Hyperinsulinemia in Cord Blood in Mothers With Type 2 Diabetes and Gestational Diabetes Mellitus in New Zealand

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OBJECTIVE — In genetically diabetes-prone populations, maternal diabetes during pregnancy increases the risk of their children developing diabetes and obesity (the vicious cycle of type 2 diabetes). Fetal hyperinsulinemia at birth acts as a marker of this risk. We therefore examined whether cord insulin and leptin concentrations are increased in offspring of Maori and Pacific Island mothers with type 2 and gestational diabetes mellitus (GDM) and varying degrees of glycemic control (HbA_{1c}).

RESEARCH DESIGNS AND METHODS — Maori and Pacific Island mothers were prospectively recruited at Middlemore Hospital, South Auckland. Cord blood was taken from umbilical vein at birth from singleton babies born after 32 weeks of gestation to 138 mothers with GDM, 39 mothers with type 2 diabetes, and 95 control mothers.

RESULTS — Babies born to mothers with both type 2 diabetes and GDM had higher birth weight and skinfold thickness and markedly higher concentrations of insulin (median [interquartile range] type 2 diabetes 77 pmol/l [42–143], GDM 67 pmol/l [42–235], and control subjects 33 pmol/l [18–62]; $P < 0.001$) and leptin (type 2 diabetes 39 ng/ml [18–75], GDM 31 ng/ml [17–58], and control subjects 13 ng/ml [8–22]; $P < 0.001$) in cord blood. Cord insulin concentrations >120 pmol/l were found in 29% of offspring of mothers with GDM and 31% of mothers with type 2 diabetes. Many mothers with GDM had abnormalities of glucose tolerance postpartum (20% type 2 diabetes, 34% impaired glucose tolerance or impaired fasting glucose). Higher cord insulin (57 pmol/l [40–94]) and leptin (26 ng/ml [17–39]) concentrations were found even in offspring of GDM mothers with normal glucose tolerance postpartum.

CONCLUSIONS — Raised cord insulin and leptin concentrations are a common finding in offspring of mothers with type 2 diabetes and GDM in this population.

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Fetal hyperinsulinemia is characteristic of pregnancy complicated by maternal diabetes and underpins complications such as macrosomia (1). Cord leptin correlates with measures of adiposity at birth (2–4) and is also raised in offspring of mothers with diabetes (3,4). Assessment of insulin and leptin at birth may be a particularly useful way of monitoring whether the fetus has been exposed to abnormally high levels of glucose in utero. Fetal hyperinsulinism may also have potential prognostic implications. Several studies have suggested that the maternal intrauterine environment might result in "programming" of later disease. An increased risk of obesity (5–8) and abnormal glucose tolerance (9–12) are observed when offspring have been exposed to maternal diabetes in utero. Fetal hyperinsulinemia acts as a marker of this increased risk, offspring of diabetic mothers with higher insulin levels in utero being at a higher risk of later metabolic complications (7,8,10).

The Pacific Island and Maori peoples of New Zealand are populations at high risk of both type 2 and gestational diabetes during pregnancy. We measured concentrations of fetal insulin, insulin propeptides, and leptin, together with weight and skinfold thickness at birth, with the following hypotheses: where the mother has type 2 diabetes and gestational diabetes mellitus (GDM), fetal hyperinsulinism is common despite treatment of disease, and fetal leptin and fat mass are similarly increased; and in subgroup analysis, these effects are most pronounced in those women with known preexisting disease and not found in those with GDM and subsequent normal postnatal oral glucose tolerance test (OGTT).

