Published in final edited form as:
Obstet Gynecol. 2014 November ; 124(5): 933–940. doi:10.1097/AOG.0000000000000509.

Laboratory Abnormalities in Pregnancy-Associated Hypertension: Frequency and Association With Pregnancy Outcomes

Jessica Cantu, M.D., **Rebecca G. Clifton, Ph.D.**, **James M. Roberts, M.D.**, **Kenneth J. Leveno, M.D.**, **Leslie Myatt, Ph.D.**, **Uma M. Reddy, M.D.**, **Michael W. Varner, M.D.**, **Ronald J. Wapner, M.D.**, **John M. Thorp Jr., M.D.**, **Brian M. Mercer, M.D.**, **Alan M. Peaceman, M.D.**, **Susan M. Ramin, M.D.**, **Philip Samuels, M.D.**, **Anthony Sciscione, D.O.**, **George Saade, M.D.**, and **Yoram Sorokin, M.D. for the Eunice Kennedy Shriver National Institute of Child and HealthHuman Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, Bethesda, Maryland**

Departments of Obstetrics and Gynecology of the University of Alabama at Birmingham, Birmingham, AL (J.C.); University of Pittsburgh, Pittsburgh, PA (J.M.R.); University of Texas Southwestern Medical Center, Dallas, TX (K.J.L.); University of Cincinnati, Cincinnati, OH (L.M.); Utah, Salt Lake City, UT (M.W.V.); Columbia University, New York, NY (R.J.W.); University of North Carolina at Chapel Hill, Chapel Hill, NC (J.M.T.); Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH (B.M.M.); Northwestern University, Chicago, IL (A.M.P.); University of Texas Health Science Center at Houston-Children's Memorial Hermann Hospital, Houston, TX (S.M.R.); The Ohio State University, Columbus, OH (P.S.); Drexel University, Philadelphia, PA (A.S.); University of Texas Medical Branch, Galveston, TX (G.S.); Wayne State University, Detroit, MI (Y.S.); and the George Washington University Biostatistics Center, Washington, DC (R.G.C.); and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (U.M.R.)

Abstract

Objective—To estimate the frequency of abnormal laboratory test results in pregnancy-associated hypertension and relationship with pregnancy outcomes.

Methods—This was a secondary analysis of a multicenter trial of vitamin C and E for prevention of pregnancy-associated hypertension in low-risk nulliparous women. Laboratory abnormalities included: platelets <100,000 per cubic millimeter, aspartate aminotransferase ≥100 u/L, creatinine ≥1.5 mg/dL, lactate dehydrogenase ≥600 u/L, total bilirubin ≥1.2 mg/dL, or evidence of hemolysis on peripheral smear. Mild pregnancy-associated hypertension was defined as blood pressure (BP) 140-159/90-109 mmHg. Severe pregnancy-associated hypertension was defined as persistent BP ≥160/110 mmHg, acute antihypertensive treatment, or any BP elevation associated with clinical

Corresponding author: Jessica Cantu, M.D., University of Alabama at Birmingham, Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, 619 19th St S, 176F 10270C, Birmingham, AL 35249, Work phone: (205) 934-5611, jesscantu27@gmail.com.
*For a list of other members of the NICHD MFMU, see the Appendix online at http://links.lww.com/xxx.

Presented in part as a poster at the 2013 SGI 60th Annual Scientific Meeting, March 20 – 24, 2013, Orlando, Florida.

Financial Disclosure: The authors did not report any potential conflicts of interest.

signs of end-organ dysfunction (one or more of headache, epigastric pain, blurred vision, pulmonary edema, eclampsia, or oliguria). Pregnancy outcomes were compared across four groups: I, mild hypertension alone; II, mild hypertension + abnormal laboratory values; III, severe pregnancy-associated hypertension alone; and IV, severe pregnancy-associated hypertension + abnormal laboratory values.

Results—Of 9,969 women, 2,752 (27.9%) developed pregnancy-associated hypertension and of these, laboratory abnormalities occurred in 7.3%. Laboratory abnormalities increased with severity of hypertension: mild hypertension alone (4.9%), severe hypertension alone (8.9%), mild or severe hypertension with clinical signs of end-organ dysfunction (12.2%); p-value (trend) <0.001. Compared with women with mild hypertension alone, the adjusted odds for the perinatal composite (2 to 4.8–fold in Category III–IV), preterm birth (2.1 to 7.8–fold in Category II–IV) and other adverse perinatal outcomes increase with disease severity, particularly with laboratory abnormalities and severe clinical signs.

