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*Obstet Gynecol.* 2016 April ; 127(4): 771–779. doi:10.1097/AOG.0000000000001353.**Pregnancy-Associated Hypertension in Glucose Intolerant Pregnancy and Subsequent Metabolic Syndrome**

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**Abstract**

**Objective**—To evaluate whether pregnancy-associated hypertension (preeclampsia or gestational hypertension), among women with varying degrees of glucose intolerance during pregnancy is associated with maternal metabolic syndrome 5-10 years later.

**Methods**—This was an observational cohort study of women previously enrolled in a treatment trial of mild gestational diabetes mellitus or an observational study of lesser degrees of glucose intolerance, evaluated 5-10 years following their index pregnancy. At follow-up, women underwent anthropometric and blood pressure measurements and analysis of fasting glucose and serum lipids.

**Results**—Eight hundred twenty five women (47% of eligible women from the original study) were included in this analysis and evaluated at a median 7 years after their index pregnancy at a median age of 35 years. Overall, 239 (29%) had subsequent metabolic syndrome. The frequency

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\*For a list of other members of the NICHD MFMU, see Appendix 1 online at <http://links.lww.com/xxx>.

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of metabolic syndrome and its components was highest in the women who had pregnancy-associated hypertension and delivered preterm. After adjusting for confounding factors, pregnancy-associated hypertension in women who delivered preterm was associated with subsequent hypertension (130/85 mmHg; relative risk [RR] 3.06, 95% confidence interval [CI] 1.95-4.80,  $p < .001$ ), high triglycerides (150 mg/dL; RR 1.82, 95% CI 1.06-3.14,  $p = .03$ ) and metabolic syndrome (per the American Heart Association and National Heart Lung and Blood Institute Scientific Statement; RR 1.78, 95% CI 1.14-2.78,  $p = .01$ ), compared with women who remained normotensive throughout their index pregnancy and were delivered at term.

**Conclusion**—Women with varying degrees of glucose intolerance who experienced pregnancy-associated hypertension and then delivered preterm had a higher frequency of subsequent hypertension, high triglycerides and metabolic syndrome 5-10 years later.

## Introduction

Several systematic reviews and meta-analyses support the association between pregnancy complications and future cardiovascular and metabolic disease in the mother.<sup>(1-4)</sup> Gestational diabetes mellitus (GDM) is a risk factor for future metabolic disease, in particular type 2 diabetes,<sup>(1,2,5)</sup> with its associated cardiovascular complications.<sup>(6,7)</sup> Preeclampsia and gestational hypertension, collectively referred to as pregnancy-associated hypertension, have both been shown to be associated with the development of hypertension and cardiovascular disease later in life.<sup>(2-5,8-16)</sup> Several studies suggested that the association is strongest with preterm pregnancy-associated hypertension possibly due to its earlier onset and/or greater severity.<sup>(8,12,17,18)</sup> Pregnancy complications may initiate vascular damage, alter metabolism, or unmask a woman's risk of future disease via pathways common to both pregnancy complications and cardiovascular disease, such as systemic inflammation and endothelial dysfunction.<sup>(2,5,10,19-22)</sup>

The American Heart Association now includes history of preeclampsia, gestational hypertension and GDM in their classification of cardiovascular risk factors in women.<sup>(23)</sup> However, much of the data on which this guideline is based were derived from retrospective identification of pregnancy complications, linked birth and death registries, and administrative data bases. Therefore, the objective of this analysis was to evaluate whether pregnancy-associated hypertension is associated with maternal metabolic syndrome at 5-10 years follow-up in an ethnically-diverse cohort of women with glucose intolerance enrolled during pregnancy with rigorously collected data.

## Materials and Methods

Women enrolled from October 2002 through mid-November 2007 in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network GDM study were evaluated 5-10 years after their index pregnancy (February 2012 through September 2013). Details regarding the GDM study have been previously described.<sup>(24)</sup> Briefly, women enrolled in the GDM study were between 24 weeks 0 days and 30 weeks 6 days of gestation and had an abnormal blood glucose concentration (135-200 mg/dl) one hour after a 50 gram glucose loading screen based on local laboratory measurement. After an overnight fast the women completed a 3-hour 100

gram oral glucose tolerance test, and those with a fasting glucose <95 mg/dl remained eligible. Women with an abnormal oral glucose tolerance test consistent with mild GDM (two or three oral glucose tolerance test timed measurements that exceeded established thresholds: one hour, 180 mg/dl; two hour, 155 mg/dl; and three hour, 140 mg/dl) who provided informed consent were randomly assigned to treatment with formal nutritional counseling and diet therapy with insulin if required or usual prenatal care. Women with a normal oral glucose tolerance test (but had an abnormal screen, and therefore had lesser degrees of glucose intolerance) who provided informed consent were enrolled and received usual prenatal care. By including this observational cohort of women with lesser degrees of glucose intolerance, the patients, their caregivers, and the study staff were unaware of whether or not women in the untreated group met the criteria for the diagnosis of mild GDM.

