Insulin Resistance and Preeclampsia in Gestational Diabetes Mellitus

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OBJECTIVE — To compare the degree of insulin resistance in women with gestational diabetes mellitus (GDM) who do and do not develop preeclampsia.

RESEARCH DESIGN AND METHODS — We conducted a prospective cohort study of initially normotensive women with GDM who underwent oral glucose tolerance tests (OGTTs), intravenous glucose tolerance tests (IVGTTs), and glucose clamp studies in the early third trimester ($n = 150$) and 15 months postpartum ($n = 89$). After delivery, the women were categorized as nonpreeclamptic or preeclamptic (systolic blood pressure [SBP] ≥140 mmHg, diastolic blood pressure [DBP] ≥90 mmHg, and at least >1+ proteinuria or >300 mg/24 h). Metabolic parameters between the groups were compared by χ^2 or Fisher's exact tests and ANOVA with $P < 0.05$ as significant.

RESULTS — A total of 29 women (19%) developed preeclampsia, which was mild in 21 and severe in 8 women. At entry, there were no differences in age, weight indexes, and glycemic measures between the nonpreeclamptic and preeclamptic groups. Those with preeclampsia were significantly taller (61.5 ± 2.4 vs. 60.1 ± 2.3 in, $P = 0.003$), were more often nulliparous (38 vs. 16%, $P = 0.01$), and had higher entry SBP (112 ± 10 vs. 103 ± 6.9 mmHg, $P < 0.0001$) and DBP (64 ± 9 vs. 59 ± 5 mmHg, $P = 0.002$). No significant differences between the groups were found in any measures of the OGTT glucose levels, insulin sensitivity index, glucose effectiveness, acute response to glucose, or disposition index, nor were there any differences found in the euglycemic clamp measures of basal or steady-state levels of glucose, insulin, free fatty acid, hepatic glucose output, peripheral glucose clearance, C-peptide, or glucagon. At 15 months postpartum, blood pressure levels remained significantly higher in the preeclamptic group ($n = 19$) compared with the nonpreeclamptic group ($n = 70$). No differences in any glycemic or insulin resistance measures were found.

CONCLUSIONS — Women with GDM were uniformly insulin resistant. Those who developed preeclampsia, when compared with those who remained nonpreeclamptic, were not more insulin resistant in either the third trimester or 15 months postpartum. However, women who developed preeclampsia had blood pressure levels that were significantly higher, although still in the normal range, than those of women who remained nonpreeclamptic.

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Abbreviations: DBP, diastolic blood pressure; FFA, free fatty acid; GDM, gestational diabetes mellitus; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

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

Hypertension, a common disorder complicating pregnancy (6–9%), remains a leading cause of maternal mortality (~15%) in the U.S. (1) and worldwide (2). Hypertensive disorders are increased two- to threefold in pregnancies complicated by diabetes, and insulin resistance has been proposed as an important etiologic factor (3). Women with pregestational and gestational diabetes mellitus (GDM) have been reported to have both increased risk of preeclampsia (10–50 and 10–30%, respectively) and insulin resistance when compared with women with normal glucose tolerance whose rate of preeclampsia is 5–7% (1–6). Several studies have reported an association between preeclampsia and insulin resistance as characterized by higher glucose and/or insulin levels when compared with normotensive women (4–6), but an association between direct measurements of insulin resistance and preeclampsia has not been demonstrated.

In this prospective, longitudinal cohort study, women with GDM underwent detailed metabolic studies in the early third trimester and were followed through delivery. Metabolic testing was repeated 15 months postpartum. The results from the women who developed preeclampsia were compared with those from the women who remained nonpreeclamptic.

RESEARCH DESIGN AND METHODS

— The women reported here are part of an ongoing longitudinal study to ascertain the evolution of the metabolic characteristics of women with previous GDM (7). All of them gave informed consent to participate in the study, which was approved by the institutional review board of the University of Southern California.