Conclusion—The frequency of abnormal laboratory values in women with pregnancy-associated hypertension increases with disease severity. Adverse perinatal outcomes increase in the presence of abnormal laboratory values, particularly in those with clinical signs, likely due in part to the decision to deliver early.

Introduction

Hypertensive disorders occur in approximately 12 to 22 percent of all pregnancies and are associated with significant maternal and neonatal morbidity and mortality (1–3). Pregnancy-associated hypertension includes a spectrum of clinical presentations from mild to severe disease and classification is dependent on the severity of hypertension, presence of clinical signs and symptoms, proteinuria and other laboratory abnormalities (1,3).

Laboratory assessment has become routine practice in the evaluation of pregnancy-associated hypertension. The cost of this surveillance can be considerable and it leads to increased interventions such as hospital admission and labor induction (4). In a study of 442 women with severe preeclampsia, approximately 20 percent were reported to develop laboratory abnormalities including hemolysis, elevated liver enzymes, thrombocytopenia, and elevated creatinine or multiple abnormalities (HELLP syndrome) (5). Severe preeclampsia with HELLP syndrome is associated with a significant increase in adverse maternal and perinatal morbidity (5–8). However, there are limited contemporary data from well-defined populations regarding the yield of these laboratory evaluations and the associated pregnancy outcomes.

Our objective was to estimate the frequency of laboratory abnormalities in women with pregnancy-associated hypertension and to assess the relationship with adverse perinatal outcomes.

Materials and Methods

This study is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network

multicenter randomized, double-masked trial of low risk nulliparous women assigned to daily vitamin C and E supplementation or matching placebo to prevent pregnancy-associated hypertension (9). Women with singleton gestations between 9 0/7 and 16 6/7 weeks of gestation at the time of randomization were followed until delivery. Gestational age was based on a previously described algorithm (10) using the date of the last menstrual period (if reliable) and results of the earliest ultrasound examination. Exclusion criteria included medical co-morbidity (including preexisting hypertension) and known fetal anomalies which have been described previously (9). All data were collected by certified research personnel and uploaded to a database managed by an independent data coordinating center.

The study was approved by the institutional review board at each clinical site and the data-coordinating center. This secondary analysis included women who developed confirmed new-onset hypertension (including gestational hypertension and preeclampsia) per the study protocol. Pregnancy-associated hypertension was confirmed via central review of de-identified medical records, using a standardized protocol by 3 reviewers not associated with the clinical site of origin. Mild pregnancy-associated hypertension was defined as BP of 140–159 mmHg systolic or 90–109 mmHg diastolic on 2 occasions, 2–240 hours apart. Severe pregnancy-associated hypertension was defined as systolic BP of 160 mmHg or higher or diastolic of 110 mmHg or higher on 2 occasions, 2–240 hours apart, or a single occurrence treated with anti-hypertensives, or any BP elevation associated with severe clinical signs or symptoms of end organ dysfunction. Severe clinical signs and symptoms were defined as one or more of the following: headache, epigastric pain, blurred vision, pulmonary edema (confirmed by radiography), eclampsia, or oliguria (<500 ml in a 24-hour urine sample).

Laboratory abnormalities in the context of pregnancy-associated hypertension were defined as one or more of the following with the worst result recorded (e.g. lowest platelet count, highest AST, etc): thrombocytopenia (platelet count <100,000 per cubic millimeter), elevated liver enzyme levels (aspartate aminotransferase ≥100 U/L), elevated serum creatinine level (≥1.5 mg/dL [132.6 μmol per liter]), or evidence of hemolysis (either a lactate dehydrogenase level ≥600 U/L or a total bilirubin level ≥1.2 mg/dL, or a peripheral-blood smear showing nucleated red cells, schistocytes, or an elevated reticulocyte count) (9). An AST ≥100 U/L (rather than twice the upper limit of normal) was chosen as the threshold because the values were obtained clinically at each center and the upper limit varied among the centers. The AST value of 100 U/L is approximately twice the upper limit of normal at the participating centers. All chart-reviewed laboratory values were included from 20 weeks gestation through discharge after delivery. The laboratory data were based on clinical routine at each center and were run in each center's laboratory. In general, all patients with suspected pregnancy-associated hypertension would undergo laboratory evaluation as part of the work-up.

For this analysis, the severity of pregnancy-associated hypertension was categorized into four groups: Category I-mild pregnancy-associated hypertension alone in the absence of laboratory abnormalities or severe clinical signs or symptoms, Category II-mild pregnancy-associated hypertension with laboratory abnormalities, Category III-severe hypertension or any BP elevation associated with severe clinical signs or symptoms with normal laboratory

values, Category IV-severe hypertension or any BP elevation associated with severe clinical signs or symptoms and laboratory abnormalities.

