Fetal Overnutrition in Polynesian Pregnancies and in Gestational Diabetes May Lead to Dysregulation of the Adipoinsular Axis in Offspring

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OBJECTIVE — To compare umbilical cord leptin concentrations in different ethnic groups and between pregnancies with and without gestational diabetes mellitus (GDM) in Auckland, New Zealand.

RESEARCH DESIGN AND METHODS — A cross-sectional study of 116 European, Polynesian, and South Asian women and their infants with and without GDM. Maternal metabolic measures were recorded at 36 weeks' gestation, umbilical cord samples were collected at birth, and neonatal anthropometric measures were recorded 24 h after delivery.

RESULTS — Compared with Europeans and South Asians, samples of Polynesian umbilical cords had higher leptin concentrations (8.7 and 9.5 vs. 14.9 ng/ml, respectively; $P = 0.026$). Umbilical cord samples from pregnancies complicated by GDM had higher leptin concentrations than those from normal pregnancies (22.3 vs. 13.8 ng/ml, respectively; $P = 0.022$). Maternal leptin concentrations at 36 weeks were similar across ethnic groups and with and without GDM. Cord leptin correlated with birth weight, measures of fetal size, and cord insulin in normal pregnancies and those complicated by GDM. In multivariate analyses, cord leptin was related to birth weight ($P < 0.001$), gestation at delivery ($P = 0.038$), and ethnic group ($P = 0.017$) in normal pregnancies and to birth weight ($P < 0.001$), gestation at delivery ($P < 0.001$), and sex ($P = 0.003$) but not maternal diabetes status ($P = 0.909$) in pregnancies complicated by GDM.

CONCLUSIONS — Offspring of Polynesian women are relatively hyperleptinemic, independent of birth size. Offspring of women with GDM are also relatively hyperleptinemic at birth, but this was associated with their increased birth weight. We speculate that this GDM-associated relative hyperleptinemia may be due to fuel-mediated teratogenesis affecting the adipoinsular axis, which in turn could also lead to leptin resistance and obesity in adult life. The reason for the ethnic difference in hyperleptinemia is unclear.

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Both prospective clinical and experimental studies have confirmed that small size or thinness at birth is associated with obesity, type 2 diabetes, dyslipidemia, cardiovascular disease, and hypertension in adult life (1,2). Furthermore, follow-up studies of the offspring of women with diabetes in pregnancy suggest that increased fuel supply in utero, more associated with larger fetal size, also increases the future risk of obesity and type 2 diabetes (3–5). This and other intrauterine metabolic impacts on organogenesis have been termed "fuel-mediated teratogenesis" (6). The mechanisms linking an adverse intrauterine environment with later obesity and disease remain unclear.

The pathogenesis of obesity in humans is complex, and although strongly associated with an energy imbalance between food consumption and energy expenditure, a variety of control mechanisms exist, including those mediated by leptin (7–9). Leptin acts at the level of the hypothalamus to regulate appetite and energy homeostasis (8). Because plasma leptin levels are increased in human obesity and proportional to adipose tissue mass, it has been proposed that leptin resistance may be a key mechanism in the pathogenesis of obesity in some populations (9,10). Although leptin is produced predominantly by white adipose tissue, expression of leptin and its long-form signaling receptor are much more widespread than originally believed. Leptin signaling has recently been demonstrated in peripheral tissues, and there is growing evidence for a feedback system between leptin and insulin (11). This endocrine system has been termed the adipoinsular axis, linking the brain and endocrine pancreas with other peripheral insulin- and leptin-sensitive tissues in the control of feeding behavior, metabolic regulation, and body energy balance (11).

Placental and fetal leptin expression have been demonstrated (12); leptin concentrations correlate with birth weight, cord blood insulin concentration, and placental weight (13). Polynesian women and women with gestational diabetes mellitus (GDM) in New Zealand have large babies (14,15), which could be anticipated to be relatively hyperleptinemic at birth. The present study investigates the relationship between leptin concentrations in cord blood and birth weight across different ethnic groups and in babies of mothers with GDM and explores

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Abbreviations: GDM, gestational diabetes mellitus; RIA, radioimmunoassay.

