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Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Preeclampsia

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group¹

Abstract

OBJECTIVE—To examine associations of fasting C-peptide, BMI, and maternal glucose with risk of preeclampsia, in a multicenter multinational study.

STUDY DESIGN—Secondary analysis of blinded observational cohort study. Subjects underwent a 75-g OGTT at 24–32 weeks gestation. Associations of preeclampsia with fasting C-peptide, BMI, and maternal glucose were assessed using multiple logistic regression analyses, adjusting for potential confounders.

RESULTS—Of 21,364 women included in analyses, 5.2% developed preeclampsia. Adjusted odds ratios (OR) for preeclampsia for 1 SD higher fasting C-peptide (0.87 ug/L), BMI (5.1 kg/m²), fasting (6.9 mg/dl), 1-hour (30.9 mg/dl), and 2-hour plasma glucose (23.5 mg/dl) were 1.28 (1.20, 1.36), 1.60 (95% CI 1.60–1.71), 1.08 (95% CI 1.00–1.16), 1.19 (95% CI 1.11–1.28), and 1.21 (1.13–1.30), respectively.

CONCLUSION—Results indicate strong, independent associations of fasting C-peptide and BMI with preeclampsia. Maternal glucose levels (below diabetes) had weaker associations with preeclampsia, particularly after adjustment for fasting C-peptide and BMI.

Keywords

preeclampsia associations; BMI; C-peptide; glucose

INTRODUCTION

Preeclampsia complicates 2–8% of pregnancies worldwide and is associated with increased risk of adverse outcomes for mother and baby (1). It is a systemic disease characterized by increased vascular resistance, endothelial dysfunction, proteinuria and coagulopathy, in addition to hypertension (2). The pathophysiology is not completely defined but probably includes immune, genetic, and placental abnormalities. Insulin resistance and secretion rise during normal pregnancy; there is growing evidence that preeclampsia is related to increased insulin resistance during pregnancy (3–9). There is also strong evidence that women with

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Study Sites: Bellflower, CA, Chicago, IL, Cleveland, OH, Providence, RI, USA; Toronto, CA, Barbados, West Indies; Belfast, UK, Manchester, UK; Petah Tiqva, Israel, Beersheba, Israel; Bangkok, Thailand; Brisbane, Australia, Newcastle, Australia; Singapore, Singapore; Hong Kong, China.

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higher pre-pregnancy body mass index (BMI) are more likely to develop preeclampsia (10–13).

Most observational studies of GDM and preeclampsia included adjustment for maternal BMI (14–16), but none included adjustment for insulin resistance. Nordin, et al (17) showed that lesser degrees of glucose intolerance are associated with risk of preeclampsia; however, it is not clear if there was an independent association as this study did not include adjustment for BMI or other potential confounders. Another study looked at the association with preeclampsia across quartiles of glucose values below those diagnostic of GDM and found a positive association that became non-significant after adjustment for confounders (18). Thus, the nature of the association between lesser degrees of hyperglycemia and preeclampsia remains uncertain.

The objective of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was to assess the risk of adverse pregnancy outcome associated with lesser degrees of hyperglycemia than overt diabetes (19,20). Participants underwent a 2-hr 75 g OGTT. Glucose results were blinded from participants and caregivers, except where results fell outside predetermined ranges (20).

We previously reported continuous positive associations between maternal glucose values and preeclampsia (20). In this report, we examine the associations of maternal C-peptide and BMI with preeclampsia and, in addition, more fully examine the associations of maternal glucose with preeclampsia, including adjustment for fasting C-peptide.

MATERIALS and METHODS

HAPO was an international, multi-center epidemiologic study. Detailed methods have been reported (19,20). The study was approved by the local institutional review board at each center. All participants gave written informed consent and the study was overseen by an external Data Monitoring Committee.

Participants

All pregnant women at each center were eligible to participate unless they had one or more exclusion criteria (20). Methods to determine gestational age and expected date of delivery have been described (20).

Oral glucose tolerance test (OGTT)

Participants underwent a standard 75 g OGTT between 24 and 32 weeks gestation (as close to 28 weeks as possible). Data concerning smoking and alcohol use, first degree family history of diabetes and hypertension and demographic data were collected using standardized questionnaires. Race/ethnicity was self-identified by participants.

