Pre-eclampsia & Eclampsia

Literature Review: Antihypertensive Medication in Pregnancy

An Update from the 2011 *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*

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Acknowledgments

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This Literature Review covers the years 2004-2014 and does not survey later contributions to the scholarship.

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List of Abbreviations

DDD	Defined Daily Dose
EML	Essential Medicines List
GDP	Gross Domestic Product
HTN	Hypertension
ICD	International Classification of Diseases
MCHIP	Maternal and Child Health Integrated Program
NEML	National Essential Medicines List
NHANES	National Health and Nutrition Examination Survey
PE	Pre-Eclampsia
PIH	Pregnancy-Induced Hypertension
PRAMS	Pregnancy Risk Assessment Monitoring System
QoC	Quality of Care
RDS	Respiratory Distress Syndrome
SAMM	Severe Acute Maternal Morbidity
WHO	World Health Organization

Scope of the Project

Hypertensive disorders of pregnancy are an important cause of maternal and neonatal morbidity globally, including maternal and fetal death. Pre-eclampsia and eclampsia are the most severe hypertensive disorders in pregnancy. The majority of mortality attributable to these conditions could be prevented through earlier diagnosis, monitoring, and effective management. In 2011, the World Health Organization (WHO) released its recommendations for the treatment and prevention of pre-eclampsia/eclampsia (WHO 2011).

Related to antihypertensive medications, WHO recommended that women who are treated with antihypertensive drugs prenatally be continued on treatment postpartum (very low evidence, strong recommendation), and to treat women with severe hypertension during pregnancy with antihypertensive medications (very low evidence, strong recommendation). Uncertainty remains, however, about the current use of antihypertensive medications and their impact during pregnancy.

The purpose of this project was to review the current use of WHO-recommended antihypertensive medications in pregnancy to prevent pre-eclampsia and manage hypertension and to update the science about the guidelines using meta-analyses, reviews, and primary studies since the publication of the latest guidelines. Estimates were also obtained from published literature for the prevalence of chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia in low-resource settings, where possible, as well as in developed countries, as the quality of data from most resource-poor settings is of concern. Finally, data were gathered from multiple sources to estimate the unmet need and potential demand for antihypertensive medications in pregnancy, with special emphasis on low-resource settings.

This report first describes prevalence estimates from both population-based and clinic- and hospital-based studies of hypertension in pregnancy, as well as among women of childbearing age. An update of studies and meta-analyses relevant to the guidelines for use of antihypertensive medications in pregnancy is then presented. A discussion follows of a non-systematic literature review of estimates of the potential demand for and availability of antihypertensive medication in resource-poor settings.

The benefit of antihypertensive therapy in pregnancy to prevent pre-eclampsia continues to be widely debated. The review, entitled *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*, provides a thorough summary of the relevant literature through its time of publication in 2011. This report summarizes the WHO recommendations and describes all relevant scientific studies since the publication of the WHO's recommendations.

Population-Based Estimates of Hypertension during Pregnancy

Population-based estimates of chronic hypertension and any hypertensive disorders among women during pregnancy in low-resource settings are not widely available. However, several large, population-based studies with data about hypertension disorders during pregnancy have been conducted in high-resource settings, including the United States, Australia, Sweden, Western Europe, Canada and several US states. Data related to prevalence were obtained from these studies for rates of chronic hypertension (HTN), pre-eclampsia (PE), and all hypertensive disorders in pregnancy. In addition, a meta-analysis was undertaken based on studies in which data were available on prevalence rates and denominators for the rates (the number of women for which prevalence was based); the majority of studies included the numerator data as well.

We identified studies in which prevalence estimates were available for chronic HTN, gestational HTN, PE, and all hypertensive disorders in pregnancy using a variety of approaches. We first undertook an extensive search of PubMed for studies of HTN in pregnancy as well as searches of pregnancy databases in the US and other developed countries, such as the EURO-PERISTAT project and the Pregnancy Risk Assessment Monitoring System (PRAMS). PRAMS data for chronic diseases such as HTN are reported for specific states that participate in PRAMS.

Search terms for PubMed included pregnancy and HTN, chronic HTN, gestational HTN and PE; incidence and prevalence; and population-based. Clinical queries (diagnosis category) were also queried in PubMed with these search terms. Finally, the search terms were used along with terms such as maternal mortality and neonatal mortality and morbidity to obtain studies for which mortality or morbidity rates were estimated for women with and without hypertensive disorders. Inclusion of the various terms yielded studies not only for which prevalence was the main focus but also other studies for which the main objective was not prevalence estimates. The additional studies also provided data to estimate rates of hypertensive disorders in pregnancy for a meta-analysis we conducted.

