ACOG and local diagnostic criteria for hypertensive disorders of pregnancy (HDP) in La Paz-El Alto, Bolivia: A retrospective case-control study

Litzi Lazo-Vega[a,#],

Lilian Toledo-Jaldin[a,#],

Abraham Badner[a],

José Luis Barriga-Vera[b],

Melany Castro-Monrroy[c],

Anna G. Euser[d],

Alison Larrea-Alvarado[a],

Ian Lawrence[e],

Carola Mérida[c],

Rodrigo Mizutani[b],

Yuri Pérez[f],

Sebastian Rocabado[g],

Manfredo Vargas[b],

Vikram Vasan[h],

Colleen G. Julian[i,^],

Lorna G. Moore[d,^,*]

[*]Corresponding author. Lorna.Moore@cuanschutz.edu (L.G. Moore).
[#]Co-first authors.
[^]Co-senior authors.

[a]Hospital Materno-Infantil, Caja Nacional de Salud, La Paz, Bolivia

[b]Hospital Boliviano Holandés, El Alto, Bolivia

[c]Universidad Major de San Andrés, Escuela de Medicina, La Paz, Bolivia

[d]Department of Obstetrics and Gynecology, University of Colorado Denver, Anschutz Medical Campus, MS 8913, 12700 E 19th Avenue, Aurora, CO 80045, USA

[e]University of Colorado Denver School of Medicine, Aurora, CO, USA

[f]Hospital de la Mujer, La Paz, Bolivia

[g]Universidad Nuestra Señora de La Paz, Escuela de Medicina, La Paz, Bolivia

[h]Krieger School of Arts and Sciences, The Johns Hopkins University, Baltimore, MD, USA

[i]Department of Medicine, University of Colorado Denver, Aurora, CO, USA

Summary

Background—Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal death in low- to middle-income countries (LMIC). The American College of Obstetricians and Gynecologists (ACOG) updated diagnostic guidelines to align signs and symptoms with those associated with maternal death. We performed an observational study to ask whether ACOG guidelines were employed and associated with adverse outcomes in La Paz-El Alto, Bolivia, an LMIC.

Methods—Medical records for all HDP discharge diagnoses ($n = 734$) and twice as many controls ($n = 1647$) were reviewed for one year at the three largest delivery sites. For the 690 cases and 1548 controls meeting inclusion criteria (singleton, 18–45 maternal age, local residence), health history, blood pressures, symptoms, lab tests, HDP diagnoses (i.e., gestational hypertension [GH]; preeclampsia [PE]; haemolysis, low platelets, high liver enzymes [HELLP] syndrome, eclampsia), and adverse outcomes were recorded. Bolivian diagnoses were compared to ACOG guidelines using accuracy analysis and associated with adverse outcomes by logistic regression.

Findings—Both systems agreed with respect to eclampsia, but only 27% of all Bolivian HDP diagnoses met ACOG criteria. HDP increased adverse maternal- or perinatal-outcome risks for both systems, but ACOG guidelines enabled more pre-delivery diagnoses, graded maternal-risk assessment, and targeting of HDP terminating in maternal death.

Interpretation—Bolivia diagnoses agreed with ACOG guidelines concerning end-stage disease (eclampsia) but not the other HDP due mainly to ACOG's recognition of a broader range of severe features. ACOG guidelines can aid in identifying pregnancies at greatest risk in LMICs, where most maternal and perinatal deaths occur.

Keywords

Eclampsia; HELLP syndrome; High altitude; Maternal mortality; Perinatal mortality; Preeclampsia

Introduction

Hypertensive disorders of pregnancy (HDP) are leading causes of maternal and perinatal deaths, especially in low- to middle-income countries (LMIC) where 98 and 99%, respectively, of such deaths occur.[1–3] HDP range from isolated hypertension in a previously normotensive woman to severe hypertension with abnormal laboratory values or symptoms indicative of multiorgan dysfunction. The American College of Obstetricians and Gynecologists (ACOG), the International Society for the Study of Hypertension in Pregnancy, and the World Health Organization updated their diagnostic guidelines to align HDP signs and symptoms with those most closely associated with maternal death.[4–6] Proteinuria was eliminated as a severe feature and focus placed on severe hypertension and other measures of organ-system dysfunction. While ACOG guidelines have been officially adopted at the national level in Latin America,[7] whether the ACOG criteria have been incorporated into clinical practice or improved the detection of adverse outcomes is unknown.

Bolivia is a Latin American LMIC with one of the highest rates of maternal and perinatal mortality.[8–10] The adjacent cities of La Paz and El Alto, located at an altitude of 3600–4100 m, house Bolivia's largest population concentration. High-altitude residence increases the frequency of HDP[11–13] but unknown are the types of HDP present in Bolivia, the criteria used for diagnosis and whether adherence to ACOG guidelines improves prediction of adverse outcomes. We, therefore, examined the prenatal, hospital and delivery records for all women with HDP discharge diagnoses (cases) and a temporally matched sample of those without such a diagnosis (controls) at the three largest delivery hospitals in La Paz-El Alto. We hypothesized that ACOG guidelines were not followed but would improve the detection of pregnancies at risk of adverse outcomes. We aimed to determine (1) the agreement or lack thereof between Bolivian and ACOG HDP diagnoses and (2) their respective associations with adverse maternal- or perinatal outcomes.

Methods

Study population

Cases were all women with any HDP discharge diagnosis (cases, $n = 734$) who gave birth from April 1, 2017 to March 31, 2018, at Hospital Materno-Infantil, Hospital de la Mujer, or Hospital Boliviano Holandés in La Paz-El Alto, Bolivia meeting our inclusion criteria; namely, singleton pregnancy, maternal age at delivery > 18 and < 45 years, and La Paz-El Alto residence (Figure 1). Controls ($n = 1647$) were women without an HDP discharge diagnosis and temporally matched to include deliveries immediately before and after an HDP case, over-sampled to ensure at least a 2:1 control-to-case ratio, and subject to the same inclusion criteria as cases. Study procedures were approved by the University of Colorado Multiple Institutional Review Board (COMIRB 17–1529) and its Bolivian counterpart. Study conduct was in keeping with the STROBE statement.[14]

Hospital Materno-Infantil and Hospital de la Mujer are tertiary-level facilities in La Paz and Hospital Boliviano Holandés is a secondary-level hospital in El Alto. All provide government-subsidized no-cost services and Hospital Materno-Infantil also serves those

insured through the country's largest insurance system, the *Caja Nacional de Salud* (National Health Care Fund). During the one-year study period, the three hospitals delivered 13,531 babies which comprised 40% of all hospital births in the La Paz-El Alto metropolitan region.