RESEARCH DESIGN AND METHODS

— The case group comprised Maori and Pacific Island women planning to deliver in Middlemore Hospital, South Auckland, who had either type 2 diabetes known before pregnancy or a positive OGTT during pregnancy. Local criteria for diagnosis of GDM were fasting glucose ≥5.5 mmol/l and/or a 2-h value after a 75-g glucose load ≥9.0 mmol/l. All women delivered between 1 February 1999 and 31 May 2001. A total of 232 women with diabetes were eligible for the study, and 218 (94%) agreed to take part. Twenty-eight women were excluded during pregnancy (12 miscarried, 10 moved out of the area, 3 twin pregnancies, 1 delivery at <32 weeks' gestation, 1 intrauterine death, and 1 termination of pregnancy for fetal abnormality). To en-

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Abbreviations: GDM, gestational diabetes mellitus; ILM, insulin-like molecule; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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sure quality of insulin assays (13), 13 case subjects were excluded after delivery if cord blood was not collected or there was gross sample hemolysis (9), if there was a delay >20 min before cord blood collection or >60 min before freezing plasma (4), or if antenatal glucocorticoids had been administered in the 24 h before birth (no exclusions). A total of 138 women with GDM and 39 women with type 2 diabetes were thus included in the analysis.

Control subjects were selected using a pseudo-random number generator (MS Excel) to produce a standardized template that was placed against clinic lists. To avoid overmatching, the only selection criteria were ethnicity (Pacific Islander or Maori), no previous history of diabetes, and no evidence of diabetes in the current pregnancy (a negative screen after 26 weeks' pregnant). The screen used was the polycose 50-g unfasted test with blood test 1 h later, normal glucose <7.8 mmol/l. One hundred and thirty control subjects were invited to participate, with 17 women declining and 18 excluded (7 twins and 11 no cord blood sample available).

All participants were given information sheets translated into Tongan and Samoan when required, and the study was explained by the research midwife (J.B.) or another member of the clinical team. Participants gave informed consent, and the trial protocol received ethical approval from the Health Funding Authority, Auckland Ethics Committee.

Clinic protocol

Pregnancy care was supervised by a combination of hospital and home visits by diabetes midwives. All women were instructed in home blood glucose monitoring at a first home visit by the diabetes midwives with recommendation to test fasting and 2 h postprandially (five tests daily). All women were routinely seen by an obstetrician and diabetologist in the clinic monthly until 28 weeks, fortnightly until 36 weeks, and weekly until delivery. Insulin, usually as lispro insulin up to three times daily along with Humulin N, was commenced if fasting glucose was ≥5.5 mmol/l on two occasions or postprandial readings were consistently ≥6.5 mmol/l. After commencement of insulin, diabetes midwives maintained twice weekly contact with all women, adjusting doses as necessary. Where daily dosage exceeded 200 units, subcutaneous insulin pumps were the preferred route of administration. No oral hypoglycemic agents were used.

All women with GDM (diabetes with first onset or recognition in pregnancy) were offered a 75-g OGTT at 8 weeks postnatally. Glucose tolerance was classified by 1998 American Diabetes Association criteria (14).

Collection of cord blood and neonatal assessment and assays

Delivery room midwives were trained by a single research midwife (J.B.) in all procedures. After delivery of the baby, but before placental delivery, either the delivering midwife or the operator at cesarean section took 20 ml cord blood from the umbilical vein. Blood was centrifuged in the delivery suite, and plasma was initially stored at −15°C for up to 48 h before final storage at −86°C.

A neonatal pediatrician (L.F.J.M.) or one specified senior neonatal nurse assessed the babies within 24 h of delivery. Crown-heel length and scapular and tricep skinfold thicknesses were measured with a Harpenden neonatometer and Harpenden calipers (Holtain Limited, Dyfed, U.K.), respectively.

Assays were performed either at Addenbrookes Hospital, Cambridge, U.K. (plasma insulin, proinsulin, 32–33 split proinsulin, and glucose) or Auckland University Laboratory, Grafton, Auckland (leptin). The methods used for analysis were as previously described (15). HbA_{1c} (A1C) assays were performed at two local laboratories using either affinity chromatography (Primus, Kansas City, MO) or ion-exchange chromatography (Bio-Rad, Hercules, CA). Regular interlaboratory comparisons were performed to ensure the comparability of results.