Women did not have a prior history of pregestational or gestational diabetes mellitus, renal or cardiovascular disease or chronic hypertension, nor did they have preeclampsia at the time of enrollment in the original study. The GDM study was approved by the institutional review board of all participating centers.

Pregnancy complications, including pregnancy-associated hypertension and gestational age at delivery, were collected as part of the original study.<sup>(24)</sup> Pregnancy-associated hypertension included both gestational hypertension and preeclampsia. Gestational hypertension was defined as meeting either of the following criteria: 1) diastolic blood pressure  $\geq 90$  or systolic blood pressure  $\geq 140$  on two occasions at least four hours apart; or 2) one elevated blood pressure subsequently treated with anti-hypertensive medication. Preeclampsia was defined as elevation in blood pressure as defined above plus meeting any of the following criteria: 1) proteinuria (24-hour urine protein  $\geq 300$  mg/24 hours or 24-hour urine not done and  $\geq 2+$  on dipstick in absence of a urinary tract infection, or 24-hour urine not done and protein-creatinine ratio  $\geq 0.35$ ); 2) elevated liver enzyme serum levels (serum glutamic oxaloacetic transaminase  $\geq 70$  unit/L or lactic acid dehydrogenase  $\geq 600$  unit/L); or 3) thrombocytopenia (platelet count  $<100,000/\text{mm}^3$ ); in absence of any other known cause of elevated pressures, proteinuria, elevated enzymes, or decreased platelets. All suspected cases of pregnancy-associated hypertension were centrally reviewed and adjudicated during the original study by two protocol subcommittee physician members. Preterm delivery was defined as delivery  $<37$  weeks, 0 days of gestation, with gestational age confirmed by ultrasound before enrollment. For the present analysis, women were categorized into one of four groups: 1) experienced pregnancy-associated hypertension and delivered preterm; 2) experienced pregnancy-associated hypertension and delivered at term; 3) remained normotensive throughout their index pregnancy and delivered preterm; 4) remained normotensive throughout their index pregnancy and delivered at term (reference group).

The follow-up study was approved by the institutional review board of all participating centers and has been previously described.<sup>(25)</sup> Maternal eligibility included that the patient had participated in the original GDM study, she was enrolled at a center still participating in the Maternal-Fetal Medicine Units Network at the time of the follow-up study, and her index child participated in the follow-up study. Following informed consent, women underwent anthropometric and blood pressure measurements, and completed a research staff-

administered questionnaire about medication use, physical activity, and diet. Weight and height were measured using a hospital grade scale and a stationary stadiometer, respectively. Waist circumference was measured by trained personnel who received standardized anthropometric training, using an AcuFitness MyoTape just above the uppermost lateral border of the right ilium of the pelvis,<sup>(26)</sup> and an average of three measurements was used in the analysis. Blood pressure was measured by trained personnel after the participant fasted and had not smoked for at least 30 minutes, and was sitting quietly for at least 10 minutes, by auscultation using aneroid sphygmomanometer instruments or a hospital grade blood pressure/pulse machine. The average of two measurements was used in the analysis. The women were queried regarding the number of minutes or hours per week in the last 7 days that they engaged in vigorous activity, moderate activity and walking. The diet questions queried about the typical number of servings per day or week of various foods, including vegetables other than potatoes or corn, dairy, and sweetened beverages. Following a minimum 6-hour fast, participants had their blood drawn. Collection, processing and storage of specimens were conducted per a standardized approach prior to being shipped on dry ice to the Northwest Lipid Metabolism and Diabetes Research Laboratories for lipid panel and glucose laboratory measurements. Laboratory analyses were performed the same day as sample arrival. Determination of fasting glucose was performed enzymatically using Roche reagents on a Roche Module-P autoanalyzer. Lipid panel determination was performed enzymatically using Roche reagent on the Roche Modular P autoanalyzer by methods standardized to the Centers for Disease Control and Prevention Reference Methods. To minimize bias, research staff involved in data collection and laboratory analyses were masked to the participant's exposures during the original study. The primary outcome, metabolic syndrome, was defined per the American Heart Association / National Heart Lung and Blood Institute Scientific Statement<sup>(27)</sup> as three or more of the following: waist circumference >88 cm, triglycerides  $\geq 150$  mg/dL, high-density lipoprotein cholesterol <50 mg/dL, blood pressure  $\geq 130/85$  mmHg, or fasting glucose  $\geq 100$  mg/dL, or relevant treatment for any of these components.