The main pre-specified outcomes of interest were i) the frequency of laboratory abnormalities overall and stratified by category of pregnancy-associated hypertension based on severity of blood pressure and presence of clinical signs, and ii) adverse perinatal outcomes across the four pre-defined categories of pregnancy-associated hypertension. The prespecified adverse outcomes examined included a primary composite neonatal morbidity (one or more of respiratory distress syndrome, sepsis, necrotizing enterocolitis, Grade III or IV intraventricular hemorrhage, retinopathy of prematurity or Apgar score ≤3 at 5 minutes), overall and indicated preterm birth (PTB) (delivery either prior to 37 weeks of gestation or prior to 32 weeks of gestation), placental abruption, small for gestational age (SGA) birthweight < 5^{th} percentile (11), fetal or neonatal death (≥20 weeks), NICU admission, neonatal length of stay, and maternal length of stay. Neonatal outcomes were defined according to the criteria in the original trial protocol (9).

Continuous variables were compared with the use of the Wilcoxon rank-sum test (2 groups) or Kruskal-Wallis test (3 groups), and categorical variables with the use of the chi-square or Fisher exact tests as appropriate. Frequency of laboratory abnormalities across pregnancy-associated hypertension categories was assessed using the Cochran-Armitage Trend test. Univariable analyses were performed and logistic regression was used for multivariable analysis of binary outcomes and included significant covariates (maternal age, race, body mass index (BMI) at enrollment, smoking, education level (total years of schooling completed for a maximum of 16 years) and family history of preeclampsia) as well as treatment group (Vitamin C & E versus placebo) to compare pregnancy-associated hypertension groups relative to the mild pregnancy-associated hypertension group. Exact logistic regression was performed as appropriate. Attempts were made to normalize the continuous outcomes; however, due to the skewness of the data this was not possible and adjusted means are not presented. Observations with missing data were excluded from the analysis. For all outcomes, nominal p-values of less than 0.05 were considered to indicate statistical significance; no adjustments were made for multiple comparisons. Analyses were performed using SAS software (Cary, NC).

Results

A total of 10,154 women were randomized in the original trial and outcome data were available for 9,969 women. For this secondary analysis, 2,779 (27.9%) women developed pregnancy-associated hypertension. Twenty-seven women had babies with major malformations and were excluded, leaving 2,752 women for analysis. In those who developed pregnancy-associated hypertension, the frequency of laboratory abnormalities was 7.3% overall (95% CI 6.3–8.3%) and the frequency increased with increasing severity of pregnancy-associated hypertension: mild hypertension alone (4.9%, 95% CI 3.9–6.0%), severe hypertension alone (8.9%, 95% CI 4.8–13.1%), mild or severe hypertension with severe clinical signs (12.2%, 95% CI 9.9–14.5%) (p-value for trend <0.001) (Table 1). The frequency of laboratory abnormalities in women without pregnancy-associated hypertension was 0.4%.

Baseline maternal characteristics of women in each of the 4 pregnancy-associated hypertension categories are presented in Table 2. The groups differed by age, baseline BMI, race, smoking status, family history of preeclampsia, and education level. Women with laboratory abnormalities (Groups II and IV) when compared to the those without abnormalities, were significantly more likely to be older, Caucasian or Hispanic, non-smokers, have a higher education level and lower BMI (data not shown).