Our primary focus was population-based studies for which the number of women or percentage of women with HTN was reported along with the sample size for the study (total number of at risk women/births in the study population). The abstracts of all potential studies were initially reviewed for this information and selected if the study was determined to be likely to provide data about prevalence. Related citations and the reference lists of identified studies were also reviewed along with their abstracts. All studies for which data appeared to be available, regardless of quality, were initially reviewed. We identified population-based studies, multi-facility studies and single-facility studies; the latter studies provided data largely from low-resource countries. A concurrent search was undertaken independently for high- (by Donna Strobino) and low-resource (by Mahua Mandal) countries. The results of the concurrent searches were compared and combined to increase completeness of studies.

Data sources used in the population-based studies included: inpatient hospital or hospital discharge data for all births in the population, sometimes linked with birth registries or birth certificates; birth certificates or birth registries; and to a lesser extent, postpartum surveys linked with birth certificate data. Definitions of hypertensive disorders varied across studies; many were based on International Classification of Diseases (ICD)-9 or ICD-10 codes when hospital discharge or inpatient data were used. Reports on birth certificates or birth records were generally based on criteria used for reporting data about hypertensive disorders on standard certificates (Osterman et al. 2009); the definitions were updated in the 2003 revision of the US birth certificate, but most studies included in this review were based on the 1989 standard certificate. PRAMS data were based on mothers' reports using the PRAMS standard items about mothers' reports of high blood pressure (HTN) in the three months prior to pregnancy or high blood pressure (including pregnancy-induced HTN [PIH], PE or toxemia) during pregnancy.

We identified specific studies in which data were available to undertake meta-analysis estimates for three HTN measures during pregnancy: chronic HTN, PE, and all hypertensive disorders in pregnancy. We used random effects estimation because of heterogeneity of the sample characteristics across studies. These

estimates are reported below for each HTN outcome for studies in which data for the outcome were reported. Some studies, as noted below, were excluded from the estimates due to concerns about the quality of the data, the diagnostic criteria or definitions used or missing information about sample size.

Estimates of Chronic Hypertension, Pre-Eclampsia and Any Hypertensive Disorder in Pregnancy

Chronic Hypertension

We identified 13 studies with population-based estimates of the percentage of women with chronic HTN who had live births, eight from developed countries (three conducted in the United States), and the remaining four from states in the United States. Two studies were not included in the meta-analysis and are not shown in Table 1 (Lawler et al. 2007; Hayes et al. 2010). The population in Lawler et al. conducted in Western New York overlapped with data from the entire state reported in Tanaka et al. (2007) and was accordingly not included in estimates reported below. The report from Hawaii by Hayes et al. (2010) included a prevalence figure but gave no actual numbers for the denominator from the PRAMS sample and was excluded as well. Specific information about all studies can be found in Table A-1 in the Appendix.

Table 1 shows population-based estimates of women with chronic HTN in pregnancy. Estimates of women with chronic HTN or a history of HTN ranged from 0.5% (Sweden) to 1.7% (Portugal) in the single-site, population-based studies, although the figure for Sweden was the only one below 1.0%. In the study reported by Roberts et al. (2011) from eight areas in Australia, Europe, Canada and the United States, prevalence figures ranged from 0.3% (Sweden) to 1.6% in Massachusetts, with several areas reporting figures below 1.0%, all of them in Western Europe or Canada.

Table 1: Prevalence Estimate of Chronic Hypertension (HTN) in Population-Based Studies

Reference	Study Location (Total N)	Source of Data	Measures	Prevalence (Number with HTN)
Zhang et al. (2003)	US, 1988–1997 (38,923,280)	National Hospital Discharge Survey	ICD-9	1.2% (483,658)
Allen et al. (2004)	Nova Scotia, Canada 1988–2000 (135,466)	Perinatal database	Coded medical records data	0.9% (1,242)
Zettenstorm et al. (2005)	Sweden, 1991–1998 (681,515)	Medical record registry	ICD-9 or ICD-10 codes	0.5% (3,374)
Tanaka et al. (2007)	New York State 1993–2002 (2,571,069)	Hospital discharge data	ICD-9	1.2% Estimated (31,190)
Bateman et al. (2012)	US, 1995–2008 (56,494,634)	Nationwide Inpatient Sample	ICD-9	1.3 % (731,994)
Kuklina, Ayala, Callaghan (2009)	US, 1998–2006 (36,537,061)	Nationwide Inpatient Sample	ICD-9	1.3% (489,153)
Roberts et al. (2005)	Australia, 2000–2002 (250,173)	Linked birth and hospital records	ICD-10 codes	1.0% (2,543)
Su et al. (2013)	Taiwan, 2005 (218,781)	Birth certificates and claims data	ICD-9	1.6% (3,569)
Bombard et al. (2012)	Multiple US states, 2005–2006 (14,990)	PRAMS linked with birth certificates	Birth certificate categories & standard PRAMS items	1.2% Estimated (181)
Alves et al. (2012)	Porto, Portugal, 2005–2006 (7,181)	Survey questionnaire	Survey items and medical records	1.7% (127)
Roberts et al. (2011)	Australia (New South Wales and Western Australia), Alberta, Denmark, Norway, Scotland, Sweden and Massachusetts; (1997–2007), N between 149,624 and 913,779	Population health data (record-linked birth and hospital data, where available)	ICD-9 or ICD-10 codes	0.3% in Sweden; 1.6% in Massachusetts; Australia and US estimates only ones above 1.0%, numbers between 1,024 and 12,204