A sample for random plasma glucose (RPG) was collected at 34–37 weeks gestation as a safety measure to identify cases with hyperglycemia above a pre-defined threshold.

Glucose analysis and unblinding

Aliquots of fasting and 2-hour OGTT and RPG samples were analyzed at field center laboratories. Values were unblinded if fasting plasma glucose (FPG) exceeded 105 mg/dL (5.8 mmol/L), if 2-hour OGTT plasma glucose (PG) exceeded 200 mg/dL (11.1 mmol/L), if RPG was greater than or equal to 160 mg/dL (8.9 mmol/L) or if any PG value was less than 45 mg/dL (2.5 mmol/L). Otherwise, women, caregivers, and HAPO Study staff (except laboratory personnel) remained blinded to glucose values. All OGTT specimens were analyzed at the

HAPO Central Laboratory and those results are used here. Only women whose results remained blinded, with no additional glucose testing outside the HAPO protocol, are included in these analyses.

Fasting C-peptide

A serum sample for fasting C-peptide was collected at the OGTT visit. Because hemolysis is known to increase insulin degradation but not to affect C-peptide (21), and because C-peptide and insulin are secreted in equimolar amounts, we measured C-peptide rather than insulin. Levels of fasting insulin or C-peptide or derived variables that also include fasting glucose concentration (e.g. HOMA) are commonly used as an index of insulin sensitivity. We used fasting C-peptide as the index so that we could look at the association of fasting C-peptide and glucose separately. C-peptide measurements were performed on an Autodelphia instrument manufactured by Perkin-Elmer. The functional sensitivity of the assay is 0.02 ng/ml with intra- and inter-assay coefficients of variation of 3.2–5.0% and 1.9–3.0% respectively, in samples with high and low C-peptide concentrations (21).

Maternal height and weight

Maternal height and weight, measured at the OGTT visit, were used to calculate maternal body mass index (BMI). Height was measured twice to the nearest 0.5 cm with a stadiometer or wall-mounted measuring tape with shoes removed and the participant's head facing forward in the horizontal plane. If results differed by more than 1.0 cm, measurements were repeated. Weight was measured twice to the nearest 0.1 kg on a calibrated scale with outer garments and shoes removed and repeated if results differed by more than 0.5 kg. Recalled maternal pre-pregnancy weight was also recorded, but is not the focus of this report due to its inherent subjectivity and the absence of data for 1,966 participants (8.4%). No center provided specific interventions to participants based on weight or BMI.

Prenatal care and delivery

Prenatal care and timing of delivery were determined by standard field center practice. No field center arbitrarily delivered patients before full term or routinely performed cesarean delivery at a specified maternal or gestational age. Medical records were abstracted to obtain data regarding maternal and delivery course.

Classification of preeclampsia and other hypertensive disorders of pregnancy

Blood pressure was measured at the OGTT visit using standardized procedures and a calibrated electronic device (Omron 711). Additional blood pressure measurements were abstracted from medical records. Hypertension which was present prior to 20 weeks gestation which did not progress to preeclampsia was classified as chronic hypertension. After 20 weeks gestation, blood pressure measurements were used to classify hypertensive disorders in pregnancy according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines (22). A woman with a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg on 2 or more occasions a minimum of 6 hours apart and proteinuria of $\geq 1+$ dipstick or ≥ 300 mg per 24 hours was classified as having preeclampsia. If the criteria for elevated blood pressure but not proteinuria were met, this was classified as gestational hypertension.

Statistical analysis

Descriptive statistics include means and standard deviations for continuous variables and numbers and percentages for categorical variables. For associations of fasting C-peptide, BMI, fasting, 1-hr, and 2-hr PG, with preeclampsia, each predictor was considered as both a categorical and continuous variable in multiple logistic regression analyses. In categorical

analyses, each predictor was divided into 7 categories, with approximately 50% of all values in the two lowest categories and 3% and 1% in the two highest categories, respectively (20). Categories for fasting plasma glucose were pre-specified in 5mg/dl increments as < 75, 75–79, 80–84, 85–89, 90–94, 95–99, and ≥ 100 mg/dl respectively. The highest and second-highest categories, accounting for 1% and 3% of participants respectively, were specifically chosen to allow for assessment of whether there were threshold effects. Categories for fasting C-peptide, BMI, and 1- and 2-hr PG were therefore also selected so that similar proportions fell into each of their 7 categories.