The incidence of the adverse perinatal outcomes in each pregnancy-associated hypertension category are presented in Table 3 with the results comparing each category of pregnancy-associated hypertension relative to the mild pregnancy-associated hypertension category after adjusting for maternal age, race, baseline BMI, smoking, treatment group (Vitamin C and E versus placebo), education level and family history of preeclampsia. Mean gestational age at delivery decreased with increasing severity of pregnancy-associated hypertension. Compared with the mild pregnancy-associated hypertension category (I), there were no increases in the rates of the composite neonatal morbidity, PTB <32 weeks of gestation, indicated PTB <37 or <32 weeks of gestation, fetal/neonatal death, SGA, or NICU admission in those with mild pregnancy-associated hypertension *plus* laboratory abnormalities (Category II), while there were increases in the rate of abruption (aOR 7.1 [1.9,27.5]) and overall PTB <37 weeks of gestation (aOR 2.1 [1.1,4.0]). In those with severe pregnancy-associated hypertension (Category III), the incidence of the composite neonatal morbidity (aOR 2.0 [1.4,2.9]), overall and indicated PTB <37 (aOR 3.6 [2.8,4.6] and aOR 8.5 [5.9,12.3]) and <32 weeks of gestation (aOR 3.8 [1.8,8.1] and aOR 11.3 [3.3,38.7]), SGA (aOR 1.5 [1.1,2.0]), and NICU admission (aOR 1.9 [1.5,2.3]) were increased compared with mild pregnancy-associated hypertension (Category I). With the exception of SGA, the incidence and adjusted odds of adverse outcomes increased further with severe pregnancy-associated hypertension in the presence of laboratory abnormalities (Category IV), when compared with mild pregnancy-associated hypertension alone (Category I): composite neonatal morbidity (aOR 4.8 [2.6,9.1]), overall PTB <37 weeks (aOR 7.8 [5.0,12.1]) and <32 weeks (aOR 24.7 [9.9,61.8]) of gestation, indicated PTB <37 weeks (aOR 20.1 [12,33.9]) and <32 weeks (aOR 82.1 [21.9,307.7]) of gestation, cesarean delivery (aOR 2.1 [1.4,3.0]), and NICU admission (aOR 3.9 [2.5,5.9]). There was no significant difference in fetal or neonatal death ≥20 weeks between any of the pregnancy-associated hypertension categories regardless of laboratory abnormalities. Neonatal and maternal length of stay were longer in pregnancy-associated hypertension categories II–IV when compared with those having mild pregnancy-associated hypertension alone (Category I) ($p<0.001$); however, the median lengths of stay were 2–3 days for all groups. The risk of cesarean delivery differed by pregnancy-associated hypertension category: 29.2%, 45.5%, 35.5%, and 45.1% for categories I –IV, respectively ($p<0.001$); categories with laboratory abnormalities were at higher risk of cesarean delivery.

In additional multivariable analyses that added gestational age at delivery to the model, there was no longer an increase in the adjusted odds of the composite neonatal morbidity (Categories III and IV), SGA (Category III) or NICU admission (Category III) compared with mild pregnancy-associated hypertension alone (Category I). However, in women with severe pregnancy-associated hypertension and laboratory abnormalities (Category IV), the

increase in NICU admission persisted after adjustment for gestational age (aOR 1.8, [1.1,3.0]). When we considered a creatinine level of 1.2 mg/dL or more to be abnormal, the results for the composite neonatal outcome were materially unchanged: aOR (95% CI) was 2.0 (0.8,4.8) for Group II vs. I, 1.9 (1.3,2.8) for Group III vs. I and 4.8 (2.7,8.8) for Group IV vs. I.

Analyses were performed to determine if outcomes were worse in women with severe pregnancy-associated hypertension or any hypertension with severe clinical signs and laboratory abnormalities (Category IV), compared with those having severe pregnancy-associated hypertension or any hypertension with severe clinical signs without abnormal laboratory values (Category III). As shown in Table 4, laboratory abnormalities were associated with an increase in the odds of the neonatal composite (aOR 2.5 [1.3,4.9]), PTB <37 (aOR 2.2 [1.4,3.4]) and <32 (aOR 6.1 [2.7,14.0]) weeks of gestation, indicated PTB <37 (aOR 2.4 [1.5,3.8]) and <32 (aOR 6.7 [2.9,15.8]) weeks of gestation and NICU admission (aOR 2.0 [1.3,3.2]) by two-fold or greater.

An additional analysis was performed to determine the association between the number of laboratory abnormalities and the composite outcome. Of the 201 women with laboratory abnormalities, 163 had 1 abnormal, 24 had 2 abnormal and 14 had 3 or more abnormal results. For the neonatal composite, there was a significant increasing trend (4.4%, 8.6%, 8.7% and 28.6% for 0, 1, 2 and 3 or more laboratory abnormalities respectively); p (trend) <0.001.

Although proteinuria was not required or used to define the category of pregnancy-associated hypertension, the frequency of proteinuria (defined as a 24-hour urine protein of 300 mg/24 hours or 2+ on dipstick (in absence of UTI) or protein-creatinine (PC) ratio of 0.35) increased across PAH categories: 16.0%, 25.0%, 41.6% and 56.6% for Categories I–IV, respectively (p-value for trend <0.001).

Discussion

This study demonstrates that abnormal laboratory results occur in 7.3% of otherwise healthy nulliparous women whose pregnancies are complicated by pregnancy-associated hypertension; and that the frequency increases from 5% to 12% with increasing severity of BP and presence of severe symptoms. Overall, the incidence of laboratory abnormalities in our study is lower than what has been reported in the literature (4,5,12). The incidence of HELLP syndrome among women with severe preeclampsia has been reported to be as high as 20%; however, this likely reflects the high-risk patient population examined, compared with our general population of nulliparous women at otherwise low-risk, including those who developed less-severe, as well as severe pregnancy-associated hypertension (5, 12). Few studies have examined laboratory abnormalities in the broad group of women with pregnancy-associated hypertension. The low prevalence of laboratory abnormalities in patients without pregnancy-associated hypertension almost certainly represents an underestimate as these women did not undergo routine clinical screening.