A meta-analysis was conducted using the data shown in Table 1. The study by Su et al. (2013) was excluded from the meta-analysis because of concerns about the quality of the data; the percentage of women with chronic HTN was among the highest reported for all studies, but estimates of PE and all HTN disorders among the lowest; these results suggested inconsistencies about diagnoses of the conditions in the available data. The study by Roberts et al. (2011) included data from several countries; the meta-analysis estimates were calculated with and without data from this study.

The meta-analysis, using random effects estimation, yielded an estimate of 0.96% (95% CI: 0.84; 1.09) for all studies combined that are reported in Table 1, excluding the data from Su et al. (2013). These estimates were somewhat higher when Su et al. was included in the analysis, but the confidence intervals overlap (data not reported). The estimate was lower when only data from Roberts et al. (2011) were included in the analysis, 0.76% (95% CI: 0.49; 1.03); it was higher when these data were excluded, 1.12% (95% CI: 1.04; 1.20). The meta-analysis estimates were more variable based on data from Roberts et al. (2011) alone; this finding was not surprising because more than half of the sites with reported data were from Western Europe and Western Canada, areas with quite homogeneous, largely white populations, while three sites were from the US and Australia with more racially and ethnically diverse populations. The percentage of women with chronic HTN at the start of pregnancy appears, on average, to be about 1% in populations with similar age distributions to the population of women with births in Australia, Sweden and the US during the years of study; it is unlikely that it exceeds 2% for these countries.

Pre-Eclampsia

Table 2 summarizes population-based estimates of the percentage of women with PE from eight single-site studies, along with the range of estimates reported by Roberts et al. (2011). Although data for gestational HTN or PE were reported in 13 studies, three studies (Allen et al. 2004; Bombard et al. 2012; Hayes et al. 2010) did not report estimates for PE, and the data from Lawler et al. (2007) were excluded for the reason described above. Data sources, again, were primarily birth registries, inpatient hospital or hospital discharge data, sometimes linked with birth registries

or birth certificates, and to a lesser extent postpartum survey data. One study reported data from middle- or low-resource countries; Conde-Agudelo et al. (2000) reported data from perinatal information systems in 19 Latin American countries. Definitions varied based on ICD-9 and ICD-10 codes and reporting of data on standard birth certificates or PRAMS items.

Estimates of PE ranged from 1.2% (Taiwan) to 5.0% (19 Latin American countries); some of the variation in PE may be due to whether or not severe PE was included in the estimate along with eclampsia. The lowest estimate for PE was reported in Taiwan, and was inconsistent with the estimate in Table 1 for chronic HTN; accordingly it was not included in the subsequent meta-analysis estimate. The estimate for Latin America was 5% when including eclampsia, and was close to the 4% noted in many of the studies from developed countries. The percentages with PE reported by Roberts et al. (2011) ranged from 1.4% in Alberta, Canada, to 4.0% in Norway.

Estimates of pre-eclampsia ranged from 1.2% in Taiwan to 5.0% in 19 Latin American countries.

Table 2: Prevalence Estimate of Pre-eclampsia (PE) in Population-Based Studies

Author	Study Location (Total N)	Source of Data	Measures	Prevalence (Number with PE)
Conde-Agudelo et al. (2000)	19 Latin American countries, 1985–1997 (878,680)	Perinatal information system	As noted in record	PE 5.0% (44,402)
Hernandez-Diaz et al. (2009)	Sweden, 1987–2004 (1,430,464)	Swedish Medical Birth Registry	ICD-9 or ICD-10 codes	PE: 3.0% (42,297)
Zhang et al. (2003)	US, 1988–1997 (38,123,280)	National Hospital Discharge Survey	ICD-9	PE: 2.7% (1,043,005) PE with HTN: 2.9% (1,111,777)
Zettenstorm et al. (2005)	Sweden, 1992–1998 (681,515)	Medical record registry	ICD-9 or ICD-10 codes	PE: 2.8% (18,966)
Tanaka et al. (2007)	New York State, 1993–2002 (2,517,069)	Hospital discharge data	ICD-9	PE: 3.3% Estimated (82,878) PE with HTN: 3.6% (90,829)

Table 2 (*continued*)

