Gestational Diabetes, Pregnancy Hypertension, and Late Vascular Disease

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Increased understanding of the epidemiologic context, pathophysiology, and treatment efficacy of gestational diabetes mellitus (GDM) has raised corollary questions regarding subsequent morbidities, in addition to diabetes, sustained by patients with this diagnosis. Both hypertension and vascular disease have been examined as conditions that may be predicted by GDM. Obesity and insulin resistance are central attributes of both GDM and the metabolic syndrome. These characteristics and dyslipidemia are associated with endothelial dysfunction, oxidative stress, and overexpression of inflammatory responses, all of which contribute to vascular disease. These associations have significant public health ramifications because of the current epidemic of obesity, affecting individuals of all age-groups. The recent report of Crowther et al. (1) confirming the efficacy of screening for and treatment of mild-to-moderate levels of glucose intolerance in mid-pregnancy in reducing both perinatal and maternal morbidity has set the stage for universal maternal screening and thereby identifies a cohort of young women (as many as 200,000 annually in the U.S.) who may be at risk for subsequent hypertension and vascular disease. Recent trials of exercise and dietary interventions and pharmacological treatments suggest that such interventions may reduce late post-gestational morbidity among women with prior GDM. Consequently, questions about the association of GDM and subsequent hypertension and vascular disease are timely and important.

NONDIABETIC AND GDM PREGNANCY

— Pregnancy produces transient insulin resistance, manifest as elevated postprandial glycemia, fasting hyperlipidemia in the form of increased triglycerides, LDL particles, and free fatty acids and accelerated ketosis. Nondiabetic pregnancy is also associated with increased blood levels of plasminogen activator inhibitor-1, tumor necrosis factor-α, and C-reactive protein (CRP), all markers of increased inflammatory response. Despite these metabolic characteristics, pregnancy also induces increased venous capacitance, reduced systemic arterial resistance, and vasodilation associated with a 50% increase in circulating blood volume.

Gravidas with GDM generally demonstrate higher degrees of postpregnancy insulin resistance, β-cell dysfunction, higher BMI, central obesity, and exaggerated hyperlipidemia, which suggests that GDM is a transient manifestation of long-standing metabolic dysfunction. As such, GDM may be expected to have an association with gestational hypertension, a hypothesis ascribed to Vorzimer et al. in 1937 (2).

INSULIN RESISTANCE, GDM, AND GESTATIONAL HYPERTENSION

— Bryson et al. (3) found significantly elevated odds ratios (ORs) for GDM among women with gestational hypertension (1.4) and preeclampsia (new-onset proteinuric hypertension during pregnancy) (1.5) among 60,000 maternal hospital discharges in Washington state. Nonproteinuric GH but no preeclampsia have been associated with insulin resistance documented by the hyperinsulinemic-euglycemic clamp technique (4,5). Caruso et al. (4) examined 26 sequential subjects with third trimester hypertension (10 with preeclampsia, 10 with gestational hypertension, 6 with chronic hypertension, and 10 normotensive control subjects) with a euglycemic-hyperinsulinemic clamp. On day 1 of the study protocol, subjects performed an oral glucose tolerance test, during which plasma glucose, insulin, lipids, and lipoprotein were measured. On day 2, bioelectrical impedance was measured and the clamp was performed. Women with gestational hypertension demonstrated a 40% reduction in the steady-state insulin sensitivity index compared with the control subjects (3.75 vs. 6.34, $P < 0.03$), but no insulin sensitivity index differences were found between control subjects and either of the two other hypertensive groups. In fact, preeclampsia subjects had lower insulin and glucose area under the curve than control subjects (85.7 vs. 146.4 μmol/l, $P < 0.006$, and 994 vs. 1,225 mmol/l, $P < 0.0005$, respectively), with there being no differences among the other groups. When the four groups were pooled, insulin sensitivity index was negatively associated with triglyceride concentration and insulin area under the curve and persisted after adjustment for percent body fat. These data suggest that insulin resistance, independent of degree of obesity, contributes to transient hypertension identified in late pregnancy. These data, from gravidas already diagnosed with hypertension, suggest that preeclampsia may not result solely from insulin resistance.