Study data

Prenatal care in Bolivia occurs at community outpatient clinics until week 28 and then at outpatient clinics at the hospital delivery site. Data are entered onto the *Centro Latinoamericano de Perinatología* (CLAP) form,[15] which study investigators used to collect maternal age, education, body mass index (BMI), health history, last menstrual period), systolic and diastolic blood pressures (SBPs, DBPs), HDP diagnoses, diagnostic symptoms, and drugs administered. Hospital records were used to obtain these same data for visits after week 28, laboratory test results, delivery mode (Caesarean section, vaginal), maternal intensive care unit (ICU) or neonatal ICU (NICU) admission, days hospitalized, stillbirths, maternal and perinatal deaths (i.e., deaths after 22 completed weeks and before seven days after birth). All maternal or perinatal deaths were verified using Bolivian Ministry of Health records. Data were entered into a Spanish-language RedCap database patterned after COLLECT.[16]

Definitions

Hypertension was defined as two or more SBPs 140 mmHg or DBPs 90 mmHg at least six hours apart in a previously normotensive woman. Hypertension was considered severe if two or more SBPs 160 mmHg or DBPs 110 mmHg. Due to the limited prenatal BP data, only data after 20 weeks were used to assign diagnoses and chronic hypertension (before 20 weeks or when nonpregnant) was not considered. Proteinuria was defined as 2+ by dipstick or >300 mg in a 24 h urine collection. Women with hypertension but without proteinuria were considered as having gestational hypertension (GH). Preeclampsia (PE) was defined as hypertension during pregnancy with proteinuria. PE was considered severe by Bolivian criteria when HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome was present and defined as hypertension during pregnancy with any two of the three followings: haemolysis (LDH>600 IU/L), low platelets (<100,000/L), or elevated serum alanine or aspartate aminotransferase liver enzymes (>80 IU/L). ACOG guidelines considered PE as severe when either serum creatinine 1.1 mg/dL, platelet count <100,000/L, liver enzymes >80 IU/L, severe hypertension, or diagnostic symptoms (i.e., severe headache, blurred vision, significant shortness of breath, or epigastric pain) were present, and HELLP as a subset of severe PE characterized by both low platelets and elevated liver enzymes. Any seizure or stroke was classified as eclampsia[4,17] by both systems. Anti-hypertensive drugs administered were calcium-channel or beta-blockers, and magnesium sulphate (MgSO4) or Zuspan were used as anti-seizure as well as anti-hypertensive medications.

Gestational age at delivery was calculated from the last menstrual period and corrected using ultrasound and/or clinical estimates following ACOG guidelines.[18] Approximately half (57%) of the women had ultrasound exams. Delivery <37 weeks was considered preterm and sex- and gestational age-adjusted birth weight less than the 10th percentile as small for gestational age (SGA).[19]

Adverse maternal outcomes were Caesarean delivery for decreased foetal movement or abnormal heart rate tracing; prolonged (>3 days) hospitalization due to maternal and/or infant problems; ICU admission; or death after 22 weeks of pregnancy and within 7 days postpartum. Adverse perinatal outcomes were preterm delivery, SGA, 5 min Apgar score <7, receiving supplemental oxygen, NICU admission, or perinatal death.

Statistics

Mean values or frequencies were compared between cases and controls or among diagnostic groups using chi-squared tests, Students t-test for unpaired data, or one-way ANOVA with Tukey's multiple comparisons, as appropriate. The strength of agreement between Bolivian and ACOG HDP diagnoses was tested using Cohen's Kappa (K) and accuracy parameters (sensitivity, specificity, positive likelihood ratio and negative likelihood ratio) for diagnostic testing. Diagnostic estimates were assessed for each Bolivian category using ACOG guidelines as the gold standard (reference) and against all other Bolivian diagnostic categories since we were predominantly concerned with misclassification. Using GH as an example, given that there were 129 true positives, 1784 true negatives, 220 false positives and 105 false negatives, sensitivity was calculated as 129/ (129 + 105) or 0.55 and specificity as 1784/ (1784 + 220) or 0.89. Logistic regression was used to estimate the association between HDP diagnostic categories (independent, categorical variable) and any adverse maternal or perinatal outcome (dichotomous, dependent variable) within each system. Each HDP category was contrasted against the no HDP category (reference). Final regression models were performed using diagnostic groups alone since risk factors (i.e., maternal age >40 yr., nonpregnant BMI >35 kg/m^2, no or primary-only education, primiparity, number of prenatal visits) were not associated with adverse maternal or perinatal outcomes in our dataset, nor were differences apparent in the frequency of adverse outcomes when baseline characteristics were compared (Supplemental Table 1). Data were excluded on a pairwise basis except for logistic regression analyses where data were excluded listwise and reported in the tables as numbers or percentages with the trait, means ± standard deviation (SD), or means with the 95% confidence interval (CI). A two-sided $p < 0.05$ was considered evidence of association or difference in sample means or frequencies, and trends reported when $0.05 < p < 0.10$. Data analyses were conducted using SPSS v.26 (IBM, Chicago, IL) and graphics prepared with GraphPad Prism v. 5.01 (Graph-Pad Software, Inc., La Jolla, CA).

Role of the funding source

Results

Maternal and infant characteristics

Of the 2381 records examined, 143 did not meet inclusion criteria, leaving 2238 maternal-infant dyads (690 cases, 1548 controls) as our study population (Figure 1). Compared to controls, HDP cases were more often >40 years old, primiparous and to have had fewer years of schooling, greater BMI, a history of HDP, Caesarean delivery, and to have died

within the first postnatal week (Table 1). Infants born to HDP cases *vs.* controls weighed less, were born at an earlier gestational age, tended to be more often male or stillborn, and had more deaths during the first postnatal week or perinatal period.

Comparison of Bolivian and ACOG diagnoses

Of the 690 women with an HDP by Bolivian criteria (Figure 2A), 50% had GH, 43% PE, 4% severe PE (HELLP), and 4% eclampsia. Application of ACOG criteria classified 746 women with an HDP, 31% of whom had GH, 3% PE, 63% severe PE, and 2% eclampsia. In short, GH was the most common HDP according to Bolivian criteria but severe PE according to ACOG guidelines. Exemplifying the source of such diagnostic differences, a woman with severe hypertension or severe headache and epigastric pain would be classified as PE by Bolivian criteria but as severe PE by ACOG.