Author	Study Location (Total N)	Source of Data	Measures	Prevalence (Number with PE)
Kuklina, Ayala, Callaghan (2009)	US, 1998–2006 (36537061)	Nationwide Inpatient Sample	ICD-9	PE: 3.3% (1,219,200)
Roberts et al. (2005)	Australia, 2000–2002 (250,173)	Linked birth and hospital records	ICD-10 codes	PE: 4.2% (10,379) PE with HTN: 4.4% (11,110)
Su et al. (2013)	Taiwan, 2005 (218,781)	Birth certificates and claims data	ICD-9	PE: 1.2% (2,712)
Roberts et al. (2011)	Australia (NSW and Western Australia), Alberta, Canada, Denmark, Norway, Scotland, Sweden and Massachusetts; (1997–2007), N between 149,624 and 913,779	Population health data (record-linked birth and hospital data, where available)	ICD-9 or ICD-10 codes	1.4% in Canada; 4.0% in Norway; numbers between 3,586 and 26,500

The meta-analysis estimate for PE was 3.02% (95% CI: 2.73; 3.31) with all studies including data from Roberts et al. (2011); the estimation results show considerable heterogeneity and across-study variance. The estimate without data from Roberts et al. (2011) was 3.47% (95% CI: 3.13; 3.81). Using data only from Roberts et al. (2011), the meta-analysis estimate was 2.63% (95% CI: 1.90; 3.35), with wider confidence intervals than for the other two estimates, although all three confidence intervals overlap. The results of three studies (Roberts et al. 2005; Tanaka et al. 2007; Zhang et al. 2003) included data for PE among women with and without chronic HTN. When data for PE superimposed on chronic HTN were included, the respective estimates of PE were 3.08% (95% CI: 2.80; 3.35) and 3.59% (95% CI: 3.31; 3.86) with and without the data from Roberts et al. (2011). The percentage of women with PE appears to be close to 3.5% in populations with similar age distributions to the population of women with births in Australia, Sweden and the US during the years of study, and it is unlikely that it exceeds 5% based on data

for Latin American countries, assuming that the reporting of data about PE from the various sources is accurate. The variability in reporting of gestational HTN and PE across studies suggests that the estimates for PE are subject to more error than those for chronic HTN or all HTN in pregnancy.

All Hypertensive Disorders

Table 3 shows estimates of all hypertensive disorders in pregnancy including chronic HTN and gestational HTN when reported from 11 population-based studies. Thirteen studies were identified; Hayes et al. (2010) and Lawler et al. (2007) were excluded for the reasons described above. The same sources of data and definitions as noted in the previous tables were used as the basis for these estimates. Estimates ranged from 2.9% in Taiwan and 3.3% in Sweden to 11.0% in Maryland. The low estimate from Su et al. (2013) for Taiwan was not included in the meta-analysis because of concerns about the quality of the data described above. The percentages reported in Roberts et al. (2011) ranged from a low of 4.0% in Denmark to a high of 10.2% in Western Australia. The figures from this study are more consistent with the estimates from other studies shown in Table 3 for all hypertensive disorders than the figures for chronic HTN or PE.

Table 3: Prevalence Estimate of All Hypertensive (HTN) Disorders in Pregnancy in Population-Based Studies

Author	Study Location (Total N)	Source of Data	Measures	Prevalence (Number with HTN)
Zhang et al. (2003)	US, 1988–1997 (38,923,280)	National Hospital Discharge Survey	ICD-9	5.9% (2,285,191)
Allen et al. (2004)	Nova Scotia, Canada 1988–2000 (135,466)	Perinatal database	Coded medical records data	10.1% (13,706)
Zettenstorm et al. (2005)	Sweden, 1991–1998 (681,515)	Medical record registry	ICD-9 or ICD-10 codes	3.3% (22,340)
Tanaka et al. (2007)	New York State, 1993–2002 (2,571,069)	Hospital discharge data	ICD-9	6.2% (161,435)

Table 3 (*continued*)

Author	Study Location (Total N)	Source of Data	Measures	Prevalence (Number with HTN)
Miranda et al. (2010)	North Carolina, 1994–2003 (350,717)	Birth certificates	Birth certificate categories	8.2% (28,697)
Kuklina, Ayala, Callaghan (2009)	US, 1998–2006 (36,537,061)	Nationwide Inpatient Sample	ICD-9	7.4% (2,704,445)
Su et al. (2013)	Taiwan, 2005 (218,781)	Birth certificates and claims data	ICD-9	2.9% (6,290)
Roberts et al. (2005)	Australia, 2000–2002 (250,173)	Linked birth and hospital records	ICD-10 codes	9.8% (24,517)
Bombard et al. (2012)	Multiple US states, 2005–2006 (14,990)	PRAMS linked with birth certificates	Birth certificate categories and standard PRAMS items	5.7% (882)
Cheng and Barra (2012)	Maryland, 2004–2010 (10,915)	PRAMS linked with birth certificates	Birth certificate categories and standard PRAMS items	11.0% (1,201)
Roberts et al. (2011)	Australia (NSW and Western Australia), Alberta, Canada Denmark, Norway, Scotland, Sweden and Massachusetts; (1997–2007), N between 149,624 and 913,779	Population health data (record-linked birth and hospital data, where available)	ICD-9 or ICD-10 codes	4.0% in Denmark; 10.2% in Western Australia, numbers between 15,262 and 73,228

