High Blood Pressure Before and During Early Pregnancy Is Associated With an Increased Risk of Gestational Diabetes Mellitus

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OBJECTIVE — While women with prior gestational diabetes mellitus (GDM) are more likely to display features of the metabolic syndrome, including hypertension, in the years after delivery, it is unclear whether these components are also present before pregnancy. We examined the relationship between blood pressure (BP) measured before and during early pregnancy (<20 weeks) and the risk of GDM in a nested case-control study.

RESEARCH DESIGN AND METHODS — Case (n = 381) and control (n = 942) subjects were selected from a cohort of women delivering between 1996 and 1998 and screened for GDM between 24 and 28 weeks' gestation. GDM was defined by the National Diabetes Data Group criteria. BP and covariates data were obtained by review of the medical records. Women were categorized according to BP levels recommended by the American Heart Association outside of pregnancy: <120/80 mmHg (normal), 120–139/80–89 mmHg (prehypertension), and ≥140 and/or ≥90 mmHg or use of antihypertensive medications (hypertension).

RESULTS — During early pregnancy, women with prehypertension had a small increased risk of GDM (odds ratio [OR] 1.56 [95% CI 1.16–2.10]), and women with hypertension had a twofold increased risk of GDM (2.04 [1.14–3.65]) compared with women with normal BP after adjusting for age, race/ethnicity, gestational week of BP, BMI, and parity. Similar results were seen among the subset of women with BP levels measured before pregnancy (1.44 [0.95–2.19] for prehypertension and 2.01 [1.01–3.99] for hypertension).

CONCLUSIONS — Clinicians should be aware that women presenting with hypertension may warrant early screening or intervention to prevent GDM.

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Type 2 diabetes and hypertension are both components of the metabolic syndrome and commonly occur together in individuals. A recent study of initially healthy middle-aged women found that blood pressure (BP) predicted the development of incident type 2 diabetes independent of BMI and other known diabetes risk factors (1). Several studies have shown that women with a history of gestational diabetes mellitus (GDM) are more likely to have features of the metabolic syndrome, including high BP, in the years after delivery (2–5). It is unclear whether elevated BP before or during early pregnancy is associated with the development of GDM.

Crowther et al. (6) showed that treatment of mild-to-moderate levels of glucose intolerance in midpregnancy effectively reduced both perinatal and maternal complications. Therefore, identifying additional variables that predict the development of GDM may help identify women who would benefit from early screening and, if needed, early treatment of pregnancy hyperglycemia to prevent perinatal complications. Because BP is a vital sign that is measured at each medical visit, it would be an easy and inexpensive clinical characteristic that could be used to identify women at risk of GDM. We therefore evaluated the relationship between BP before and during early pregnancy (<20 weeks' gestation) and risk of GDM in a nested case-control study among women who delivered singleton live infants at a large U.S. group practice prepaid health plan and received uniform screening and a standardized diagnostic test for GDM.

RESEARCH DESIGN AND METHODS

Setting

The study setting was the Kaiser Permanente Medical Care Program of Northern California (KPMCP-NC), which at the time provided comprehensive medical services through 15 hospitals and 23 outpatient clinics to over 3 million members located in a 14-county region in northern California. The KPMCP-NC membership represents ~30% of the surrounding population, and it is representative of the population living in the same geographic area demographically, ethnically, and socioeconomically, except that the KPMCP-NC membership underrepresents the very poor and the very wealthy (7).