Inclusion criteria

Criteria for enrollment included GDM according to the diagnostic criteria of the Third International Workshop-Conference on Gestational Diabetes (8); gestational age between 28 and 34 weeks as determined by a clinical examination before 12 weeks and/or an ultrasound be-

Table 1—*Demographic and metabolic parameters at the time of metabolic testing during the third trimester (antepartum) and 15 months after delivery (postpartum) in women with GDM who subsequently remained nonpreeclamptic and those who developed preeclampsia*

Antepartum clinical parameters	Nonpreeclamptic	Preeclampsia	*P*
n	121 (80.7%)	29 (19.3%)	
Age	30.5 ± 5.6	30.1 ± 6.2	NS
Nulliparous	20 (16.4%)	11 (37.9%)	0.01
First-degree relative with diabetes	28 (30.8%)	6 (27.3%)	NS
Birthweight of largest prior infant (lb)	8.0 ± 1.3	8.2 ± 1.5	NS
Prepregnancy weight (lb)	148.8 ± 29.0	153.5 ± 28.5	NS
Prepregnancy BMI (kg/m^2)	28.9 ± 5.0	28.6 ± 5.2	NS
1-h 50-g glucose challenge test (mg/dl)	170.1 ± 35.3	165.4 ± 37.7	NS
Highest fasting plasma glucose (mg/dl)	101.8 ± 18.5	103.9 ± 10.6	NS
Required insulin during pregnancy	18 (19.8%)	5 (22.7%)	NS
Preterm delivery (<37 weeks)	17 (13.9%)	3 (10.3%)	NS
Antepartum entry (early third trimester)			
Gestational age at entry (weeks)	30.9 ± 2.3	31.3 ± 2.5	NS
Height (in)	60.1 ± 2.3	61.5 ± 2.4	0.003
Maternal weight (entry, lb)	164.4 ± 30.3	170.5 ± 31.9	NS
BMI (entry, kg/m^2)	31.9 ± 5.1	31.8 ± 5.8	NS
SBP (mmHg)	103.1 ± 6.9	112.1 ± 10.0	<0.0001
DBP (mmHg)	58.9 ± 4.6	64.4 ± 8.8	0.002
Mean arterial blood pressure (mmHg)	73.6 ± 4.7	80.3 ± 8.6	0.003
Postpartum (15 months after delivery)	70 (78.7%)	19 (21.3%)	
SBP (mmHg)	106.3 ± 8.2	114.1 ± 11.7	0.01
DBP (mmHg)	62.2 ± 5.9	65.7 ± 8.0	0.04
Mean arterial blood pressure (mmHg)	76.9 ± 6.1	81.8 ± 8.7	0.03

Data are means ± SD and *n* (%). NS, no significant difference between non-preeclamptic and preeclampsia groups.

fore 20 weeks; entry fasting serum glucose concentration <130 mg/dl; uncomplicated singleton pregnancy with no previous insulin use and no history of hypertension, renal, or other chronic medical disease; and negative antipancreatic islet cell antibodies. All women were ethnically Latina (parents and at least three of four grandparents were from Mexico, Guatemala, or El Salvador). A total of 150 women met the criteria for enrollment and completed the metabolic testing.

Testing protocol

The protocol used in this study has been previously published in detail (7) and will be briefly summarized. All the studies were performed at the clinical research center on 3 separate days, at least 48-h apart. An oral glucose tolerance test (OGTT) was done on day 1, an euglycemic clamp study on day 2, and an intravenous glucose tolerance test (IVGTT) on day 3 (9,10). Measurements during both the basal and the steady state of the euglycemic clamp included levels of plasma free fatty acids (FFAs), glucose, [6,6-$^2H_2$]glucose, insulin, C-peptide, and glucagon.

Postpartum testing

Of the 150 women initially studied in the third trimester, 122 completed their first postpartum metabolic evaluation at 6 months postpartum. Diabetes was diagnosed in 12 subjects, leaving 110 nondiabetic women eligible for the second metabolic evaluation at 11–26 months (11). A total of 89 subjects (59% of the original antepartum cohort) returned for metabolic testing at a mean of 15 months postpartum and are reported in this study (12). None were breastfeeding or taking any medications. Detailed descriptions of the longitudinal study design and patient follow up have been previously described (9,11–12). The 3-day testing protocol performing an OGTT, clamp studies, and IVGTT was repeated following the same methods described above.

