Pregnancy Insulin, Glucose, and BMI Contribute to Birth Outcomes in Nondiabetic Mothers

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OBJECTIVE — We investigated the effects of normal variations in maternal glycemia on birth size and other birth outcomes.

RESEARCH DESIGN AND METHODS — Women in two unselected birth cohorts, one retrospective ($n = 3,158$) and one prospective ($n = 668$), underwent an oral glucose challenge at 28 weeks of gestation. In the retrospective study, glycemia was linked to routine birth records. In the prospective study, offspring adiposity was assessed by skinfold thickness from birth to age 24 months.

RESULTS — In the retrospective study, within the nondiabetic range (2.1–7.8 mmol/l), each 1 mmol/l rise in the mother's 60-min glucose level was associated with a (mean ± SEM) 2.1 ± 0.8% ($P = 0.006$) rise in absolute risk of assisted vaginal delivery, a 3.4 ± 0.8% ($P < 0.0001$) rise in emergency cesarean delivery, a 3.1 ± 0.7% ($P < 0.0001$) rise in elective cesarean delivery, and a 46 ± 8 g ($P < 0.0001$) increase in offspring birth weight. In the prospective study, fetal macrosomia (birth weight >90th centile) was independently related to the mother's fasting glucose (odds ratio 2.61 per +1 mmol/l [95% CI 1.15–5.93]) and prepregnancy BMI (1.10 per +1 kg/m^2 [1.04–1.18]). The mother's higher fasting glycemia ($P = 0.004$), lower insulin sensitivity ($P = 0.01$), and lower insulin secretion ($P = 0.02$) were independently related to greater offspring adiposity at birth. During postnatal follow-up, the correlation between the mother's glycemia and offspring adiposity disappeared by 3 months, whereas prepregnancy BMI was associated with offspring adiposity that was only apparent at 12 and 24 months (both $P < 0.05$).

CONCLUSIONS — Prepregnancy BMI, pregnancy glycemia, insulin sensitivity, and insulin secretion all contribute to offspring adiposity and macrosomia and may be separate targets for intervention to optimize birth outcomes and later offspring health.

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The international multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study recently reported that maternal fasting and stimulated glucose levels showed linear effects on risks for macrosomia, cesarian delivery, and neonatal hypoglycemia at birth (1). These findings question the optimal indicators used to manage maternal glucose levels during pregnancy.

The elevation in maternal glycemia during pregnancy is consequent to a rise in maternal insulin resistance, which in turn is attributed to hormonal changes, such as placental growth hormone (2), or to a maternal inflammatory response to placental cells (3). Higher maternal glucose levels facilitate glucose transport across the placenta, which in turn promotes fetal insulin secretion and fetal growth (4). In addition to higher glucose levels, maternal insulin resistance also elevates circulating amino acids and fatty acids, and these nutrients could also stimulate fetal insulin secretion and fetal growth. Therefore, maternal BMI, insulin sensitivity, and insulin secretion could all contribute to offspring birth size and birth outcomes.

We investigated the relationships between maternal insulin, glucose, and BMI during pregnancy and offspring birth size and adiposity in a prospective study with follow-up of offspring to age 24 months. In a separate large retrospective study, we explored the nature of the relationship between maternal glycemia on birth weight and mode of delivery.

RESEARCH DESIGN AND METHODS

— The retrospective cohort (the Cambridge Wellbeing Study) comprised mothers identified from routine clinical data in an electronic database of all deliveries at the Rosie Maternity Hospital, Cambridge, U.K., between 1999 and 2000. The data were merged to a biochemistry database of maternal venous blood glucose levels 60 min after a 50-g oral glucose load at 27–29 weeks of gestation as a routine screening test for gestational diabetes mellitus. Women with 60-min glucose levels >7.8 mmol/l were excluded from this study, as these women would have been considered at high risk of gestational diabetes mellitus (5). We identified data for 3,158 Caucasian women with normal glucose tolerance, who denied smoking or taking any medication at the time of glucose testing and who had a subsequent full-term (≥37 weeks of gestation) singleton delivery. Birth weight was measured at delivery by the midwife.