Cohort identification

The methods used to identify this cohort have been described in detail elsewhere (8). Briefly, we identified all pregnancies that resulted in a singleton live birth between 1 January 1996 and 30 June 1998 among women without recognized diabetes before the index pregnancy. All pregnancies resulting in a singleton live birth, screened for GDM between 24–28 weeks' gestation, and without a diagnosis of GDM in a prior pregnancy were eligible to be selected for this study (Fig. 1). Briefly, we had 46,727 singleton pregnancies that

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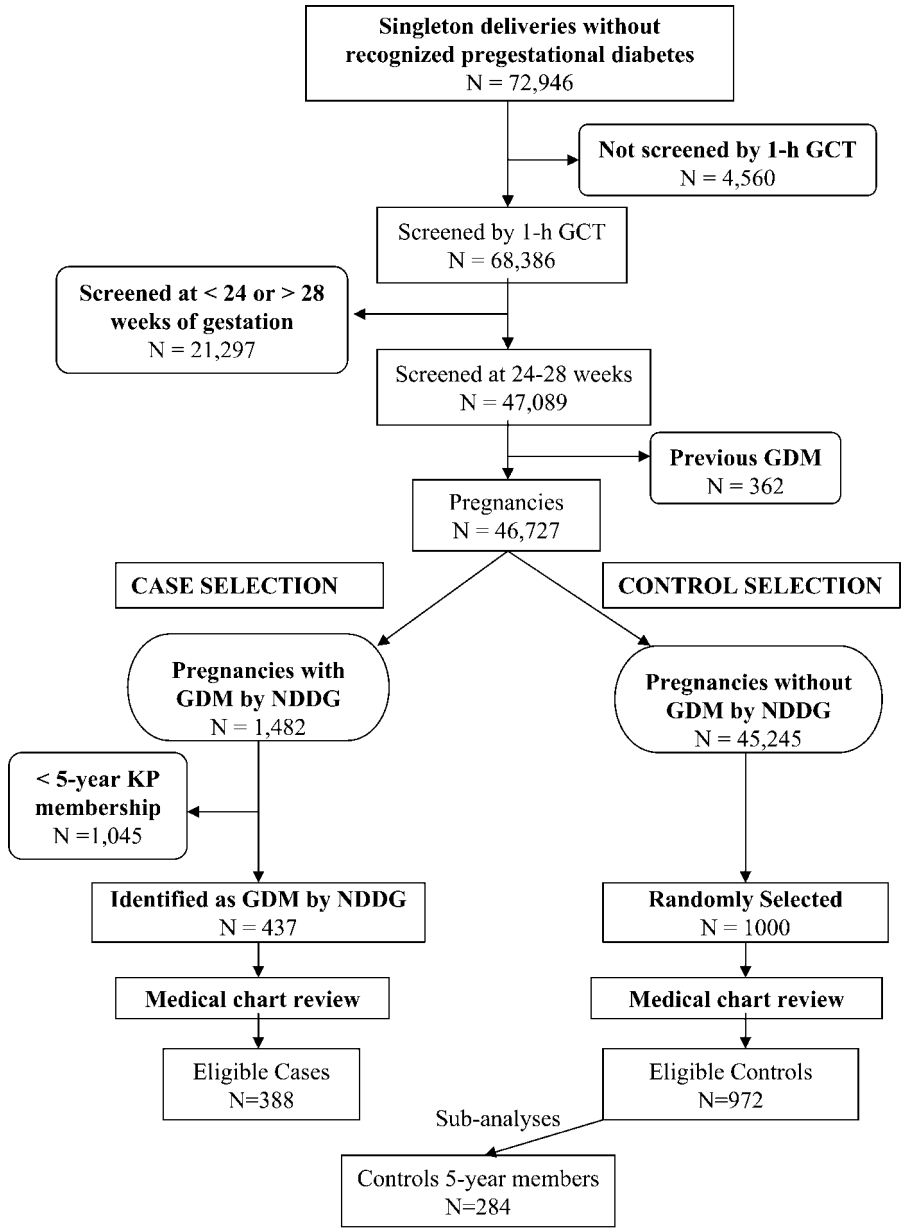

Figure 1—*GCT, glucose challenge test; NDDG, National Institute of Diabetes and Digestive and Kidney Diseases.*

were screened for GDM at 24–28 weeks, according to the earliest ultrasound. All 437 GDM case subjects (according to the NDDG criteria) that had been in the health plan for at least 5 years were selected for medical chart review, and 388 were included in the study. A total of 1,000 control subjects were randomly selected among 45,245 pregnancies with normoglycemia; 972 met the eligibility criteria after medical chart review, and 29% were members of the health plan for at least 5 years and served as control subjects for the subanalyses on "prepregnancy" BP levels and risk of GDM.