The presence of abnormal laboratory values was associated with an increased risk of selected adverse outcomes, which increased with the number of abnormal laboratory values. While the increase in adverse outcomes may be a direct consequence of a higher degree of disease severity associated with abnormal laboratory values, the decision to deliver early after observing an abnormal laboratory finding is likely also a contributing factor. Laboratory abnormalities in women with pregnancy-associated hypertension is considered a marker of disease severity and an important factor in the clinical decision to deliver preterm. This is supported by the lack of association of most pregnancy-associated hypertension categories with perinatal outcomes observed in the additional analyses adjusting for gestational age. However, this is not meant to imply that laboratory testing results should not be factored into the decision to deliver, a question that cannot be addressed using our data.

The results of this study are consistent with the available literature in that adverse neonatal outcomes are relatively low in women with mild pregnancy-associated hypertension (gestational hypertension or preeclampsia) (3,6,12–15), while those who develop severe pregnancy-associated hypertension including HELLP syndrome have higher rates of PTB, maternal and neonatal morbidity and mortality (7,8,14–16). Our study is unique in that we are able to quantify the prevalence of laboratory abnormalities in women with varying severity of pregnancy-associated hypertension including those with otherwise mild disease.

We found a 7-fold increase in the incidence of placental abruption in those women with mild pregnancy-associated hypertension and abnormal laboratory values compared to those with mild pregnancy-associated hypertension and normal laboratory values which was not seen with increasing severity of pregnancy-associated hypertension. This observation may be because patients with abruption are more likely to have less severe blood pressure elevation as a result of the bleeding associated with abruption.

Traditionally, a diagnosis of preeclampsia is made in the setting of new-onset hypertension after 20 weeks of gestation associated with proteinuria (1,3). The literature suggests that laboratory abnormalities (HELLP syndrome) may occur in the absence of proteinuria in approximately 10–15% of women (13,17). Therefore, proteinuria was not required or used to define the category of pregnancy-associated hypertension. This is consistent with the recent guidelines released from the ACOG task force in that proteinuria is no longer required to make a diagnosis of preeclampsia if other systemic findings are present (18).

In this secondary analysis, we used the terminology of pregnancy-associated hypertension to coincide with that of the primary trial. However, the defined BP categories can be extrapolated to the new ACOG classification of hypertensive disorders in pregnancy (18). Category I (mild pregnancy-associated hypertension alone) corresponds to BP in the setting of either gestational hypertension or preeclampsia with non-severe features; Category II (mild pregnancy-associated hypertension + abnormal laboratory values) corresponds to a subgroup of preeclampsia with severe features regardless of proteinuria given the abnormal laboratory values. Category III (severe hypertension or any BP elevation associated with severe clinical signs with normal laboratory values) corresponds to either preeclampsia with severe features or severe gestational hypertension. Category IV (severe hypertension or any BP elevation associated with severe clinical signs with laboratory abnormalities) also

corresponds to a subgroup of preeclampsia with severe features given abnormal laboratory values.

The strengths of our study include the relatively large proportion of women with pregnancy-associated hypertension, central validation of key outcomes and data abstraction by trained and certified research staff – factors that minimize bias. Limitations include the relatively small number of women with laboratory abnormalities reducing our ability to fully evaluate less frequent outcomes and delineate differences between pregnancy-associated hypertension categories I and II. Factors such as use of corticosteroids or magnesium sulfate could have resulted in additional confounding with regard to neonatal outcomes; however, these data were not available. Those with laboratory abnormalities were delivered earlier, and, therefore, might have been more likely to receive corticosteroids biasing the results towards the null. Also, since only nulliparous women were enrolled in the study, generalizability of our findings to parous women is uncertain. Furthermore, we have not addressed whether the relationship with adverse outcomes is modified by the presence or absence of proteinuria (and the definition of proteinuria differs slightly from the recent ACOG task force document) (18)– we focused on hypertension, which is essential for the diagnosis of pregnancy-associated hypertension. Finally, when multiple comparisons are conducted, the likelihood of chance findings increases. Given that we prespecified the composite as the primary outcome of interest for this analysis, and secondary findings are consistent, this is less of a concern.