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

whether differences in cord leptin concentrations solely relate to birth weight or to the metabolic status of the mother during pregnancy.

RESEARCH DESIGN AND METHODS

The study was undertaken in Auckland, New Zealand as previously described (16,17). Auckland is a multiethnic city with a large proportion of Polynesians (indigenous Maori and those from the South Pacific). The original study was designed to compare maternal and neonatal characteristics among Europeans, Polynesians, and South Asians and between Polynesians and South Asians with and without GDM. Samples that had been stored at –70°C were thawed and leptin and IGF-1 concentrations measured as described below. Paired samples were available for 26 of 32 Europeans, 55 of 63 Polynesians, and 11 of 28 South Asians without GDM and for 20 of 27 Polynesians and 4 of 8 South Asians with GDM.

Consecutive eligible women were recruited into the study. All four grandparents were of the same ethnic group, except among Maori, in which at least three of the four grandparents were considered Maori. Women smoking >10 cigarettes per day or with any medical disorder were excluded. Pregnancies were excluded if they were complicated by intrauterine growth retardation, hypertension/preeclampsia, premature delivery (<37 weeks by clinical assessment or ultrasound), significant meconium, or fetal distress on cardiotocography at delivery. All women underwent 100-g oral glucose tolerance testing between the 28th and 32nd weeks of the pregnancy, and an additional fasting venous sample was collected at 36–38 weeks. GDM was diagnosed using modified O'Sullivan criteria (16) (if fasting glucose + 3-h glucose + 2 × (1-h glucose + 2-h glucose) ≥ 50).

At delivery, umbilical cord samples were collected. Gestational age was assessed using Dubowitz criteria. Neonatal skinfold measurements were recorded within 24 h. The protocol for the study was approved by the Auckland Area Health Board Ethics Committee, and informed consent for the study was obtained from each woman. Management of women with GDM has been described elsewhere (16) and followed a standard protocol (18).

Assays

Glucose and triglyceride concentrations were measured in batches on a Hitachi 717 autoanalyzer (Hitachi, Japan; interassay precision 1.9 and 2.0%, respectively). Nonesterified fatty acids were measured using an enzymatic colorimetric system (interassay precision 3.6%). Insulin was assayed by an in-house two-site radioimmunoassay (RIA; interassay precision 5.0%) and C-peptide (collected in aprotonin) was measured by RIA kit (Novo Nordisk, Copenhagen, Denmark; interassay precision 5.0%).

We measured IGF-1 in blood plasma using the IGF binding protein–blocked RIA (19). We used a polyclonal antibody (no. 878/4), which has high affinity and specificity for IGF-1 and low cross-reactivity with IGF-2 (20). This assay uses a nonextraction process with samples diluted in acidic buffer and coincubated with an excess of IGF-2. Dilution and acidification to pH 2.8 followed by addition of excess IGF-2 serves to functionally block IGF binding protein interference. This IGF binding protein–blocked RIA for IGF-1 shows complete parallelism between serial dilutions of human plasma and the rhIGF-1 assay standard (no. GO80AB; Genentech, South San Francisco, California). The recovery of unlabeled rhIGF-1 added before assay was 95 ± 6.6% (n = 16). The ED-50 was 0.1 ng per tube, the detection limit was 0.7 ng/ml, and the interassay and intra-assay coefficients of variation were 10.1 and 5.0%, respectively.