Medical chart review

Trained medical records abstractors completed chart review on the selected case and control subjects and confirmed if criteria for inclusion were met and if any of the exclusion criteria were present.

Case definition

Women were classified as having GDM at the index pregnancy if two or more of the four plasma glucose values obtained during the 100-g 3-h OGTT were abnormal according to the NDDG criteria (9): fasting ≥105 mg/dl (5.8 mmol/l), 1 h ≥190 mg/dl (10.5 mmol/l), 2 h ≥165 mg/dl (9.1 mmol/l), and 3 h ≥145 mg/dl (8.0 mmol/l). All plasma glucose measurements were performed using the hexokinase method by the regional laboratory of Kaiser Permanente Northern California. This laboratory participates in the College of American Pathologists' accreditation and monitoring program.

Data collection

Trained medical chart abstractors reviewed all available medical records to obtain information on subjects' measured BP before and during early pregnancy and potential confounders. Abstractors recorded the first BP measured during a prenatal visit provided it was performed before 20 weeks' gestation, according to the earliest ultrasound. For pregravid BP, the BP measured closest to but before the last menstrual period and no more than 5 years before pregnancy was recorded. The BP measured before pregnancy was not recorded if it was from an emergency or urgent-care visit. Information on use of BP medications was obtained from the medical chart.

Other information obtained on potential confounders during the medical record review included any body weights measured before pregnancy in a nonpregnant state. Last menstrual period before the index pregnancy, gestational week at the earliest ultrasound used to calculate gestational age at screening for GDM, marital status, family history of diabetes, family history of hypertension, self-reported prepregnancy weight, weight at first prenatal visit, parity, and height were abstracted from the prenatal form completed at the first prenatal visit. Prepregnancy weight was defined as the last recorded weight found in the chart before the woman's last menstrual period for the index pregnancy. For the 14.4% of women for whom these data were not available, the self-reported prepregnancy weight on the prenatal form was used. Prepregnancy BMI was calculated as prepregnancy weight in kilograms divided by the square of height in meters. BMI at first prenatal visit was calculated as weight in kilograms measured at first prenatal visit divided by the square of height in meters. Women's self-reported race/ethnicity and education were obtained by linkage to the electronic birth certificate database. Gestational age at first prenatal visit with a BP measurement was calculated from the earliest ultrasound performed before 24 weeks' gestation.

Exposure definition

For both prepregnancy BP and BP at first prenatal visit, women were classified into three predefined BP categories according the American Heart Association's criteria: <120 mmHg for systolic and <80 mmHg for diastolic BP (subsequently call normal BP), 120–139 mmHg for systolic and/or 80–89 mmHg for diastolic (subsequently called prehypertension), and at least 140 mmHg for systolic or at least 90 mmHg for diastolic or a prescription for antihypertensive treatment found in the medical chart (subsequently referred to as hypertension) (10).

Missing data

Women for whom information on either early pregnancy or prepregnancy BP was unavailable were excluded from that particular analysis. BP measured during the first prenatal visit was missing for 7 (1.8%) case subjects and 30 (3.1%) control subjects.

BP before pregnancy was not abstracted for 185 of the control subjects. Among case and control subjects who had BP before pregnancy abstracted, these data were missing for 6 (1.5%) case subjects and 186 (23.6%) control subjects. Information on BP before pregnancy was missing for a larger proportion of control subjects in part because the question was not initially included on the questionnaire at the beginning of the study (11) that provided data on control subjects.

A total of 381 case subjects and 942 control subjects remained for the analysis of early pregnancy BP, and 381 case subjects and 289 control subjects remained for the subanalysis of prepregnancy BP.