Statistical analysis

Differences between groups were analyzed by either χ^2 test (for categorical variables) or by general linear model and post hoc Student-Newman-Keuls test. *Z* scores were calculated for babies of 38–41 weeks' gestation using ethnic-specific birth weight centiles developed from deliveries at National Women's Hospital, Auckland (16), for babies of Maori, Samoan, and Tongan ethnicity or "other" (other Pacific Island ethnicity including Cook Island) in keeping with the derivation of the centile charts. Simple correlations of insulin-like molecules (ILMs) to fetal and maternal variables were assessed by Spearman's rank correlation. The hypothesis that correlation coefficients of the ILMs versus birth weight or leptin were different from those of insulin versus birth weight or leptin was assessed by standard methods (17).

RESULTS — Mothers with both GDM and type 2 diabetes were older, more parous, heavier, more likely to have labor induced, and more likely to be delivered by cesarean section compared with control subjects (Table 1). Mothers with type 2 diabetes were more likely to have had essential hypertension noted before pregnancy (28% type 2 diabetes vs. 4% control subjects and 2% GDM subjects; $P < 0.001$), and booking blood pressure was higher in both diabetic groups (Table 1). No differences in other medical diagnoses were observed. A1C was significantly higher in mothers with type 2 diabetes compared with GDM subjects at 30 weeks of gestation and at the end of pregnancy (Table 1).

Despite being born ~2 weeks earlier than control subjects, offspring of mothers with GDM were ~300 g heavier at birth, and birth weight adjusted for sex and gestation (expressed as birth weight *Z* score) was significantly greater in offspring of mothers with both type 2 and diabetes and GDM (Table 2). Offspring of diabetic mothers had higher skinfold thickness as well as markedly higher concentrations of insulin, insulin propeptides, and leptin, with median values generally two to three times those of control subjects. These relationships persisted after multivariate analysis controlling for delivery method, sex, and ethnicity and, in the case of insulin, insulin propeptides and leptin even after adjusting for those variables and standardized birth weight. Neither mode of delivery nor use of intravenous dextrose in delivery (recorded for 88% of case subjects and used in 82% of GDM and 95% of type 2 diabetes deliveries) were independent predictors of cord insulin.

For most variables, offspring of mothers with GDM and type 2 diabetes were similar (Table 2). In general, concentrations of leptin, insulin, and the insulin propeptides were higher in offspring of mothers with type 2 diabetes, while absolute values of birth weight and *Z* score of birth weight were higher in the offspring of mothers with GDM. However, none of the differences between the two diabetic groups were significant. Values of all three ILMs (insulin, proinsulin, and 32–33 split proinsulin) were highly intercorrelated. In general, these relationships were stron-

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Table 1—*Maternal demographic and delivery details*

	Control subjects	GDM subjects	Type 2 diabetic subjects
n	95	138	39
Age (years)	29.3 ± 6.4	33.0 ± 5.9*	34.8 ± 5.2*
Parity			
0	23	12	10
1–2	44	38*	41
≥3	32	51	49
Early pregnancy weight (kg)	86.5 ± 19.7	102.0 ± 19.9*	98.5 ± 21.5*
BMI in early pregnancy (kg/m^2)	32.5 ± 6.9 (*n* = 70)	38.0 ± 6.9 (*n* = 111)*	36.4 ± 7.4 (*n* = 35)*
Booking systolic blood pressure (mmHg)	111 ± 11 (*n* = 85)	120 ± 14 (*n* = 100)*	126 ± 15 (*n* = 26)*†
Booking diastolic blood pressure (mmHg)	69 ± 9 (*n* = 85)	74 ± 11 (*n* = 100)*	77 ± 12 (*n* = 26)*
A1C week 30 (%)	—	6.0 ± 0.9 (*n* = 69)†	6.5 ± 1.3 (*n* = 32)
A1C end of pregnancy (%)	—	6.0 ± 0.7 (*n* = 111)†	6.4 ± 1.3 (*n* = 28)
Current smoker	31	30	31
Ethnic group			
Maori	38	21	15
Samoan	32	33	46
Tongan	16	24	21
Cook Island	9	13	8
Other	5	9	10
Previous LSCS	18	20	36*†
Labor induced	22 (*n* = 91)	69 (*n* = 119)*	71 (*n* = 31)*
Delivery			
Elective cesarean	4	14	21
Emergency cesarean	19	20	23
Operative vaginal	4	3	10*
Spontaneous	72	63	46