For analyses of fasting C-peptide, BMI, and glucose as continuous variables, odds ratios (OR) and 95% confidence intervals (CI) were calculated for each predictor higher by 1 standard deviation (SD). To assess whether or not the log of the odds of preeclampsia was linearly related to each of these variables, we added squared terms in each predictor. Because of the large sample size in HAPO and the large number of women with preeclampsia, squared terms were considered statistically significant only for $p < 0.001$.

For each predictor, 3 logistic models (I, II, and III) were fit. Model I included adjustment only for field center. Model II included adjustment for multiple potential pre-specified confounders, including: maternal age, height, smoking, alcohol use, family history of diabetes, family history of high blood pressure, gestational age at the OGTT, baby's sex, parity (0, 1, 2+), and any maternal urinary tract infection (UTI) during the pregnancy. For fasting C-peptide and measures of glycemia, Model II also included adjustment for BMI, and for analyses focusing on BMI as the predictor of interest, Model II also included adjustment for fasting PG. For analyses of fasting C-peptide, Model III included further adjustment for fasting glucose. For BMI and measures of glycemia, Model III included further adjustment for fasting C-peptide.

All analyses were conducted in SAS version 9.1 or Stata 10.0.

RESULTS

There were 1,116 cases of preeclampsia among the 23,316 blinded participants. In addition, 582 had chronic hypertension and 1,370 developed gestational hypertension. Only women who remained normotensive (20,248) or who developed preeclampsia are included in these analyses. Characteristics of these 21,364 women are shown in Table 1. Maternal age, BMI, and glucose values at the OGTT, and gestational age at delivery are similar to those that have been reported for the entire cohort (20). Our primary objective was to determine associations of glucose, BMI, and C-peptide with risk of preeclampsia. Because of center-by-center differences in frequency of preeclampsia and other variables (maternal age, BMI, parity) a comparison of characteristics of those who developed preeclampsia to those who remained normotensive would optimally use a case-control design which is outside the scope of this report.

Table 2 shows associations between maternal fasting C-peptide and preeclampsia, including ORs and 95% CIs for each category compared with the lowest or referent category. A fasting C-peptide level was available for 21,141 of the 21,364 women with either no hypertension or preeclampsia. The frequency of preeclampsia rose from 1.7% in the lowest category (≤ 1.2 ug/L) of fasting C-peptide to 16.9% in the highest (≥ 4.8 ug/L). Odds ratios rose across categories in each of the models and were highest in the second highest category. With adjustment for confounders including BMI (Model II), there was substantial attenuation. However, there was very little additional attenuation with further adjustment for FPG (Model III). With fasting C-peptide considered as a continuous variable, ORs for C-peptide higher by 1 SD (0.87 ug/L) were 1.61, 1.32, and 1.28, in the three models, respectively. In each model, there was a

significant non-linear association of fasting C-peptide with preeclampsia ($p < 0.001$ when C-peptide squared was added to the model).

Associations between maternal BMI at OGTT and preeclampsia are shown in Table 3. The frequency of preeclampsia increased from 2.1% in the lowest BMI category ($\leq 23.2 \text{ kg/m}^2$) to 30.4% in the highest ($> 44.0 \text{ kg/m}^2$). The field center adjusted OR (Model I) was 14.11 in the highest category. With adjustment for additional confounders including FPG (Model II), there was little change in the odds ratios and the OR in the highest category became slightly larger. With further adjustment for maternal fasting C-peptide (Model III), odds ratios were substantially attenuated but remained significant in all but the next to lowest BMI category. Continuous variable analyses showed strong positive associations for each of the models for BMI higher by 1 SD or 5.1 kg/m^2 (OR of 1.82 in Model I and 1.60 in Model III).