The meta-analysis estimates based on studies with and without the data from Roberts et al. (2011) were 7.28% (95% CI: 6.67; 7.90) and 7.52% (95% CI: 6.74; 8.29), respectively. The estimate using data from the eight sites reported by Roberts et al. was 7.02% (95% CI: 5.41; 8.63), indicating both a lower estimate and greater heterogeneity across populations they studied than the remaining population-based studies we identified. Differences in the degree of diversity among populations were discussed above as a possible reason for this greater heterogeneity. Thus, it appears that the percentage of women with any hypertensive disorder during pregnancy was approximately 7.5% in populations with similar age distributions to the population of women with births

in Australia, Sweden and the US during the years of study. It may, on average, be as high as 8.5%, and in some populations may exceed 10%.

Some additional population-based studies from developed countries were available for eclampsia; the results suggested that eclampsia in these settings was quite rare, less than 1 per 1,000 women (Zhang et al. 2003, Bouvier-Colle et al. 2012, Callaghan et al. 2012; see Appendix for these data). Two studies attempted to estimate severe PE in middle- or low-resource countries based on survey data. Souza et al. (2008) reported the results of interviews with women in the 1996 Demographic and Health Survey in Brazil, showing that 2.7% reported experiencing convulsions in any one of their pregnancies, which included a maximum of six live births in the five preceding years; this figure was accordingly an overestimate for the cross-sectional estimates from other studies for any given birth. Data from a subsample of households from the 2007 Ghana Maternal Health Survey indicated that 2.0% of women reported edema during pregnancy (Ghana Statistical Service 2009). The data from the latter two studies were not included in estimates for PE because they were based on self-reported data about a single symptom that may or may not have reflected PE.

Hypertension among Women of Childbearing Age

Table 4 shows population-based estimates for HTN among women of childbearing age. We identified three population-based studies from the US and Canada. One study, although not population-based, was found from Zambia among a sample of women aged 18–45 who attended one of two hospitals in Lusaka City for routine gynecologic visits. It was the only study in a low-resource setting for women of childbearing age. The data from Canada were based on linking of health administrative data from the Canadian Chronic Disease Surveillance System with health insurance registries, a physician billing database and the Canadian Institute of Health Information Discharge Abstract Database for 1998/99 to 2007/08 (Robitaille et al. 2012).

The prevalence estimates for women are shown in five-year age groups starting at age 20; prevalence increased from 0.5% at ages 20–24 to 8.7% among women aged 40–44 and exceeded 5%

after age 35, suggesting that the age distribution of women giving birth in a population had an effect on estimates of chronic HTN among pregnant women.

The percentage of women 20–44 with HTN based on a blood pressure reading of 140/90 mmHg or self-reported use of antihypertensive medication (Bateman et al. 2012) was 7.7%, based on data from five National Health and Nutrition Examination Survey (NHANES) cycles in the US (1999–2008). Data from the 2003–2009 Behavioral Risk Factor Surveillance System on women's reports that they were ever told by a doctor or other health professional that they had high blood pressure indicate that 9.0% reported the condition in 2003, rising to 10.1% in 2009 (Hayes et al. 2011); the reports may include women who were told about HTN during pregnancy and may not reflect only chronic HTN. The data from NHANES may be the most accurate estimate of HTN because of the use of actual blood pressure measurement and report of medication use for HTN.

The Zambia report (Chowa et al. 2011) defined HTN as blood pressure 140/90 mmHg or greater; 18.6% of women in urban areas and 6.7% in rural areas were found to have HTN based on this definition. The former estimate was considerably higher than estimates from Canada or the US, but may have also been due to a selectively biased sample of women in the study seeking care at clinic facilities or the limited resources in Zambia to identify and treat chronic HTN.