Laboratory analysis. Glucose was measured by glucose oxidase (Glucose Analyzer II; Beckman, Brea, CA). Insulin and proinsulin were measured by a charcoal precipitation radioimmunoassay (Novo Pharmaceuticals, Danbury, CT). C-peptide and glucagon were measured in aprotinin-preserved plasma radioimmunoassay (Linco Research, St. Charles, MO). FFAs were measured by 63 Ni precipitations. [6,6-$^2H_2$]glucose concentrations in infusates and perchloric acid supernatants of plasma were measured by gas chromatography and mass spectrometry after conversion of glucose to its aldonitrile penta-acetate derivative (13). Islet cell antibodies were measured by an indirect immunofluorescence assay using human pancreas (detection limit of 1 JDFU [Juvenile Diabetes Foundation International unit]).

Study group assignment

After delivery, the medical records were systematically abstracted and reviewed to determine which women had developed preeclampsia according to the criteria of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (14). The women were categorized as nonpreeclamptic if they maintained all clinically measured SBP levels <140 mmHg, DBP <90 mmHg, and urine dipstick <1+ during antepartum and intrapartum care; as mild preeclampsia if they had at least two elevated blood pressure levels 6 h apart of SBP 140–149 mmHg or DBP 90–99 mmHg and >1+ urine protein; and as severe preeclampsia if they had SBP ≥160 mmHg or DBP ≥110 mmHg and ≥2+ proteinuria. The presence of proteinuria was determined by the laboratory on urine specimens obtained by sterile catheterization. Women diagnosed with preeclampsia were treated with intrapartum intravenous magnesium sulfate therapy according to standardized protocols (1).

Data analysis. The areas under the OGTT glucose curves were calculated by the trapezoid method. Glucose turnover rates during the euglycemic clamps were calculated by the Steele equation for non–steady-state conditions, as modified by Finegood et al. (10). IVGTT glucose and insulin data were subjected to minimal model analysis (9,15) using the MINMOD program provided by Dr. R. Bergman. β-Cell insulin release in response to glucose was assessed as the incremental area under the insulin curve during the first 10 min after the glucose injection (acute insulin response to glucose