In conclusion, women with pregnancy-associated hypertension have a relatively low incidence of laboratory abnormalities. This is useful contemporary information for counseling women with the condition regarding laboratory abnormalities. In women with mild pregnancy-associated hypertension and no signs or symptoms of severity, routine laboratory evaluation may not be beneficial or cost-effective, given the low frequency of laboratory abnormalities. Studies comparing outcomes with and without (or masked) routine laboratory assessment are needed to further clarify this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Alan T. N. Tita for his role in proposal development and project oversight, Sabine Bousleiman, R.N.C., M.S.N., M.P.H. and Margaret Cotroneo, R.N, for protocol development and coordination between clinical research centers (.), Elizabeth Thom, Ph.D, for protocol/data management and statistical analysis, and John C. Hauth, M.D., Gail D. Pearson, M.D., Sc.D., and Catherine Y. Spong, M.D., for protocol development and oversight.

Supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) [HD34208, HD27869, HD40485, HD40560, HD40544, HD34116, HD40512, HD21410, HD40545, HD40500, HD27915, HD34136, HD27860, HD53118, HD53097, HD27917, and HD36801]; the National Heart, Lung, and Blood Institute; and the National Center for Research Resources [M01 RR00080, UL1 RR024153, UL1 RR024989]. Comments and views of the authors do not necessarily represent the views of the NICHD.

References

1. ACOG Practice Bulletin No. 33. Diagnosis and management of preeclampsia and eclampsia. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2002; 99:159–167. [PubMed: 16175681]
2. Cunningham, Gary; Leveno, Kenneth J.; Bloom, Steven L.; Hauth, John C.; Rouse, Dwight J.; Spong, Catherine Y. Williams Obstetrics. 23. McGraw Hill; 2010.
3. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000; 183:S1–S22.
4. Bailey DJ, Walton SM. Routine investigations might be useful in pre-eclampsia, but not in gestational hypertension. Aust N Z J Obstet Gynaecol. 2005 Apr; 45(2):144–7. [PubMed: 15760317]
5. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol. 1993; 169:1000–1006. [PubMed: 8238109]
6. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003 Jul; 102(1):181–92. [PubMed: 12850627]
7. Cavkaytar S, Ugurlu EN, Karaer A, Tapisiz OL, Danisman N. Are clinical symptoms more predictive than laboratory parameters for adverse maternal outcome in HELLP syndrome? Acta Obstet Gynecol Scand. 2007; 86(6):648–51. [PubMed: 17520393]
8. Haddad B, Barton JR, Livingston JC, Chahine R, Sibai BM. Risk factors for adverse maternal outcomes among women with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol. 2000 Aug; 183(2):444–8. [PubMed: 10942484]
9. Roberts JM, Myatt L, Spong CY, Thom EA, Hauth JC, Leveno KJ, Pearson GD, Wapner RJ, Varner MW, Thorp JM Jr, Mercer BM, Peaceman AM, Ramin SM, Carpenter MW, Samuels P, Sciscione A, Harper M, Smith WJ, Saade G, Sorokin Y, Anderson GB. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med. 2010 Apr 8; 362(14):1282–91. [PubMed: 20375405]
10. Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, Heine RP, Nugent RP, Fischer ML, Leveno KJ, Wapner R, Varner M. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med. 2000 Feb 24; 342(8):534–40. [PubMed: 10684911]
11. Alexander GR, Himes JH, Kaufman RB, Kogan M. A United States Reference for Fetal Growth. Obstet and Gynecol. 1996; 87:163–168.
12. Audibert F, Friedman S, Frangieh A, Sibai B. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol. 1996; 175:460–464. [PubMed: 8765269]
13. Sibai B, Dekker G, Kupferminc M. Prefeclampsia. Lancet. 2005 Feb-Mar;365(9461):785–99. [PubMed: 15733721]
14. Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. Obstet Gynecol. 2000; 95:24–28. [PubMed: 10636496]
15. Buchbinder A, Sibai B, Caritis S, MacPherson C, Hauth J, et al. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. Am J Obstet Gynecol. 2002; 186:66–71. [PubMed: 11810087]
16. Abramovici D, Friedman S, Mercer B, Audibert F, Kao L, Sibai B. Neonatal outcome in severe preeclampsia at 24 to 36 weeks' gestation: Does the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome matter? Am J Obstet Gynecol. 1999; 180:221–5. [PubMed: 9914607]
17. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004 May; 103(5 Pt 1):981–91. [PubMed: 15121574]

18. American College of Obstetricians and Gynecologists. Hypertension in Pregnancy: Executive Summary. Obstet and Gynecol. 2013 Nov; 122(5):1122–1131.