Data are means ± SD or percent, unless otherwise indicated. *$P < 0.05$ vs. control; †$P < 0.05$ type 2 diabetes vs. GDM. LSCS, lower-segment cesarean section.

gest between 32–33 split proinsulin and proinsulin (data not shown). ILMs were significantly related to birth weight and leptin in all three groups (Table 3). In general, 32–33 split proinsulin showed a stronger relationship to birth weight and leptin than insulin, but this was only significantly greater in the case of leptin in type 2 diabetes (Table 3). By contrast, insulin was only significantly correlated to cord glucose in offspring of mothers with diabetes (GDM or type 2 diabetes) and more strongly related to cord glucose concentrations than to either 32–33 split proinsulin (in GDM and type 2 diabetes) or proinsulin (in type 2 diabetes).

In mothers with diabetes (data for type 2 diabetes and GDM combined), maternal A1C at the end of pregnancy was significantly correlated with standardized birth weight ($r = 0.24$, $n = 123$, $P = 0.008$), skinfold thickness (triceps: $r = 0.39$, $n = 105$, $P < 0.001$; scapular: $r = 0.35$, $n = 105$, $P = 0.002$), cord insulin ($r = 0.30$, $n = 132$, $P = 0.004$), 32–33 split proinsulin ($r = 0.31$, $n = 135$, $P = 0.003$), and leptin ($r = 0.40$, $n = 136$, $P < 0.001$).

Among mothers with GDM, 107 (79%) underwent postnatal glucose tolerance testing. A high number of mothers (57 of 107) had persisting abnormalities of glucose tolerance (20% type 2 diabetes and 34% impaired glucose tolerance or impaired fasting glucose), suggesting that many women may have had preexisting, but clinically undetected, abnormalities of glucose tolerance before pregnancy. In general, birth weight, skinfold thickness, insulin, insulin propeptides, and leptin were higher in mothers with GDM and abnormal glucose tolerance after pregnancy. In those with GDM, values of A1C were highest in those subsequently found to have type 2 diabetes on OGTT postpartum (A1C at end of pregnancy: postpartum type 2 diabetes 6.5 ± 0.8%, $n = 29$; postpartum impaired glucose tolerance/impaired fasting glucose 6.0 ± 0.6%, $n = 19$; postpartum normal OGTT 5.7 ± 0.6%, $n = 43$; $P < 0.0002$). Notably, values of insulin, 32–33 split proinsulin, and leptin were higher than in control subjects even in offspring of those GDM mothers with entirely normal glucose tolerance after pregnancy (Table 2).

CONCLUSIONS — Exposure of the fetus to maternal diabetes results in characteristic changes in birth weight, adiposity, and fetal insulin production. We have used cord insulin and leptin as indicators of exposure to an abnormal intrauterine environment. Notably, birth weight, skinfold thickness, insulin, insulin propeptides, and leptin are significantly increased in our population, not only in offspring of mothers with type 2 diabetes but also offspring of mothers with GDM. Further, cord hormonal measures indicate that insulin and leptin are higher in offspring of mothers with GDM even when glucose tolerance returns to normal postpartum. Fetal hyperinsulinemia is a frequent outcome of pregnancy complicated by diabetes in our population, and this is associated with increased fetal growth and adiposity.

