Increased Risk of Hypertension After Gestational Diabetes Mellitus

Findings from a large prospective cohort study

Deirdre K. Tobias, sm[1]
Frank B. Hu, md, phd[1,2]
John P. Forman, md, msc[2,3]
Jorge Chavarro, md, scd[1,2]
Cuilin Zhang, md, phd[4]

OBJECTIVE—Whether a history of gestational diabetes mellitus (GDM) is associated with an increased risk of hypertension after the index pregnancy is not well established.

RESEARCH DESIGN AND METHODS—We investigated the association between GDM and subsequent risk of hypertension after the index pregnancy among 25,305 women who reported at least one singleton pregnancy between 1991 and 2007 in the Nurses' Health Study II.

RESULTS—During 16 years of follow-up, GDM developed in 1,414 women (5.6%) and hypertension developed in 3,138. A multivariable Cox proportional hazards model showed women with a history of GDM had a 26% increased risk of developing hypertension compared with those without a history of GDM (hazard ratio 1.26 [95% CI 1.11–1.43]; $P = 0.0004$). These results were independent of pregnancy hypertension or subsequent type 2 diabetes.

CONCLUSIONS—These results indicate that women with GDM are at a significant increased risk of developing hypertension after the index pregnancy.

Diabetes Care 34:1582–1584, 2011

Increasing evidence suggests the effect of gestational diabetes mellitus (GDM) extends beyond pregnancy for both the mother and child (1). For instance, women with a history of GDM are at a substantially higher risk of type 2 diabetes (2); small- and large-vessel vascular dysfunction (3); cardiovascular disease; and metabolic syndrome and its components, including hypertension (4–7). In the current study, we examined longitudinally whether GDM is associated with an increased risk of hypertension later in life independent of other known risk factors.

RESEARCH DESIGN AND METHODS

Study population

Our analysis was conducted among the 116,671 participants of the Nurses' Health Study II, a longitudinal prospective cohort established in 1989 and described in detail elsewhere (8). Questionnaires are distributed biennially to update lifestyle characteristics and health-related outcomes. Our analysis included women if they reported at least one pregnancy lasting >6 months between 1991 and 2001 and were free of chronic disease. Participants were censored during follow-up at death or if they reported a cardiovascular disease event. In all, 25,305 participants were included.

Assessment of exposure and outcome

A physician diagnosis of GDM was ascertained by self-report on biannual questionnaires from 1989 through 2001, and has been previously validated. GDM is an established risk factor for type 2 diabetes (2), which is a well-known correlate of hypertension. Thus, we recategorized our exposure in a secondary analysis to examine the joint effect of GDM and type 2 diabetes: without self-reported GDM or type 2 diabetes, GDM only, type 2 diabetes only, or both GDM and subsequent type 2 diabetes.

Participants were asked on each questionnaire if they received a physician's diagnosis of high blood pressure (yes/no) and the date of diagnosis, which was also previously validated. Incident cases were counted from the first follow-up questionnaire (1993) through June 2007.

Statistical analysis

Participants' person-time was computed from the date of questionnaire return reporting the index pregnancy until the date of the diagnosis of hypertension, date of death or cardiovascular disease event, or the date of their latest questionnaire return, whichever came first. GDM-exposed person-time was defined from the date of the first reported GDM diagnosis through the end of follow-up.

Multivariable Cox proportional hazards models estimated the relative risk (hazard ratio [HR]) and 95% CI for the association between GDM and the subsequent risk of hypertension. In addition to computing an age-adjusted model, we adjusted for a priori potential confounders of the association between GDM and hypertension. We conducted −2 log likelihood ratio tests to assess whether the association of GDM with a future risk of hypertension was modified by family history of hypertension (yes/no), race

From the [1]Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the [3]Renal Division, Brigham and Women's Hospital, Boston, Massachusetts; and the [4]Epidemiology Branch, Division of Epidemiology, Statistics, and Prevention Research, *Eunice Kennedy Shriver* National Institute of Child Health & Development (NICHD), Bethesda, Maryland.
Corresponding authors: Deirdre K. Tobias, dbanel@hsph.harvard.edu, and Cuilin Zhang, zhangcu@mail.nih.gov.
Received 10 February 2011 and accepted 20 April 2011.
DOI: 10.2337/dc11-0268
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0268/-/DC1.

(Caucasian vs. non-Caucasian), and BMI category (<25, 25–29, and ≥30 kg/m^2).

RESULTS—Of the 25,305 participants included in our analysis, 1,414 (5.6%) were first exposed to GDM during their index or a subsequent pregnancy. Women with GDM were generally more likely to be obese, have a history of preeclampsia/toxemia, have a family history of diabetes/hypertension, and were less likely to perform vigorous physical activity than women without GDM (Supplementary Table 1).

We documented 3,138 cases of hypertension during 317,892 person-years of follow-up. The unadjusted incidence rate of hypertension was 1.76 cases per 100 person-years among women with GDM, and 0.95 cases per 100 person-years among the unexposed (Supplementary Fig. 1). Table 1 reports the age-, BMI-, and multivariable-adjusted associations between GDM and incident hypertension. In the multivariable-adjusted model, the association was significant: exposure to GDM was associated with a 26% increased risk of hypertension (HR 1.26 [95% CI 1.11–1.43]; $P = 0.0004$). There was no evidence of effect modification by family history of hypertension ($P = 0.9$ for interaction), race and ethnicity ($P = 0.6$), or BMI status ($P = 0.3$).

