Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus

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OBJECTIVE

To characterize physiologic subtypes of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

Insulin sensitivity and secretion were estimated in 809 women at 24–30 weeks' gestation, using oral glucose tolerance test–based indices. In women with GDM (8.3%), defects in insulin sensitivity or secretion were defined below the 25th percentile in women with normal glucose tolerance (NGT). GDM subtypes were defined based on the defect(s) present.

RESULTS

Relative to women with NGT, women with predominant insulin sensitivity defects (51% of GDM) had higher BMI and fasting glucose, larger infants (birth weight *z* score 0.57 [−0.01 to 1.37] vs. 0.03 [−0.53 to 0.52], $P = 0.001$), and greater risk of GDM-associated adverse outcomes (57.6 vs. 28.2%, $P = 0.003$); differences were independent of BMI. Women with predominant insulin secretion defects (30% of GDM) had BMI, fasting glucose, infant birth weights, and risk of adverse outcomes similar to those in women with NGT.

CONCLUSIONS

Heterogeneity of physiologic processes underlying hyperglycemia exists among women with GDM. GDM with impaired insulin sensitivity confers a greater risk of adverse outcomes.

Gestational diabetes mellitus (GDM) is associated with adverse outcomes, including macrosomia, neonatal hypoglycemia, and increased rate of cesarean delivery, but it is unclear if the risk is equally distributed among all women with this condition (1). Hyperglycemia in both pregnant and nonpregnant individuals results from inadequate insulin secretion for the level of insulin sensitivity. In many nonpregnant individuals, a defect in either insulin secretion or insulin sensitivity can be identified as the predominant driver of hyperglycemia (2,3). We hypothesized that there would similarly be heterogeneity of physiologic processes contributing to hyperglycemia in women with GDM. We aimed to define physiologic subtypes of GDM and test whether phenotypic characteristics and pregnancy outcomes differed among these GDM subtypes and women who maintained normal glucose tolerance (NGT).

RESEARCH DESIGN AND METHODS

The Genetics of Glucose regulation in Gestation and Growth (Gen3G) cohort is a prospective pregnancy study that has been previously described in detail (4–6). The

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ethics committee at Centre Hospitalier Universitaire de Sherbrooke approved the study; participants gave written informed consent. Women with overt diabetes by history or by laboratory in the first trimester (hemoglobin A_{1c} ≥6.5% or glucose ≥185 mg/dL after a 50-g glucose load) were excluded. All women underwent a fasting 75-g oral glucose tolerance test (OGTT) at 24–30 weeks' gestation. Based on OGTT results, we defined GDM according to International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria (7). We used insulin and glucose levels during the OGTT to estimate insulin secretion (using the Stumvoll first-phase estimate) and insulin sensitivity (using the Matsuda index) (8–10). These indices were multiplied to calculate the oral disposition index (DI_o), which assesses β-cell compensation for insulin resistance (11). To define GDM subtypes, we used the distributions of insulin sensitivity and secretion in women with NGT. We considered women with GDM to have an insulin secretion or sensitivity defect if insulin secretion or sensitivity was below the 25th percentile, respectively. We classified women with GDM into physiologic subtypes based on the defects present: GDM with a predominant insulin secretion defect (GDM-secretion), GDM with a predominant insulin sensitivity defect (GDM-sensitivity), or GDM with both defects (GDM-mixed). One participant with GDM had both insulin secretion and sensitivity above the 25th percentile and was excluded from subgroup analyses.

Birth weight *z* scores were calculated using the 2013 Fenton growth chart (12). Large for gestational age (LGA) was defined as weight ≥90th percentile. A composite outcome of any GDM-related adverse pregnancy outcome (LGA, hypoglycemia, or cesarean delivery) was created.

We compared characteristics, adipokines, and pregnancy outcomes across GDM subtypes and the NGT group using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. When the *P* value obtained was significant (<0.05), Dunn test or Fisher exact test was performed, comparing each GDM subtype with the NGT group. *P* values for pairwise comparisons were adjusted using Bonferroni correction. To test whether differences between groups were due to maternal weight status, we created linear or logistic regression models to adjust for maternal BMI (measured at the time of the OGTT). Nonnormally distributed variables were natural log transformed prior to regression analysis. Two-tailed *P* values of <0.05 were considered significant. Analyses were conducted with STATA, version 11 (StataCorp LP, College Station, TX). Dunn test was performed using the dunntest package (13).