However, these and other studies of gravidas with established hypertension did not address whether obesity per se or insulin resistance was primarily associated with new-onset hypertension in late pregnancy. Cohort studies, in which metabolic characteristics were measured before the onset of hypertension in pregnancy, have provided more insight into this association. Mid-pregnancy fasting hyperinsulinemia has been associated with subsequent development of preeclampsia alone in African-Americans (6) and with GH alone in a Japanese cohort (7), both independent of maternal BMI. In contrast, another mixed

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

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racial cohort found no association between mid-pregnancy hyperinsulinemia and subsequent gestational hypertension when controlling for BMI and race (8).

The possible independent effect of insulin resistance on gestational hypertension was examined in a cohort study of 320 gravidas, documented free of GDM, who were examined initially at 24–30 weeks' gestation and who delivered at ≥36 weeks (9). No subjects had any history of hypertension or thyroid disease, and they had BMIs of 25 ± 6 kg/m^2. The investigators measured fasting and 1-h glucose, insulin, and C-peptide at the time of the 1-h 50-g glucose challenge test at 27 ± 1 week. Multivariate analysis, controlling for BMI, gestational age, and mean arterial pressure at the time of the glucose challenge test, identified fasting C-peptide and glucose-stimulated C-peptide concentrations, both surrogate markers for insulin resistance, as significantly associated with the later development of gestational hypertension (OR 1.7 [1.1–2.7] and 3.8 [1.5–9.6], respectively). This association suggests that insulin resistance, rather than obesity, is more proximately related to nonproteinuric hypertension.

Several other cohort studies of surrogate markers for insulin resistance in early pregnancy suggest that it is insulin resistance that predisposes to new-onset hypertension in pregnancy. A prospective cohort case-control study (10) examined first trimester sex hormone–binding globulin and second trimester glucose challenge test glucose values in 45 patients with preeclampsia and 90 normotensive control subjects. Sex hormone–binding globulin production is inhibited by insulin and thereby serves as evidence of hyperinsulinemia and insulin resistance. Those who later developed preeclampsia had lower sex hormone–binding globulin (302 ± 130 vs. 396 ± 186 nmol/l, $P < 0.01$) and higher glucose challenge test values (122.4 ± 25.2 vs. 111.6 ± 23.4 mg/dl, $P = 0.3$), suggesting an association between early insulin resistance and late pregnancy preeclampsia. Of note, the sex hormone–binding globulin association with preeclampsia reached statistical significance only among women with BMI values <25 kg/m^2, suggesting an obesity-related threshold effect.

Further, among nondiabetic gravidas, mid-pregnancy postprandial glycemia has been noted to be positively associated with odds of subsequent gestational hypertension and preeclampsia. A retrospective case-control study (11) of 97 women with new-onset hypertension in late pregnancy and 77 normotensive control gravidas demonstrated that after adjustment of BMI and baseline systolic and diastolic blood pressures, the post–50-g challenge 1-h glucose value at 24–28 weeks was significantly higher among those developing hypertension. The Toronto Tri-Hospital Project cohort study (12) of 4,274 screened gravidas ≥24 years of age with singleton pregnancies examined 3,836 who went on to have a 3-h 100-g oral glucose tolerance test and a secondary outcome of preeclampsia (accepted as the caregiver's assignment of the diagnosis), with the first being cesarean delivery. Postprandial glucose but not fasting glucose values showed an association with the probability for subsequent preeclampsia, with the most significant being the 2-h value. Among those with values of <5.6 mmol/l, 3.3% had preeclampsia, with rates rising to 4.7, 6.5, and 6.4% among those in the 5.6–6.4, 6.5–7.3, and >7.3 mmol/l strata. A secondary analysis of the Calcium for Preeclampsia Prevention multicenter calcium prophylaxis preeclampsia trial (13) examined the association between glucose tolerance and subsequent gestational hypertension or preeclampsia among 3,381 screened nulliparous gravidas. The adjusted (by study center) relative risk of gestational hypertension and preeclampsia of those with GDM compared with those with 50-g 1-h values of <7.8 mmol/l was 1.48 (95% CI 0.99–2.22) and 1.67 (0.92–3.05), respectively, and reached statistical significance when the two hypertensive outcomes were combined 1.54 (1.28.–2.11). When the 227 gravidas with screening test values of ≥7.8 mmol/l but without GDM were compared with those with values <7.8 mmol/l, no difference in hypertension incidence could be detected. However, as in earlier studies, the 1-h 50-g glucose value among all gravidas correlated strongly ($P < 0.0001$) with preeclampsia risk after adjustment for clinical center, race, and BMI.