Table 4 shows associations of maternal glucose with preeclampsia. Rates of preeclampsia increased with higher levels of fasting, 1-, and 2-hr PG. For example, the frequency of preeclampsia was 3.1% in the lowest FPG category ($< 75 \text{ mg/dL}$) and rose to 17.6% in the highest ($> 100 \text{ mg/dL}$). The rise in frequency of preeclampsia was less steep across categories of 1- and 2-hr PG. With adjustment for field center (Model I), the OR was 4.72 in the highest category for FPG and 2.94 and 2.91 for 1-, and 2-hr PG, respectively. With adjustment for additional confounders including BMI (Model II), there was attenuation of the ORs for all 3 glucose measures and further adjustment for maternal fasting C-peptide (Model III) produced additional attenuation. In continuous variable models, ORs ranged from 1.36 to 1.47 in Model I for each glucose measure higher by 1 SD. In Model II they were reduced to 1.21 to 1.29. With additional adjustment for maternal C-peptide in Model III, they were further reduced to 1.08 to 1.21, and the association was no longer statistically significant for FPG.

COMMENT

We previously reported continuous positive associations between maternal glucose values and preeclampsia (20). In this report, we examined the associations of insulin levels (measured as fasting C-peptide) and maternal BMI with preeclampsia. Fasting indices of C-peptide provide an acceptable measure of insulin sensitivity in pregnancy (23). We also more fully examined the relationship of maternal glucose values with preeclampsia, including the effect of adjustment for fasting C-peptide. Our main findings are: 1) higher fasting C-peptide is an independent predictor of preeclampsia, including after adjustment for BMI and fasting glucose; 2) higher maternal BMI is associated with greater risk for preeclampsia, with the odds of preeclampsia increasing approximately 8 fold from the lowest to highest category of BMI; and 3) the frequency of preeclampsia rises with increasing OGTT plasma glucose (fasting, 1- and 2-hr). The glucose associations were independent of field center and maternal BMI but were weaker with adjustment for C-peptide.

Strengths of this study include the large cohort, the large number developing preeclampsia, 1,116 of 21,364 analyzable participants, and use of a contemporary definition of preeclampsia, which should eliminate potential confounding by gestational hypertension or chronic hypertension uncomplicated by preeclampsia. Inclusion of multiple field centers distributed globally allows for widespread generalizability of the findings. Careful quality control with all research glucose and C-peptide analyses performed in a central laboratory also served to maximize measurement accuracy.

Weaknesses of the study include the fact that no research measurement of BMI was made prior to pregnancy. Thus, we do not have accurate data on weight gain to the time of the OGTT or to any specific later time in gestation. Weight gain after development of preeclampsia would be confounded since preeclampsia is detected at variable gestational ages. All data regarding

maternal prepregnancy weight are potentially tainted by recall bias and it was decided that use of the carefully measured maternal weight and height at the 24–32 week OGTT was preferable. Adjustment for gestational age in analyses negates the potential impact of differing gestational age at the time of OGTT. Another potential weakness is the lack of a direct measure of insulin sensitivity; however for large populations the use of fasting indices, in this case C-peptide, is commonly employed.

The strengths of HAPO in relation to other studies include blinding of participants and caregivers, availability of glucose results across a broad range, and careful research measurements of weight, height, glucose and fasting C-peptide (as an index of insulin sensitivity [resistance]). While other observational studies of GDM and preeclampsia included adjustment for maternal BMI (14–16), none included adjustment for insulin resistance. One study showed that lesser degrees of glucose intolerance are associated with risk of preeclampsia; however, it was not clear if there was an independent association since there was no adjustment for BMI or other potential confounders (17).

The prevalence of obesity has increased dramatically worldwide over the past two decades (24). A systematic meta-analysis showed a doubling of preeclampsia risk with each 5 to 7 kg/m² increase in pre-pregnancy BMI (25). In the current study, risk of developing preeclampsia was higher with greater maternal BMI, even after controlling for fasting plasma glucose and level of fasting C-peptide. Thus, maternal obesity is a strong risk factor for preeclampsia.

A number of studies suggest an association of preeclampsia with insulin resistance (3–9). It is uncertain whether women destined to develop preeclampsia have pre-existing insulin resistance or whether it is acquired with development of hypertension. Moreover, it has been unclear if insulin resistance is independently associated with preeclampsia or only reflects an association with higher BMI. Moran et al (8) found higher levels of fasting insulin in normal weight and obese women with preeclampsia than in those without preeclampsia. Some have suggested that women who subsequently develop preeclampsia have insulin resistance before the onset of clinical manifestations (9,26,27).