RESULTS

Of 809 women, 67 (8.3%) developed GDM (Table 1). Among all women, the relationship between insulin secretion and insulin sensitivity appeared to be that of a hyperbola (Supplementary Fig. 1). Women with GDM had a lower DI_o compared with women with NGT, resulting in a downshift of the hyperbolic curve. Among women with GDM, 30% were in the GDM-secretion group, 51% were in the GDM-sensitivity group, and 18% were in the GDM-mixed group. In contrast, two women (0.3%) who maintained NGT had both insulin secretion and sensitivity below the 25th percentile.

Subject characteristics and pregnancy outcomes in each GDM subtype are compared with the NGT group in Table 1. Women in the GDM-sensitivity group had higher BMI, while women in the GDM-secretion group and GDM-mixed group had BMIs similar to those in the NGT group. Women in the GDM-secretion group had late second-trimester fasting glucose similar to women who maintained NGT, whereas women in the other two GDM subgroups had elevated fasting glucose as compared with the NGT group, independent of BMI ($P < 0.001$). The GDM-sensitivity group had higher leptin and lower adiponectin compared with the NGT group; after adjustment for BMI, only the adiponectin difference remained significant ($P = 0.01$).

A similar proportion of women with each GDM subtype was treated with insulin (25–42%, $P = 0.51$); in insulin-treated women, there were no significant differences between the subtypes in the type of insulin regimen (basal vs. prandial vs. both, $P = 0.87$). Compared with women with NGT, women in the GDM-sensitivity group had infants with greater birth weight *z* scores and had a greater risk of GDM-associated adverse outcomes (Table 1). Women in the GDM-secretion and GDM-mixed groups were similar to the NGT group in terms of outcomes. The between-group differences in pregnancy outcomes persisted after adjustment for BMI (GDM-sensitivity vs. NGT: $P = 0.02$ for infant birth weight and $P = 0.01$ for adverse outcomes; GDM-secretion or GDM-mixed vs. NGT: $P > 0.2$ for infant birth weight and adverse outcomes).

In women without GDM, the median birth weight *z* score of infants born to mothers with insulin sensitivity below the 25th percentile was greater than in infants born to mothers with insulin sensitivity at or above the 25th percentile (0.11 [−0.45 to 0.74] vs. 0 [−0.57 to 0.47], $P = 0.01$), although this was attenuated by adjustment for BMI ($P = 0.16$). Among women without GDM, infants of women with insulin secretion below the 25th percentile had greater median infant birth weight *z* score only after accounting for insulin sensitivity ($\beta = 0.17$, $P = 0.03$), without attenuation by BMI adjustment.

CONCLUSIONS

Here, in a large pregnancy cohort, we have demonstrated heterogeneity of physiologic processes underlying hyperglycemia in GDM. Almost one-third of women with GDM had predominant insulin secretion defects without impaired insulin sensitivity, and one-half had predominant insulin sensitivity defects with hyperinsulinemia. Unlike women with GDM who had predominant insulin secretion defects, women with GDM with predominant insulin sensitivity defects had altered adipokine profiles, had larger infants, and were at greater risk of GDM-related complications. Our findings have important implications for the understanding of glycemic physiology in pregnancy and for the development of treatment strategies for GDM.

Usually women with GDM are considered together, as a single group. However, previous small studies in selected patients have suggested that, like type 2 diabetes, GDM is a heterogeneous disease (14,15). Unlike previous studies that used lean and obese phenotypes to characterize GDM, we initiated our investigation using validated indices to define subtypes based on underlying glycemic physiology. In the future, studying each subtype separately may provide

Table 1—Characteristics and pregnancy outcomes of women with NGT and GDM, by physiologic subtype