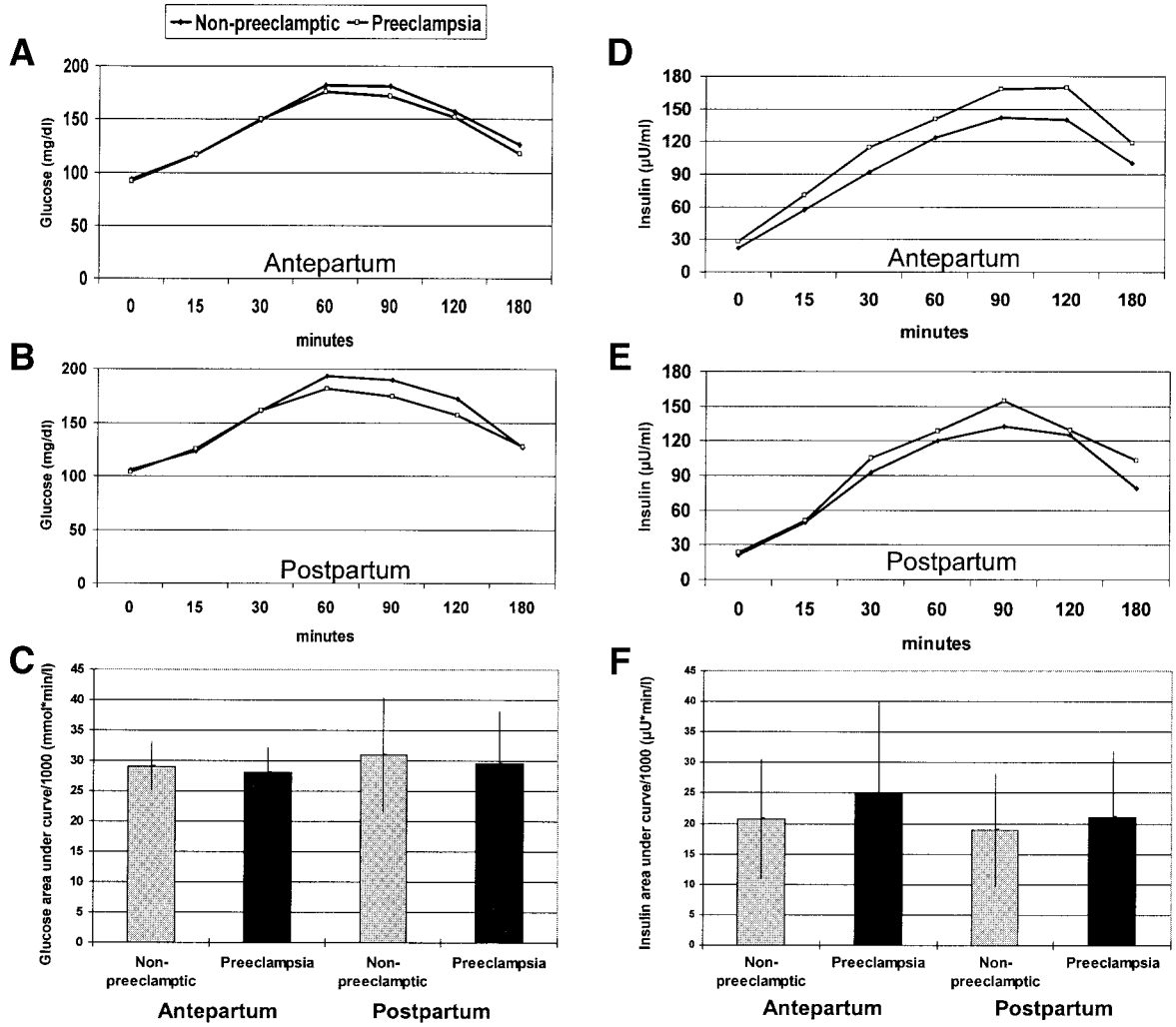

Figure 1—*Glucose and insulin levels during OGTT performed antepartum and repeated postpartum in subjects who remained normotensive and developed preeclampsia at delivery. There were no significant differences in either glucose or insulin measurements between the normotensive and preeclampsia groups.* A*: Antepartum mean glucose levels during OGTT performed in the early third trimester.* B*: Postpartum mean glucose levels during OGTT performed 15 months after delivery.* C*: Mean glucose area under the curve from OGTTs performed antepartum and postpartum.* D*: Antepartum mean insulin levels during OGTT performed in the early third trimester.* E*: Postpartum mean insulin levels during OGTT performed 15 months after delivery.* F*: Mean insulin area under the curve from OGTTs performed antepartum and postpartum.*

[AIR_g]). The appropriateness of β-cell insulin release in relation to ambient insulin sensitivity was assessed as the product of the minimal model insulin sensitivity index (S_I) and AIR_g as originally proposed by Bergman et al. (16,17).

Statistical analysis. The calculations included means and SDs for continuous variables and the number and proportion of subjects per group for categorical variables. For categorical variables, χ^2 tests or Fisher's exact tests were used to compare proportions. For continuous variables, ANOVA and two-tailed *t* tests were used to detect trends among groups. To detect trends across groups, ANOVA (continuous variables) and the Cochran-Armitage test (categorical variables) were used. Non-normally distributed data, such as insulin-related measurements, were subjected to logarithmic or square-root transformation. Pearson correlation coefficients were calculated to examine relationships among metabolic, body mass, and blood pressure variables. For multiple comparisons, a Bonferroni correction was used to maintain an overall α level of 0.05, and all tests were performed at this level.

RESULTS

Antepartum testing

The mean gestational age at entry was 31.0 ± 2.3 weeks. Twenty-nine (19.2%) women developed preeclampsia, which was mild in 21 and severe in 8 women. Two additional subjects had transiently elevated blood pressure at delivery without proteinuria. At entry, and before the development of preeclampsia, the initial demographic and metabolic parameters were not significantly different between those who remained nonpreeclamptic ($n = 121$) and the 29 who later developed preeclampsia. The women who developed preeclampsia were significantly taller, were more often nulliparous, and had significantly higher SBP, DBP, and mean arterial pressure than those who remained nonpreeclamptic (Table 1).