Mechanisms by which insulin resistance could increase the risk for preeclampsia are not clearly established. Systemic inflammation, reflected in higher levels of CRP, has been implicated (28), but efforts to demonstrate a role for specific cytokines such as TNF-alpha have had inconsistent results (29,30).

The goal of predicting and preventing preeclampsia has not been reached and the impact of preeclampsia extends beyond perinatal outcomes. Preeclampsia is a risk factor for future type 2 diabetes, hypertension and cardiovascular morbidity (metabolic syndrome) and mortality (28,31). It is encouraging that in two randomized controlled trials which included women with glucose values that overlapped the new IADPSG proposed thresholds for GDM (32), treatment of mild GDM (33,34) reduced risk of preeclampsia. It remains to be determined whether similar results can be achieved in general clinical practice as in research settings. If so, and if the IADPSG thresholds for the diagnosis of GDM are adopted, treatment of GDM may help reduce the adverse effects of and costs of treatment for preeclampsia.

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References

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–137. [PubMed: 19464502]
2. Solomon CG, Seely EW. Hypertension in pregnancy: a manifestation of the insulin resistance syndrome? *Hypertension* 2001;37:232–239. [PubMed: 11230277]
3. Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. *J Clin Endocrinol Metab* 2003;88:2393–2398. [PubMed: 12788833]
4. Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL, Thadhani R. First trimester insulin resistance and subsequent pre-eclampsia: a prospective study. *J Clin Endocrinol Metab* 2002;87:1563–1568. [PubMed: 11932283]
5. Lorentzen B, Birkeland KI, Endresen MJ, Henriksen T. Glucose intolerance in women with pre-eclampsia. *Acta Obstet Gynecol Scand* 1998;77:22–27. [PubMed: 9492712]
6. Martinez AE, Gonzalez OM, Quinones GA, Ferrannini E. Hyperinsulinemia in glucose-tolerant women with preeclampsia. A controlled study. *Am J Hypertens* 1996;6:610–614. [PubMed: 8783787]
7. Kaaja R, Laivuori H, Laakso M, Tikkanen MJ, Ylikorkala O. Evidence of a state of increased insulin resistance in preeclampsia. *Metabolism* 1999;48:892–896. [PubMed: 10421232]
8. Moran C, Sandoval T, Duque X, Gonzalez S, Moran S, Bermudez JA. Increased insulin levels independent of gestational overweight in women with preeclampsia. *Arch Med Res* 2006;37(6):749–54. [PubMed: 16824935]
9. Emery SP, Levine RJ, Qian C, et al. CPEP study group. Twenty-four-hour urine insulin as a measure of hyperinsulinaemia/insulin resistance before onset of pre-eclampsia and gestational hypertension. *BJOG* 2005;112(11):1479–85. [PubMed: 16225566]
10. Sowers JR, Sokol RJ, Standley PR, et al. Insulin resistance and increased body mass index in women developing hypertension in pregnancy. *Nutr Metab Cardiovasc Dis* 1996;6:141–146.
11. Thadani R, Stampfer MJ, Hunder DJ, Manson JE, Solomon CG, Curhan GC. High body mass index and hypercholesterolemia: risk of hypertensive disorders of pregnancy. *Obstet Gynecol* 1999;94:543–550. [PubMed: 10511356]
12. Sibai BM, Gordon T, Thom E, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1995;172:642–8.
13. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol* 1997;177:1003–1010. [PubMed: 9396883]
14. Joffe GM, Esterlitz JR, Levine RJ, et al. for the Calcium for Preeclampsia Prevention (CPEP) Study Group. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. *Am J Obstet Gynecol* 1998;179:1032–1037. [PubMed: 9790393]
15. Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Forti ACE, Spichler ER, Pousada JMDC, Teixsira MM, Yamashita T. for the Brazilian Gestational Diabetes Study Group. Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. *Diabetes Care* 2001;24:1151–1155. [PubMed: 11423494]
16. Yogev Y, Xenakis EMJ, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *Am J Obstet Gynecol* 2004;191:1655–1660. [PubMed: 15547538]
17. Nordin NM, Wei JWH, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. *J Obstet Gynaecol Res* 2006;32:107–114. [PubMed: 16445535]
18. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JWK, Farine D, Cohen HW, McArthur K, Holzapfel S, Biringier A, Chen E. for the Toronto Tri-Hospital Gestational Diabetes Investigators. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital Gestational Diabetes Project. *Am J Obstet Gynecol* 1995;173:146–156. [PubMed: 7631672]

19. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Intl J Gyn Ob* 2002;78:69–77.
20. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. *N Engl J Med* 2008;358:1991–2002. [PubMed: 18463375]
21. Nesbitt GS, Smye M, Sheridan B, Lappin TR, Trimble ER. for the HAPO Study Cooperative Research Group. Integration of local and central laboratory functions in a worldwide multicentre study: experience from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Clin Trials* 2006;3:397–407. [PubMed: 17060214]
22. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:ix–xiv. [PubMed: 12044323]
23. McIntyre HD, Chang AM, Callaway LK, et al. for the HAPO Study Cooperative Research Group. Hormonal and metabolic factors associated with variations in insulin sensitivity in human pregnancy. *Diabetes Care*. 2009 Oct 30; (Epub ahead of print).
24. World Health Organization. Obesity: preventing and managing a global epidemic. *World Health Organ Tech Rep Ser* 2000;894:1–4.
25. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic review. *Epidemiology* 2003;14:368–374. [PubMed: 12859040]
26. Sierra-Laguado J, Garcia RG, Celedon J, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy-induced hypertension. *Am J Hypertens* 2007;20(4):437–42. [PubMed: 17386353]
27. Parretti E, Lapolla A, Dalfra MG, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension* 2006;47:449–453. [PubMed: 16446386]
28. Srinivas SK, Sammel MD, Bastek J, et al. Evaluating the association between all components of the metabolic syndrome and pre-eclampsia. *J Matern Fetal Neonatal Med* 2009;22(6):501–9. [PubMed: 19479639]
29. Kaaja R, Laivuori H, Pulkki P, Tikkanen MJ, Hiilesmaa V, Ylikorkala O. Is there any link between insulin resistance and inflammation in established preeclampsia? *Metabolism* 2004;53(11):1433–5. [PubMed: 15536597]
30. Anim-Nyame N, Sooranna SR, Jones J, Alagband-Zadeh J, Steer PJ, Johnson MR. Insulin resistance and pre-eclampsia: a role for tumor necrosis factor- α ? *Gynecol Endocrinol* 2004;18(3):117–23. [PubMed: 15255279]
31. Lykke JA, Langhoff-Ross J, Sibai B, Funai EF, Triche EW, Paides MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53(6):944–51. [PubMed: 19433776]
32. IADPSG Consensus Panel. International Association of Diabetes and Pregnancy Study Groups (IADPSG) Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. *Diabetes Care*. in press.
33. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486. [PubMed: 15951574]
34. Landon M, Spong CY, Thom E, et al. for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:11–20. [PubMed: 19571279]

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The Writing Group takes responsibility for the content of this article.

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Table 1Characteristics of HAPO Participants with either no Hypertension or with Preeclampsia¹

Characteristics of Mothers ²	N	Mean	SD
Age (yrs)	21,364	29.2	5.8
Body Mass Index (BMI) (kg/m ²) ³	21,364	27.4	4.9
Fasting Plasma Glucose (mg/dL) ^{3, 4}	21,364	80.7	6.8
1-hr Plasma Glucose (mg/dL) ^{3, 4}	21,364	133.4	30.8
2-hr Plasma Glucose (mg/dL) ^{3, 4}	21,364	110.5	23.4
Fasting C-peptide (ug/L) ³	21,141	1.9	0.8
Gestational Age (wks) ³	21,364	27.8	1.8
	N	%	
Prenatal Smoking (any)	1,429	6.7	
Prenatal Alcohol Use (any)	1,476	6.9	
Family Hx of Diabetes	4,795	22.5	
Family Hx of Hypertension	7,427	34.8	
Parity (prior delivery ≥ 20 wks)	11,246	53.1	
Prenatal Urinary Tract Infection	1,483	6.9	
Newborn Characteristics	N	Mean	SD
Gestational Age (wks)	21,364	39.4	1.7
	N	%	
Gender - Male	10,974	51.4	

¹ Hypertension: Hypertension present prior to 20 weeks which did not progress to preeclampsia was classified as chronic hypertension. After 20 weeks gestation, hypertensive disorders in pregnancy were categorized according to International Society for the Study of Hypertension (ISSHP) guidelines (26). Preeclampsia = systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on 2 or more occasions a minimum of 6 hours apart and proteinuria of ≥ 1+ dipstick or ≥ 300 mg per 24 hours. If the criteria for elevated BP but not proteinuria were met, this was classified as gestational hypertension.

