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Maternal Weight Gain Is Associated With Infant Insulin Concentrations During the 1st Year of Life

Since hyperinsulinemia tracks from childhood to adulthood and is associated with diabetes risk, identifying modifiable conditions during gestation that may impact insulin metabolism in offspring is important. We conducted a pilot study to investigate associations between maternal weight gain and infant insulin concentrations in an underserved population at high risk for diabetes. Mexican or Native American women with an infant <1 year of age provided written consent. Infant weight-for-age Z scores (WAZ) were calculated, and nonfasting plasma samples were analyzed for insulin by standard assay. Pearson's bivariate test was used to assess relationships between variables, and the unpaired *t* test was used to examine differences between means.

A total of 16 women ([means ± SE] 21.8 ± 1.7 years) and their infants (6.4 ± 0.9 months; 9 males and 7 females) completed the study, and medical records were available for 9 of these pairs. Based on combined self-reports and medical records, the mean prepregnancy weight was 71.5 ± 4.0 kg, and the mean pregnancy weight gain was 10.7 ± 2.4 kg. Infants were full term with birth weights ranging from 2,495 to 4,309 g (3,381 ± 121.0 g); WAZ scores averaged 0.47 ± 0.23. Blood insulin concentrations averaged 11.5 ± 1.6 mU/l. Gestational weight gain was significantly correlated to infant insulin concentrations ($r = 0.662$; $P = 0.005$); however, for nondiabetic women with verifiable pregnancy weight gain ($n = 8$), this association was strengthened ($r = 0.763$, $P = 0.028$; Fig. 1). Infant insulin concentrations ($n = 16$) were not associated with birth weight, infant age, WAZ scores, prepregnancy weight, or maternal age.

These data show that maternal weight gain predicted infant insulin concentrations, explaining nearly 60% of the vari-
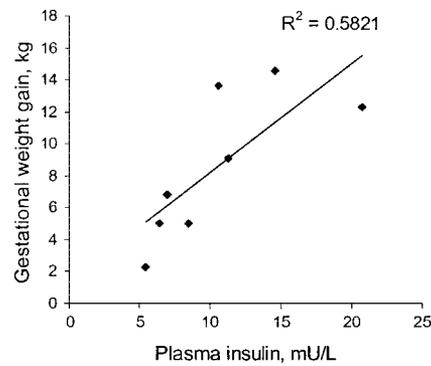

Figure 1—*Correlation of maternal weight gain and infant insulin concentrations (n = 8 mother/infant pairs;* r = 0.763, P = 0.028*).*

ance in these values. Diabetes during pregnancy has been associated with cord blood insulin and with insulin concentrations in adolescence (1), and in nondiabetic pregnancies, maternal weight gain was related to cord blood insulin in macrosomic neonates (2). Currently, a weight gain of 6.8–11.5 kg is recommended for overweight women, and obese women are advised to gain a minimum of 6.8 kg. In obese, nondiabetic women, minimal gestational weight gain (<5 kg) normalized obstetric outcomes, including hypertension, cesarean section, induction of labor, and macrosomia, and did not adversely affect fetal outcomes (3). Utilizing an emerging obstetric outcome, infant insulin concentrations, our preliminary data support the contention that gestational weight gain should be carefully considered in overweight populations at high risk for diabetes. Differential analyses of our data show that minimal gestational weight gain in the nondiabetic women (≤5 vs. >5 kg) was associated with lower infant insulin concentrations (7.2 ± 0.6 vs. 13.4 ± 2.0 mU/l; $P = 0.013$). Together, the available data indicate that controlling weight gain during obese pregnancies may be advantageous and that more studies of this nature are warranted.

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Soluble Tumor Necrosis Factor Receptor 1 Is Strongly and Independently Associated With Serum Homocysteine in Nonobese Japanese Type 2 Diabetic Patients

The major clinical consequence of type 2 diabetes is mortality and morbidity from atherosclerotic vascular disease. With regards to the risk factors responsible for the evolution of atherosclerosis, Bierman (1) estimated that typical risk factors, including smoking, cholesterol, and blood pressure, can account for no more than 30% of excess cardiovascular risk factors in diabetic patients. Thus, other factors seem to play a key role in the progression of atherosclerosis in diabetes.

One potential factor is homocysteine. Homocysteine has been shown to contribute to the development of atherosclerosis in diabetic patients (2). Whereas the deficiencies of folate and vitamin B_{12} lead to hyperhomocysteinemia, these deficiencies alone do not completely account for atherosclerotic changes induced by homocysteine in diabetic patients.

