone profiles compared with normoglycemic mothers, and that the associations varied by infant sex. These hormonal changes may underlie the developmental programming of obesity and dysmetabolism seen among children, especially boys, born to mothers with gestational diabetes mellitus.

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Abbreviations

BMI	body mass index
CI	confidence interval
GDM	gestational diabetes mellitus
GIGT	gestational impaired glucose tolerance
IGF	insulin-like growth factor
IH	isolated hyperglycemia
OGTT	oral glucose tolerance test
SD	standard deviation

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Table 1

Characteristics of 976 pregnant women and their infants in Project Viva according to maternal gestational glucose tolerance status

Maternal Characteristics	All Women	Normal Glycemia	Isolated Hyperglycemia	Gestational Impaired Glucose Tolerance	Gestational Diabetes Mellitus
	n=976	N=799 (81.9%)	N=86 (8.8%)	N=31 (3.2%)	N=60 (6.1%)
N (%) or Mean (SD)					
Age, years	31.8 (5.2)	31.5 (5.3)	33.2 (4.9)	33.1 (4.2)	33.3 (4.8)
Pre-pregnancy BMI, kg/m ²	24.9 (5.5)	24.6 (5.4)	25.4 (5.6)	27.1 (6.0)	28.1 (5.7)
Pre-pregnancy BMI category					
18.5 - <25.0 kg/m ²	611 (62.9)	526 (66.2)	50 (58.8)	14 (45.2)	21 (35.0)
25.0 - <30.0 kg/m ²	205 (21.1)	158 (19.9)	18 (21.2)	9 (29.0)	20 (33.3)
>=30.0 kg/m ²	155 (16.0)	111 (14.0)	17 (20.0)	8 (25.8)	19 (31.7)
Race/ethnicity, %					
Black	140 (14.4)	118 (14.8)	7 (8.1)	4 (12.9)	11 (18.3)
Hispanic	66 (6.8)	47 (5.9)	6 (7.0)	2 (6.5)	11 (18.3)
White	686 (70.5)	565 (71.0)	68 (79.1)	22 (71.0)	31 (51.7)
Other	81 (8.3)	66 (8.3)	5 (5.8)	3 (9.7)	7 (11.7)
College graduate, %					
No	361 (37.1)	292 (36.7)	30 (34.9)	13 (41.9)	26 (43.3)
Yes	612 (62.9)	504 (63.3)	56 (65.1)	18 (58.1)	34 (56.7)
Nulliparous, %					
No	533 (54.6)	427 (53.4)	50 (58.1)	21 (67.7)	35 (58.3)
Yes	443 (45.4)	372 (46.6)	36 (41.9)	10 (32.3)	25 (41.7)
Married or cohabitating, %					
No	81 (8.3)	69 (8.7)	8 (9.3)	1 (3.2)	3 (5.0)
Yes	891 (91.7)	726 (91.3)	78 (90.7)	30 (96.8)	57 (95.0)
Household income %					
<=\$70,000/yr;	349 (39.8)	279 (39.3)	35 (42.2)	12 (40.0)	23 (43.4)
>\$70,000/yr,	527 (60.2)	431 (60.7)	48 (57.8)	18 (60.0)	30 (56.6)
Smoking status					

Maternal Characteristics		All Women	Normal Glycemia	Isolated Hyperglycemia	Gestational Impaired Glucose Tolerance	Gestational Diabetes Mellitus
		n=976	N=799 (81.9%)	N=86 (8.8%)	N=31 (3.2%)	N=60 (6.1%)
Never		655 (67.6)	541 (68.1)	54 (62.8)	22 (71.0)	38 (65.5)
Former		190 (19.6)	153 (19.3)	19 (22.1)	5 (16.1)	13 (22.4)
During pregnancy		124 (12.8)	100 (12.6)	13 (15.1)	4 (12.9)	7 (12.1)
Prenatal glycemic status, %						
Normal glycemia		799 (81.9)	799 (100)	--	--	--
IH		86 (8.8)	--	86 (100)	--	--
IGT		31 (3.2)	--	--	31 (100)	--
Gestational diabetes mellitus		60 (6.1)	--	--	--	60 (100)
Child Characteristics						
Sex, %						
Male		512 (52.5)	425 (53.2)	35 (40.7)	16 (51.6)	36 (60.0)
Female		464 (47.5)	374 (46.8)	51 (59.3)	15 (48.4)	24 (40.0)
Birth weight, g		3529 (528)	3508 (518)	3617 (600)	3677 (579)	3612 (509)
Gestation length, wk		39.7 (1.6)	39.7 (1.6)	39.7 (1.7)	39.7 (1.5)	39.2 (1.3)
Birth weight for gestational age, z-score		0.24 (0.95)	0.19 (0.93)	0.46 (1.03)	0.57 (1.04)	0.44 (0.97)
Cesarean delivery, %						
No		807 (82.7)	668 (83.6)	75 (87.2)	21 (67.7)	43 (71.7)
Yes		169 (17.3)	131 (16.4)	11 (12.8)	10 (32.3)	17 (28.3)

GDM – gestational diabetes mellitus; IH – isolated hyperglycemia; IGT –impaired glucose tolerance; BMI – body mass index

Table 2

Correlations among cord blood hormone concentrations from 976 infants born to pregnant women in Project Viva