² Participants with chronic or gestational hypertension excluded

³ Measured at the OGTT visit

⁴ For glucose to mmol/L, divide by 18

Table 2

Relationship between maternal fasting C-peptide and preeclampsia.

Fasting C-peptide (ug/L)	N	#	%	Model I OR	95% CI	Model II OR	95% CI	Model III OR	95% CI
≤ 1.2	4,546	79	1.7	1.00		1.00		1.00	
1.3-1.7	6,648	230	3.5	1.88	(1.45-2.45)	1.54	(1.18-2.01)	1.49	(1.14-1.95)
1.8-2.3	5,297	259	4.9	2.54	(1.95-3.30)	1.71	(1.31-2.24)	1.61	(1.22-2.12)
2.4-2.8	2,299	169	7.4	3.82	(2.89-5.05)	2.14	(1.59-2.88)	1.97	(1.45-2.67)
2.9-3.7	1,631	209	12.8	6.44	(4.89-8.48)	3.07	(2.28-4.14)	2.76	(2.02-3.78)
3.8-4.7	525	113	21.5	11.69	(8.51-16.06)	4.34	(3.05-6.19)	3.77	(2.59-5.49)
≥ 4.8	195	33	16.9	9.39	(6.00-14.71)	3.66	(2.23-5.99)	3.08	(1.84-5.16)
Continuous *	21,141	1,092	5.2	1.61 **	(1.53, 1.69)	1.32 **	(1.25, 1.40)	1.28 **	(1.20, 1.36)

* Fasting C-peptide higher by 1 SD (0.87 ug/L)

** Significant quadratic association ($p < 0.001$)

N = total number in the fasting C-peptide category # = number in the glucose category with preeclampsia, % = proportion in the fasting C-peptide category with preeclampsia

Model I: Adjusted for field center

Model II: Adjusted for field center, age, age squared, BMI, parity, height, gestational age at the OGTT, smoking, alcohol use, any family history of diabetes, any family history of hypertension, baby's gender

Model III: Model II adjustments plus fasting plasma glucose

Table 3

Relationship between maternal BMI and preeclampsia.

BMI (kg/m ²)	N	#	%	Model I OR	95% CI	Model II OR	95% CI	Model III* OR	95% CI
≤ 23.2	3,917	81	2.1	1.00		1.00		1.00	
23.3–26.7	7,136	205	2.9	1.33	(1.02–1.73)	1.34	(1.03–1.75)	1.23	(0.94–1.62)
26.8–30.5	5,684	273	4.8	2.06	(1.60–2.67)	2.13	(1.63–2.77)	1.75	(1.33–2.30)
30.6–33.6	2,378	195	8.2	3.47	(2.64–4.56)	3.60	(2.72–4.78)	2.61	(1.94–3.52)
33.7–38.3	1,552	188	12.1	5.17	(3.92–6.82)	5.38	(4.02–7.18)	3.52	(2.58–4.80)
38.4–44.0	539	126	23.4	10.00	(7.34–13.64)	10.17	(7.33–14.11)	5.94	(4.17–8.46)
> 44.0	158	48	30.4	14.11	(9.26–21.50)	14.50	(9.29–22.65)	8.35	(5.22–13.36)
Continuous**	21,364	1,116	5.2	1.82	(1.72–1.92)	1.83	(1.73–1.95)	1.60	(1.50–1.71)

* Model based on N of 21,141

** BMI higher by 1 SD (5.1 kg/m²)

N = total number in the BMI category # = number in the glucose category with preeclampsia, % = proportion in the BMI category with preeclampsia

Model I: Adjusted for field center

Model II: Adjusted for field center, age, age squared, parity, height, gestational age at the OGTT, smoking, alcohol use, any family history of diabetes, any family history of hypertension, fasting plasma glucose, baby's gender

Model III: Model II adjustments plus fasting C-peptide, fasting C-peptide squared

Table 4

Relationship between maternal glucose and preeclampsia.