The crosstabulation and accuracy analysis in Figure 2B assesses diagnostic agreement, or lack thereof, between the two classificatory systems. Both systems generally agreed with respect to identifying women with no HDP and agreed entirely with respect to eclampsia, but there was a poor or very poor agreement concerning the other three HDP diagnoses (GH, PE, severe PE). Specifically, among the 349 Bolivian GH diagnoses, only 129 or 37% met ACOG criteria; the others were, in order, severe PE, no HDP, or PE. Of the 294 Bolivian PE diagnoses, only 10 or 3% met ACOG criteria for PE; most would have been classified as severe PE by ACOG. All 28 Bolivian severe PE (HELLP) diagnoses met ACOG criteria for severe PE, but ACOG guidelines identified an additional 445 women with severe PE, including six with HELLP syndrome who were diagnosed as GH or PE by Bolivian criteria (data not shown). Using ACOG as the gold standard, the positive and negative likelihood ratios in Figure 2B show that Bolivian criteria were moderately or very good for ruling in or out no-HDP status. Bolivian diagnoses had modest positive predictive values for ruling in GH or PE but were comparatively poor in ruling them out. All women with a Bolivian diagnosis of severe PE met ACOG severe-PE guidelines, preventing the calculation of a positive-predictive value, but since many more cases also met ACOG criteria for severe PE, Bolivian diagnoses were ineffective for ruling out such a diagnosis. Overall, as shown by the diagonal numbers in Figure 2B, only 27% of the 690 Bolivian HDP diagnoses agreed to ACOG guidelines.

The source of discrepancies between Bolivian and ACOG diagnoses are detailed in Table 2. Specifically, 25% of the Bolivian GH women had proteinuria and hence met ACOG criteria for PE. Severe PE diagnostic symptoms were present prenatally, at delivery or immediately postpartum in 8%, 76% or 22%, respectively, of the Bolivian PE women. Twenty per cent of the Bolivian PE cases had abnormal laboratory values, which qualified them for an ACOG diagnosis of severe PE. Of the 28 Bolivian HELLP diagnoses, 23 met Bolivian criteria for HELLP, with the other 5 having diagnostic symptoms alone (data not shown). All Bolivian HELLP cases met ACOG criteria for severe PE, but only 8 were considered by ACOG as severe PE with HELLP; the other 20 were classified by ACOG as severe PE without HELLP based on low platelets, high serum creatinine, or high liver enzymes ($n = 14$); severe hypertension ($n = 4$); or symptoms alone ($n = 2$) (data not shown). The time of diagnosis also varied: 29 Bolivian HDP diagnoses were made before delivery whereas 2.5-times as

many ($n = 74$) could have been made had ACOG criteria been employed. While half the maternal deaths occurred in eclamptic women, all the other deaths were in women who met ACOG guidelines for severe PE but were distributed among Bolivian HELLP ($n = 2$), no HDP ($n = 2$), or PE ($n = 1$) cases.

In terms of treatments, administration of anti-hypertensives or $MgSO_4$ was common in HDP patients regardless of the classificatory system. Unknown, however, was whether the anti-hypertensive medication continued to be taken after the outpatient visit or period of hospitalization.

Comparison of adverse maternal or perinatal outcomes

Whether based on Bolivian or ACOG criteria, HDP increased the risks of adverse maternal and perinatal outcomes and did so to a greater extent in mothers than offspring (Table 3). The pattern of increase differed somewhat, with adverse maternal-outcome risks being greater for each Bolivian HDP diagnosis but only for the ACOG severe PE or eclampsia groups. The risk of any adverse maternal outcome was greatest for women with eclampsia, five (26%) of whom died, and greater in those with a Bolivian diagnosis of severe PE (HELLP) than an ACOG severe-PE diagnosis. The greater risk seen for Bolivian compared to ACOG severe PE diagnoses was due to most (23 of 28) of the Bolivian diagnoses being based on abnormal laboratory values whereas only 14 of the 473 ACOG severe-PE women met ACOG criteria for HELLP, the remainder having severe hypertension ($n = 58$); at least one abnormal serum creatinine, platelet count or liver enzyme value ($n = 103$); or diagnostic symptoms alone ($n = 298$). As shown in Supplemental Table 2, the risk of any adverse maternal or perinatal outcome is markedly greater for Bolivian HELLP diagnoses than for Bolivian diagnoses of PE with abnormal labs or severe hypertension, and least (but still significantly elevated) in those with diagnostic symptoms alone or undetermined criteria. Similarly, the risk of any adverse maternal or perinatal outcome was greater for ACOG severe PE with *vs.* without HELLP and, among those without HELLP, showed a gradient whereby risk was greater when any abnormal lab value or severe hypertension was present than for those whose diagnosis was based on diagnostic symptoms alone. Supplemental Table 3 details the individual adverse outcomes for subsets of women whose diagnoses differed between the two classificatory systems. Women without HDP by Bolivian criteria but having severe PE according to ACOG guidelines were more often admitted to the ICU, had more adverse maternal outcomes, more often delivered SGA babies, and tended for their babies to be treated more often with supplemental oxygen. Babies born to women diagnosed as GH by Bolivian criteria who met ACOG guidelines for severe PE were also more often admitted to the NICU.

Discussion

We found that Bolivia and ACOG diagnostic criteria agreed well with respect to identifying women without HDP or the end-stage disease, eclampsia. But there was considerable disagreement for GH, PE, and severe PE diagnoses such that, overall, only 27% of Bolivian HDP diagnoses agreed with ACOG guidelines and greatly underestimated the number of women with severe PE. ACOG guidelines permitted more HDP diagnoses to be made

before admission for delivery and, while both classificatory systems showed that HDP raised adverse-outcome risks and did so to a greater extent for mother than baby, application of ACOG criteria provided a more graded assessment of risk and better targeted HDP cases terminating in maternal death.

Differences between Bolivian diagnoses and those recommended by ACOG arose chiefly as the result of ACOG's recognition of a broader range of severe features. Specifically, the only severe feature for Bolivian PE diagnoses was HELLP whereas ACOG guidelines included severe hypertension; any abnormal serum creatinine, liver enzyme or platelets value; or any diagnostic symptom. Other differences were due to the inclusion of some women with proteinuria in the Bolivian GH category, and the use of slightly different criteria for HELLP; that is, both high liver enzymes and low platelets were required by ACOG but only two of three abnormal liver enzyme, platelet, or LDH values for a Bolivian diagnosis.

Like previous studies, we found women with HDP to be older, more often obese, primiparous, with fewer years of schooling, and history of PE or eclampsia.[20] The ~5% crude HDP incidence rate using either Bolivian or ACOG criteria was slightly higher than the 4% global LMIC rate and much higher than the 0.5% all-country rate.[8,20] One contributor may have been the high altitude at which our study was conducted. In Colorado, the only high-altitude region where complete birth records are available, high-altitude residence increases the incidence of the full spectrum of HDP by 33%.[13] Several studies in Bolivia or elsewhere in Latin America also report an altitude-related rise.[11,12,21] The chronic hypoxia of residence at high altitude interferes with the normal maternal vascular adjustments to pregnancy[22] and lower arterial O_2 saturation is a component of the fullPIERS model for predicting adverse maternal outcomes.[23] Thus, high-altitude residents may be especially susceptible to HDP and could benefit from therapies such as low-dose aspirin or other treatments aimed at preventing or delaying HDP onset.