How important is the finding of raised fetal insulin levels at birth? Several studies suggest that exposure to maternal diabetes in utero exerts programming effects to increase the risk of adiposity and type 2 diabetes in early life. In the Pima Indian population of southwestern U.S., maternal diabetes is clearly associated

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Table 2—*Neonatal outcomes by maternal diabetes status*

	Control	GDM	Type 2 diabetes (prepregnancy)	GDM*		
				Normal OGTT postnatally	IGT/IFG postnatally	Type 2 diabetes postnatally
n	95	138	39	50	21	36
Male (%)	57	48	38	46	62	47
Gestation (weeks)	40.3 ± 1.4	38.6 ± 1.5†	38.2 ± 1.2†	38.9 ± 1.6	38.8 ± 1.0	38.3 ± 1.4
Birthweight (kg)	3.6 ± 0.6	3.9 ± 1.5†	3.6 ± 0.6	3.7 ± 0.5	4.0 ± 0.7	4.1 ± 0.6
Macrosomia (birth weight ≥4 kg)	21 (22)	54 (39)	13 (33)	14 (28)	11 (52)	18 (50)
Z score for birth weight‡	−0.08 ± 1.10 (*n* = 90)	0.94 ± 1.31 (*n* = 119)†	0.53 ± 1.14 (*n* = 30)†	1.26 ± 1.40 (*n* = 19)†	1.31 ± 1.4* (*n* = 29)	
Length (cm)	50.8 ± 2.1	50.9 ± 2.0	50.1 ± 2.4	50.5 ± 2.2 (*n* = 40)	51.3 ± 2.2 (*n* = 19)	51.4 ± 1.7 (*n* = 27)
Head circumference (cm)	35.5 ± 1.7 (*n* = 62)	35.8 ± 1.3 (*n* = 108)	35.2 ± 1.9 (*n* = 28)	35.5 ± 1.4 (*n* = 40)	36.2 ± 1.3 (*n* = 19)	36.1 ± 1.25 (*n* = 27)
Tricep thickness (cm)	0.44 ± 0.1 (*n* = 61)	0.50 ± 0.12 (*n* = 108)†	0.53 ± 0.13 (*n* = 28)†	0.46 ± 0.10 (*n* = 40)	0.51 ± 0.13 (*n* = 19)†	0.55 ± 0.10 (*n* = 27)†
Scapula thickness (cm)	0.44 ± 0.1 (*n* = 61)	0.56 ± 0.16 (*n* = 108)†	0.57 ± 0.19 (*n* = 28)†	0.49 ± 0.14 (*n* = 40)	0.58 ± 0.20 (*n* = 19)†	0.63 ± 0.12 (*n* = 27)†
Insulin (pmol/l)	33 (18–62) (*n* = 92)	67 (42–135) (*n* = 133)†	77 (42–143) (*n* = 36)†	57 (40–94)†	83 (31–162) (*n* = 20)†	101 (61–198) (*n* = 32)†
Proinsulin (pmol/l)	10 (8–13) (*n* = 93)	14 (10–19) (*n* = 134)†	16 (10–26) (*n* = 38)†	13 (9–15) (*n* = 48)	12 (10–16)†	19 (14–24) (*n* = 34)†
32–33 split proinsulin (pmol/l)	7.6 (5.6–15.6) (*n* = 93)	27 (10–52) (*n* = 134)†	26 (13–70) (*n* = 38)	21 (12–42) (*n* = 48)†	31 (8–50)†	42 (25–78) (*n* = 34)†
Glucose (mmol/l)	5.2 ± 0.9 (*n* = 91)	5.4 ± 1.1 (*n* = 132)	5.1 ± 1.4 (*n* = 37)	5.3 ± 1.1 (*n* = 49)	5.4 ± 1.1 (*n* = 20)	5.3 ± 1.2
Leptin (ng/ml)	13 (8–22) (*n* = 92)	31 (17–58) (*n* = 134)†	39 (18–75) (*n* = 37)†	26 (17–39)†	38 (17–62)†	52 (29–78) (*n* = 33)†

Data are means ± SD, median (interquartile range), *n* (%), or percent, unless otherwise indicated. *Results for participants with gestational diabetes subdivided by results of oral glucose tolerance after pregnancy. Postnatal OGTT results not available for 31 participants. †$P < 0.05$ vs. control. ‡Calculated for gestations 38–41 weeks. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

with an increase in risk of type 2 diabetes and obesity in offspring, in keeping with in utero programming of disease (9,18) and forming a "vicious cycle of type 2 diabetes" (19). More recently, studies (20,21) in hepatocyte nuclear factor-1α mutation carriers (maturity-onset diabetes of the young 3) have supported a role of the intrauterine environment in modifying risk of diabetes. Such studies are of great importance to Pacific Island and Maori women, as these populations are also believed to be at high genetic risk of obesity and type 2 diabetes and therefore likely to be prone to the same programming effects. Importantly, the risk of later adverse metabolic consequences appears to relate to fetal insulin levels (7,8,10). In this context, our finding of increased concentrations of insulin in cord blood offspring of mothers with type 2 diabetes and GDM suggests that such a cycle is also potentially present in Pacific Island and Maori peoples.