Table 1

Frequency of laboratory abnormalities among women with pregnancy-associated hypertension

	No laboratory abnormalities (n=2,551)	**Laboratory Abnormalities (n=201)**
Mild hypertension without clinical signs	Category I – 1,690 (95.1)	Category II – 88 (4.9; 95% CI 3.9,6.0)
Severe hypertension without clinical signs	Category III – 163 (91.1)	Category IV – 16 (8.9; 95% CI 4.8,13.1)
Mild or severe hypertension with severe clinical signs**	Category III – 698 (87.8)	Category IV – 97 (12.2; 95% CI 9.9,14.5)

Data are n (%) or 95% confidence interval.

** Defined as at least one of the following: headache, blurred vision, epigastric pain, pulmonary edema, eclampsia, or oliguria

Table 2

Baseline characteristics of women according to pregnancy-associated hypertension category

	Pregnancy-Associated Hypertension Category				
Characteristic	**I (n=1690)**	**II (n=88)**	**III (n=861)**	**IV (n=113)**	**p-value**
Age (yr)	23.6±5.3	24.9±5.3	22.9±5.1	24.8±5.3	<**0.001**
Prior pregnancy < 20 weeks	413 (24.4)	21 (23.9)	199 (23.1)	24 (21.2)	0.80
Baseline body mass index	28.0±7.0	26.9±6.7	29.4±7.3	26.8±6.3	<**0.001**
Race or ethnic group					
Black	593 (35.1)	25 (28.4)	334 (38.8)	26 (23.0)	<**0.001**
Hispanic	322 (19.1)	22 (25.0)	197 (22.9)	29 (25.7)	
Caucasian/Other	775 (45.9)	41 (46.6)	330 (38.3)	58 (51.3)	
Smoker	304 (18.0)	10 (11.4)	179 (20.8)	15 (13.3)	**0.040**
Vitamins	874 (51.7)	46 (52.3)	477 (55.4)	50 (44.2)	0.09
Placebo	816 (48.3)	42 (47.7)	384 (44.6)	63 (55.8)	
Family history of preeclampsia	226 (13.4)	8 (9.1)	169 (19.6)	22 (19.5)	<**0.001**
Taking multivitamins	1421 (84.1)	71 (80.7)	709 (82.3)	94 (83.2)	0.63
Educational level (yrs)	13.0±2.5	13.3±2.6	12.5±2.5	13.2±2.5	<**0.001**

I, Mild hypertension alone; II, Mild hypertension + abnormal laboratory values; III, Severe hypertension alone or any hypertension with severe clinical signs; IV, Severe hypertension alone or any hypertension with severe clinical signs + abnormal laboratory values.

Data are n (%) or mean ± standard deviation unless otherwise specified. Boldface indicates p-value <0.05.

Table 3

Adverse pregnancy outcomes among women with pregnancy-associated hypertension by presence or absence of abnormal laboratory values