Currently, nearly all maternal deaths worldwide occur in LMIC, with the proportion due to HDP being higher in Latin America than in African or South Asian LMICs.[2,3,5,8,24–26] Since ACOG and other international agencies updated their diagnostic criteria ~10 years ago to identify those most closely associated with maternal death[4,6,17] and the ACOG guidelines have been officially adopted in Bolivia,[7] our study was designed to address whether ACOG guidelines have been incorporated into practice and, if not, whether their adoption would improve detection of adverse maternal or perinatal outcomes. We chose Bolivia since, while HDP is known to be common[8–10,27] and maternal and perinatal mortality rates are among the highest in Latin America, little is known regarding the diagnostic criteria being used in Bolivia or their ability to predict adverse outcomes.

The strengths of our study stemmed from its detailed analyses of prenatal, delivery and immediate postpartum records for all HDP discharge diagnoses at the three largest hospitals in the La Paz-El Alto metropolitan region, which together deliver 40% of all hospital births. We also reasoned that the increased incidence of HDP at high altitude would enable us to collect sufficient HDP cases over one year and hence avoid artefacts introduced by changes in other factors during the study period. Another advantage was that Bolivia's *Seguro Integral de Salud* (Comprehensive Health Care System) began in 2013 increased access to

prenatal care and, in turn, enabled us to acquire more prenatal data than in some reports. To overcome the difficulties for detecting maternal or perinatal deaths when patients are transferred to other hospital units,[28] we used Ministry of Health records to identify such deaths and then reviewed the hospital emergency, intensive care, or paediatric department records to obtain the adverse outcome data required. Unlike other LMIC studies,[20,25,26,29] we considered the full spectrum of HDP and separated adverse maternal and perinatal outcomes which enabled us to determine that maternal and perinatal risks rose progressively with the severity of HDP and were greater for given diagnoses for mother than baby. Finally, while low platelets or severe hypertension have been shown to raise maternal mortality risk in Latin America,[30] our observation that diagnostic symptoms alone raised risks was novel.[31]

Our study also suffered from certain limitations. As in other retrospective case-control studies, ours was subject to selection bias and the possibility that cases and controls were not representative of the same population. Additionally, identifying cases and controls by discharge diagnoses can be misleading, subject to recall bias by whoever has filled out the CLAP form or hospital record, and the controls may have had pregnancy complications other than HDP. Difficulties in record-keeping also limited the availability or accuracy of the information available. In particular, the CLAP form from which we acquired much of our prenatal data lists HELLP as the only kind of severe PE and thus likely resulted in women with severe hypertension or diagnostic symptoms being classified as PE or GH. Logistic regression can only demonstrate association, not causation, and hence other factors could have been responsible for the adverse outcomes observed. Missing data were also common: less than a third of women had first trimester visits, most lacked data for pre-pregnancy blood pressure or other comorbidity data (e.g., heart or renal disease), 18% of prenatal visits lacked any diagnostic-symptom data, and laboratory values were infrequently obtained since outpatient prenatal clinics cannot perform even dipstick proteinuria determinations. Thus, only 13% of all women were tested for proteinuria at any time during pregnancy, and serum creatinine, platelets or liver enzyme tests were performed in only 15% of HDP cases before admission for delivery.

In summary, we concluded that the criteria used for diagnosing HDP in La Paz-El Alto, Bolivia appropriately identified women at the two extremes of risk for adverse outcomes; namely, those who remained normotensive during pregnancy or developed eclampsia. However, Bolivian diagnoses for GH, PE, or severe PE did not conform to ACOG guidelines and resulted in an underestimation of severe PE cases. These findings strongly recommend the usage of ACOG guidelines to better identify those mothers at greatest risk of adverse outcomes in La Paz-El Alto and perhaps elsewhere in Bolivia. While diagnosis itself is not a treatment, accurate diagnoses are essential for closer monitoring of pregnancies likely to develop life-threatening conditions and for the allocation of scarce healthcare resources. Implementing ACOG guidelines could (1) increase the number of diagnoses made before admission for delivery, thus affording time for closer monitoring; (2) provide a more graded assessment of risk; and (3) better target those pregnancies likely to terminate in maternal death. Adoption of ACOG guidelines at the La Paz-El Alto hospitals studied here requires wider laboratory testing, particularly during the third trimester when visits are carried out at the outpatient clinics at the hospital delivery site where laboratory facilities are

available, and closer monitoring as well use of symptoms as a referral criterion for the conduct of laboratory tests of organ-system dysfunction. Future, prospective studies are also required with comprehensive documentation of blood pressure, proteinuria, diagnostic symptoms, laboratory tests of organ dysfunction, foetal deaths, and maternal as well as perinatal outcomes to define the incidence of PE and other HDP in Bolivia, identify the diagnostic criteria most predictive of adverse outcomes, inform clinical decisions as to when to deliver, and reduce Bolivia's alarmingly high maternal and infant mortality rates. Given the increased incidence of HDP at high altitudes[13] and the consequent reduction in the number needed to treat,[32] such locales are also ideal for determining the efficacy of low-dose aspirin or novel HDP therapies. Follow-up studies in mothers with HDP and their offspring are also important given the known association between HDP and susceptibility to cardiovascular or other diseases later in life, especially given Bolivia's very high rate of maternal cardiovascular disease.[10] Finally, better coordination among prenatal care providers, obstetric, emergency, and perinatal services is also essential for earlier diagnosis, identification of pregnancies at greatest risk and tracking of adverse outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Duley L The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–137. [PubMed: 19464502]

2. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–e333. [PubMed: 25103301]

3. ACOG practice bulletin no. 222 gestational hypertension and preeclampsia. Obstet Gynecol. 2020;135(6):e237–e260. Jun. [PubMed: 32443079]

4. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. WHO guidelines approved by the guidelines review committee. Geneva 2011.

5. Gestational hypertension and preeclampsia: ACOG practice bulletin summary, number 222. Obstet Gynecol. 2020;135(6):1492–1495. [PubMed: 32443077]

6. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72 (1):24–43. [PubMed: 29899139]

7. Giachini FR, Galaviz-Hernandez C, Damiano AE, et al. Vascular dysfunction in mother and offspring during preeclampsia: contributions from Latin-American countries. Curr Hypertens Rep. 2017;19(10):83. [PubMed: 28986756]

8. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7. [PubMed: 23746796]

9. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9947):980–1004. [PubMed: 24797575]

10. Roser M Maternal mortality: our world in data; 2019 [Available from: https://ourworldindata.org/maternal-mortality.

11. Keyes LE, Armaza JF, Niermeyer S, Vargas E, Young DA, Moore LG. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. Pediatr Res. 2003;54(1):20–25. [PubMed: 12700368]

12. Campero Nava A, Parada Barba C, Mamani Huallpa G, Rios Vacaflor M, Flores Velasco O, Enriquez Nava M, Salud M. Estudio Nacional de Mortalidad Materna 2011 Bolivia: Resumen Ejecutivo. La Paz, BO: Ministerio de Salud; 2016:1–98. editor.