The prospective cohort (the Cambridge Baby Growth Study) was recruited from mothers attending ultrasound clinics during early pregnancy at the Rosie Maternity Hospital between 2001 and

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2006. At 28 weeks of gestation, a 75-g oral glucose load (oral glucose tolerance test [OGTT]) was given. Venous blood glucose and insulin levels were measured at fasting and at 60 min, and capillary blood glucose was measured at 30, 90, and 120 min. Of a total of 708 women who underwent an OGTT, we excluded 34 (4.8%) who had known diabetes, a further 4 women who had a 120-min capillary glucose level >8.6 mmol/l, and 2 women who had fasting venous glucose >6.1 mmol/l. Complete data on glucose and insulin levels and offspring birth weight were available for 668 nondiabetic pregnant women with normal fasting glucose and glucose tolerance. Birth weight was measured by the midwife. Offspring skinfold thicknesses (biceps, triceps, subscapular, and suprailiac) were measured at birth (<7 days old). Measurements were performed in duplicate by trained research nurses using a Harpenden Skinfold Caliper (Holtain, Crosswell, Crymych, Pembrokeshire, U.K.).

Ethical approval

Both studies were approved by the local ethics committee, Addenbrooke's Hospital, Cambridge, U.K. For the retrospective Cambridge Wellbeing Study, we only analyzed routinely collected and anonymized data, and therefore consent was not required. For the prospective Cambridge Baby Growth Study, written informed consent was obtained from all mothers by a research nurse.

Assays

In both cohorts, mother's whole blood glucose levels were taken from routine measurements in the Clinical Biochemistry Department, Addenbrooke's Hospital, U.K., using a standard glucose oxidase–based assay. In the Cambridge Baby Growth Study, fasting and stimulated insulin levels were measured in the Department of Pediatrics. Insulin was measured by enzyme-linked immunosorbent assay using a commercial kit (DSL, London, U.K.). Sensitivity was 0.26 mU/l. Intra-assay coefficients of variation (CVs) were 4.4 and 5.1% at 10.3 and 35.8 mU/l, and equivalent inter-assay CVs were 8.7 and 2.9%; this assay has no cross-reactivity with proinsulin at levels up to 1,000 pmol/l.

Calculations

Insulin sensitivity was estimated using homeostasis model assessment (HOMA) (6). To estimate insulin secretion independent of insulin sensitivity, we calculated the disposition index as the insulinogenic index [(insulin 60 − insulin 0)/(glucose 60 − glucose 0)] (7) divided by the insulin resistance index (8). Offspring adiposity at ages 0, 3, 12, and 24 months was estimated as the average of the standardized scores for the four skinfold thickness measurements adjusted for age and sex.

Statistics

For the retrospective Cambridge Wellbeing Study, glucose levels were categorized into five groups (≤4, 4.1–5.0, 5.1–6.0, 6.1–7.0, and 7.1–7.8 mmol/l). Differences in birth weight and birth outcomes between these five groups were analyzed by ANOVA and χ^2 tests for trend. Regression analyses were also performed using the continuous variables glucose and glucose^2 to test for nonlinearity.

For the prospective Cambridge Baby Growth Study, correlations between continuous variables were tested by linear regression, adjusted for potential confounding factors (maternal age, height, smoking in pregnancy, parity, offspring sex, and gestational age). Results of these analyses are displayed as standardized regression coefficients (β). Insulin levels were positively skewed, and logarithms were calculated to achieve normal distributions.

RESULTS

Maternal glucose levels and birth outcomes

In the retrospective Cambridge Wellbeing study, associations were identified between various birth outcomes and maternal glucose levels within the normal nondiabetic range (glucose level ≤7.8 mmol/l 60 min after a 50-g glucose load) (Table 1). Offspring birth weights increased by (mean ± SEM) 46 ± 8 g for each 1 mmol/l rise in maternal 60-min stimulated glucose level ($P < 0.0001$, n = 3,158), and a continuous trend was apparent across the range of normal glucose levels (Table 1). Each 1 mmol/l increase in maternal postchallenge glucose levels was also associated with a rise in the absolute risk of assisted vaginal deliveries (2.1 ± 0.8%, $P = 0.006$), emergency cesarean delivery (3.4 ± 0.8%, $P < 0.0001$), and elective cesarean delivery (3.1 ± 0.7%, $P < 0.0001$) (Table 1). No significant deviation from linearity was observed for any outcome (data not shown).