A double-antibody RIA was developed and validated for measurement of leptin in human plasma. The antibody was raised in rabbits against a synthetic fragment (aa 30–45) of bovine leptin. The standard preparation for the RIA was rh-leptin (no. CR-6781; Crystalchem) used in concentrations ranging from 0.5 to 20 ng/ml. Samples were assayed neat or diluted 1:2–1:4 in assay buffer (0.05 mol/l PBS, pH 7.4, containing 0.1 mol/l NaCl, 0.5% BSA, 10 mmol/l EDTA, 0.05% Na_3N). In brief, 100 μl of primary antibody (1:25,000) was added to tubes containing 100 μl of sample or standard. After incubation for 24 h at 4°C, 100 μl of tracer (^{125}I-rh-leptin, 20,000 cpm per tube) was added to all tubes, followed by further incubation for 24 h at 4°C. A second antibody technique was used to separate bound from free ligand (21). Human plasma samples showed parallel displacement to the standard curve, and recovery of unlabelled rh-leptin was 101.4 ± 2.7% (mean ± SEM, n = 26). The ED-50 was 0.4 ng/ml, and the intra-assay and interassay coefficients of variation were <5 and <8%, respectively.

Statistics

All tests are two-tailed; $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS for Windows software (SPSS, Chicago). Mean ± SD are shown. Non-normally distributed variables (insulin, leptin, IGF-1, nonesterified fatty acids, and triglycerides) were logarithmically transformed for analysis and geometric mean shown. For the comparison of pregnancies with and without GDM, Polynesians and South Asians were in the same ratio in each group (5:1), and therefore, no adjustment for ethnic group has been made. Univariate correlations were undertaken using Pearson's correlations. The comparison of cord leptin between ethnic groups and between pregnancies with and without GDM were adjusted for covariates using ANCOVA. Regression lines and 95% CIs for slope and constant were calculated using simple linear regression without logarithmic transformation.

RESULTS

Table 1 shows the maternal characteristics of the three ethnic groups and compares Polynesians and South Asians with and without GDM. These differ slightly from the original study due to the loss of some subjects because of insufficient sample volume (especially among South Asians) (16,17). There were no significant differences in gestation at delivery (40 ± 1 weeks) or placental weight (670 ± 130 g) overall. There were no significant ethnic differences in parity (1 ± 1), but women with GDM had higher parity (1 ± 1 vs. 2 ± 1) than women without GDM. In Table 1, the neonatal characteristics by ethnic group and maternal GDM status are compared. Cord leptin, but not cord IGF-1, was significantly higher among offspring of Polynesian women and women with GDM. Table 2 shows the statistically significant univariate correlations between maternal and neonatal leptin and other parameters. Numbers of normal South Asians were too small but are shown for completeness. Maternal leptin concentrations did not correlate with any neonatal measures. Cord leptin concentrations did