Indirect evidence for an association with early-pregnancy insulin resistance and subsequent preeclampsia (14) has been provided in a nested case-control study of 24-h urine insulin excretion (at 17 weeks' gestational age) in a cohort of nondiabetic singleton pregnancies. Patients with preeclampsia ($n = 70$) and nonproteinuric gestational hypertension ($n = 142$) were compared with 429 normotensive control subjects, matched by enrollment site and specimen storage time. The association of 24-h insulin secretion and preeclampsia or gestational hypertension was adjusted for BMI and smoking. Patients with mild preeclampsia, but not those with gestational hypertension, demonstrated increased 24-h insulin secretion. Possible confounding by variable hepatic insulin clearance notwithstanding, the increased 24-h insulin excretion suggests that insulin resistance, not hyperglycemia, characterizes a predisposition to preeclampsia.

Patients with GDM have a high prevalence of insulin resistance and were studied to examine the effect of insulin resistance versus other potential pathogenic factors in the development of preeclampsia. Among 184 gravidas with diagnosed GDM, mid-pregnancy anthropometry, blood pressure, microalbuminuria, fasting lipids, inflammatory and endothelial damage markers, and family disease history were examined in a predictive model for subsequent preeclampsia (15). Compared with the remaining patients, the 22 who developed preeclampsia demonstrated increased mid-pregnancy BMI, blood pressure, fasting glucose and insulin, urate, CRP, and microalbuminuria and a higher prevalence of family history of hypertension and gestational diabetes. No association of preeclampsia with mid-pregnancy lipid measurements was found. These data suggest that among gravidas with characteristics of the metabolic syndrome, fasting dyslipidemia is not an independent pathogenic factor in the development of preeclampsia.

SYSTEMIC INFLAMMATION AND GDM — Subclinical inflammation is associated with insulin resistance in groups at high risk for diabetes, and acute-phase biomarkers may predict the incidence of newly diagnosed type 2 diabetes. In a 2-year follow-up study of 396 male and female subjects with hyperlipidemia, obesity, or a family history of diabetes, normal glucose tolerance was noted in 271, impaired glucose tolerance in 82, and asymptomatic diabetes in 43. Insulin resistance, estimated by homeostatic model assessment, was found to be correlated with BMI ($r = 0.545$, $P < 0.001$), CRP ($r = 0.243$, $P < 0.001$), and leukocyte count ($r = 0.103$, $P = 0.04$) (16).

A similar association may be found in

women with recent GDM. Among women with and without a history of GDM, diastolic blood pressure and BMI were comparable. However, waist-to-hip circumference ratio, CRP, and fibrinogen values were significantly increased in the post-GDM group. In another study performed during pregnancy, those with GDM ($n = 48$) demonstrated increased CRP levels (5.5 mg/l, BMI 29.3 ± 5.0 kg/m^2) compared with those with only one elevated glucose value ($n = 39$) but of similar BMI (4.4 mg/l, BMI 28.4 ± 4.7 kg/m^2). Among all 180 subjects, CRP was more strongly associated with BMI ($r = 0.38$, $P < 0.0001$) than fasting insulin ($r = 0.27$, $P = 0.0002$) and fasting glucose ($r = 0.18$ $P = 0.016$) (17).