Table 1—*Birth weight and birth outcomes by maternal glucose levels within the nondiabetic range (≤7.8 mmol/l 60 min after a 50-g glucose load) in the retrospective Cambridge Wellbeing Study*

Outcome	Maternal glucose level (mmol/l)*					Trend (per + 1 mmol/l)	P_{trend}
	<4.0	4.1–5.0	5.1–6.0	6.1–7.0	7.1–7.8		
n	311	1,050	1,016	554	227		
Birth weight (g)	3,446 (3,398–3,496)	3,514 (3,488–3,540)	3,529 (3,502–3,555)	3,606 (3,570–3,642)	3,622 (3,555–3,690)	46 ± 8	<0.0001
Assisted delivery (%)	14.4 (9.6–19.3)	19.9 (17.1–22.6)	21.5 (18.6–24.3)	20.4 (16.5–24.3)	27.8 (21.3–34.3)	2.1 ± 0.8	0.006
Emergency cesarean delivery (%)	10.9 (6.1–15.8)	15.5 (12.8–18.3)	17.7 (14.8–20.5)	20.4 (16.5–24.2)	27.8 (21.5–34.1)	3.4 ± 0.8	<0.0001
Elective cesarean delivery (%)	9.1 (4.5–13.6)	13.3 (10.7–15.8)	14.3 (11.7–17.0)	16.2 (12.6–19.8)	26.5 (20.8–32.3)	3.1 ± 0.7	<0.0001

Data are means (95% CI) or means ± SEM adjusted for sex and parity. n = 3,158. *After a 50-g oral glucose challenge at 27–29 weeks of gestation.

Table 2—*Characteristics of mothers in the prospective Cambridge Baby Growth Study with normal glycemia (fasting glucose <6.1 mmol/l and 120 min post–75-g OGTT glucose level ≤8.6 mmol/l) and reportedly nondiabetic*

	Mean	Median	SD	Minimum	Maximum
Age (years)	33.3	33.3	4.1	18.1	47.5
Prepregnancy weight (kg)	66.3	63.5	13.1	40.0	143.2
Prepregnancy BMI (kg/m^2)	24.1	23.0	4.4	16.6	48.0
Height (cm)	165.9	165.1	7.1	146.0	190.0
Venous glucose					
0 min (mmol/l)	4.3	4.3	0.4	2.7	6.0
60 min (mmol/l)	6.6	6.5	1.5	3.0	13.1
Capillary glucose 120 min (mmol/l)	6.5	6.5	1.0	2.7	8.6
Insulin					
0 min (pmol/l)	51.5	43.6	28.1	5.3	347.0
60 min (pmol/l)	406.4	354.7	239.0	38.9	2,315.8

N = 668.

Maternal BMI and glucose levels related to offspring birth size

Maternal characteristics of the prospective Cambridge Baby Growth Study are displayed in Table 2. Among women with normal glycemia (fasting glucose <6.1 mmol/l and 120-min post–75-g OGTT glucose level ≤8.6 mmol/l and reportedly nondiabetic), distinct effects of maternal glucose levels and prepregnancy BMI were seen on infant birth size (Fig. 1). Mother's fasting glucose level was more strongly related to offspring skinfolds ($\beta = 0.207$, $P < 0.0001$) and weight at birth ($\beta = 0.180$, $P < 0.0001$) than to birth length ($\beta = 0.097$, $P = 0.02$). Conversely, mother's prepregnancy BMI was independently related to offspring birth length ($\beta = 0.104$, $P = 0.009$) and birth weight ($\beta = 0.090$, $P = 0.04$) but not to skinfolds at birth ($\beta = 0.048$, $P = 0.2$) (Fig. 1).

The risk of fetal macrosomia (birth weight >90th centile for gestational age and sex) was independently related to both the mother's fasting glucose (odds ratio 2.61 per +1 mmol/l [95% CI 1.15–5.93]) and prepregnancy BMI (1.10 per +1 kg/m^2 [1.04–1.18]).