13. Bailey BA, Euser AG, Bol K, Julian CG, Moore LG. High-altitude residence alters blood-pressure course and increases hypertensive disorders of pregnancy. J Matern Fetal Neonatal Med. 2020;30:1–8.

14. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344–349. [PubMed: 18313558]

15. Fescina RH, Butrón B, De Mucio B, et al. Sistema Informatico Perinatal: Historia Clínica Perinatal, Instrucciones de llenado y definición de términos: Publicación Científica CLAP/SMR; 2017 Junio 2017.

16. Myatt L, Roberts JM, Redman CWG. Global Pregnancy C. Availability of COLLECT, a database for pregnancy and placental research studies worldwide. Placenta. 2017;57:223–224. [PubMed: 28864015]

17. ACOG. Hypertension in pregnancy. Report of the American college of obstetricians and gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122–1131. [PubMed: 24150027]

18. ACOG. Committee opinion no 700: methods for estimating the due date. Obstet Gynecol. 2017;129(5):e150–e1e4. [PubMed: 28426621]

19. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol. 2014;124(1):16–22. [PubMed: 24901276]

20. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLoS One. 2014;9(3):e91198. [PubMed: 24657964]

21. Tejera E, Sanchez ME, Henriquez-Trujillo AR, Perez-Castillo Y, Coral-Almeida M. A population-based study of preeclampsia and eclampsia in Ecuador: ethnic, geographical and altitudes differences. BMC Pregnancy Childbirth. 2021;21(1):116. [PubMed: 33563238]

22. Moore LG. Reproductive challenges at high altitude: fertility, pregnancy and neonatal well-being. Reproduction. 2021;161(1):F81–F90. [PubMed: 33112770]

23. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219–227. [PubMed: 21185591]

24. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891–900. [PubMed: 15752534]

25. Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization multicountry survey on maternal and newborn health. BJOG. 2014;121(Suppl 1):14–24.

26. Vogel JP, Souza JP, Mori R, et al. Maternal complications and perinatal mortality: findings of the World Health Organization multicountry survey on maternal and newborn health. BJOG. 2014;121(Suppl 1):76–88. [PubMed: 24641538]

27. Roser M Our world in data: neonatal mortality 2017 [Available from: https://ourworldindata.org/grapher/neonatal-mortality-wdi.

28. Villar J, Say L, Lindheimer M, et al. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. Int J Gynecology Obstet. 2004;85(S1):S28–S41.

29. Nakimuli A, Nakubulwa S, Kakaire O, et al. The burden of maternal morbidity and mortality attributable to hypertensive disorders in pregnancy: a prospective cohort study from Uganda. BMC Pregnancy Childbirth. 2016;16:205. [PubMed: 27492552]

30. Vigil-De Gracia P, Rojas-Suarez J, Ramos E, et al. Incidence of eclampsia with HELLP syndrome and associated mortality in Latin America. Int J Gynaecol Obstet. 2015;129(3):219–222. the official organ of the International Federation of Gynaecology and Obstetrics. [PubMed: 25687238]

31. Thangaratinam S, Gallos ID, Meah N, et al. How accurate are maternal symptoms in predicting impending complications in women with preeclampsia? A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2011;90(6):564–573. [PubMed: 21355860]

32. Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia. Cochrane Database Syst Rev. 2000:(2):CD000492. [PubMed: 10796208]

Research in context panel

Evidence before this study

Hypertensive disorders of pregnancy (HDP) are leading causes of maternal and perinatal deaths especially in low- to middle-income countries (LMIC) where nearly all deaths occur. The American College of Obstetricians and Gynecologists (ACOG) and other international agencies updated diagnostic guidelines a decade ago to align HDP signs and symptoms with those most closely associated with maternal death. While HDP accounts for more maternal deaths in Latin America than elsewhere in the world, whether ACOG criteria have been incorporated into clinical practice or improved the detection of adverse outcomes in the region remains unknown.

Added value of this study

We chose Bolivia, a Latin American LMIC with one of the highest maternal and perinatal mortality rates, and its adjacent cities of La Paz-El Alto as our study site. Prenatal and delivery hospital records were examined for all HDP discharge diagnoses at the three largest delivery hospitals (cases) and twice as many without such diagnoses (controls) during a one-year period. We found that local criteria agreed with ACOG guidelines for identifying women with the end-stage disease, eclampsia, but for only 27% of all HDP (i.e., gestational hypertension, preeclampsia, severe preeclampsia with HELLP [haemolysis, low platelets, high liver enzymes] or without HELLP syndrome, eclampsia). HDP increased risks of any adverse maternal- or perinatal-outcome according to both classificatory systems, but ACOG guidelines improved the ability to diagnose HDP prior to admission for delivery, grade maternal risk, and target those HDP terminating in maternal death.