Table 1—*Maternal and neonatal characteristics by ethnic group and GDM status*

	Normal Europeans	Normal South Asians	Normal Polynesians	Ethnic Difference	Polynesians and South Asians		GDM Difference
					Normal*	GDM*	
N	26	11	55		66	24	
Maternal							
Age (years)	27 ± 5	25 ± 5	26 ± 5	0.497	26 ± 5	31 ± 5	<0.001
BMI (kg/m^2)	25.3 ± 4.9	20.9 ± 3.3	29.2 ± 6.3	<0.001	27.8 ± 6.6	33.8 ± 7.0	<0.001
Weight at delivery (kg)	77 ± 13	62 ± 11	88 ± 17	<0.001	83.2 ± 19.1	94.6 ± 18.8	0.014
Fasting glucose (mmol/l)	4.4 ± 0.4	4.5 ± 0.4	4.5 ± 0.3	0.625	4.5 ± 0.3	5.4 ± 1.5	<0.001
36/40-week maternal glucose (mmol/l)	5.2 ± 0.5	4.7 ± 0.6	5.1 ± 0.5	0.054	5.0 ± 0.6	5.9 ± 0.9	<0.001
Nonesterified fatty acids (mmol/l)	0.37 ± 0.14	0.42 ± 0.14	0.37 ± 0.16	0.698	0.38 ± 0.16	0.43 ± 0.18	0.261
Triglycerides (mmol/l)	2.4	2.2	2.5	0.592	2.5	2.8	0.109
Insulin† (mU/l)	17.8	16.8	23.7	0.007	22.4	39.1	<0.001
Insulin: C-peptide†	45.6	47.4	59.9	0.009	57.6	95.7	<0.001
Maternal leptin† (ng/ml)	32.7	37.2	36.8	0.732	36.9	45.0	0.234
Maternal IGF† (ng/ml)	145.6	118.1	149.6	0.258	143.8	173.4	0.072
Neonatal							
Birthweight (g)	3,430 ± 630	2,820 ± 380	3,590 ± 500	<0.001	3,460 ± 560	3,730 ± 550	0.046
Sum of callipers (mm)	187 ± 37	171 ± 9	193 ± 37	0.147	190 ± 36	211 ± 34	0.012
Crown rump (mm)	332 ± 17	315 ± 10	338 ± 14	<0.001	334 ± 16	338 ± 14	0.237
Cord insulin (mU/l)	12.4	11.2	13.2	0.558	12.9	20.0	<0.001
Insulin: C-peptide	45.2	43.4	53.6	0.042	51.8	66.4	0.004
Nonesterified fatty acids (mmol/l)	0.21 ± 0.09	0.24 ± 0.07	0.19 ± 0.07	0.139	0.20 ± 0.07	0.23 ± 0.17	0.192
Triglycerides (mmol/l)	0.41	0.50	0.43	0.326	0.44	0.48	0.349
Cord leptin (ng/ml)	8.7	9.5	14.9	0.026	13.8	22.3	0.022
Cord IGF (ng/ml)	42.8	34.0	33.5	0.271	33.6	40.3	0.231

Data are means ± SD. *Normal subjects include 55 Polynesians and 11 South Asians; Europeans were excluded as no GDM. Subjects with GDM include 20 Polynesians and 4 South Asians. Triglyceride, insulin, insulin:C-peptide ratio, maternal leptin, and maternal IGF-1 are geometric means and hence do not show SD.

not correlate with any maternal measures except with BMI and weight at delivery among Europeans.

In Table 3, cord leptin is compared between the three ethnic groups and between those with and without GDM after adjustment for covariates using ANCOVA. The higher geometric mean cord leptin concentration among Polynesians persisted ($P = 0.017$; adjusted leptin concentrations 8.6 in Europeans, 14.1 in South Asians, and 19.2 in Polynesians) after adjusting for covariates. Significant covariates were gestational age and birth weight. The analysis accounted for 39.5% of the variance in leptin concentrations. However, after adjusting for covariates, the difference in cord leptin concentration between pregnancies with and without GDM disappeared ($P = 0.909$). Significant covariates were sex, gestational age, and birth weight. The cord insulin from diabetic pregnancies was higher than that for nondiabetic pregnancies at higher cord leptin values (Fig. 1).

Table 2—*Pearson univariate correlations between maternal and umbilical cord leptin concentrations and other parameters*

	Normal Europeans	Normal South Asians	Normal Polynesians	Polynesians and South Asians	
				Normal	GDM
N	26	11	55	66	24
Cord leptin—maternal					
Weight at delivery	0.563†	0.023	0.106	0.187	0.152
BMI	0.444‡	0.054	0.055	0.143	0.175
36/40-week maternal glucose	0.429‡	0.502	0.186	0.261‡	0.405‡
Cord leptin—neonatal					
Birthweight	0.626*	0.477	0.490*	0.514*	0.688*
Placenta weight	0.268	−0.257	0.570†	0.584*	0.732†
Sum callipers	0.495†	0.145	0.438*	0.447*	0.744*
Crown rump	0.469*	0.550	0.373†	0.428*	0.532†
Cord insulin	0.400*	0.149	0.402†	0.379†	0.643*
Cord IGF-1	0.179	0.564	0.486*	0.333†	0.299
Maternal leptin					
Weight at delivery	0.536†	0.592	0.615*	0.514*	0.556†
BMI	0.490*	0.452	0.473*	0.400*	0.641*
Cord leptin	0.286	0.355	0.128	0.171	0.044

None of the neonatal anthropometric or metabolic measurements were significantly correlated with maternal or cord leptin concentrations. *P <0.001; †P <0.01; ‡P < 0.05.