There were no statistically significant

Table 2—*Results of IVGTT and euglycemic clamp studies performed during the early third trimester and 15 months postpartum in women who remained nonpreeclamptic and those who developed preeclampsia at delivery*

	Antepartum			Postpartum		
	Non-preeclamptic	Preeclampsia	*P*	Non-preeclamptic	Preeclampsia	*P*
n	121 (80.7%)	29 (19.3%)		70 (78.4%)	19 (21.6%)	
IVGTT						
S_I [$min^{-1} \cdot (\mu U/ml)^{-1}$]$10^4$	0.63 ± 0.49	0.64 ± 0.37	0.72	1.49 ± 1.06	1.43 ± 0.92	0.53
Glucose effectiveness ($min^{-1} \cdot 10^2$)	0.019 ± 0.004	0.020 ± 0.004	0.10	0.016 ± 0.004	0.016 ± 0.004	0.78
AIR_g ($\mu U \cdot ml^{-1} \cdot min$)	923.7 ± 1,098.8	928.3 ± 637.9	0.43	550.9 ± 479.0	502.0 ± 472.2	0.21
Disposition index	517.4 ± 584.3	547.3 ± 428.3	0.53	772.5 ± 630.2	705.2 ± 587.8	0.63
Euglycemic clamp study						
Basal glucose clamp						
Plasma glucose (mmol/l)	5.39 ± 0.50	5.42 ± 0.60	0.81	6.19 ± 1.52	6.06 ± 1.16	0.73
Plasma insulin (μU/ml)	23.4 ± 9.0	29.6 ± 26.1	0.23	20.8 ± 8.1	21.1 ± 7.8	0.82
Plasma FFA (μmol/ml)	435.9 ± 111.7	476.9 ± 143.7	0.13	—	—	
Plasma C-peptide (ng/ml)	2.26 ± 0.50	2.37 ± 0.65	0.30	—	—	
Plasma glucagon (pg/dl)	37.5 ± 12.1	35.6 ± 9.9		—	—	
Glucose production (mmol · $min^{-1} \cdot m^2$)	0.494 ± 0.72	0.508 ± 0.075	0.38	0.381 ± 0.065	0.382 ± 0.045	0.81
Glucose clearance (ml · $min^{-1} \cdot m^2$)	0.097 ± 0.011	0.096 ± 0.012	0.69	0.068 ± 0.013	0.068 ± 0.11	0.89
Steady-state glucose clamp						
Plasma glucose (mmol/l)	4.81 ± 0.11	4.81 ± 0.13	0.77	4.80 ± 0.14	4.85 ± 0.32	0.80
Plasma insulin (μU/ml)	101.6 ± 23.1	107.0 ± 31.0	0.37	89.9 ± 20.9	90.3 ± 18.5	0.82
Plasma FFA (μmol/ml)	180.9 ± 70.3	181.1 ± 71.5	0.99	—	—	
Plasma C-peptide (ng/ml)	1.48 ± 0.56	1.52 ± 0.71	0.79	—	—	
Glucose production (mmol · $min^{-1} \cdot m^2$)	0.161 ± 0.060	0.180 ± 0.090	0.32	0.122 ± 0.067	0.149 ± 0.061	0.29
Glucose clearance (ml · $min^{-1} \cdot m^2$)	0.586 ± 0.137	0.555 ± 0.71	0.64	0.172 ± 0.042	0.171 ± 0.064	0.93

Data are means ± SD. Antepartum data were obtained in the early third trimester prior to the development of preeclampsia and postpartum data at a mean of 15 months after delivery. Data for the basal clamp were obtained during the last 90 min of a 180-min basal tracer infusion, before insulin infusion; those for the steady-state glucose clamp were obtained during the last 30 min of insulin infusion. Postpartum measures of FFA, C-peptide, and glucagons were not evaluated. There were no significant differences between nonpreeclamptic and preeclampsia metabolic parameters measured in antepartum or postpartum tests.

differences in the multiple metabolic parameters measured during the third trimester between the women with preeclampsia and those who remained nonpreeclamptic. During the OGTT, the fasting and postload levels of glucose and insulin at all time points (0–180 min) and the areas under the curves after glucose ingestion were not significantly different (Fig. 1), nor were there any differences in the IVGTT values, including the S_I, glucose effectiveness, AIR_g, and disposition index (Table 2). During the euglycemic clamps there was no difference in the basal and steady-state levels of glucose, insulin, FFA, glucose clearance, hepatic glucose output, glucagon, and C-peptide (Table 2).

Postpartum testing

Eighty-nine of the 150 women, 70 who remained nonpreeclamptic and 19 who had developed preeclampsia during pregnancy, returned for metabolic testing at a mean of 15 months postpartum. The entry demographics of those who returned did not differ from those who did not return with respect to age, weight, and blood pressure. Postpartum blood pressure measurements remained significantly different between the women who had developed preeclampsia during pregnancy and those who had remained nonpreeclamptic (Table 1). There were no significant differences in the OGTT glucose and insulin levels (Fig. 1), measures of insulin sensitivity during the IVGTT, or basal and steady-state measurements during the euglycemic clamp studies between the groups (Table 2).