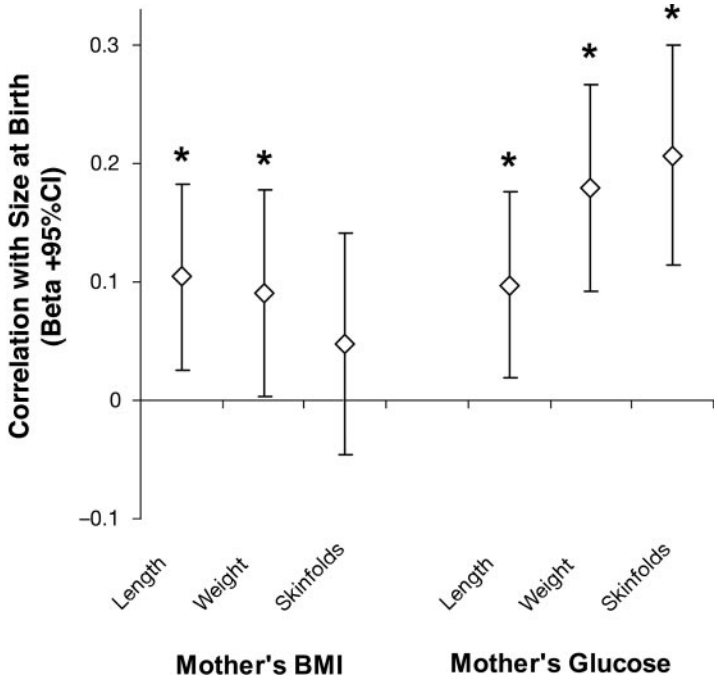

Figure 1— *Distinct influences of the mother's prepregnancy BMI and gestational fasting glucose level on offspring size at birth (length, weight, and skinfolds). Standardized correlation coefficients (β ± 95% CI) from multivariable models that included both BMI and fasting glucose as determinants are shown. *P < 0.05, also adjusted for maternal age, height, smoking in pregnancy, parity, offspring sex, and gestational age.*

Maternal insulin and glucose metabolism and offspring adiposity

Offspring skinfolds at birth were more strongly related to fasting glucose ($\beta = 0.222$, $P < 0.0001$) than to 30-min glucose ($\beta = 0.086$), 60-min glucose ($\beta = 0.094$), 90-min glucose ($\beta = 0.074$), or 120-min glucose ($\beta = 0.114$, all $P < 0.05$). Beyond the effect of fasting glucose, stimulated glucose levels did not further contribute to the variance in offspring skinfolds at birth (data not shown).

However, independent of the mother's glucose levels, the mother's insulin sensitivity ($\beta = -0.129$, $P = 0.01$) and insulin secretion (disposition index, $\beta = -0.137$, $P = 0.02$) were both inversely related to offspring skinfolds at birth (Table 3).

Correlations with adiposity during infancy

In the prospective Cambridge Baby Growth Study, prepregnancy BMI correlated positively with offspring adiposity at ages 12 and 24 months (both $P < 0.05$). However, the correlation between the mother's glycemia and offspring adiposity, which had been apparent at birth, disappeared from age 3 months onward (Fig. 2). Accordingly, higher maternal fasting glucose levels were associated with a decline in offspring adiposity between birth to age 12 months ($\beta = -0.218$, $P < 0.0001$).

CONCLUSIONS — In two contemporary U.K. cohorts, we observed that increasing maternal glucose levels within the normal nondiabetic range were consistently related to larger offspring birth size and increased risk of interventional deliveries. Maternal glucose levels specifically enhanced offspring adiposity at birth, and additional influences of maternal insulin sensitivity and insulin secretion were apparent. Postnatally, the effect of maternal glycemia on offspring adiposity rapidly disappeared during infancy, and over the same period a positive effect of maternal BMI became apparent.

Although gestational diabetes mellitus has long been associated with fetal macrosomia (9), our data support a growing number of studies that report a continuous effect of maternal glucose levels,

Table 3—*Final multivariable model of determinants of offspring skinfold thicknesses at birth in the Cambridge Baby Growth Study*

	Standardized coefficient (β)	*P* value
Significant factors		
Gestation	0.221	<0.001
Female sex	0.111	0.02
Parity	0.127	0.01
Venous glucose 0 min	0.170	0.004
Mother's insulin sensitivity (HOMA)	−0.129	0.01
Mother's disposition index	−0.137	0.02
Nonsignificant factors		
Mother's age	−0.081	0.1
Mother's height	0.077	0.1
Mother's BMI	0.049	0.3
Smoking	0.004	0.9
Venous glucose 60 min	−0.012	0.9

even in the absence of maternal diabetes, on offspring birth weight and pregnancy outcomes (1,10–13). Most recently, the international multicenter HAPO Study reported that maternal fasting, 60-min, and 120-min glucose levels all showed similar linear effects on risks for macrosomia, cesarian delivery, neonatal hypoglycemia, and insulinemia at birth (1). Such findings indicate that the current criteria used to diagnose and manage gestational hyperglycemia need urgent reconsideration.

Our study shows for the first time that in addition to maternal glycemia, differences in maternal insulin sensitivity, insulin secretion, and BMI also have an impact on offspring size and adiposity. These findings suggest that maternal energy substrates other than glucose, such as free fatty acids or amino acids, may have an important independent influence on fetal growth. Although we used the HOMA model of fasting insulin sensitivity, smaller studies using the insulinemic-euglycemic clamp method showed that maternal insulin sensitivity during pregnancy contributes to both offspring body fat and fat-free mass (14).