Descriptive analyses used the chi-square test or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Continuous variables were assessed to evaluate whether they were normally distributed and log-transformed when appropriate. Metabolic syndrome (3 or more components) was evaluated as a binomial outcome using log-Poisson multiple regression to estimate the relative risk (RR) and 95% confidence interval (CI) adjusting for potentially confounding factors. Log-Poisson multiple regression was also used to evaluate the binomial components of metabolic syndrome. A post hoc analysis using log-Poisson multiple regression evaluated presence of four or more components of metabolic syndrome (vs. 0-3 components). The components of metabolic syndrome were also evaluated as continuous outcomes using least squares means general linear regression. The multivariable models included adjustment for baseline characteristics (mild GDM, age, race/ethnicity and body mass index at time of enrollment in the original study during the index pregnancy and smoking during the index pregnancy), as well as duration of follow-up. Mild GDM treatment was evaluated for potential confounding and was shown to not confound observed associations. The models evaluating the continuous outcomes were also adjusted for relevant treatments at follow-up. Because smoking is an

important cardiovascular risk factor, and because log-Poisson multiple regression allows for zero cells (none of the women who experienced pregnancy-associated hypertension and delivered preterm smoked during the index pregnancy), the multivariable models included adjustment for smoking. However, a sensitivity analysis was conducted in which the multivariable models did not include adjustment for smoking. The main analysis did not adjust for follow-up characteristics because exposure to pregnancy complications may affect subsequent lifestyle, and therefore in the same causal pathway. However, a sensitivity analysis was conducted to evaluate whether associations changed after adjusting for follow-up lifestyle characteristics (i.e., whether there is any indication that lifestyle explained some of the observed associations), specifically vegetable consumption and vigorous physical activity. A third sensitivity analysis adjusted for pre-pregnancy body mass index rather than pregnancy body mass index. Pre-pregnancy body mass index was not used in the main analysis because it was not measured in a standardized way, included patient self-report, and was missing in 66 women. A fourth sensitivity analysis excluded 19 women with pre-pregnancy body mass index  $\geq 40$  as an assumption that they may have had metabolic syndrome at baseline. SAS software version 9.2 was used for the analyses. All tests were two-tailed and  $p < .05$  was used to define statistical significance. No imputation for missing data was performed.

## Results

This analysis included 825 women (47% of eligible women from the original study) who participated in the follow-up study and were not pregnant at the time of follow-up (Figure 1). The maternal baseline characteristics were generally similar between women who did and did not participate in the follow-up study, although some differences were observed (Appendix 2, available online at <http://links.lww.com/xxx>). Most notably, a higher percentage of the non-Hispanic white women participated in the follow-up study. The percent of women who experienced pregnancy-associated hypertension and/or were delivered preterm was similar between participants and non-participants (Appendix 2, <http://links.lww.com/xxx>).

Among the 825 women included in this analysis, 20 (2%) developed pregnancy-associated hypertension during the index pregnancy and delivered preterm (40% gestational hypertension; 60% preeclampsia), 64 (8%) developed pregnancy-associated hypertension and delivered at term (70% gestational hypertension; 30% preeclampsia), 48 (6%) remained normotensive throughout their index pregnancy and delivered preterm, and 693 (84%) remained normotensive throughout their index pregnancy and delivered at term. Among those who were delivered preterm, spontaneous delivery (31 women experienced preterm spontaneous labor and 6 women were induced after experiencing preterm premature rupture of membranes) occurred in 71% of those who remained normotensive throughout their index pregnancy and 15% of those who experienced pregnancy-associated hypertension.

The follow-up evaluation occurred at a median 7 (interquartile range 6-8) years after the index pregnancy at a median age of 35 (interquartile range 32-40) years. Fifty-six percent of the women included in this analysis were Hispanic, 31% non-Hispanic white, 10% non-Hispanic black and 3% other. Body mass index was highest in the women who experienced

pregnancy-associated hypertension and delivered preterm (Table 1). Among the women with preterm birth, the median gestational age at birth was 36.1 weeks in the women with pregnancy-associated hypertension and 35.9 in the women with normotensive pregnancies.

Subsequent high waist circumference (>88 cm) and low high-density lipoprotein cholesterol (<50 mg/dL) were observed in the majority of the women (63% and 57%, respectively). The frequency of each component of metabolic syndrome was highest in the women who experienced pregnancy-associated hypertension and delivered preterm (Table 2). When evaluating components of metabolic syndrome, and after adjusting for baseline confounding factors, pregnancy-associated hypertension was significantly associated with subsequent hypertension in women who were delivered preterm (RR 3.06, 95% CI 1.95-4.80,  $p<.001$ ) and at term (RR 1.76, 95% CI 1.22-2.53,  $p=.002$ ) (Table 2), and correspondingly significantly higher adjusted mean measures of systolic and diastolic blood pressures (Figure 2, Panels A and B), compared with women who remained normotensive and were delivered at term. Pregnancy-associated hypertension in women who delivered preterm was significantly associated with subsequent high triglycerides (RR 1.82, 95% CI 1.06-3.14,  $p=.03$ ) (Table 2), and correspondingly significantly higher adjusted mean measure of triglycerides (Figure 2, Panel C). Preterm delivery in women who remained normotensive throughout their index pregnancy was not associated with any of the components of metabolic syndrome.