Overall, type 2 diabetes developed in 244 participants (1.0%) after the index pregnancy and before hypertension or the end of follow-up (Supplementary Fig. 2), of whom 114 (47%) had been exposed to GDM before type 2 diabetes developed. Compared with participants without exposure to GDM or to type 2 diabetes, the multivariable HR of incident hypertension was 2.55 (95% CI 1.84–3.55; $P < 0.0001$) among those who had both GDM and subsequent type 2 diabetes. This was similar to the HR among women who had type 2 diabetes only (2.98 [2.17–4.08]; $P < 0.0001$). The association between GDM and incidence of hypertension remained significant among the participants who had GDM but did not subsequently develop type 2 diabetes (1.18 [1.03–1.36]; $P = 0.02$).

CONCLUSIONS—In a large prospective cohort, we found that women exposed to GDM had an increased risk of hypertension in the years after pregnancy, even after adjusting for other major risk factors of hypertension. The precise underlying mechanisms for the observed association are unclear. During a normal pregnancy, insulin resistance in maternal tissues occurs to increase the glucose supply for the developing fetus (9). Previous research has demonstrated that women who developed GDM had an underlying high susceptibility to glucose tolerance (i.e., β-cell dysfunction and chronic insulin resistance) such that they are more likely to develop GDM when facing the metabolic challenges in pregnancy. Defects in insulin sensitivity and secretion are both related to elevated hypertension risk. It is plausible that the association of GDM and subsequent hypertension reflects pre-existing common risk factors for both GDM and hypertension (10,11). It is also biologically plausible that our results reflect a causal association between GDM and subsequent hypertension, such that lasting metabolic and vascular damage inflicted during a pregnancy complicated by GDM increases the risk that hypertension will develop years later. However, prospective studies evaluating biologic risk factors before, during, and after pregnancy are needed to further evaluate the causal association hypothesis.

Our results indicate that women with GDM are at a significantly increased risk of hypertension compared with women who do not have GDM. A diagnosis of GDM may provide an opportunity to intervene with high-risk women years before hypertension would normally present. Further research is needed to understand the underlying biologic mechanisms, as well as to measure the effect of GDM prevention or postpartum interventions on the long-term risk of hypertension.

Table 1—*Association of GDM with future risk of hypertension*

Model	HR (95% CI)	*P*
Model 1: age	1.83 (1.65–2.12)	<0.0001
Model 2: + BMI	1.42 (1.25–1.61)	<0.0001
Model 3: + history of pregnancy, HTN	1.29 (1.14–1.46)	<0.0001
Model 4: + family history of HTN/T2D, parity, DASH score, alcohol, total physical activity, smoking status, race/ethnicity, analgesic use, OC use, birth weight, BMI at age 18 years	1.26 (1.11–1.43)	0.0004

DASH, Dietary Approaches to Stop Hypertension; HTN, hypertension; OC, oral contraceptive; T2D, type 2 diabetes.

Acknowledgments—C.Z. was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* NICHD, National Institutes of Health (NIH). This study was funded by NIH research grants CA-50385 and DK-58845 and the Intramural Research Program of the *Eunice Kennedy Shriver* NICHD.

No potential conflicts of interest relevant to this article were reported.

D.K.T. conceived and designed the research, analyzed and interpreted data, performed statistical analyses, and drafted the manuscript. F.B.H. conceived and designed the research and made critical revisions of the manuscript for important intellectual content. J.P.F. made critical revisions of the manuscript for important intellectual content. J.C. analyzed and interpreted data and made critical revisions of the manuscript for important intellectual content. C.Z. conceived and designed research, handled funding and supervision, and made critical revisions of the manuscript for intellectual content.

References

1. Yogev Y, Visser GH. Obesity, gestational diabetes and pregnancy outcome. Semin Fetal Neonatal Med 2009;14:77–84
2. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773–1779
3. Banerjee M, Cruickshank JK. Pregnancy as the prodrome to vascular dysfunction and cardiovascular risk. Nat Clin Pract Cardiovasc Med 2006;3:596–603
4. Ko GT, Chan JC, Tsang LW, Li CY, Cockram CS. Glucose intolerance and other cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus. Aust N Z J Obstet Gynaecol 1999;39:478–483
5. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care 2008;31:1668–1669
6. Meyers-Seifer CH, Vohr BR. Lipid levels in former gestational diabetic mothers. Diabetes Care 1996;19:1351–1356
7. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance

in pregnancy and postpartum risk of metabolic syndrome in young women. J Clin Endocrinol Metab 2010;95:670–677
8. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997;278:1078–1083
9. Knopp RH, Warth MR, Charles D, et al. Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes. Biol Neonate 1986;50:297–317
10. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl. 2):S251–S260
11. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. J Clin Endocrinol Metab 2001; 86:989–993