	GDM-secretion		GDM-sensitivity		GDM-mixed		NGT	All GDM
	Median (IQR)/*n* (%)	*P**	Median (IQR)/*n* (%)	*P**	Median (IQR)/*n* (%)	*P**	Median (IQR)/*n* (%)	Median (IQR)/*n* (%)
n‡	20 (29.9% of GDM)		34 (50.7% of GDM)		12 (17.9% of GDM)		742 (91.7% of total *n*)	67 (8.3% of total *n*)
Age (years)	29.5 (28–32)	—	28 (25–35)	—	31 (23–33)	—	28 (25–31)	29 (26–33)+
% Primigravid	2 (10.0%)	—	13 (38.2%)	—	2 (16.7%)	—	262 (35.3%)	17 (25.4%)
% Nulliparous	3 (15.0%)	0.01	16 (47.1%)	>0.99	3 (27.3%)	0.68	362 (48.9%)	23 (34.9%)+
% European descent	18 (90.0%)	—	34 (100.0%)	—	12 (100.0%)	—	705 (96.2%)	65 (97.0%)
Family history of diabetes	5 (25.0%)	—	10 (29.4%)	—	3 (25.0%)	—	138 (18.6%)	18 (26.9%)
First-trimester study visit								
Gestational age (weeks)	8.8 (7.5–10.8)	—	9.4 (7.2–11.6)	—	10.2 (8.2–12.1)	—	9.2 (8.1–11.4)	9.3 (7.4–12.0)
BMI (kg/m^2)	21.9 (20.7–26.0)	0.15	30.1 (26.9–37.7)	<0.001	25.3 (21.3–29.8)	0.98	23.9 (21.5–27.5)	27.0 (22.0–32.4)+
Hemoglobin A_{1c} (%)	5.3 (5.1–5.5)	0.88	5.4 (5.2–5.6)	0.001	5.5 (5.2–5.7)	0.02	5.2 (5.1–5.4)	5.4 (5.1–5.6)+
Hemoglobin A_{1c} (mmol/mol)	34 (32–37)	0.88	36 (33–38)	0.001	37 (33–39)	0.02	33 (32–36)	36 (32–38)+
Second-trimester study visit								
Gestational age (weeks)	26.4 (25.9–27.7)	—	26.3 (25.6–26.6)	—	26.2 (25.3–27.8)	—	26.2 (25.6–27.1)	26.3 (25.6–27.1)
BMI (kg/m^2)	25.0 (23.7–28.3)	0.21	32.3 (28.9–40.9)	<0.001	28.7 (24.6–32.8)	0.65	26.6 (24.2–30.1)	29.3 (25.6–34.5)+
Weight gain (kg)	6.5 (4.8–8.1)	—	7.0 (4.8–8.9)	—	7.5 (4.3–10.2)	—	6.8 (4.8–8.4)	6.8 (4.8–8.9)
Fasting glucose (mg/dL)	76 (72–79)	0.85	90 (81–94)	<0.001	88 (83–93)	<0.001	76 (70–79)	83 (76–92)+
1-h glucose OGTT (mg/dL)	182 (177–196)	<0.001	179 (164–189)	<0.001	187 (176–202)	<0.001	126 (106–142)	182 (169–196)+
2-h glucose OGTT (mg/dL)	155 (133–165)	<0.001	150 (135–164)	<0.001	153 (141–169)	<0.001	101 (86–115)	151 (135–164)+
Fasting insulin (μU/mL)	6.0 (4.6–6.7)	0.03	13.6 (9.9–20.5)	<0.001	7.6 (6.7–9.0)	0.62	6.9 (4.9–9.8)	9.1 (6.6–13.7)+
1-h insulin OGTT (μU/mL)	40.1 (32.0–52.2)	0.33	84.6 (68.3–108.3)	<0.001	55.5 (49.2–66.8)	0.07	45.8 (34.2–61.3)	63.9 (45.4–84.9)+
2-h insulin OGTT (μU/mL)	43.9 (34.4–53.2)	0.43	96.7 (78.0–122.2)	<0.001	56.9 (50.1–64.1)	0.003	38.3 (26.9–54.3)	58.1 (45.3–97.6)+
Insulin sensitivity (Matsuda)	7.4 (6.2–8.5)	>0.99	2.9 (2.3–4.0)	<0.001	5.4 (4.7–5.5)	<0.001	7.9 (5.8–11.1)	4.6 (2.9–6.2)+
Insulin secretion (Stumvoll)	594 (501–739)	<0.001	1,364 (1,063–1,677)	<0.001	748 (694–870)	<0.001	1,122 (936–1,289)	969 (676–1368)+
DI_o	4,491 (3,947–5,318)	<0.001	4,038 (3,655–4,613)	<0.001	4,082 (3,824–4,374)	<0.001	8,587 (6,837–11,125)	4,144 (3,760–4,850)+
Adiponectin (μg/mL)	12.7 (8.8–15.4)	0.71	9.0 (6.8–11.3)	<0.001	10.6 (8.4–12.6)	0.22	12.4 (9.7–15.3)	10.4 (7.1–13.0)+
Leptin (pg/mL)	11,306 (7,361–15,364)	0.14	25,463 (19,866–34,279)	<0.001	21,173 (8,373–25,343)	0.40	13,808 (8,509–21,311)	21,092 (12,061–26,579)+
TNF-α (pg/mL)	1.72 (1.22–2.34)	—	1.80 (1.37–2.94)	—	1.65 (1.14–1.80)	—	1.60 (1.18–2.17)	1.71 (1.25–2.39)
Delivery								
Gestational age	38.8 (38.4–39.7)	0.14	38.8 (38.2–39.6)	0.01	38.8 (38.0–39.3)	0.06	39.5 (38.5–40.3)	29.0 (38.3–39.6)+
Infant birth weight (g)	3,400 (2,978–3,685)	—	3,505 (3,209–3,800)	—	3,243 (2,800–3,620)	—	3,403 (3,130–3,690)	3,460 (3,055–3,755)
Infant birth weight (*z* score)	0.20 (−0.54 to 0.86)	0.71	0.57 (−0.01 to 1.37)	0.001	0.16 (−0.57 to 0.70)	>0.99	0.03 (−0.53 to 0.52)	0.39 (−0.44 to 0.87)+
LGA	2 (10.0%)	>0.99	9 (26.5%)	<0.001	0 (0.0%)	>0.99	47 (6.3%)	11 (16.4%)+
Cesarean delivery‡	4 (20.0%)	>0.99	11 (33.3%)	0.03	3 (25.0%)	>0.99	111 (15.2%)	18 (27.3%)+
LGA or cesarean delivery‡	5 (25.0%)	>0.99	16 (48.5%)	<0.001	3 (25.0%)	>0.99	144 (19.7%)	24 (36.4%)+
Infant hypoglycemia‡	1 (5.6%)	—	8 (23.5%)	—	1 (8.3%)	—	74 (10.7%)	10 (15.4%)
Any adverse outcome‡	6 (33.3%)	>0.99	19 (57.6%)	0.003	3 (25.0%)	>0.99	196 (28.2%)	28 (43.8%)+