Overall, 239 (29%) had metabolic syndrome; 33% in those with mild GDM and 24% in those with lesser degrees of glucose intolerance. The frequency of metabolic syndrome was similar between the women who experienced gestational hypertension and the women who experienced preeclampsia, 43% and 45%, respectively. The frequency of metabolic syndrome ranged from 21% in the women who remained normotensive throughout their index pregnancy and delivered preterm to 70% in the women who experienced pregnancy-associated hypertension and delivered preterm (Table 2). Furthermore, the percent of women experiencing 4 or more metabolic syndrome components was highest in the women who experienced pregnancy-associated hypertension and then delivered preterm (30%, compared with 8% in those who remained normotensive and delivered at term;  $p<.001$ ) (Table 2). After adjusting for baseline confounding factors, pregnancy-associated hypertension in women who delivered preterm was significantly associated with subsequent metabolic syndrome (3 or more components) (RR 1.78, 95% CI 1.14-2.78,  $p=.01$ ) (Table 2), compared with women who remained normotensive and delivered at term. Pregnancy-associated hypertension was significantly associated with experiencing 4 or more (vs. 0-3) metabolic syndrome components in women who were delivered preterm (RR 3.00, 95% CI 1.74-5.18,  $p<.001$ ) and at term (RR 1.64, 95% CI 1.05-2.58,  $p=.03$ ) (Table 2).

The associations remained consistent between models with and without adjustment for smoking, adjustment for lifestyle characteristics at the time of follow-up (diet and physical activity), adjustment for pre-pregnancy body mass index rather than pregnancy body mass index, or adjustment for pre-pregnancy body mass index and excluding women with a pre-pregnancy body mass index  $\geq 40$  (Appendix 3, available online at <http://links.lww.com/xxx>). We observed several modifiable risk factors significantly associated with metabolic syndrome: enrollment smoking (OR 1.71, 95%CI 1.18-2.47,  $p=.005$ ); enrollment body mass

index (OR 14.67, 95%CI 8.15-26.41 per unit increase in log body mass index,  $p < .001$ ); and follow-up vegetable intake (OR 0.77, 95%CI 0.67-0.87 per unit increase in daily servings,  $p < .001$ ).

## Discussion

In an obstetric population without known pre-existing conditions, but with varying degrees of glucose intolerance, women who experienced pregnancy-associated hypertension and then delivered preterm had a significantly higher likelihood of experiencing hypertension, high triglycerides, metabolic syndrome (3 or more components) and 4 or more metabolic syndrome components 5-10 years later. Furthermore, although the magnitude of the association was weaker, pregnancy-associated hypertension in women who were delivered at term had a significantly higher likelihood of subsequent hypertension and experiencing 4 or more metabolic syndrome components.

Studies performed outside of the United States, in primarily white European populations, have also observed an association between pregnancy-associated hypertension and subsequent metabolic syndrome. In a United Kingdom prospective population-based study of 3,416 women followed up 18 years after delivery, gestational hypertension was associated with higher waist circumference, higher blood pressure, higher triglycerides and lower high-density lipoprotein cholesterol, and preeclampsia was associated with higher blood pressure and higher glucose.<sup>(14)</sup> In a study of 15,065 Norwegian women, with retrospectively linked registry delivery data, followed prospectively 16.5 years after pregnancy, both gestational hypertension and preeclampsia were associated with high triglycerides, low high-density lipoprotein cholesterol and high systolic blood pressure.<sup>(13)</sup> In a time frame of 7.8 years after delivery, 168 nulliparous Canadian women who had either gestational hypertension or preeclampsia were followed prospectively, and had a higher frequency of metabolic syndrome, high waist circumference, low high-density lipoprotein cholesterol and high blood pressure, compared with 168 retrospectively matched controls.<sup>(11)</sup> Also, the metabolic syndrome risk profile was similar between the women with gestational hypertension and the women with preeclampsia. In another Canadian study of women prospectively followed after delivery, preeclampsia was associated with metabolic syndrome at the one-year ( $n=99$  preeclampsia,  $n=118$  controls) and three-year ( $n=73$  preeclampsia,  $n=47$  controls) follow-ups.<sup>(28)</sup> In a study from The Netherlands, 306 women with either gestational hypertension or preeclampsia at term who participated in a pregnancy trial were prospectively followed up 2.5 years after delivery, and found to have a higher frequency of metabolic syndrome and high blood pressure compared with 99 retrospectively matched normotensive term controls.<sup>(15)</sup>