CONCLUSIONS — In this prospective cohort study, and before there was any evidence of preeclampsia, women with GDM underwent detailed metabolic investigations in the early third trimester, including OGTT, IVGTT, and euglycemic clamp studies. The women with GDM who later developed preeclampsia were not metabolically different from those who remained nonpreeclamptic in the multiple parameters measured. There were no differences in fasting or postchallenge glucose levels, glucose production and clearance rates, or insulin resistance measurements between the two groups. This absence of metabolic differences remained at 15 months after delivery. The women with GDM who later developed preeclampsia were more likely to be nulliparous, were taller, and had entry blood pressure levels in the early third trimester that were consistently higher than those of women who remained nonpreeclamp-

tic, although the blood pressure levels were still within the normal range. The blood pressure levels remained significantly higher 15 months after delivery in the preeclampsia group, but again, the means were well within the normal range.

Our diagnosis of preeclampsia relied on clinical criteria (elevated blood pressure readings and 1+ proteinuria from a catheterized urine specimen) (1,14). As a qualitative determination of one positive proteinuria, a dipstick is influenced by the concentration of the urine and false positive and negative diagnosis may occur. Future protocols will use a urine protein-to-creatinine ratio now shown to be consistent with 24-h collections.

Although we did not find metabolic differences between the women who did and did not develop preeclampsia, it is important to recognize that relative to non-GDM control subjects, our GDM cohort has marked defects in regulation of glucose clearance, glucose production, and plasma FFA concentrations as well as a 67% impairment of pancreatic β-cell compensation for insulin resistance (7). This cohort was predicted to have a 65% risk of developing type 2 diabetes within 5 years of delivery (18). Because both insulin resistance and β-cell defects characterize GDM, it can be difficult to determine their role in the development of preeclampsia during pregnancy. Several studies have reported a higher incidence of preeclampsia during pregnancy in women with abnormal glucose tolerance (3–6,19–22), using either plasma glucose or insulin levels pre- or postglucose load.

A few studies have directly measured insulin in relation to preeclampsia during pregnancy. Utilizing hyperinsulinemic-euglycemic clamp studies, Caruso et al. (23) demonstrated increased insulin resistance in 8 women with GDM and chronic hypertension compared with 15 women with GDM alone. Fasting and post-OGTT insulin levels tended to be higher in women with GDM and chronic hypertension compared with women with GDM alone, but the difference did not reach statistical significance. No women with preeclampsia were included in their report. Roberts et al. (24) studied 11 women with preeclampsia and 11 nonpreeclamptic control subjects in the third trimester using the minimal model technique and found no differences between the groups. In a retrospective review, Van Hoorn et al. (25) found no difference in preeclampsia rates in women with GDM (19.6%, $n = 51$) compared with control subjects (17.1%, $n = 258$). They also report that the preeclamptic women were taller (by 1.9 cm; $P < 0.05$) and had higher DBP at booking ($P < 0.001$) than the control subjects. Cioffi et al. (26) measured fasting and 1-h postchallenge glucose and insulin levels in 292 pregnant women between 26 and 28 weeks of gestation. There were no significant differences in glucose or insulin levels in those who subsequently developed preeclampsia ($n = 11$) compared with those who remained nonpreeclamptic. The entry SBP, DBP, and mean arterial pressure were higher in the 11 women who later developed preeclampsia.

The women who went on to develop preeclampsia had significantly higher blood pressure levels, although still in the normal range, either at the initial prenatal visit or in the early third trimester. This finding has been observed by others as well (25,26) and suggests an underlying vascular pathology that might predate pregnancy and result in abnormal placentation (27), leading to placental hypoperfusion and the release of circulating compounds able to alter the maternal vascular endothelium (28).

In conclusion, the role of insulin resistance contributing to the etiology of preeclampsia has yet to be determined. Our detailed metabolic studies in women with GDM, a subgroup that has been associated with an increased preeclampsia risk, did not find any correlation between multiple measures of insulin resistance and β-cell function with the subsequent development of preeclampsia during pregnancy.

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