SUBCLINICAL INFLAMMATION, VASCULAR DYSFUNCTION, AND GDM

— A case-control study (18) of patients with ($n = 25$) and without ($n = 23$) prior GDM demonstrated that post-GDM women had higher mean levels of inflammatory biomarkers and peripheral vascular resistance and decreased stroke volume, measured ~4 years postpartum, compared with those without. Though maternal age (37 ± 5 vs. 39 ± 6 years) and years postpartum (4.0 ± 3.3 vs. 4.6 ± 4.3 years) were comparable, those with a history of GDM had higher levels of CRP (3.58 ± 3.86 vs. 0.52 ± 0.16 mg/l, $P <$ 0.001), interleukin-6 (1.81 ± 1.04 vs. 0.99 ± 0.52 pg/ml; $P = 0.001$), and plasminogen activator inhibitor-1 (29.6 ± 17.6 vs. 16.5 ± 14.0 ng/ml; $P = 0.001$). The same subjects also demonstrated increased vascular resistance (1,658 ± 290 vs. 1,462 ± 340 dyn per sec/cm [5]) (measured by arterial tonometry and simultaneous electrocardiographic recordings obtained from the brachial, radial, femoral, and carotid arteries with a custom pulse transducer) and decreased stroke volume (65 ± 13 vs. 75 ± 14 ml/beat) (measured by simultaneous tonometry of the carotid artery and pulsed Doppler of the left ventricular outflow tract) after adjustment for BMI. These data suggest that the gestational diabetic condition, characterized by inflammatory dysregulation and vascular dysfunction, both independent risks for cardiovascular disease, may predict its later clinical development.

The mechanisms that may link GDM with pregnancy hypertension are only partly examined. Brachial artery post-occlusion flow-mediated vasodilation but not nitrate-dependent vasodilation has been found to be reduced in gravidas with impaired glucose tolerance (19,20). Paradisi et al. (20) performed stepwise linear regression analysis of data among 10 gravidas with impaired glucose tolerance, 13 gravidas with GDM (1979), and 15 gravidas with normal glucose tolerance (National Diabetes Data Group criteria) and found that glucose area under an oral 3-h glucose tolerance test curve could account for 35%, and fasting free fatty acid levels accounted for 5% of the variance in flow-mediated vasodilation. However, neither BMI nor insulin response to an oral glucose challenge were independently associated with flow-mediated vasodilation. Moreover, moderate (8%) weight reduction does not affect the reduced brachial artery flow-mediated vasodilation in women with a history of GDM (21). These data suggest that, at least macrovascular, endothelial dysfunction may be a response to mildly elevated ambient glucose concentrations but may not reflect insulin resistance.

The association between preeclampsia and later hypertension also appears to be partly independent of insulin resistance and β-cell function. In a 15-month cohort study (22) of 150 gravidas with GDM enlisted between 28 and 34 weeks' gestational age, 29 were found to meet criteria for preeclampsia. A thorough characterization of insulin response and glucose disposal was carried out during and after pregnancy, including oral glucose tolerance test glucose levels, insulin sensitivity index, glucose effectiveness, acute response to glucose, disposition index, and euglycemic clamp measures of basal or steady-state levels of glucose, insulin, free fatty acid, hepatic glucose output, peripheral glucose clearance, C-peptide, and glucagon. In the third trimester and at 15 months after delivery, compared with the remainder of the cohort, those with preeclampsia did not demonstrate greater insulin resistance, but did demonstrate significantly higher blood pressures. Though no subjects in this short follow-up study became clinically hypertensive, this cohort study suggests that new-onset proteinuric hypertension in pregnancy may reflect underlying vascular dysfunction that is independent of insulin resistance or hyperglycemia.

LATE VASCULAR SEQUELAE AFTER PREGNANCY HYPERTENSION

— GDM may be linked to subsequent vascular disease. GDM predicts later manifestation of the metabolic syndrome including type 2 diabetes, both associated with vascular dysfunction and atherogenesis. Additionally, the association of glucose intolerance and insulin resistance in early and mid-pregnancy with subsequent gestational hypertension and preeclampsia suggests that patients with GDM may already have subclinical vasculopathy that results in later hypertension and vascular disease.