CONCLUSIONS — Our results suggest that there may be separate mechanisms

Table 3—*ANCOVA of umbilical cord leptin concentration by ethnic group and GDM status*

Comparison of cord leptin between ethnic groups among normal pregnancies		
Source	*F*	*P*
Birth weight	14.129	0.000
Gestation	4.479	0.038
Ethnic group	4.301	0.017
Age	0.277	0.600
BMI	0.450	0.504
Parity	0.543	0.464
Fasting glucose	0.207	0.651
Weight at delivery	0.227	0.635
36-week maternal glucose	3.024	0.086
Sum of calipers	1.512	0.223
Log maternal triglyceride	0.263	0.610
Log maternal nonesterified fatty acids	0.028	0.867
Sex	1.004	0.320
Ethnic group–sex interaction	1.844	0.165
Corrected model	4.637	0.000
Intercept	2.215	0.141

$R^2 = 0.504$ (Adjusted $R^2 = 0.395$)

ANCOVA between the three ethnic groups with birth weight, gestation, age, BMI, parity, glucose, weight at delivery, sum of calipers, log maternal triglyceride, and log maternal nonesterified fatty acids as continuous variables, and sex of offspring as a discrete variable.

Comparison of cord leptin between pregnancies with and without GDM (Polynesian/South Asian)		
Source	*F*	*P*
Birth weight	19.865	0.000
Gestation	13.304	0.000
Diabetes status	0.013	0.909
Age	0.299	0.586
BMI	0.249	0.619
Parity	0.131	0.718
Fasting glucose	0.322	0.572
Weight at delivery	0.016	0.899
36-week maternal glucose	1.215	0.274
Sum of calipers	1.594	0.211
Log maternal triglyceride	0.019	0.892
Log maternal nonesterified fatty acids	0.092	0.763
Sex	9.520	0.003
Diabetes–sex interaction	0.003	0.957
Corrected model	7.066	0.000
Intercept	9.985	0.002

$R^2 = 0.579$ (Adjusted $R^2 = 0.497$)

ANCOVA between those with and without GDM with birth weight, gestation, age, BMI, parity, glucose, weight at delivery, sum of calipers, log maternal triglyceride, and log maternal nonesterified fatty acids as continuous variables, and sex of offspring as a discrete variable.

explaining *1*) the relative hyperleptinemia in the offspring of women with relative hyperglycemia and GDM during the last trimester of pregnancy and *2*) the relative hyperleptinemia in Polynesian infants of normoglycemic mothers. Evidence for the former is suggested by the initial relative hyperleptinemia in the cord blood of the offspring of the women with GDM being lost on adjusting for birth weight in our ANCOVA. These findings have relevance not only to the very high prevalence of obesity and type 2 diabetes among adult Polynesians (22) but to the obesity seen in later life in the offspring of women with diabetes in pregnancy (3–5). Our observations may relate, at least in part, to the mechanistic principles that explain the growing pandemic of obesity in the Western World and in developing countries.

Hyperleptinemia in offspring of women with relative hyperglycemia and GDM

The finding that women with diabetes in pregnancy have hyperleptinemic babies has been described elsewhere (23). Our observations suggest that hyperleptinemia may be due to maternal hyperglycemia and/or the supply of other fuels during fetal development. This hypothesis is supported by our previous observation that antenatal insulin therapy among women with GDM is associated with less subsequent adiposity in offspring, consistent with reduced fuel-mediated teratogenesis (24).