Table 4: Prevalence of Hypertension (HTN) among Women of Childbearing Age

Author	Site	Source of Data	Measures	Prevalence
Chowa et al. (2011)	Zambia	150 women ages 18–45 years who came for a routine gynecological visit at the Department of Gynecology at the University Teaching Hospital, Lusaka City, and 104 women at Liteta Hospital, Chibombo District.	Hypertension was defined as 140/90 mmHg or greater.	HTN 18.6 (Urban) HTN 6.7 (Rural)
Robitaille et al. (2012)	Canada	Retrospective cohort of more than 26 million Canadian men and women 20 years and older from 1998/99 to 2007/08. Women 20–54 years with suspected PIH (HTN 120 days before or 180 days after any pregnancy-related visit) excluded. Linked databases: Canadian Chronic Disease Surveillance System, collaborative network of surveillance systems conditions; health insurance registries; billing database; Canadian Institute for Health Information Discharge Abstract Database. Denominator: total number of people eligible for health insurance	Individuals with HTN: 2 or more physician claims for HTN within 2 years, or one recording of HTN in hospital discharge abstract. ICD codes used to identify HTN cases. Cases incident in first year in which met case definition. Prevalence cases remained while patient was alive and resided in province or territory and health insurance number was valid.	Prevalence (%); Incidence, per 100 per year Women-only: 20–24 yrs: Pr=0.5; In=0.2 25–29 yrs: Pr=1.6; In=0.3 30–34 yrs: Pr=3.2; In=0.4 35–39 yrs: Pr=5.2; In=0.7 40–44 yrs: Pr=8.7; In=1.2
Bateman et al. (2012)	US	5,521 women aged 20–44 years from 1999–2008 NHANES, a nationally representative cross-sectional survey (with physician examination) designed to assess the health and nutritional status of the US civilian, non-institutionalized population. Data were analyzed from 5 survey periods. Overall examination survey response rates ranged from 75–80%.	HTN defined as having an average BP ≥140/90 mmHg (as measured by physician using an appropriately sized cuff); or those who self-reported taking antihypertensive medications.	Survey cycle: %(CI) 1999–2000: 8.0 (6.3–10.1) 2001–2002: 7.3 (5.5–9.6) 2003–2004: 7.3 (5.7–9.1) 2005–2006: 6.0 (4.6–7.8) 2007–2008: 9.3 (7.5–11.4) Overall: 7.7 (6.9–8.5)
Hayes et al. (2012)	US	327,917 women 18–44 from 2001–2009 Behavioral Risk Factor Surveillance System, telephone survey of health behavior in US adults. 2003–2009 data only, due to a different question about blood pressure in the 2001 survey. Women pregnant at time of survey or with missing data on any chronic condition risk factor, or covariates excluded in specific analyses. Missing data ranged from .05–6.4%.	High blood pressure was considered present if the woman reported she had ever been told by a doctor or other health professional that she had the condition.	Chronic high blood pressure by survey year % (95% CI) 2003: 9.0 (8.6–9.4) 2005: 9.2 (8.8–9.6) 2007: 9.8 (9.4–10.2) 2009: 10.1 (9.7–10.5)

The percentage of women between ages 18 and 44 with HTN appeared to be between 7% and 8% based on data from the US and Canada. As noted above, the most accurate estimate was likely from NHANES. The age-specific data from Canada were interesting because they showed that the percentage of incident cases of chronic HTN rose slowly with age, although the trajectory for prevalence was more pronounced than for incidence. Although data were not reported, the prevalence was lower for women than men until age 55, after which it was greater for women. These estimates have implications for prevention of pregnancies at older ages especially in low-resource settings, and suggest the need to promote more family planning and family planning options among women in their late 30s.

Limitations of the Population-Based Data

The data from which the above estimates were derived had limitations that warrant comment here. Although the population-based estimates reduced the likelihood of selection bias, the data sources were secondary and may have resulted in under- or over-estimates of hypertensive disorders. Hospital discharge and inpatient data measured conditions based on diagnostic ICD-9 or ICD-10 codes, which were also used for billing for services, at least in the US, and may not have reflected the true incidence of disease. In Australia, hospital data had been linked to medical records to provide estimates in the tables; the prevalence rates were higher than for several other countries, but the higher rates may have reflected a more heterogeneous population than in European countries and Canada. The Australian estimates tended to be closer to those from the US, which also had a more racially and ethnically diverse population. Birth registries, while capturing the population in European countries, may not have achieved the level of precision needed to rely on the reported data. Certainly the data for hypertensive disorders occurring in pregnancy from Taiwan were of concern when compared to data for chronic HTN.

Under-reporting of chronic conditions and complications had been noted for birth certificate data from the US, although current trends showed increases in these conditions in national data that likely reflected improved reporting of these conditions. Only the reports for Maryland and Hawaii looked at recent data. None of the studies reported here used data from US birth certificates

only. When birth certificate data were combined with PRAMS data, they may have overestimated hypertensive disorders if women's reports were not accurate; for example, one elevated blood pressure reading during a prenatal visit may have been reported by a woman as high blood pressure during pregnancy. The one study that used these data for chronic HTN (Bombard et al. 2012) showed prevalence similar to that in the studies using hospital discharge data. The figures from Bombard et al. (2012) and Cheng and Barra (2012) were quite different, suggesting the prevalence estimates may be related more to population characteristics than to the data source.