Statistical methods

Unconditional logistic regression was used to obtain odds ratios (ORs) as estimates of the relative risk of GDM in relation to category of BP. Women with normal BP were used as the reference group. To assess confounding, we entered covariates into a logistic regression model one at a time and then compared the adjusted and unadjusted odds ratios (12). Final logistic regression models included covariates that altered unadjusted odds ratios for BP by at least 10% as well as those covariates of a priori interest (i.e., parity). Variables evaluated for confounding were maternal age, race/ethnicity, pregravid BMI (kilograms divided by the square of height in meters), parity, maternal education in years, family history of diabetes (yes/no), and family history of hypertension (yes/no). BMI at first prenatal visit when the BP was measured and gestational week at BP measurement were also included in the adjusted model assessing BP during early pregnancy. For the analysis of BP before pregnancy and GDM, we adjusted for prepregnancy BMI and time between BP measurement and pregnancy. To assess the potential modifying effects of BMI (overweight ≥25

Table 1—*Selected characteristics of case and control subjects*

	GDM case subjects*	Control subjects
n	381	942
Age (years)		
<25	26 (6.8)	229 (24.3)
25–29	52 (13.6)	226 (24.0)
30–34	132 (34.6)	303 (32.2)
≥35	171 (44.9)	184 (19.5)
Race/ethnicity		
Non-Hispanic white	168 (44.1)	502 (53.3)
Hispanic	75 (19.7)	166 (17.6)
Asian	47 (12.3)	82 (8.7)
African American	29 (7.6)	90 (9.6)
Other	58 (15.2)	99 (10.5)
Unknown	4 (1.0)	3 (0.3)
Marital status		
Never married	54 (14.2)	226 (24.0)
Married	300 (78.7)	689 (73.1)
Widowed, divorced, or separated	16 (4.2)	21 (2.2)
Unknown	11 (2.9)	6 (0.6)
Education (years)		
≤12	142 (37.3)	392 (41.6)
13–15	124 (32.5)	267 (28.3)
16	73 (19.2)	159 (16.9)
≥17	37 (9.7)	115 (12.2)
Unknown	5 (1.3)	9 (1.0)
Parity		
0	148 (38.8)	405 (43.0)
1	125 (32.8)	343 (36.4)
≥2	108 (28.3)	194 (20.6)
Family history of diabetes		
First-degree relative	87 (22.8)	104 (11.0)
Second-degree relative	98 (25.7)	204 (21.7)
None	154 (40.4)	561 (59.6)
Unknown	42 (11.0)	73 (7.7)
Family history of hypertension		
First-degree relative	113 (29.7)	233 (24.7)
Second-degree relative	41 (10.8)	100 (10.6)
None	168 (44.1)	532 (56.5)
Unknown	59 (15.5)	77 (8.2)
BMI at first prenatal visit (kg/m^2)		
<20	14 (3.7)	98 (10.4)
20.1–24.9	96 (25.2)	423 (44.9)
25.0–29.9	126 (33.1)	250 (26.5)
≥30	142 (37.3)	149.0 (15.8)
Unknown	3 (0.8)	22.0 (2.3)
Blood pressure during pregnancy		
Normal	197 (51.7)	668 (70.9)
Prehypertenison	147 (38.6)	240 (25.5)
Hypertension	37 (9.7)	34 (3.6)

Data are *n* (%). *GDM equals NDDG criteria. Normal BP: ≤120/80 mmHg; prehypertension: 120–139/80–89 mmHg; and hypertension: ≥140 and/or ≥90 mmHg or use of antihypertensive drugs.

kg/m^2 vs. not overweight <25 kg/m^2), age (<30 vs. ≥30 years), family history of diabetes (first- or second-degree versus none), parity (one or more live births vs. none), and race/ethnicity (non-Hispanic white vs. African American, Asian, and Hispanic women), we examined interaction terms and repeated analyses within these subgroups. This study was approved by the human subjects committee of the Kaiser Foundation Research Institute.

