Increased Risk of Hypertension After Gestational Diabetes Mellitus

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Increased Risk of Hypertension After Gestational Diabetes Mellitus

Findings from a large prospective cohort study

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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.

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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.
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.

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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.

Table 1—Association of GDM with future risk of hypertension

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<tr>
<th>Model</th>
<th>HR (95% CI)</th>
<th>P</th>
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<td>Model 1: age</td>
<td>1.83 (1.65–2.12)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Model 2: + BMI</td>
<td>1.42 (1.25–1.61)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Model 3: + history of pregnancy, HTN</td>
<td>1.29 (1.14–1.46)</td>
<td>&lt;0.0001</td>
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<td>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</td>
<td>1.26 (1.11–1.43)</td>
<td>0.0004</td>
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DASH, Dietary Approaches to Stop Hypertension; HTN, hypertension; OC, oral contraceptive; T2D, type 2 diabetes.

References
7. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance...
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