Tumor necrosis factor (TNF) is a potent candidate involved in the pathogenesis of atherosclerosis. Rauchhaus et al. (3) demonstrated that elevated soluble TNF receptor 1 (sTNF-R1) has shown to be predictive of cardiovascular mortality in patients with chronic heart failure. We

found that sTNF-R1 is independently associated with albuminuria in type 2 diabetic patients (4). To the best of our knowledge, however, it is not clear whether serum homocysteine is associated with TNF receptor in type 2 diabetic patients. The aim of the present study was therefore to investigate the relationships between serum homocysteine and TNF receptor in patients with type 2 diabetes.

Fifty nonobese Japanese type 2 diabetic patients were studied. Their BMI, HbA_{1c}, and serum creatinine were 22.6 ± 0.3 kg/m2 (range 17.6–26.2), 7.8 ± 0.2% (5.5–12.3), and 0.70 ± 0.02 mg/dl (0.46–0.98), respectively. They had not been treated with insulin or any medications known to alter homocysteine level. In conjunction with homocysteine, systolic and diastolic blood pressure, HbA_{1c}, glucose, lipids, serum creatinine, TNF-α, sTNF-R1, and sTNF-R2 were measured after an overnight fast.

With univariate analysis, serum homocysteine was positively correlated with age ($r = 0.361$, $P = 0.012$), diabetes duration ($r = 0.292$, $P = 0.045$), serum creatinine ($r = 0.623$, $P < 0.001$), sTNF-R1 ($r = 0.415$, $P < 0.005$), and sTNF-R2 ($r = 0.371$, $P < 0.01$). Other variables including TNF-α, however, were not associated with homocysteine. Multiple regression analyses showed that serum homocysteine was independently associated with serum creatinine ($F = 20.1$) and sTNF-R1 ($F = 6.9$), which explained 49.3% of the variability of homocysteine. Thus, TNF system activity may be responsible for the evolution of atherosclerosis induced by homocysteine in nonobese Japanese type 2 diabetic patients.

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Phenformin-Induced Lactic Acidosis in an Older Diabetic Patient

A recurrent drama (phenformin and lactic acidosis)

Editor's note: The authors had the following statement in their letter to me, with which I agree, "Most physicians are aware of the risk of lactic acidosis in patients taking phenformin. However, this side effect is continuously observed because phenformin is still used in Italy, Brazil, and China. We believe that the publication of our observation in an important journal like Diabetes Care *may help to prompt governments of these countries to ban phenformin, just like in the rest of the world. This is the only way to prevent further cases of this avoidable, unacceptable and life-threatening complication."*

A 73-year-old man with diabetes presented with upper-abdominal pain and nausea. He also had a history of hypertension, a pace-maker implant, and peripheral arterial disease treated with amputation of his left leg. His therapy included ticlopidine, enalapril, omeprazole, and 2 mg glibenclamide/30 mg phenformin b.i.d. The patient was alert and cognitively intact. Blood pressure and heart rate were 120/70 mmHg and 70 bpm, respectively. Radiographs of the chest and abdomen and an abdominal ultrasound study were normal. Laboratory tests disclosed a severe lactic acidosis (pH 6.8, pCO_2 14.1 mmHg, pO_2 108 mmHg, HCO_3 4.9 mmol/l, lactate 21 mmol/l, and anion gap 31 mmol/l). After phenformin discontinuation, the patient's conditions rapidly improved. He was treated with intravenous insulin and glucose (1) and discharged 7 days later in good condition.

This report confirms that phenformin-induced lactic acidosis (PLA) is still a public health problem (1,2). To our knowledge, phenformin is still used in Italy, China, and Brazil. In a Medline search, we found 12 cases that occurred in Italy between 1981 and 1998 (2). In two patients phenformin was even brought back into use soon after, thereby questioning the belief that PLA is adequately recognized (2). More importantly, according to data by Intercontinental Marketing Services (www.imshealth.com), 838,000 preparations of phenformin and a sulfonylurea have been sold in Italy between January and October 2005. Because PLA occurs in 1 of 4,000 patients (3) with a mortality rate of ~50%, these data raise worrying health care considerations. In fact, diabetic patients often have comorbid conditions known to favor PLA.

Phenformin was removed from the U.S. market in 1977, but, surprisingly, cases of patients who have been prescribed the drug abroad are continuously reported (1). Phenformin can also be illegally obtained online or through mail orders to replace metformin, which is more costly. Furthermore, herbal medicines containing phenformin are also consumed in developed countries. In February 2000, the Food and Drug Administration recalled five Chinese herbal medications containing phenformin (4), while Health Canada is currently warning consumers not to take "Shortclean," a phenformin-based Chinese "natural" medicine (5).

Phenformin can always be replaced by metformin, which should not be associated with a higher risk of lactic acidosis compared with nonbiguanide therapies (6). Despite most clinicians being aware of PLA, the only way for preventing further cases is to forbid phenformin in countries where it is still used.

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