Preeclampsia's association with subsequent vascular disease has been explored in several recent reports. Hannaford et al. (23) used data from the Royal College of General Practitioners' oral contraception study. A structured questionnaire was performed in over 23,000 parous control women throughout the U.K. who weren't using oral contraception, exploring medical history, including "toxemia." Their 1,400 general practitioners were polled at regular intervals about newly identified vascular diseases in study patients. Age-, social class–, and smoking-standardized rates of these disorders were calculated. Compared with parous women without a recollection of toxemia, those reporting toxemia demonstrated increased relative risks (RRs) of hypertension (RR 2.35, 2.08–2.65), acute myocardial infarction (RR 1.74, 1.26–2.16), angina pectoris (RR 1.53, 1.09–2.15), and venous thromboembolism (RR 1.62, 1.09–2.41). There was a nonsignificant association with "total cerebral vascular disease" (RR 1.39, 0.89–2.16). However, the study's methods did not stipulate criteria for toxemia, the interval time between the recalled diagnosis of toxemia, and the identification of a vascular disorder, nor the degree of hypertension.

Wilson et al. (24) performed a similar controlled cohort study of women living in Aberdeen, Scotland, who had gestational hypertension ($n = 1,197$), preeclampsia, or eclampsia ($n = 1,199$) during their first singleton pregnancy from 1951 to 1970. Control subjects with documented normotensive pregnancies ($n = 1,197$) were matched for age and year of delivery. The diagnosis of gestational hypertension, preeclampsia, or eclampsia (or its absence) was defined a priori and was confirmed by record review of the Aberdeen maternity and neonatal databank. Patients with an asso-

Table 1—*ORs (control group = 1.0) for measures of hypertensive and other cardiovascular disease among questionnaire respondents*

	Gestational hypertension		Preeclampsia/eclampsia	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Doctor-diagnosed hypertension	2.47 (1.74–3.51)	<0.001	3.98 (2.82–5.61)	<0.001
Medicated hypertension	1.89 (1.23–2.88)	0.003	1.90 (1.27–2.86)	0.002
Doctor-diagnosed stroke	2.42 (0.59–9.98)	0.22	3.41 (0.95–12.2	0.06
Doctor-diagnosed angina	1.02 (0.58–1.81)	0.94	1.61 (0.95–2.73)	0.08
Doctor-diagnosed possible myocardial infarction	0.73 (0.32–1.63)	0.44	0.76 (0.35–1.63)	0.48
Intermittent claudication, Rose criteria	1.54 (0.38–6.19)	0.55	1.57 (0.41–6.05)	0.51
Doctor-diagnosed DVT	0.65 (0.35–1.20)	0.17	0.75 (0.42–1.34)	0.32
Doctor-diagnosed kidney disease (NOS)	0.64 (0.22–1.82)	0.40	2.39 (1.01–5.65)	0.05

DVT, deep venous thrombosis; NOS, not otherwise specified.

ciated contemporaneous history of chronic hypertension were excluded. Outcomes were ascertained by questionnaire (n = 295, 445, and 572, respectively), clinical examination (n = 206, 343, and 443, respectively), and hospital discharge data (n = 513, 599, and 717, respectively). Odds ratios were adjusted for maternal age, BMI, and smoking. Subjects with either gestational hypertension or preeclampsia/eclampsia had higher BMI, high proportions for late pregnancy care registration, and lower rates of administrative or professional employment. Adjusted ORs from patient questionnaire data (Table 1) demonstrated significant positive associations between both gestational hypertension and preeclampsia/eclampsia disorders and subsequent diagnosed and treated hypertension. Of interest, only stroke and claudication had a positive, albeit nonsignificant, association with pregnancy hypertensive disorders, whereas disorders of coronary and renal vascular disease were not associated (Table 1).

The questionnaire data were confirmed by clinical examination insofar as the ORs of medicated hypertension were greater in both gestational hypertension and preeclampsia/eclampsia groups (OR 1.95 [1.18–3.24], P = 0.009, and 2.77 [1.72–4.47], $P < 0.001$, respectively). However, there was no increase in the rate of new-onset electrocardiogram abnormalities in either group compared with control subjects (20/205 and 32/342, respectively).