An important remaining question relates to the cause of hyperleptinemia in these babies and its long-term consequences. Although leptin was initially believed to act solely by reducing appetite through its hypothalamic effects, there is growing evidence for an endocrine feedback system between adipose tissue and pancreatic β-cells via the hormones leptin and insulin, respectively. Insulin is adipogenic and increases the production of leptin by adipose tissue, whereas leptin inhibits the production of insulin in pancreatic β-cells (8). As fat stores increase, increasing plasma leptin concentrations reduce circulating insulin levels under normal conditions, thereby directing less energy to the formation of adipose tissue. Conversely, when adipose stores are reduced, decreasing plasma leptin concentrations allow increased insulin production, thereby resulting in the deposition of additional fat. The suppressive effect of leptin on insulin production is mediated, in part, by direct actions via leptin receptors on β-cells (11).

Our data (Fig. 1) suggest that the hyperglycemia in utero in GDM mothers leads to increased insulin secretion and adiposity in the fetus, which may reflect an inability of rising plasma leptin concentrations to control the release of insulin. Therefore, we hypothesize that dysregulation within the adipoinsular axis induced by fetal hyperglycemia in mothers with GDM may be the trigger for a permanent resetting of a positive feedback loop that leads to hyperinsulinemia and further adiposity and hyperleptinemia during postnatal life.

We have previously shown that the relative hyperinsulinemia in Polynesian cord blood is not confined to pregnancies complicated by GDM but is also present in cord blood of more obese mothers (25). We speculate that in conditions of fetal overnutrition, chronic hyperleptinemia may lead to a defect at the pancreatic β-cells such that insulin secretion cannot be controlled by further elevation of cir-

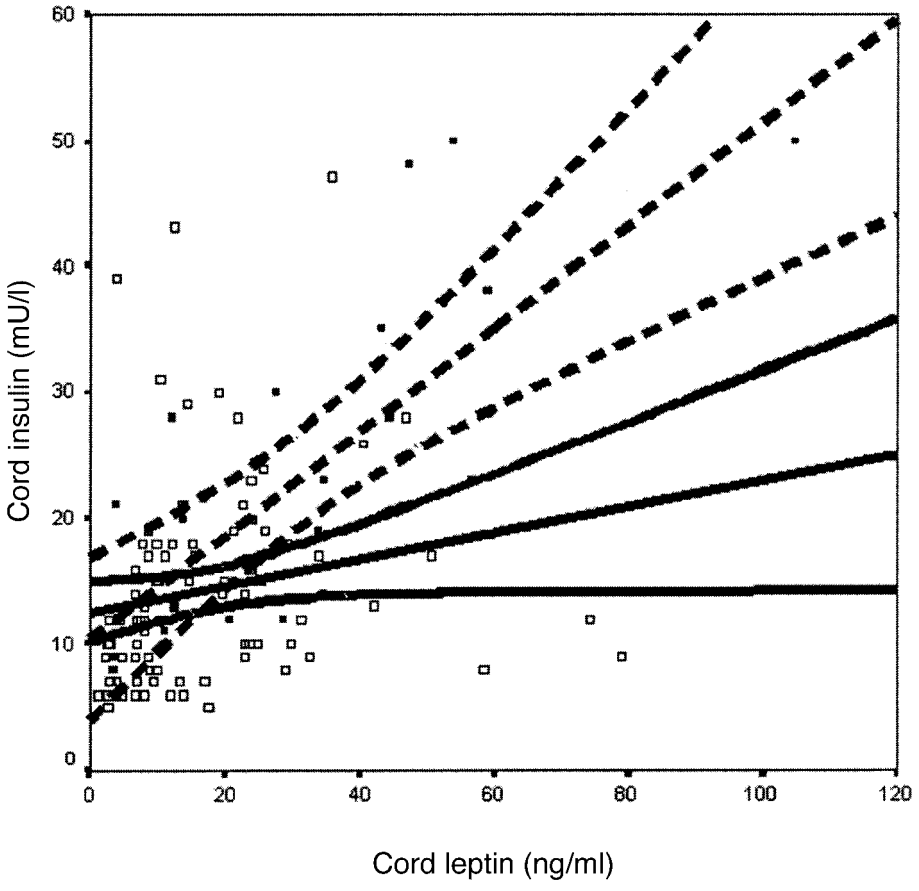

Figure 1—*Closed and open squares represent pregnancies complicated and not complicated by diabetes, respectively. Broken and unbroken lines represent the line of best fit and 95% CIs for pregnancies complicated and not complicated by diabetes, respectively. Slopes (95% CIs) were 1.30 (0.76–1.84) and 0.390 (−0.004 to 0.783), respectively.*