Spearman r	IGF-1	IGF-2	IGFBP-3	Insulin	C-peptide	Leptin	Adiponectin
IGF-1	1.00	0.26	0.65	0.38	0.33	0.23	0.11
IGF-2	0.26	1.00	0.65	0.19	0.28	0.23	0.14
IGFBP-3	0.65	0.65	1.00	0.28	0.31	0.22	0.12
Insulin	0.38	0.19	0.28	1.00	0.80	0.35	0.09
C-peptide	0.33	0.28	0.31	0.80	1.00	0.34	0.04
Leptin	0.23	0.23	0.22	0.35	0.34	1.00	0.39
Adiponectin	0.11	0.14	0.12	0.09	0.04	0.39	1.00

Hormone levels in venous umbilical cord blood collected at delivery among 976 participants in Project Viva, according to gestational glucose tolerance status

Table 3

Umbilical cord blood hormone concentration	All Women	Normal Glycemia	Isolated Hyperglycemia	Gestational Impaired Glucose Tolerance	Gestational Diabetes Mellitus
Mean (SD) concentration in cord blood					
IGF-1, ng/mL	56.5 (24.2)	55.9 (23.6)	56.2 (22.9)	60.8 (31.8)	62.0 (29.2)
IGF-2, ng/mL	409.2 (92.8)	406.8 (91.6)	406.2 (92.5)	431.0 (117)	432.4 (92.0)
IGFBP-3 ng/mL	1084 (317)	1073 (311)	1088 (299)	1153 (390)	1178 (361)
Insulin uU/mL	6.5 (7.1)	6.1 (6.4)	7.8 (7.3)	6.6 (5.1)	10.4 (12.9)
C-peptide ng/mL	1.0 (0.6)	1.0 (0.6)	1.1 (0.6)	1.1 (0.5)	1.4 (1.1)
Leptin, ng/mL	9.0 (6.6)	8.6 (6.5)	10.4 (6.7)	11.2 (8.0)	11.2 (7.3)
Adiponectin, µg/mL	28.7 (6.7)	28.7 (6.6)	28.9 (8.1)	29.9 (5.9)	28.6 (7.4)

IGF – insulin-like growth factor; IGFBP – insulin-like growth factor binding protein

Multivariable* associations of maternal gestational glucose tolerance status with cord blood hormone concentrations at delivery, among boys and girls

Table 4

Cord blood hormones	All Women	Normal Glycemia	Isolated Hyperglycemia	Gestational Impaired Glucose Tolerance	Gestational Diabetes Mellitus
Boys (n=512)	Mean (SD)	Adjusted* β (95% CI)			
IGF-1 ng/mL	52.9 (22.8)	0.0 (ref)	-6.45 (-14.3, 1.41)	0.76 (-10.2, 11.71)	-1.30 (-9.13, 6.54)
IGF-2, ng/mL	403.1 (91.3)	0.0 (ref)	-27.0 (-60.0, 6.09)	4.36 (-41.7, 50.42)	35.55 (2.60, 68.50)
IGFBP-3 ng/mL	1028 (297)	0.0 (ref)	-45.3 (-151, 60.65)	25.95 (-122, 173.6)	111.2 (5.53, 216.8)
Insulin uU/mL	6.2 (6.8)	0.0 (ref)	3.62 (1.33, 5.91)	1.14 (-2.05, 4.33)	4.66 (2.38, 6.95)
C-peptide ng/mL	1.0 (0.6)	0.0 (ref)	0.32 (0.11, 0.53)	0.22 (-0.08, 0.51)	0.46 (0.25, 0.67)
Leptin, ng/mL	7.7 (5.7)	0.0 (ref)	1.99 (-0.11, 4.09)	3.14 (0.26, 6.02)	3.51 (1.37, 5.64)
Adiponectin, μ g/mL	28.3 (7.1)	0.0 (ref)	-1.84 (-4.50, 0.81)	1.53 (-2.11, 5.17)	-0.24 (-3.02, 2.54)
Girls (n=464)	Mean (SD)	Adjusted* β (95% CI)			
IGF-1 ng/mL	60.4 (25.1)	0.0 (ref)	2.03 (-5.02, 9.09)	5.07 (-7.33, 17.46)	16.83 (6.53, 27.14)
IGF-2, ng/mL	415.8 (94.0)	0.0 (ref)	4.59 (-23.1, 32.28)	40.00 (-8.63, 88.63)	10.83 (-29.6, 51.25)
IGFBP-3 ng/mL	1144 (327)	0.0 (ref)	1.92 (-92.9, 96.70)	96.20 (-70.2, 262.6)	86.90 (-51.4, 225.2)
Insulin uU/mL	6.8 (7.4)	0.0 (ref)	0.10 (-2.08, 2.28)	-1.02 (-4.85, 2.80)	0.71 (-2.47, 3.89)
C-peptide ng/mL	1.0 (0.6)	0.0 (ref)	-0.02 (-0.21, 0.17)	-0.11 (-0.44, 0.22)	0.03 (-0.24, 0.31)
Leptin, ng/mL	10.4 (7.3)	0.0 (ref)	1.31 (-0.99, 3.61)	1.12 (-3.43, 5.66)	-0.39 (-3.98, 3.20)
Adiponectin, μ g/mL	29.2 (6.3)	0.0 (ref)	1.54 (-0.44, 3.52)	0.56 (-3.08, 4.20)	1.66 (-1.42, 4.73)

* Models adjusted for maternal pre-pregnancy body mass index, education, smoking, race/ethnicity, and parity.

IGF – insulin-like growth factor; IGFBP