IQR, interquartile range. *Differences across the four groups (NGT and three GDM subtypes) were compared using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. When the *P* value from the Kruskal-Wallis test or Fisher exact test was <0.05, pairwise comparisons between the NGT group and each GDM group were made using Dunn test or Fisher exact test. Bonferroni-adjusted *P* values are given for these pairwise comparisons in the third, fifth, and seventh columns. +The All GDM group was significantly different from the NGT group when compared using the rank sum test or χ^2 test. ‡Missing data on infant hypoglycemia for 50 participants and delivery route for 12 participants; all other variables had data missing for <10 participants.

greater insight into the hormonal alterations that lead to GDM.

Women with GDM due to a predominant insulin sensitivity defect appeared to be at particularly high risk for fetal overgrowth and GDM-associated adverse outcomes. This increased risk might be partly due to the higher BMI or fasting glucose in this group, although maternal BMI did not completely explain this (1,16). Discovering and targeting both glycemia and nonglycemic factors that influence fetal growth in women with GDM characterized by impaired insulin sensitivity has the potential to reduce the morbidity associated with this condition.

Limitations of our study included lack of data on insulin secretion or insulin sensitivity before and after pregnancy; small sample size, which limited power to directly compare GDM subtypes; and a relatively homogeneous cohort composed predominantly of women of European descent.

In summary, we have demonstrated that GDM is a heterogeneous condition on the basis of glycemic physiology and have linked underlying physiologic processes to important adverse perinatal outcomes. GDM subtypes, based on the relative contribution of insulin sensitivity and secretion defects, appear to have distinct biology, as evidenced by their differing adipokine and risk profiles. Future research should consider the heterogeneity present in the population of women with GDM.

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