Are insulin levels raised to a similar degree as found in these previous studies? Weiss et al. (22) have suggested that cord insulin concentrations >120 pmol/l (20 μU/ml) are indicative of hyperinsulinemia relative to control subjects. Less than 1% of control pregnancies had insulin concentrations >120 pmol/l compared with 21% of offspring of mothers with GDM and 49% of offspring of mothers with type 1 diabetes. In our series, 3 of 91 offspring (3%) of control mothers, 29% of offspring of mothers with GDM, and 31% of offspring of mothers with type 2 diabetes had cord insulin concentrations >120 pmol/l. Results for the control subjects are similar to those of Weiss et al. and would suggest that insulin levels are indeed markedly raised in our offspring of diabetic mothers. Proinsulin and 32–33 split proinsulin have longer half-lives (23–25) and are poorer substrates for insulin-degrading enzymes (26) than insulin. We have previously demonstrated that insulin propeptides are more stable in cord blood than insulin and have closer relationships to fetal growth and leptin concentrations at birth than insulin (13). Insulin propeptides are also raised in offspring of mothers with GDM and comprise ~30–40% of all ILMs. Further, they are significantly correlated with birth weight and cord leptin. In general, 32–33 split proinsulin was more closely related to leptin (but not birth weight) in the diabetic groups. Taken together, these results would confirm that measurement of insulin propeptides are a useful indicator

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Table 3—*Relationship of ILMs to birth weight, leptin, and cord glucose*

	Control			GDM			Type 2 diabetes		
	Insulin	32–33 split proinsulin	Proinsulin	Insulin	32–33 split proinsulin	Proinsulin	Insulin	32–33 split proinsulin	Proinsulin
Z weight	**0.36**	**0.43**	**0.38**	**0.48**	**0.48**	**0.46**	**0.40**	**0.43**	**0.34**
Leptin	**0.49**	**0.61**	**0.40**	**0.53**	**0.59**	**0.50**	**0.46**	**0.68***	**0.59**
Cord glucose	*0.08*	*0.12*	*−0.04*	0.27	*0.17**	*0.17*	0.42	*0.16**	*0.06**

Spearman's correlation coefficients of insulin and insulin propeptides to variables from mother and child in offspring of control subjects ($n = 86$) and mothers with GDM ($n = 134$) or type 2 diabetes ($n = 39$) . Where the P value for simple Spearman's correlation is <0.01, r value is shown in bold type; where $0.01 < P < 0.05$, r is in standard type; where $P > 0.05$, r is in italics. For relationships with Z weight, leptin, and cord glucose, *r value for proinsulin or 32–33 split proinsulin significantly different from that of insulin at significance level $P < 0.05$.

of overall fetal insulinemia with potentially stronger relationships to important fetal outcomes.