Implications of all the available evidence

Educational and other efforts are required to better acquaint health-care providers in community outpatient clinics and delivery hospitals with ACOG diagnostic guidelines and to ensure their implementation. Also needed is revision of the CLAP prenatal form to include severe preeclampsia without HELLP, better documentation of diagnostic criteria, more frequent laboratory testing, and more complete recording of laboratory-test results and diagnostic symptoms. Such information is needed to define the incidence of HDP in Bolivia, help identify the diagnostic criteria most predictive of adverse outcomes, inform clinical decisions as to when to deliver, and reduce Bolivia's alarmingly high maternal and infant mortality rates.
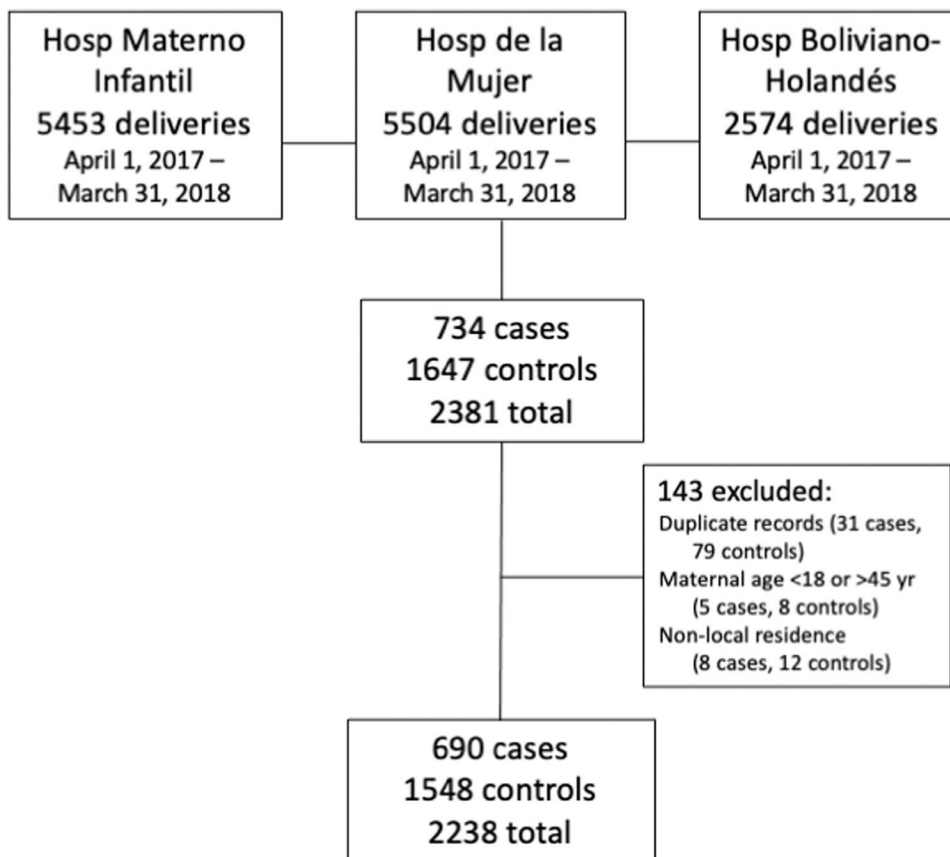
Figure 1.

Flow chart showing selection of study sample. Discharge diagnoses were examined at the three largest delivery hospitals in the adjacent cities of La Paz and El Alto, Bolivia for the period April 1, 2017 through March 31, 2018. All women with a discharge diagnosis of any HDP was selected as a case. Approximately twice as many without such diagnoses and who delivered immediately before or after the HDP case were selected as controls. Inclusion criteria were maternal age at delivery greater than 18 and less than 45 years, singleton pregnancy, and residence in either La Paz or El Alto. A total of 143 records were excluded due to duplicate records ($n = 110$), non-qualifying maternal age at delivery ($n = 13$) or non-local residence ($n = 20$).

A.

Bolivian distribution

☐ No HDP (n=1548)
☐ GH (n=349)
☐ PE (n=294)
☐ Severe PE (n=28)
■ Eclampsia (n=19)

Total=2238, 690 with HDP

ACOG distribution

☐ No HDP (n=1492)
☐ GH (n=234)
☐ PE (n=20)
☐ Severe PE (n=473)
■ Eclampsia (n=19)

Total=2238, 746 with HDP
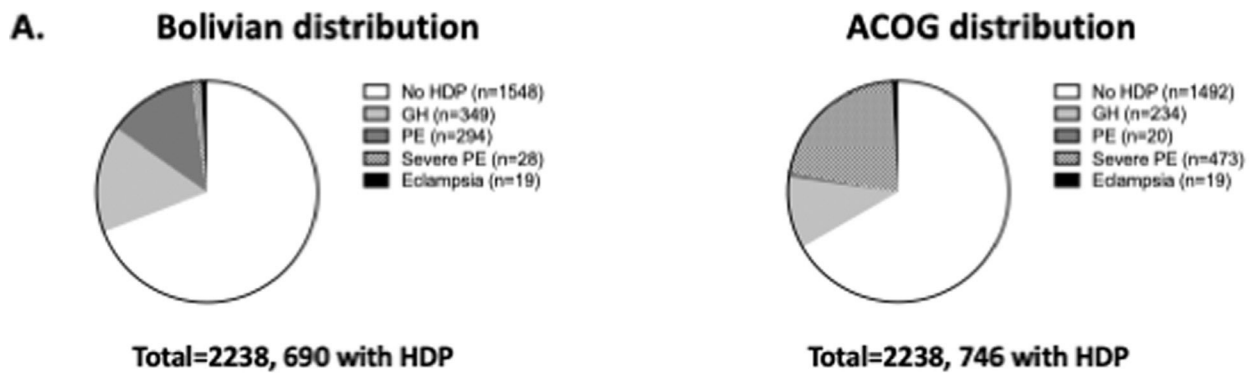
B. Crosstabulation and accuracy analysis

		ACOG Guidelines					
		No HDP	GH	PE	Severe PE	Eclampsia	Row totals
Bolivian Diagnoses	No HDP	**1436**	78	3	31	0	1548
	GH	49	**129**	7	164	0	349
	PE	7	27	**10**	250	0	294
	Severe PE (HELLP)	0	0	0	**28**	0	28
	Eclampsia	0	0	0	0	**19**	19
Column totals		1492	234	20	473	19	690, HDP / 746, HDP
Sensitivity, %		96	55	50	6	100	
Specificity, %		85	89	87	100	100	
Cohen's K		0.83	0.36	0.05	0.09	1.00	
Agreement		Good	Poor	Very poor	Very poor	Perfect	
+ likelihood ratio		6.4 [5.4, 7.6]	5.0 [4.2, 6.0]	3.9 [2.5, 6.1]	---	---	
- likelihood ratio		0.0 [0.0, 0.1]	0.5 [0.4, 0.6]	0.57 [0.4, 0.9]	0.9 [0.9, 1.0]	0 [0, 0.39]	

Figure 2.

Distribution of the diagnoses for 2238 study subjects (Panel A), crosstabulation and accuracy analysis of Bolivian diagnoses vs. those arrived at by application of ACOG diagnostic guidelines (Panel B). Panel A shows that similiar numbers or women with no HDP and the same number of women with eclampsia are identified but considerable differences exist with respect to the numbers with GH, PE or severe PE. The bolded, boxed values in the crosstabulation in Panel B indicate the numbers of women whose Bolivian and ACOG diagnoses agreed: overall 93% ($n = 1436$) of women with no HDP agreed with ACOG guidelines but only 27% ($n = 186$) of the 690 Bolivian HDP diagnoses. With respect to GH or PE, the agreement between Bolivian and ACOG diagnoses was poor to very poor, with the ability for Bolivian diagnoses to rule in these diagnoses being modest and to rule them out being poor. All women with a Bolivian diagnosis of severe PE or eclampsia met the respective ACOG guidelines, preventing calculation of the positive likelihood ratio, but many additional women met ACOG guidelines for severe PE which indicated that the Bolivian diagnoses were ineffective in ruling out

severe PE. All women with a Bolivian diagnosis of eclampsia also met ACOG eclampsia criteria, yielding perfect agreement and a very good negative likelihood ratio. Abbreviations: GH=gestational hypertension; HELLP=haemolysis, elevated liver enzymes, low platelets; K=kappa; −=negative; +=positive; PE=preeclampsia.