Our study provided a unique opportunity to prospectively evaluate the association between pregnancy-associated hypertension and subsequent metabolic syndrome in an ethnically diverse U.S. population. A limitation of this study, however, was the relatively modest sample size with only 20 women who experienced pregnancy-associated hypertension and then delivered preterm. We therefore were not able to evaluate gestational hypertension and preeclampsia separately. However, the frequency of metabolic syndrome was similar in these groups, also observed by Forest et al<sup>(11)</sup> who suggested that gestational hypertension

and preeclampsia may have similar long-term risks. Another limitation is that although the women did not have known preexisting clinically-diagnosed conditions, it is uncertain whether some of the women may have met criteria for metabolic syndrome before the index pregnancy but were not diagnosed. Even so, pregnancy may unmask not only future health but also existing preclinical conditions that may not be routinely screened for in women of reproductive age. It should also be noted that women with chronic hypertension or preeclampsia at the time of enrolment were excluded from the original study, so none had the hypertension component at baseline. An additional limitation is that a higher percentage of the non-Hispanic white women participated in the follow-up study. Despite this, 56% of the women included in this analysis were Hispanic. With regards to generalizability, although our study included women with mild GDM or lesser degrees of glucose intolerance, our results are consistent with studies in other obstetric cohorts.

There are numerous strengths of this study. Women were enrolled during pregnancy and therefore pregnancy complications were prospectively collected and defined in a standardized research setting, rather than relying on vital statistics or administrative data sets. Cases of pregnancy-associated hypertension were reviewed and adjudicated and gestational age at delivery was confirmed by ultrasound. Likewise, data at the follow-up visit were prospectively collected using rigorous definitions, trained research staff performed anthropometric measurements, and lipids and glucose were measured at a central laboratory. Furthermore, our analysis controlled for several potentially confounding factors, including baseline cardiovascular-related risk factors, and we observed several modifiable risk factors associated with metabolic syndrome (smoking, higher body mass index and lower vegetable consumption).