The hospital admission rate was marginally higher in those with prior preeclampsia/eclampsia (69%) than in those with gestational hypertension (63%) and among control subjects (64%). Admissions for hypertension (OR 3.72 [1.43–9.65], P = 0.007, and 3.19 [1.21–8.39], P = 0.019) and "other circulatory" disorders (1.51 [1.06–2.14], P = 0.021, and 1.49 [1.05–2.11], P = 0.024) occurred more frequently in subjects with gestational hypertension and preeclampsia/eclampsia. By 1999, ~39 years since the subjects' first singleton pregnancy, 265 deaths were identified in the cohort subgroup for which some vital statistic information was available, 72/796 control, 89/951 gestational hypertension, and 104/1,043 preeclampsia/eclampsia groups. Though the overall mortality rate did not differ, that associated with cerebrovascular disease among those in the preeclampsia/eclampsia group was increased (OR 3.59 [1.04–12.4], P = 0.044).

This study's quantification of absolute incidences of adverse outcomes in a geographically determined cohort, its use of multiple independent data sources, and its use of a priori criteria for pregnancy hypertension and outcome conditions minimized data biases that characterize most retrospective studies. Though its hypothesis did not address the interaction of gestational hypertension and glucose intolerance effects on subsequent vascular disease, its consistent finding of an association between gestational hypertension and preeclampsia with subsequent chronic hypertension and cerebrovascular disease raises important public health questions about pregnancy follow-up.

SUMMARY — The complexity of the several pathogenic pathways that cause hypertension and vascular disease and the prolonged interval that appears to predate clinical morbidity have hindered inquiry into the association between GDM and vascular disorders. As a *forme fruste* of later type 2 diabetes, GDM-affected gravidas are identified as at risk of diabetes-related atherosclerosis, glomerular disruption, and pathogenic retinal angiogenesis. That GDM is evidence for underlying chronic conditions such as dysregulation of innate immune response that, independent of the diabetic state, produces vascular disease is difficult to assert with the present published literature. Cross-sectional studies of patients with established gestational hypertension or preeclampsia are ambiguous as to the possible pathogenic effect of insulin resistance. Cohort studies initiated in early and mid-pregnancy show evidence that both gestational hypertension and preeclampsia may be more prevalent in gravidas with greater insulin resistance. The association of gestational glucose intolerance with gestational hypertension appears to be independent of obesity and ambient glycemia but explained in part by insulin resistance.

Late pregnancy preeclampsia is associated with elevated mid-pregnancy BMI, blood pressure, fasting glucose and insulin, urate, and C-reactive protein, suggestive of metabolic and immune dysregulation. GDM appears to be associated with overexpressed innate immune response, which, in turn, is associated with vascular dysfunction and vascular disease. Among women with GDM, markers of insulin resistance do not appear to correlate with hypertension in short-term cohort studies. However, when non-GDM subjects are compared with subjects with GDM, postpregnancy studies do show an association of insulin resistance with both inflammatory dysregulation and vascular dysfunction.

Cohort studies that have used population-based pregnancy databases consistently identify a clinically significant association of both gestational hypertension and preeclampsia with later hypertensive disorders. Associations with coronary artery

disease or stroke are less consistent, requiring further investigation.

Preventing the evolution of diabetes and lipid and immune dysregulation of the metabolic syndrome has become a salient public health issue because of the epidemic of childhood and early adulthood obesity and the opportunity at hand to treat insulin resistance by behavioral and pharmacological interventions. However, limited available literature highlights the need for long-term cohort studies of women with well-characterized metabolic and vascular profiles during pregnancy and decades later. Our present knowledge suggests that screening for GDM provides an opportunity of pregnancy outcome improvement. Limited studies of diabetes prevention in at-risk patient groups suggest that we may have the opportunity to reduce the risk of later diabetes. Additional investigation is required to determine if interventions that prevent or postpone diabetes also delay the onset of vascular disease.

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