Table 1:

Maternal and infant characteristics for women with discharge diagnoses at Bolivian study sites of HDP (cases) or of no HDP (controls).

	CASES *n* = 690	CONTROLS *n* = 1548	p value
Maternal characteristics			
Age at delivery, *n*	688	*1548*	
18–29 yr., *n* (%)	347 (50%)	843 (54%)	<0·05
30–39 yr., *n*(%)	293 (42%)	639 (42%)	
>40 yr., *n*(%)	48 (7%)	66 (4%)	
Parity, no. prior deliveries, *n*	*682*	*1538*	
0, *n*(%)	290 (42%)	531 (34%)	<0·01
1, 2, *n*(%)	287 (42%)	782 (51%)	
>3, *n*(%)	105 (15%)	225 (15%)	
Education, *n*	*645*	*1468*	
None or primary only, *n*(%)	80(12%)	145 (9%)	<0·0001
Secondary, *n*(%)	453 (70%)	1007 (69%)	
University, *n*(%)	112 (17%)	316(21%)	
Prepregnant body mass index, *n*	*438*	*1000*	
<25 k/m²	148 (34%)	434 (44%)	<0·0001
25.0–29.9 k/m²	162 (37%)	403 (40%)	
30–34.9 k/m²	90 (20%)	121 (12%)	
35 k/m²	38 (8%)	42 (4%)	
Health history of	*573*	*1300*	
Preeclampsia or Eclampsia, *n*(%)	36 (6%)	9 (1%)	<0·0001
Number of prenatal visits, *n*	*690*	1548	
0 or 1, *n*(%)	128(19%)	235 (15%)	NS[§]
2–5, *n*(%)	474 (69%)	1072 (69%)	
>6, *n*(%)	88(13%	241 (16%)	
Caesarean section, *n*(% all deliveries)	494 (72%)	688 (44%)	<0·0001
Death, *n*(%)	8(1.2%)	2 (0.1%)	<0·01
Infant characteristics			

	CASES n = 690	CONTROLS n = 1548	p value
Birth weight, gm (n)	2872 ± 762 (679)	3234 ± 469(1541)	<0·0001
Gestational age at delivery, wk (n)	37·6 ± 3·0(687)	39±1 ± 1·7(1545)	<0·0001
Male sex, $n(\%)$	368 (54%)	765 (50%)	NS§
Perinatal mortality, $n(\%)$	20 (2.9%)	14 (0.9%)	<0·001
Stillbirths	10(1.5%)	11 (0.7%)	NS§
Early neonatal deaths	10(1.5%)	3 (0.2%)	<0·001

Notes: Numbers of women with data for each variable are shown in italics. Values are numbers and percentages in parentheses for categorical variables with the particular trait or means ± standard deviations with sample sizes in parentheses for continuous variables. Two-tailed p values <0.05 obtained by chi-squared or by t-tests, respectively, are shown. NS=not significant, NS

§= 0.05 p<0.10.

Table 2:

Diagnostic characteristics and adverse outcomes for hypertensive disorders of pregnancy as classified by Bolivian or ACOG criteria.

	BOLIVIAN				BOLIVIAN or ACOG	ACOG			
	No HDP n = 1548	GH n = 349	PE n = 294	Severe PE (HELLP) n = 28	Eclampsia n = 19	No HDP n = 1492	GH n = 234	PE n = 20	Severe PE n = 473
Diagnostic characteristics									
Hypertension, prenatal	42 (3%)	92 (28%)	107 (40%)	7 (29%)	2 (18%)	4 (0.3%)	66 (30%)	7 (37%)	171 (39%)
At delivery	71 (5%)	283 (81%)	272 (93%)	26 (93%)	12 (79%)	8 (0.5%)	194 (83%)	20(100%)	430 (92%)
Postpartum	45 (3%)	90 (26%)	148 (52%)	17 (65%)	10 (67%)	42 (3%)	40(18%)	12 (60%)	206 (45%)
Sev pren hypertension	7 (0.5%)	8 (2%)	17 (6%)	4 (16%)	1 (9%)	3 (0.2%)	0	0	33 (8%)
At delivery	0	9 (3%)	19 (6%)	5 (18%)	3 (20%)	0	0	0	33 (8%)
Postpartum	0	4 (1%)	8 (3%)	5 (19%)	1 (6%)	0	0	0	17 (4%)
Any proteinuria	4 (14%)	28 (25%)	74 (54%)	11 (73%)	2 (29%)	5 (14%)	0	20(100%)	92 (44%)
Diag symptoms, pren	38 (3%)	29 (9%)	22 (8%)	1 (4%)	0	41 (3%)	0	0	49(11%)
At delivery	44 (3%)	132 (38%)	222 (76%)	23 (82%)	13 (87%)	47 (3%)	0	0	374 (80%)
Postpartum	43 (3%)	29 (9%)	62 (22%)	10 (38%)	11 (65%)	39 (3%)	0	0	105 (23%)
Any abnormal labs	26 (2%)	40 (12%)	57 (20%)	22 (79%)	10 (59%)	26 (2%)	0	0	119(26%)
Delivery week	39·1 ±1·7[a]	38·7±2·0[b]	37·0±3·2[c]	32·7±3·9[d]	35·7±2·8[c, cc]	39·0±1·7[aa]	38·9±1·8[aa]	37·1±3·5[bb]	37·3±3·2[bb]
Diagnosis predelivery	..	25 (7%)	4(1%)	0	0	..	27 (12%)	2 (10%)	45 (9%)
At delivery	..	322 (92%)	282 (96%)	19 (68%)	13 (68%)	..	207 (88%)	18(90%)	427 (87%)
Postpartum	..	2 (0.6%)	8 (3%)	9 (32%)	6 (32%)	..	0	0	20 (4%)
Anti-Hypertensive Rx	114(7%)	194 (56%)	248 (84%)	27 (96%)	16 (84%)	126 (8%)	70 (29%)	14(70%)	373 (79%)
MgSO4 Rx	32 (2%)	73 (21%)	192 (65%)	23 (82%)	16 (84%)	39 (3%)	28 (12%)	2 (10%)	251 (53%)
Adverse maternal outcomes									
Caesarean delivery	16 (2%)	12 (6%)	20 (8%)	6 (21%)	5 (33%)	15 (2%)	5 (4%)	1 (7%)	33 (9%)
ICU admission	6 (0.4%)	1 (0.3%)	4 (1%)	11 (58%)	15 (83%)	5 (0.3%)	1 (0.4%)	0	16 (4%)
Prolonged hosp	16(1%)	15 (4%)	23 (8%)	11 (41%)	3 (21%)	17(1%)	4 (2%)	0	44 (10%)
Death	2 (0.1%)	0	1 (0.3%)	2 (7%)	5 (26%)	0	0	0	5 (1%)
Any adverse outcome	35 (2%)	24 (7%)	44(15%)	16 (57%)	16 (84%)	34 (2%)	9 (4%)	1 (5%)	75 (16%)
Adverse outcomes, #	0·03±0·18[a]	0·08±0·31[b]	0·16±0·41[c]	1·07±1·09[d]	1·47±1·07[e,cc]	0·02±0·17[aa]	0·04±0·22[aa]	0·05±0·22[aa]	0·21±0·52[bb]