culating leptin levels. A recent report (26) also proposes that in conditions of obesity and prolonged elevation of plasma leptin levels, the leptin receptor system in pancreatic β-cells becomes desensitized. Therefore, overnutrition-induced leptin resistance during fetal development may be a trigger for a positive feedback loop that leads to hyperinsulinemia, which promotes further adipogenesis and an additional increase in hyperleptinemia, initiating a cycle of increasing insulin resistance, compensatory hyperinsulinism, and progression to adipogenic diabetes during postnatal life. Hyperinsulinemia and hyperleptinemia may also be an important determinant in the development of postnatal hyperphagia (27). It is of interest to note that, in obese individuals, elevated levels of plasma leptin are proposed to uncouple leptin action on its receptors in the hypothalamus, thereby disrupting signal transduction pathways that exert the effects of leptin on satiety and energy expenditure (28). This defect may further amplify obesity and adipogenic diabetes, as observed in Polynesian populations.

Hyperleptinemia in offspring of normal Polynesian women

The hyperleptinemia found in the offspring of normal Polynesian women was not lost on adjusting for covariates, suggesting a more complex situation, and may involve an expression of inherited factors. Polynesians are genotypically distinctive: 93% of Polynesians share a single mtDNA motif that distinguishes them from European haplotypes and that includes the 16189 variant (29–31). It has been suggested that the 16189 mtDNA variant may represent the "thrifty gene" (31). However, this variant is associated with lower rather than higher birth weight (32) and, among Europeans, is associated with insulin resistance and abnormal glucose tolerance later in life (33). Although Polynesians are at high risk for type 2 diabetes, adult Polynesians do not seem to be intrinsically insulin resistant (22). This differs from other ethnic groups, such as South Asians, who are intrinsically hyperinsulinemic, independent of any given level of obesity (34). An inherited change to adapt to this mitochondrial haplotype may have occurred, therefore, to assist with survival of babies (i.e., as a counterbalance to the "small baby" drive while maintaining any benefits of the mitochondrial haplotype later in life).

Another, not necessarily mutually exclusive adaptation, mechanism to enhance survival is obesity-driven fuel-mediated teratogenesis. We have previously shown in this cohort (25) that cord hyperinsulinemia, possibly reflecting fuel-mediated teratogenesis and driven by increasing maternal obesity with associated mild perturbations in glycemic control, may contribute to the increased risk of developing obesity in offspring. One further piece of evidence that has been recently reported from basic research studies in animals (35) is that an adipose tissue and/or hepatic dysfunction, mediated by hyperleptinemia, may trigger the pathogenesis of obesity and type 2 diabetes. Further studies are required to test these hypotheses.

There are a number of caveats to our findings. The present results are from cord samples collected during delivery with its potential confounding factors. We did not measure the serum leptin levels in the children from our follow-up study, and therefore, our hypotheses are based on cross-sectional rather than prospective data. Furthermore, the use of multivariate analyses to adjust for potential confounders, which in reality are not independent (e.g., birth weight may mask the diabetes status entrant as well as the metabolite entrants), also emphasize the need for further studies in GDM and obesity as well as in Polynesians and other ethnic groups.

We conclude that offspring of Polynesian women are relatively hyperleptinemic, independent of birth size. Our data suggest that there may be a distinct, perhaps inherited, mechanism that may trigger altered leptin action. Offspring of women with GDM are also relatively hyperleptinemic at birth, but this was associated with increased birth weight. We speculate that this GDM-associated rela-

tive hyperleptinemia may be due to fuel-mediated teratogenesis affecting the adipoinsular axis, which could, in turn, also lead to leptin resistance and obesity in adult life.

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