The effect of maternal overweight or obesity on larger offspring size has been attributed mainly to higher pregnancy glucose levels. We now show that, independent of glycemia, prepregnancy BMI appears to influence offspring body length and weight, rather than adiposity. In contrast, the major effect of maternal glycemia on fetal growth was on adiposity (15). Fetal length may be determined at a very early stage during gestation, whereas increased adiposity may result largely from glucose transport to the fetus during the third trimester. In animal models, maternal nutrition during the periconceptual period may have important effects on subsequent fetoplacental growth (16). In humans, differences in fetal length may therefore reflect early gestational placentation and periconceptual maternal nutrition. Our findings therefore indicate that the overweight or obese mother might somehow enhance early placentation and early transport of nutrient to the fetus, possibly by affecting gene methylation (17).

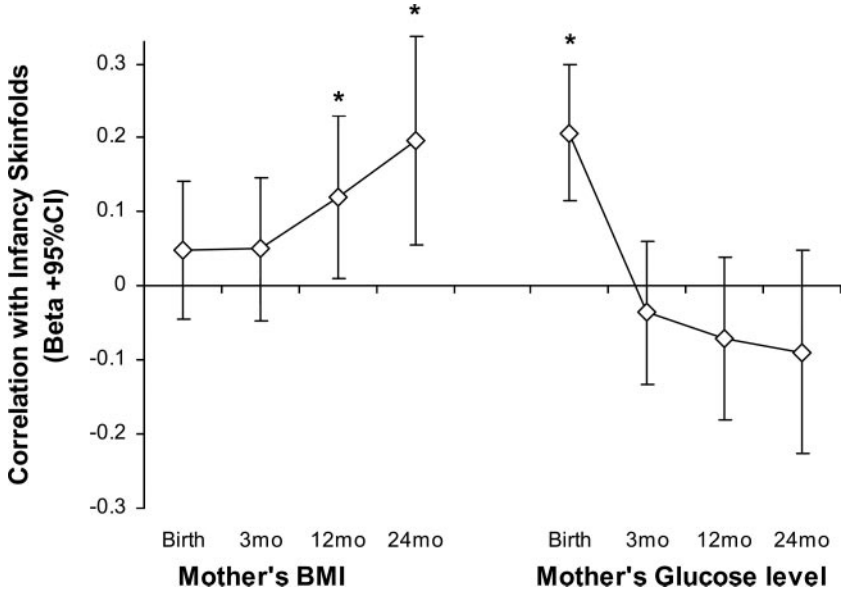

Figure 2— *Distinct postnatal influences of the mother's prepregnancy BMI and gestational fasting glucose level on offspring skinfold thicknesses during infancy (birth to 24 months). Standardized correlation coefficients (β ± 95% CI) from multivariable models that included both BMI and fasting glucose as determinants are shown.* *P < *0.05.*

Offspring of diabetic pregnancies appear to have increased long-term risks of obesity (18,19) and impaired glucose tolerance (18). It has been suggested that fetal exposure to glucose increases risks of overweight and type 2 diabetes in later life (13). However, such observational studies cannot completely separate the specific effects of gestational glucose levels from inherited genetic susceptibility to overweight and type 2 diabetes. Our data show that the effect of maternal glycemia on offspring adiposity is only transitory and disappears soon after birth. Therefore, any deleterious long-term effects of fetal glucose exposure on type 2 diabetes risk must be more subtle, possibly affecting fetal β-cell capacity or adipocyte distribution and function rather than overall adiposity. In contrast, we observed that the "transgenerational" effects of maternal BMI on offspring adiposity emerge early in infancy and could be explained by transmission of genetic susceptibility to obesity (20) or by parental influences on infant nutrition.

In summary, the linear nature of the associations between maternal glycemia and adverse birth outcomes leads to uncertainties in the optimal definition of gestational hyperglycemia. In addition to intensive interventions in high-risk individuals, according to epidemiological principles, such linear associations indicate that population-based strategies to reduce glycemia in all pregnant women would have a greater impact on reducing adverse pregnancy outcomes in similar Westernized settings (21). Furthermore, the aim of such strategies should also be

to reduce maternal prepregnancy BMI and improve insulin sensitivity as these factors may influence fetal growth independent of maternal glycemia.

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