Another limitation was related to pooling of the data across populations. Roberts et al. (2011) did not estimate absolute population rates because of different diagnostic criteria and sources of data and data collection procedures, rather, they evaluated trends in rates. They, nevertheless, discussed the generally good reliability and validity of the data about hypertensive disorders in pregnancy. Perhaps more important, the variability in population characteristics was a greater challenge in estimating rates, as evidenced by the divergence of the estimates for the Northern/ Western European countries compared to those for the US and Australia. The US and Australia had more racially and ethnically diverse populations than the European countries, and this diversity was likely to contribute to their higher percentages. When the data were pooled in the meta-analysis for Roberts et al. (2011) and the other population-based studies, the estimates may have appropriately reflected the average rates of hypertensive disorders among women in high-resource settings across diverse populations.

Data from Hospital- or Clinic-Based Studies

Clinic- and hospital- based studies were also reviewed in addition to the population-based data for HTN in pregnancy. The majority of the facility-based studies reported here were conducted in low-resource countries. In fact, these studies were the primary source of data about HTN in pregnancy among women in low-resource settings. Table 5 shows the results from studies in which the data were deemed to be of reasonable quality based on the source of data, sample size and description of methods of data collection

and ascertainment; most data were collected from medical records at single or multiple facilities.

Two large studies, one in Brazil (Gaio et al. 2001) and another in Panama (Vigil-De Gracia et al.), provided estimates of chronic HTN among women giving birth in study facilities. In Brazil, using diagnostic data noted in medical records, 4.0% of women were estimated to have chronic HTN, 4.5% if women with super-imposed PE or eclampsia were included. In the Panama City study, 2.2% were reported to have chronic HTN based on medical records data from a tertiary care facility. In a smaller study in southwest Iran, Zareian et al. (2004) reported that 2.7% of women had chronic HTN noted in their medical records at Shadid Mottahari Clinic; when superimposed PE was included for women with chronic HTN, the estimate increased to 4.0%, similar to the figure from Brazil. The percentage from Portugal, 1.5%, reported for women who delivered in public maternity facilities, was similar to figures reported in Table 1. The other estimates are higher than those reported in Table 1 and may reflect the use of a sample from women delivering in facilities in the study areas.

Estimates for gestational HTN and PE from facility-based studies largely applied to PE only. They ranged from 2.0% in Taiwan and Portugal to 4.6% in Iran when PE superimposed on chronic HTN was included in the estimate. The data for gestational HTN were inadequate to make any inferences.

Table 5 shows data from five studies in which information was available for all hypertensive disorders in pregnancy; all reported data were from medical records, and the sample from Brazil included multiple hospitals. The estimates, ranging from 6.0% in Portugal to 10.1% of women in Cuba, were similar, except for Cuba, to the meta-analysis estimates for population data reported in Table 3.

Table 5 also shows estimates of severe PE and eclampsia in facility-based studies. The estimates for eclampsia were likely more accurate because symptoms of eclampsia were very distinct and did not require evaluation of proteinuria in the absence of other readily reported symptoms; they were all under 1% with

two exceptions. The estimate from a single facility in Karachi, Pakistan, was 1.3%. More concerning was the estimate of 9.4% in the Federal Medical Center, a tertiary facility, in Nigeria. Although this figure likely reflected the fact that women with severe complications are referred to the hospital, it may also be because of higher underlying levels of hypertensive disorders in the population or to limited clinical management of PE in the facilities in Nigeria.

Table 5: Prevalence Estimate of Hypertensive Disorders in Pregnancy in Facility-Based Studies