In conclusion, our results provide further support that women who experience pregnancy-associated hypertension, particularly if then delivered preterm, are at an especially higher risk of developing metabolic syndrome. Moreover, physicians should carefully monitor and counsel these women concerning their long-term health risks.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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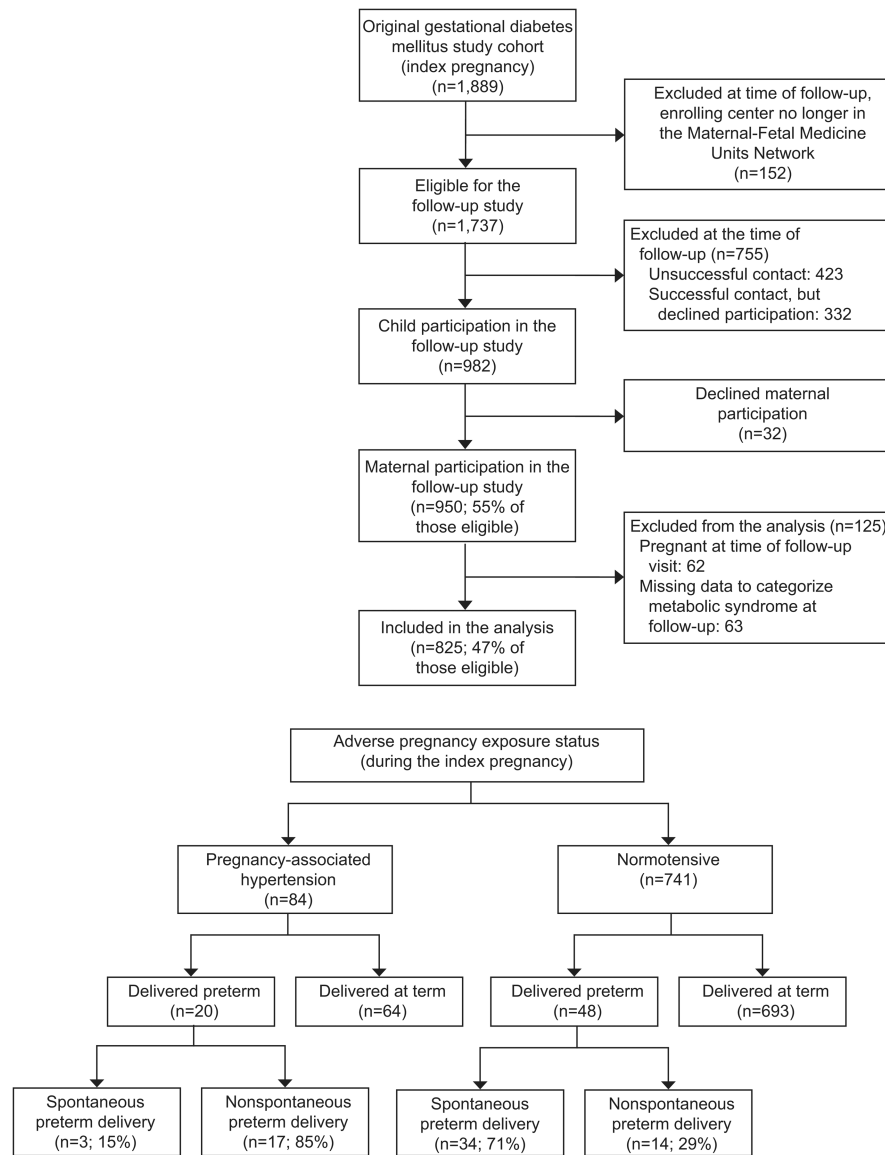
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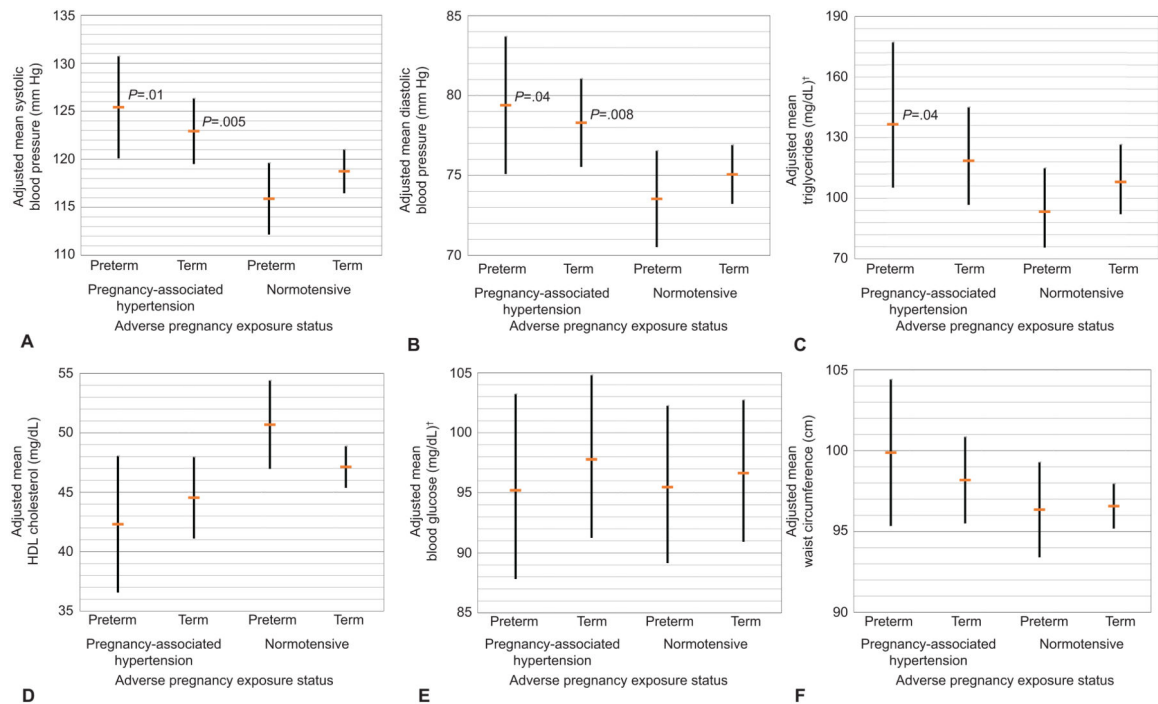
## References

1. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002; 25:1862–8. [PubMed: 12351492]
2. Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. *JAMA*. 2005; 294:2751–7. [PubMed: 16333011]
3. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007; 335:974–7. [PubMed: 17975258]
4. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008; 156:918–30. [PubMed: 19061708]
5. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ*. 2002; 325:157–60. [PubMed: 12130616]
6. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 1979; 241:2035–8. [PubMed: 430798]
7. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB Sr, et al. Trends in cardiovascular complications of diabetes. *JAMA*. 2004; 292:2495–9. [PubMed: 15562129]
8. Sibai BM, el-Nazer A, Gonzalez-Ruiz A. Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis. *Am J Obstet Gynecol*. 1986; 155:1011–6. [PubMed: 3777042]
9. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003; 326:845. [PubMed: 12702615]
10. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? *Atherosclerosis*. 2004; 175:189–202. [PubMed: 15262174]
11. Forest JC, Girouard J, Massé J, Moutquin JM, Kharfi A, Ness RB, et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. *Obstet Gynecol*. 2005; 105:1373–80. [PubMed: 15932832]
12. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009; 53:944–51. [PubMed: 19433776]
13. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. *Obstet Gynecol*. 2009; 114:961–70. [PubMed: 20168095]
14. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. *Circulation*. 2012; 125:1367–80. [PubMed: 22344039]
15. Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, et al. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *Am J Obstet Gynecol*. 2013; 208:474.e1–8. [PubMed: 23399350]
16. Männistö T, Mendola P, Väärasmäki M, Järvelin MR, Hartikainen AL, Pouta A, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. *Circulation*. 2013; 127:681–90. [PubMed: 23401113]
17. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension*. 2010; 56:166–71. [PubMed: 20516394]
18. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001; 323:1213–7. [PubMed: 11719411]
19. Roberts JM. Endothelial dysfunction in preeclampsia. *Semin Reprod Endocrinol*. 1998; 16:5–15. [PubMed: 9654603]
20. Williams D. Pregnancy: a stress test for life. *Curr Opin Obstet Gynecol*. 2003; 15:465–71. [PubMed: 14624211]

21. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Ther Adv Cardiovasc Dis*. 2008; 2:249–59. [PubMed: 19124425]
22. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010; 376:631–44. [PubMed: 20598363]
23. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation*. 2011; 123:1243–62. [PubMed: 21325087]
24. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med*. 2009; 361:1339–48. [PubMed: 19797280]
25. Landon MB, Rice MM, Varner MW, Casey BM, Reddy UM, Wapner RJ, et al. Mild gestational diabetes mellitus and long-term child health. *Diabetes Care*. 2015; 38:445–52. [PubMed: 25414152]
26. National Health and Nutrition Examination Survey (NHANES). [Accessed February 21, 2012] Anthropometry Procedures Manual. Jan. 2009 [http://www.cdc.gov/nchs/data/nhanes/nhanes\\_09\\_10/BodyMeasures\\_09.pdf](http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/BodyMeasures_09.pdf)
27. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112:2735–52. [PubMed: 16157765]
28. Smith GN, Pudwell J, Walker M, Wen SW. Risk estimation of metabolic syndrome at one and three years after a pregnancy complicated by preeclampsia. *J Obstet Gynaecol Can*. 2012; 34:836–41. [PubMed: 22971452]



**Figure 1.** Enrollment, follow-up, and adverse pregnancy exposure status of the study participants.



**Figure 2.**

Mean adjusted\* cardiometabolic measures (components of the metabolic syndrome at follow-up) according to adverse pregnancy exposure status during the index pregnancy. Systolic blood pressure (A); diastolic blood pressure (B); triglycerides (C); high-density lipoprotein (HDL) cholesterol (D); blood glucose (E); waist circumference (F). \*Adjusted for baseline mild gestational diabetes mellitus, age, race or ethnicity, smoking, log body mass index, and duration of follow-up. The models were also adjusted for relevant treatments at follow-up. <sup>†</sup>Log values back transformed.

**Table 1**  
**Baseline, delivery and follow-up characteristics by pregnancy-associated hypertension**

Characteristic	Pregnancy-associated hypertension			Normotensive		P*
	Preterm (n=20)	Term (n=64)	Preterm (n=48)	Term (n=693)		
Baseline						
Age (y)	29 (23-33)	28 (25-32)	26 (22-31)	28 (25-32)		.12
Race/ethnicity						.69
Hispanic	11 (55.0)	33 (51.6)	22 (45.8)	399 (57.6)		
Non-Hispanic white	6 (30.0)	23 (35.9)	17 (35.4)	207 (29.9)		
Non-Hispanic non-white	3 (15.0)	8 (12.5)	9 (18.8)	87 (12.6)		
Mild GDM in the index pregnancy	12 (60.0)	33 (51.6)	30 (62.5)	353 (50.9)		.40
Smoking	0 (0.0)	5 (7.8)	8 (16.7)	45 (6.5)		.06
Pre-index pregnancy body mass index (kg/m <sup>2</sup> ) <sup>†‡</sup>	28.5 (24.7-31.0)	27.8 (24.0-32.0)	25.3 (20.7-29.0)	25.9 (23.1-29.3)		.01
Body mass index at enrollment (kg/m <sup>2</sup> ) <sup>‡</sup>	34.0 (29.8-35.8)	31.3 (28.0-35.4)	28.9 (25.5-32.6)	29.7 (26.9-32.9)		.003
Delivery						
Gestational age at delivery (wk)	36.1 (34.3-36.6)	38.6 (38.0-39.6)	35.9 (34.6-36.5)	39.4 (38.7-40.1)		<.001
Follow-up						
Breast fed index child	16 (80.0)	51 (79.7)	37 (77.1)	549 (79.2)		.99
Duration of follow-up (y)	8 (7-9)	7 (6-8)	7 (6-8)	7 (6-8)		.37
Age at follow-up (y)	37 (29-41)	35 (32-40)	33 (30-38)	36 (32-40)		.19
Number of pregnancies since index pregnancy	1 (0-1)	1 (0-2)	1 (0-2)	0 (0-1)		.005
Body mass index (kg/m <sup>2</sup> )	31.5 (30.1-38.5)	30.4 (26.5-35.2)	28.1 (23.7-34.1)	28.5 (25.1-32.4)		.003
Smoking	1 (5.0)	6 (9.4)	7 (14.6)	53 (7.7)		.34
Vegetable servings (1/2 cup/d) <sup>§</sup>	0.9 (0.4-2.0)	1.0 (0.4-2.0)	1.0 (0.4-2.0)	1.0 (0.4-2.0)		.79
Dairy servings (1/2 cup/d)	1.0 (0.4-2.0)	1.0 (0.6-2.0)	1.0 (0.7-2.0)	1.0 (0.4-2.0)		.80
Sweetened beverages (cups/d)	0.4 (0.1-1.1)	0.4 (0.1-1.0)	0.4 (0.0-1.5)	0.3 (0.1-1.1)		.47
Vigorous exercise (min/wk)	0 (0-45)	0 (0-30)	0 (0-60)	0 (0-60)		.93
Resting pulse (beats/min)	69 (62-85)	72 (66-80)	70 (64-82)	70 (64-78)		.71