The importance of GDM as a clinical entity has recently been demonstrated by an Australian randomized trial in which the identification and treatment of GDM significantly reduced the rate of fetal macrosomia and serious adverse perinatal outcome (27). Our data demonstrating that GDM is associated with fetal hyperinsulinemia in Maori and Pacific Island women provides biochemical confirmation that GDM is associated with an abnormal intrauterine environment that has at least short-term consequences for the neonate. As noted, Pacific Island and Maori women are at high risk of type 2 diabetes, and our results may not be generalizable to other populations. Notably, there was a very high rate of persistent abnormality of glucose tolerance in women with GDM, with 20% subsequently diagnosed as having type 2 diabetes and 34% having persisting impaired fasting glucose or impaired glucose tolerance. A high percentage of those with GDM (defined as first onset or recognition in pregnancy) in our study probably had clinically undetected abnormalities of glucose tolerance before pregnancy. Further, it is a population with high levels of insulin resistance. Over half of the women with preexisting type 2 diabetes ($n = 22$, 56%) and 13 (9%) of the women with GDM required >200 units of insulin and hence used an insulin pump. This is a warning for clinicians who are not used to such populations and who may be inclined to dismiss the significance of GDM. Cundy et al. (28), describing their extensive experience in Auckland, have already pointed to the poor pregnancy outcome associated with type 2 diabetes, regardless of whether the diagnosis is made before or during pregnancy. In keeping with this birth weight, skinfold thickness and cord insulin and leptin were equivalent in mothers with type 2 diabetes prepregnancy and those with type 2 diabetes diagnosed postnatally. Indeed, these measures were generally higher in mothers with type 2 diabetes diagnosed postnatally, although this did not achieve significance. Our second hypothesis rested on the expectation that the fetal hormonal and biometric data in those women with GDM and a normal postnatal OGTT would not differ from the control population. We postulated that this less-marked abnormality of glucose tolerance would be below threshold stimulus. In fact, this condition does seem to be part of the spectrum of significant disease. These fetuses had significantly raised insulin, insulin propeptides, and leptin concentrations. Cord insulin concentrations were on average double those of the control subjects, and cord insulin was >120 pmol/l in 16% of these offspring. Thus, the finding that fetal hyperinsulinemia is a common outcome of pregnancy in women with GDM in this population would support the importance of detection and careful monitoring of this group and suggests that similar studies might be carried out in other groups. Finally, our study confirms the expected modest but significant relationship of maternal glycemia with birth weight and cord insulin. A1C at the end of gestation correlated with standardized birth weight and cord measures of insulin, insulin propeptides, and leptin in mothers with GDM and type 2 diabetes and is in keeping with previous results in mothers with type 1 diabetes (13). This relationship offers some support for current treatment paradigms and the expectation that careful monitoring and treatment of blood glucose will return these outcomes toward normal. By contrast, birth weights of offspring mothers with type 2 diabetes were lower (although not significantly so) than those with GDM despite slightly higher A1C at the end of pregnancy. It is not clear to what extent this reflects influences of other maternal factors (such as microvascular complications, essential hypertension, or treatment of hypertension) to modify birth weight, although it is of interest that a similar trend was not seen for cord insulin.

In conclusion, hyperinsulinemia was found throughout the spectrum of severity of maternal diabetes. Our study does not demonstrate that the vicious cycle of type 2 diabetes is occurring in this population. Nevertheless, it does demonstrate that maternal diabetes is commonly resulting in fetal hyperinsulinemia at birth in a population genetically prone to obesity and diabetes. Further studies examining the health of children of mothers with diabetes in this population, and whether maternal glycemic control can impact upon this risk, are clearly critical.