	BOLIVIAN				BOLIVIAN or ACOG	ACOG			
	No HDP $n = 1548$	GH $n = 349$	PE $n = 294$	Severe PE (HELLP) $n = 28$	Eclampsia $n = 19$	No HDP $n = 1492$	GH $n = 234$	PE $n = 20$	Severe PE $n = 473$
Adverse perinatal outcomes									
Preterm delivery	117 (8%)	50 (14%)	109 (37%)	23 (82%)	12 (67%)	121 (8%)	22 (9%)	8 (40%)	148 (32%)
SGA	209 (14%)	72 (21%)	82 (28%)	12 (43%)	2 (12%)	203 (14%)	40 (17%)	6 (30%)	1261 (27%)
5 min APGAR <7	8 (0.5%)	4 (1%)	9 (3%)	3 (11%)	1 (6%)	9 (0.6%)	2 (1%)	1 (5%)	12 (2%)
Supplemental O_2	122 (8%)	44 (13%)	43 (15%)	9 (33%)	2 (14%)	116 (8%)	27 (12%)	1 (5%)	74 (16%)
NICU admission	28 (2%)	24 (7%)	60 (20%)	15 (56%)	8 (53%)	30 (2%)	8 (3%)	2 (10%)	87 (19%)
Perinatal death	13 (0.8%)	7 (2%)	8 (3%)	1 (4%)	2 (13%)	13 (0.9%)	3 (1%)	0	13 (3%)
Any adverse outcome	411 (27%)	138 (40%)	175 (60%)	28 (100%)	15 (79%)	402 (27%)	74 (32%)	12 (60%)	264 (56%)
Adverse outcomes, #	032±060[a]	058±087[b]	106±114[c]	225±100[d]	142±096[e,bb]	033±061[aa]	044±072[aa]	090±091[bb]	097±114[bb]

Notes: Shown are the number and percentages (in parentheses) or X ± standard deviation for women in each diagnostic group. Different superscripts designate different values between groups within each system by ANOVA. All other characteristics differed among Bolivian or among ACOG categories by Chi-squared analysis. Abbreviations: Diag=diagnostic; HELLP=haemolysis, elevated liver enzymes and low platelets; hosp=hospitalization; ICU=intensive\care unit; NICU=neonatal ICU; No.=number; Pren=prenatal; Rx=medication; Sev=severe; SGA=small for gestational age.

Table 3:

Binary logistic regression analyses for the association between any adverse maternal or perinatal outcomes (dependent variable) and Bolivian or ACOG HDP diagnostic categories (independent variable).

A. ANY ADVERSE MATERNAL OUTCOME

| | BOLIVIAN CATEGORIES | | | | | | ACOG CATEGORIES | | | | | | |
Group	B	S.E.	Wald	df	P	Adjusted OR	Group	B	S.E.	Wald	df	P	Adjusted OR
No HDP, *n* = 1548 (reference)			172·68	4	0·000	..	No HDP, n= 1492 (reference)			143·0	4	0·000	..
GH, *n* = 349	116	0·27	18·21	1	0·000	3·2 (1·9,5·4)	GH, *n* = 234	0·54	0·38	2·00	1	0·157	1·7 (0·8, 3·6)
PE, all, *n* = 294	203	0·24	73·58	1	0·000	7·6 (4·8,12·1)	PE, *n* = 20	0·81	1·04	0·61	1	0·434	2·2 (0·3,17·3)
Severe PE, *n* = 28	4·05	0·42	93·89	1	0·000	57·6 (25·4,130·9)	Severe PE, all, *n* = 473	2·09	0·21	95·03	1	0·000	8·1 (5·3,12·3)
Eclampsia, *n* = 19	5·44	0·65	69·63	1	0·000	230·6 (64·2, 827·4)	Eclampsia, *n* =19	5·43	0·65	69·29	1	0·000	228·7(63·6, 821·9)
Constant	−1·23	0·16	58·84	1	0·000	0·3	Constant	−1·98	0·2	61·08	1	0·000	0·14

B. ANY ADVERSE PERINATAL OUTCOME

| | BOLIVIAN CATEGORIES | | | | | | ACOG CATEGORIES | | | | | | |
Group	B	S.E.	Wald	df	P	Adjusted OR	Group	B	S.E.	Wald	df	P	Adjusted OR
No HDP, *n* = 1548 (reference)			132·93	4	0·000		No HDP, *n* = 1492 (reference)			144·82	4	0·000	–
GH, *n* = 349	0·59	0·12	0·000	1	0·000	1·8 (1·4,2·3)	GH, *n* = 234	0·23	0·15	2·21	1	0·137	1·2 (0·9,1·7)
PE, all, *n* = 294	1·40	0·13	0·000	1	0·000	4·1 (3·1,5·3)	PE, *n* = 20	1·40	0·46	9·30	1	0·002	4·1 (1·6,10·0)
Severe PE, *n* = 28	..	..	..	..	..	..	Severe PE, all, *n* = 473	1·23	0·11	126·54	1	0·000	3·4 (2·8,4·2)
Eclampsia, *n* = 19	2·34	0·57	17·10	1	0·000	10·4 (3·4,31·4)	Eclampsia, *n* =19	2·32	0·57	16·80	1	0·000	10·2 (3·4,30·8)
Constant	4·29	1519	0·000	1	0·998	73·2	Constant	0·04	0·15	0·07	1	0·797	1·0

Parentheses indicate the 95% confidence limits for odds ratios. ORs that could not be calculated are indicated by midline dots and were due either to the women with no HDP being the reference category or because all Bolivian Severe PE cases (all had HELLP) had at least one adverse perinatal outcome. Abbreviations: B=beta coefficient; df=degrees of freedom; GH=gestational hypertension; HDP=hypertensive disorders of pregnancy; HELLP=haemolysis, high liver enzymes, low platelets syndrome; OR=odds ratios; PE = preeclampsia; S.E.=standard error.