GDM, gestational diabetes mellitus.

Data are median (interquartile range) or n (%) unless otherwise specified.

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\* Based on the chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

<sup>†</sup> Missing in 66 participants (2 in pregnancy associated hypertension and preterm, 5 in pregnancy associated hypertension and preterm, 2 in normotensive and preterm, 57 in normotensive and term).

<sup>‡</sup> Pre-index pregnancy body mass index was based on the participant's pre-pregnancy weight as reported by the patient or as recorded in the patient's chart; body mass index at enrollment was based on the weight measured by the study nurse on the day of the oral glucose tolerance test visit, between 24 weeks 0 days and 30 weeks 6 days of gestation; both body mass index measurements used the height measured by the study nurse on the day of the oral glucose tolerance test visit.

<sup>§</sup> Other than potatoes or corn.

**Table 2**  
**Association between pregnancy-associated hypertension and subsequent metabolic syndrome and its components**

Outcome	Pregnancy-associated hypertension				Normotensive			
	Preterm (n=20)		Term (n=64)		Preterm (n=48)		Term (n=693)	
	n (%)	RR (95%CI)*	n (%)	RR (95%CI)*	n (%)	RR (95%CI)*	n (%)	
Metabolic syndrome, 3-5 components <sup>†</sup> (vs. 0-2)	14 (70.0)	1.78 (1.14-2.78)	23 (35.9)	1.15 (0.81-1.62)	10 (20.8)	0.70 (0.42-1.17)	192 (27.7)	
4-5 components (vs. 0-3)	6 (30.0)	3.00 (1.74-5.18)	9 (14.1)	1.64 (1.05-2.58)	5 (10.4)	1.23 (0.69-2.22)	54 (7.8)	
Metabolic syndrome components								
Waist circumference >88 cm	17 (85.0)	1.05 (0.74-1.50)	49 (76.6)	1.13 (0.91-1.39)	28 (58.3)	0.92 (0.70-1.22)	422 (60.9)	
Triglycerides 150 mg/dL	9 (45.0)	1.82 (1.06-3.14)	17 (27.0)	1.17 (0.78-1.75)	7 (14.6)	0.61 (0.33-1.12)	157 (22.7)	
High-density lipoprotein cholesterol <50 mg/dL	15 (75.0)	1.27 (0.84-1.93)	44 (71.0)	1.23 (0.96-1.58)	24 (50.0)	0.85 (0.61-1.19)	383 (55.4)	
Blood pressure 130/85 mmHg	12 (60.0)	3.06 (1.95-4.80)	18 (28.1)	1.76 (1.22-2.53)	10 (20.8)	1.35 (0.84-2.18)	101 (14.6)	
Fasting blood glucose 100 mg/dL	8 (40.0)	1.34 (0.76-2.38)	13 (20.3)	0.82 (0.52-1.29)	12 (25.0)	1.05 (0.65-1.69)	158 (22.8)	

RR, relative risk; CI, confidence interval

\* Compared with women who remained normotensive throughout their index pregnancy and were delivered at term; adjusted for baseline mild gestational diabetes mellitus, age, race/ethnicity, smoking, log body mass index and duration of follow-up.

<sup>†</sup> Three or more of the following: waist circumference >88 cm, triglycerides 150 mg/dL, high-density lipoprotein cholesterol <50 mg/dL, blood pressure 130/85 mmHg, or fasting glucose 100 mg/dL, or relevant treatment for any of these components. Relevant treatments at follow-up included: among those with pregnancy-associated hypertension and preterm, 1 for diabetes, 2 for hyperlipidemia, and 5 for hypertension; among those with pregnancy-associated hypertension and term, 2 for diabetes, 1 for hyperlipidemia, and 6 for hypertension; among those with a normotensive pregnancy and preterm, 1 for diabetes, 0 for hyperlipidemia, and 3 for hypertension; and among those with a normotensive pregnancy and term, 5 for diabetes, 10 for hyperlipidemia, and 27 for hypertension.