RESULTS — Characteristics of women with GDM and control subjects are presented in Table 1. Women with GDM were more likely to be Hispanic, Asian, or from other nonwhite racial groups; to be older than 35 years; to have ≤12 years of education; to have a family history of diabetes; to have two or more prior livebirths; and to be overweight or obese at the first prenatal visit. GDM case subjects were also more likely to have hypertension or prehypertension both before and early in pregnancy. Mean gestational age at first BP measurement was 11.5 weeks for case subjects and 11.7 weeks for control subjects. Pregravid BP was measured on average 9.7 ± 12.3 months (mean ± SD) before the woman's last menstrual period for case subjects and 8.1 ± 8.5 months for control subjects.

After adjustment for age, race/ethnicity, parity, BMI, family history of diabetes, and gestational age at BP measurement, GDM risk increased among women with prehypertension and to a stronger degree among women with hypertension during early pregnancy (OR 1.41 [95% CI 1.04–1.90] and 2.08 [1.17–3.69], respectively) (Table 2). We examined the interaction terms between covariates presented in Table 2 and BP in the association with GDM risk; however, none of the interaction terms were statistically significant and the *P* values ranged from 0.25 for age and BMI to 0.91 for family history of diabetes. We also reran the analysis after excluding 11 case subjects and 8 control subjects who were taking antihypertensive medications, and the associations did not change significantly.

Stratified analyses suggested that the association between elevated early pregnancy BP and GDM was stronger among women known to be at high risk for GDM. Women who were overweight or obese (BMI ≥25.0 kg/m^2) before pregnancy presenting with hypertension during the first trimester of pregnancy had an almost threefold increased risk of developing GDM (OR 2.76 [95% CI 1.46–5.23]), whereas the corresponding OR for women who were not overweight was 1.26 (95% CI 0.35–4.35).

In the subsample of women who had been members of KPMCP-NC for 5 years before pregnancy and with information on BP before pregnancy and smoking status, GDM risk was associated with an increased risk among women with prehypertension and hypertension, and the magnitude of the association was similar to that found with BP during pregnancy (Table 3).

We also reran the analysis after excluding 11 case subjects and 8 control subjects who took antihypertensive medications before pregnancy, and the associations did not change.

CONCLUSIONS — In this study, women with hypertension either during the 5 years before pregnancy or during the first trimester of pregnancy had a twofold increased risk of developing GDM during pregnancy. While attenuated, these associations persisted after adjusting for BMI, suggesting that the association is independent of BMI. However, the association between BP and GDM was stronger among women who were overweight (BMI ≥25.0 kg/m^2).

A recent study among initially healthy women found high BP was associated with a twofold increased risk of developing type 2 diabetes during 4 years of follow-up after adjusting for known predictors of diabetes (1). Data on BP before or during pregnancy in relation to the occurrence of GDM are sparse. Our results are generally consistent with the one previous study of BP and risk of GDM (13). Lao and Ho (13) examined first-trimester BP and risk of GDM among 131 high-risk Chinese women and found that systolic BP above the median (109 mmHg) had a fourfold increased risk of GDM (OR 4.20 [95% CI 1.97–8.94]). While the magnitude of the association they found was greater than our findings, they examined only high-risk women referred to a clinic providing antenatal care, categorized women according to a dichotomous cut-

Table 2—*ORs and 95% CI for GDM associated with GDM risk factors and BP during the first prenatal visit*

	Case subjects	Control subjects	Crude OR (95% CI)	Adjusted OR* (95% CI)
n	381	942		
Blood pressure				
Normal	197 (51.7)	668 (70.9)	1.00	1.00
Prehypertension	147 (38.6)	240 (25.5)	2.08 (1.60–2.60)	1.56 (1.16–2.10)
Hypertension	37 (9.7)	34 (3.6)	3.69 (2.26–6.04)	2.04 (1.14–3.65)
Age ≥30 years	308 (79.4)	502 (51.7)		3.54 (2.57–4.88)
BMI ≥25 kg/m^2	276 (56.4)	426 (44.7)		2.43 (1.82–3.25)
Nonwhite	219 (56.4)	458 (47.1)		1.77 (1.34–2.34)
First- or second-degree relative with diabetes	189 (54.7)	320 (35.7)		1.73 (1.32–2.28)
1+ live births	238 (61.3)	556 (57.2)		0.77 (0.57–1.04)

Data are *n* (%) unless otherwise indicated. *ORs from multivariate model adjusted for age, BMI at first prenatal visit, race/ethnicity, family history of diabetes, parity, and gestational week at BP measurement.