	I (N=1690)	II (N=88)	II. vs I. aOR (95% CI)*	III (N=861)	III. vs I. aOR (95% CI)*	IV (N=113)	IV. vs I. aOR (95% CI)*
Composite neonatal morbidity†	56/1685 (3.3)	6/88 (6.8)	2.2 (0.9,5.3)	56/856 (6.5)	**2.0 (1.4,2.9)**+	14/111 (12.6)	**4.8 (2.6,9.1)**+
RDS	44/1680 (2.6)	0/86 (0)		45/855 (5.3)		12/111 (10.8)	
Sepsis	7/1680 (0.4)	1/86 (1.2)		8/855 (0.9)		0/111 (0)	
NEC	3/1680 (0.2)	0/86 (0)		1/855 (0.1)		3/111 (2.7)	
IVH	1/1680 (0.1)	0/86 (0)		0/854 (0)		0/111 (0)	
ROP	2/1680 (0.1)	0/86 (0)		4/855 (0.5)		0/111 (0)	
Apgar ≤3 at 5 min	11/1687 (0.7)	5/88 (5.7)		9/860 (1.0)		2/112 (1.8)	
Fetal or neonatal death (≥20 weeks)	12/1688 (0.7)	2/88 (2.3)	3.6 (0.8,16.8)	5/857 (0.6)	0.7 (0.3,2.1)	2/111 (1.8)	3.5 (0.7,16.5)
PTB < 37 weeks	112/1690 (6.6)	11/88 (12.5)	**2.1 (1.1,4.0)**	174/861 (20.2)	**3.6 (2.8,4.6)**+	38/113 (33.6)	**7.8 (5.0,12.1)**+
PTB < 32 weeks	10/1690 (0.6)	2/88 (2.3)	4.6 (0.96,21.6)	21/861 (2.4)	**3.8 (1.8,8.1)**+	11/113 (9.7)	**24.7 (9.9,61.8)**+
Indicated PTB < 37 weeks	39/1690 (2.3)	4/88 (4.5)	2.0 (0.7,5.9)	140/861 (16.3)	**8.5 (5.9,12.3)**+	34/113 (30.1)	**20.1 (12.0,33.9)**+
Indicated PTB < 32 weeks	3/1690 (0.2)	1/88 (1.1)	7.6 (0.8,75.3)	18/861 (2.1)	**11.3 (3.3,38.7)**+	11/113 (9.7)	**82.1 (21.9,307.7)**+
Placental Abruption	9/1690 (0.5)	3/88 (3.4)	**7.1 (1.9,27.5)**++	9/861 (1.0)	1.8 (0.7,4.6)	1/113 (0.9)	1.7 (0.2,13.8)
Cesarean Delivery	494/1690 (29.2)	40/88 (45.5)	**2.1 (1.3,3.2)**++	306/861 (35.5)	**1.2 (1.0,1.5)**	51/113 (45.1)	**2.1 (1.4,3.0)**+
SGA (<5th%)	96/1682 (5.7)	5/85 (5.9)	1.0 (0.4,2.6)	69/858 (8.0)	**1.5 (1.1,2.0)**	10/112 (8.9)	1.6 (0.8,3.2)
NICU Admission	203/1689 (12.0)	13/88 (14.8)	1.3 (0.7,2.4)	178/860 (20.7)	**1.9 (1.5,2.3)**+	37/113 (32.7)	**3.9 (2.5,5.9)**+
Neonatal LOS (days)	2 [2–3]	3 [2–4]	**	2 [2–4]	**	3 [2–5]	**
Maternal LOS (days)	2 [2–3]	3 [2–4]	**	2 [2–3]	**	3 [2–4]	**

I, Mild hypertension alone; II, Mild hypertension + abnormal laboratory values; III, Severe hypertension alone or any hypertension with severe clinical signs; IV, Severe hypertension alone or any hypertension with severe clinical signs + abnormal laboratory values. Data are n/Total (%) or median [interquartile range]. Boldface indicates p-value <0.05.

*Adjusted for maternal age, race, baseline BMI, smoking, treatment group (Vitamin C and E or placebo), education level, & family history of preeclampsia

** Adjusted means not reported due to inability to normalize the data

† RDS, Sepsis, NEC, IVH (Grade III or IV), ROP, Apgar ≤3 at 5 min

+ Indicates p-value <0.001

++ Indicates p-value <0.01

Table 4

Univariable and multivariable analysis of adverse pregnancy outcomes among women with severe pregnancy-associated hypertension by presence or absence of abnormal laboratory values

	III (n=861)	IV (n=113)	
		OR (95%CI)	aOR (95%CI)*
Composite neonatal morbidity†	1 (referent)	**2.1 (1.1,3.8)**	**2.5 (1.3,4.9)++**
PTB < 37 weeks	1 (referent)	**2.0 (1.3,3.1)++**	**2.2 (1.4,3.4)+**
PTB < 32 weeks	1 (referent)	**4.3 (2.0,9.2)+**	**6.1 (2.7,14.0)+**
Indicated PTB < 37 weeks	1 (referent)	**2.2 (1.4,3.4)+**	**2.4 (1.5,3.8)+**
Indicated PTB < 32 weeks	1 (referent)	**5.1 (2.3,11.0)+**	**6.7 (2.9,15.8)+**
Placental Abruption	1 (referent)	0.85 (0.02,6.2)	**
Fetal or neonatal death (≥20 weeks)	1 (referent)	3.1 (0.3,19.3)	**
SGA (<5th%)	1 (referent)	1.1 (0.6,2.2)	1.1 (0.5,2.2)
NICU Admission	1 (referent)	**1.9 (1.2,2.9)++**	**2.0 (1.3,3.2)++**

III, Severe hypertension alone or any hypertension with severe clinical signs; IV, Severe hypertension alone or any hypertension with severe clinical signs + abnormal laboratory values. Boldface indicates p-value <0.05.

*Adjusted for maternal age, race, baseline BMI, smoking, treatment group (Vitamin C and E or placebo), education level, & family history of preeclampsia

†RDS, Sepsis, NEC, IVH (Grade III or IV), ROP, Apgar ≤3 at 5 min

**Numbers too small to calculate adjusted OR

+Indicates p-value <0.001

++Indicates p-value <0.01