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References

1. Freinkel N: Banting lecture 1980: Of pregnancy and progeny. *Diabetes* 29: 1023–1035, 1980
2. Schubring C, Siebler T, Kratzsch J, Englaro P, Blum WF, Triep K, Kiess W: Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and growth hormone levels, skinfold thickness, body mass index and weight. *Clin Endocrinol (Oxf)* 51:199–204, 1999
3. Okereke NC, Uvena-Celebrezze J, Hutson-Presley L, Amini SB, Catalano PM: The effect of gender and gestational diabetes mellitus on cord leptin concentration. *Am J Obstet Gynecol* 187:798–803, 2002
4. Manderson JG, Patterson CC, Hadden DR, Traub AI, Leslie H, McCance DR: Leptin concentrations in maternal serum and cord blood in diabetic and nondiabetic pregnancy. *Am J Obstet Gynecol* 188: 1326–1332, 2003
5. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 308:242–245, 1983
6. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dorner G: Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obes Relat Metab Disord* 21: 451–456, 1997
7. Silverman BL, Landsberg L, Metzger BE: Fetal hyperinsulinism in offspring of diabetic mothers: association with the subsequent development of childhood obesity. *Ann N Y Acad Sci* 699:36–45, 1993
8. Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH: Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 23:905–911, 2000
9. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC: Congenital susceptibility to NIDDM: role of intrauterine environment. *Diabetes* 37:622–628, 1988
10. Silverman BL, Metzger BE, Cho NH, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 18:611–617, 1995
11. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dorner G: Glucose tolerance and insulin secretion in children of mothers with pregestational IDDM or gestational diabetes. *Diabetologia* 40:1094–1100, 1997
12. Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F, Gautier JF: Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet* 361:1861–1865, 2003
13. Lindsay RS, Walker JD, Halsall I, Hales CN, Calder AA, Hamilton BA, Johnstone FD, the Scottish Multicentre Study of Diabetes in Pregnancy: Insulin and insulin propeptides at birth in offspring of diabetic mothers. *J Clin Endocrinol Metab* 88: 1664–1671, 2003
14. American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1): S5–S10, 2004
15. Simmons D, Breier BH: Fetal overnutrition in polynesian pregnancies and in gestational diabetes may lead to dysregulation of the adipoinsular axis in offspring. *Diabetes Care* 25:1539–1544, 2002
16. McCowan L, Stewart AW: Term birthweight centiles for babies from New Zealand's main ethnic groups. *Aust N Z J Obstet Gynaecol* 44:432–435, 2004
17. Kleinbaum DG, Kupper LL, Muller KE, Nizam A: *Applied Regression Analysis and Other Multivariable Methods*. North Scituate, MA, Duxbury Press, 1978
18. Dabelea D, Hanson RL, Bennett PH, Pettitt DJ, Lindsay RS, Imperatore G, Gabir MM, Roumain J, Knowler WC: Intrauterine exposure to diabetes conveys risk for diabetes and obesity in offspring above that attributable to genetics (Abstract). *Diabetes* 48 (Suppl. 1): A52, 1999
19. Pettitt DJ, Nelson RG, Saad MF, Bennett PH, Knowler WC: Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. *Diabetes Care* 16:310–314, 1993
20. Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Hattersley AT: Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1α gene mutation carriers. *Diabetes Care* 25:2287–2291, 2002
21. Klupa T, Warram JH, Antonellis A, Pezzolesi M, Nam M, Malecki MT, Doria A, Rich SS, Krolewski AS: Determinants of the development of diabetes (maturity-onset diabetes of the young-3) in carriers of HNF-1α mutations: evidence for parent-of-origin effect. *Diabetes Care* 25:2292–2301, 2002
22. Weiss PA, Kainer F, Haas J: Cord blood insulin to assess the quality of treatment in diabetic pregnancies. *Early Hum Dev* 51:187–195, 1998
23. Glauber HS, Revers RR, Henry R, Schmeiser L, Wallace P, Kolterman OG, Cohen RM, Rubenstein AH, Galloway JA, Frank BH, Olefsky JM: In vivo deactivation of proinsulin action on glucose disposal and hepatic glucose production in normal man. *Diabetes* 35:311–317, 1986
24. Zilker TR, Gray IP, Hales CN, Wahl K, Ermler R, Lebender A, Heinzel G, Bottermann P: Pharmacokinetics of biosynthetic human proinsulin following intravenous and subcutaneous administration in metabolically healthy volunteers. *Horm Metab Res Suppl* 18:37–43, 1988
25. Tillil H, Frank BH, Pekar AH, Broelsch C, Rubenstein AH, Polonsky KS: Hypoglycemic potency and metabolic clearance rate of intravenously administered human proinsulin and metabolites. *Endocrinology* 127:2418–2422, 1990
26. Duckworth WC, Bennett RG, Hamel FG: Insulin degradation: progress and potential. *Endocr Rev* 19:608–624, 1998
27. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS: Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 352:2477–2486, 2005
28. Cundy T, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB: Perinatal mortality in type 2 diabetes mellitus. *Diabet Med* 17:33–39, 2000

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