Table 3—*ORs and 95% CI for GDM associated with BP before pregnancy*

	Case subjects	Control subjects	Crude OR (95% CI)	Adjusted OR* (95% CI)
n	381	289		
Blood pressure				
Normal	152 (39.9)	329 (54.7)	1.00	1.00
Prehypertension	181 (47.5)	230 (38.3)	1.66 (1.20–2.30)	1.44 (0.95–2.19)
Hypertension	48 (12.6)	42 (7.0)	2.18 (1.26–3.79)	2.01 (1.01–3.99)

Data are *n* (%) unless otherwise indicated. Data are from the subset of women who were members of KPNC 5 years before pregnancy. *Adjusted for age, race/ethnicity, prepregnancy BMI, parity, smoking status, family history of diabetes, and time between BP measurement and pregnancy.

off for systolic BP, and had limited information on confounders.

This study is the first to our knowledge to examine BP and GDM in an ethnically diverse population of women who underwent uniform screening for GDM. This study has several strengths, including the ability to assess measured BPs obtained pregravid and risk of GDM. A clear definition of GDM was based on objective measures of pregnancy glycemia among a cohort with universal screening performed at 24–28 weeks' gestation. Given the extensive chart review, we were also able to identify and exclude women with recognized preexisting diabetes before pregnancy. Finally, we were able to control for several important potential confounding factors.

This study also has several limitations. During normal pregnancy, BP steadily decreases up to 21 weeks' gestation and then increases during the second half of pregnancy (14). Our assessment of hypertension during pregnancy probably only captured severe case subjects in whom BP remained elevated even during early pregnancy. Other limitations of this study include the reliance on a single measure of BP, which may be influenced by external and internal stimuli, such as physical activity, diet, and emotional state. For the main analysis, we lacked information on smoking, a potential confounder; however, in a subanalysis limited to women who were members of the health plan for 5 years before pregnancy, we had smoking history and it did not confound the association. For the analysis of pregravid BP and GDM, we were missing information on BP on a large portion of control subjects; however, the magnitude of the association between early pregnancy BP and GDM was similar and had very little missing data. Use of certain types of antihypertensive medications may be associated with risk of type diabetes (15); however, sensitivity analyses excluding the small number of women who used antihypertensive drugs pregravid did not change our results.

Several studies have examined the metabolic syndrome or its components 2–11 years after pregnancy, and in most of these studies, mean BP levels were significantly higher among the women with prior GDM compared with women who had normal glycemia during pregnancy (3–5,16). We found the association between high BP and GDM was stronger among overweight or obese women, suggesting that these two components of the metabolic syndrome may interact synergistically to produce adverse metabolic effects that predispose to GDM during pregnancy.

There are several common pathogenic pathways to hypertension and GDM that may be underlying the association between the two conditions. Insulin resistance has been shown to be a contributing factor to both chronic (17) and gestational hypertension (18), and it is known to be involved in the pathogenesis of GDM (19). Endothethial dysfunction has been found in women with GDM both during (20) and after (21) pregnancy and is also closely related to hypertension (22). Finally, markers of inflammation such as C-reactive protein have been associated with increased BP levels (23), and elevated early pregnancy CRP levels have been related to increased risk of GDM (24).

In summary, our data suggest that women presenting with high BP, especially those who are overweight, are at increased risk of developing GDM during pregnancy. Clinicians should be aware that this subgroup of women may warrant the initiation of early screening or dietary and exercise interventions to prevent the development of GDM.

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