PG (mg/dl)	N	#	%	Model I OR	95% CI	Model II OR	95% CI	Model III* OR	95% CI
Fasting									
< 75	3,876	122	3.1	1.00		1.00		1.00	
75-79	7,065	252	3.6	0.99	(0.79-1.24)	0.83	(0.66-1.05)	0.76	(0.60-0.96)
80-84	5,624	271	4.8	1.25	(1.00-1.56)	0.94	(0.74-1.18)	0.77	(0.61-0.99)
85-89	2,455	188	7.7	1.93	(1.52-2.46)	1.31	(1.01-1.68)	1.01	(0.78-1.32)
90-94	1,604	184	11.5	2.90	(2.27-3.71)	1.69	(1.30-2.20)	1.21	(0.91-1.60)
95-99	558	67	12.0	2.90	(2.10-4.00)	1.41	(1.00-2.00)	0.92	(0.63-1.33)
> = 100	182	32	17.6	4.72	(3.05-7.30)	2.13	(1.33-3.44)	1.28	(0.78-2.10)
Continuous**	21,364	1,116	5.2	1.47	(1.39-1.56)	1.21	(1.14-1.30)	1.08	(1.00-1.16)
1-hour									
< 105	3,961	130	3.3	1.00		1.00		1.00	
106-132	6,991	294	4.2	1.34	(1.08-1.66)	1.20	(0.96-1.49)	1.16	(0.93-1.45)
133-155	5,492	340	6.2	2.10	(1.70-2.59)	1.74	(1.40-2.17)	1.56	(1.24-1.95)
156-171	2,489	163	6.5	2.26	(1.77-2.88)	1.85	(1.43-2.39)	1.61	(1.24-2.09)
172-193	1,654	128	7.7	2.78	(2.15-3.60)	2.08	(1.58-2.74)	1.71	(1.29-2.27)
194-211	570	45	7.9	2.82	(1.97-4.05)	2.10	(1.43-3.08)	1.60	(1.08-2.36)
>= 212	207	16	7.7	2.94	(1.69-5.11)	2.33	(1.31-4.17)	1.62	(0.88-2.97)
Continuous**	21,364	1,116	5.2	1.39	(1.30-1.47)	1.29	(1.20-1.38)	1.19	(1.11-1.28)
2-hour									
<= 90	4,036	147	3.6	1.00		1.00		1.00	
91-108	6,879	295	4.3	1.24	(1.01-1.52)	1.09	(0.88-1.35)	1.03	(0.83-1.27)
109-125	5,381	302	5.6	1.69	(1.38-2.08)	1.44	(1.16-1.78)	1.29	(1.04-1.61)
126-139	2,721	193	7.1	2.28	(1.82-2.86)	1.79	(1.41-2.28)	1.55	(1.21-1.98)
140-157	1,545	110	7.1	2.37	(1.82-3.08)	1.93	(1.46-2.55)	1.62	(1.22-2.15)
158-177	608	52	8.6	2.74	(1.96-3.84)	2.16	(1.50-3.10)	1.72	(1.19-2.49)
>= 178	194	17	8.8	2.91	(1.70-4.99)	2.75	(1.57-4.83)	2.06	(1.16-3.65)

PG (mg/dl)	N	#	%	Model I OR	95% CI	Model II OR	95% CI	Model III* OR	95% CI
Continuous**	21,364	1,116	5.2	1.36	(1.28–1.44)	1.29	(1.21–1.38)	1.21	(1.13–1.30)

* Model based on N of 21,141

** Glucose higher by 1 SD (6.9 mg/dL or 0.4 mmol/L for FPG, 30.9 mg/dL or 1.7 mmol/L for 1-hour, and 23.5 mg/dL or 1.3 mmol/L for 2-hour PG)

N = total number in the glucose category # = number in the glucose category with preeclampsia, % = proportion in the glucose category with preeclampsia

Model I: Adjusted for field center

Model II: Adjusted for field center, age, age squared, BMI, parity, height, gestational age at the OGTT, smoking, alcohol use, any family history of diabetes, any family history of hypertension, any urinary tract infection during pregnancy, baby's gender

Model III: Model II adjustments plus fasting C-peptide, fasting C-peptide squared