AUTHOR	STUDY LOCATION	DATA SOURCE	MEASURES	HTN DISORDERS PREVALENCE
Chronic HTN				
Gaio et al. (2001)	Selected centers of Brazilian National Health System in 6 Brazilian capitals	Medical records	As noted in medical records	Chronic HTN: 4.0% With PE: 4.5%
Vigil-De Gracia et al. (2004)	Complejo Hospitalario "Arnulfo Arias Madrid" de la Caja de Seguro Social in Panama City, tertiary care facility and referral hospital for all of Panama	Medical records	Mutually exclusive categories: chronic HTN and severe chronic HTN	Chronic HTN: 2.2%
Zareian et al. (2004)	Shahid Mottahari Clinic of Jahrom (southwest Iran)	Medical records	Disorders as noted in medical records using WHO definition to determine PE	Chronic HTN: 2.7% With PE/Eclampsia: 1.3%
Povoa et al. (2008)	Portuguese public maternity wards (85%)	Medical records	BP 140/90 mmHg or greater before pregnancy or before 20 weeks	Chronic HTN: 1.5% (1.2; 1.8%)
Gestational HTN and PE				
Gaio et al. (2001)	Selected centers of Brazilian National Health System in 6 Brazilian capitals	Medical records	As noted in medical records	PE/eclampsia: 2.3% With Chronic HTN: 2.8% Transitory HTN: 0.7%
Urasa et al. (2003)	Tanzania, 30% of antenatal care facilities at dispensary, health, center, and hospital levels in Rufiji District	Measured by research observer	As measured with newly purchased aneroid sphygmomanometer	Pregnancy related HBP: 3.2%
Zareian et al. (2004)	Shahid Mottahari Clinic of Jahrom (southwest Iran)	Medical records	Disorders as noted in medical records using WHO definition to determine PE	All hypertensive disorders (PIH, PE and eclampsia): 3.3% With chronic HTN: 4.6%
Chen et al. (2000)	Taiwan, 14 medical centers and regional hospitals. Multiple facilities	Patient charts	PE defined as PIH (systolic BP $>$140 mmHg or diastolic BP $>$90 mmHg) with proteinuria and independent part edema; complications included eclampsia	PE and eclampsia: 2.0%
Povoa et al. (2008)	Portuguese public maternity wards (85%)	Medical records	Gestational HTN: BP 140/90 mmHg or greater noted first in pregnancy; PE: BP 140/90 mmHg or greater after 30 weeks with proteinuria, eclampsia or HELLP syndrome	Gestational HTN: 2.5% PE: 2.0%

Table 5 (*continued*)

AUTHOR	STUDY LOCATION	DATA SOURCE	MEASURES	HTN DISORDERS PREVALENCE
All Hypertensive Disorders in Pregnancy				
Gaio et al. (2001)	Selected centers of Brazilian National Health System in 6 Brazilian capitals	Medical records	As noted in medical records	7.5%
Yucesoy et al. (2005)	Turkey, Kocaeli University, School of Medicine, Dept. of Obstetrics and Gynecology	Medical records	Criteria defined by the National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy	8.5%
Zareian et al. (2004)	Shahid Mottahari Clinic of Jahrom (southwest Iran)	Medical records	Disorders as noted in medical records using WHO definition to determine PE	7.3%
Perez et al. (2004)	Cuba (Havana), Enrique Cabrera General Teaching Hospital	Medical records	HTN recorded as a pre-existing illness or the patient ICU discharge status	10.1%
Povoa et al. (2008)	Portuguese public maternity wards (85%)	Medical records	Chronic HTN, Gestational HTN: BP 140/90 mmHg or greater noted first in pregnancy or PE: BP 140/90 mmHg or greater after 30 weeks with proteinuria, eclampsia or HELLP	6.0% (5.4; 6.6%)
Severe PE and Eclampsia				
Siddiqui et al. (2012)	Pakistan (Karachi), single facility	Patient charts and daily case discussions	Disease-specific criteria, used by Waterstone et al. to classify hypertensive disorders: included severe PE and eclampsia	Severe PE: 0.7% Eclampsia: 1.3%
Vigil-De Gracia et al. (2004)	Complejo Hospitalario "Arnulfo Arias Madrid" de la Caja de Seguro Social in Panama City, tertiary care facility and referral hospital for all of Panama	Medical records	Severe HTN: if maximum systolic BP was at least 160 or maximum diastolic at least 110 on 2 occasions more than 4 hours apart after receiving first dose of antihypertensive drugs only in second half of pregnancy	Severe HTN: 0.6%
Ghazal-Aswad et al. (2013)	United Arab Emirates, 4 maternal units in Abu Dhabi	Medical records	Eclampsia, HELLP and severe PE based on clinical criteria	PE 0.37% Eclampsia: 0.057% HELLP: 0.02%
Chantry et al. (2011)	France, 4 hospitals in Caen, Cochin, Grenoble, and Lille	Medical records	PMSI ICD 10 code: O15; Medical records	Eclampsia: 0.14% (PMSI) Eclampsia: 0.065% (Medical records)
Ghandi et al. (2004)	South Africa, 4 primary hospitals in the Jozini Health District of KwaZulu Natal	Medical records	Identified severe acute maternal morbidity (SAMM) cases as eclampsia by the local team and external specialist	Eclampsia: 0.2%
Tukur et al. (2007)	Nigeria from Federal Medical Centre (tertiary hospital)	Medical records	Eclampsia as noted in medical record; diagnostic measure not articulated	Eclampsia: 9.42%
Moodely et al. (1993)	South Africa, King Edward VIII Hospital	Medical records	Eclampsia as noted in hospital record; diagnostic measure not articulated	Eclampsia, 1980: 0.3 Eclampsia, 1990: 0.6

The Quality of the Data

The quality of the data from facility-based studies in low-resource countries is of more concern than the population-based estimates because of potential self-selection of women who use the facilities from which data are reported. Selection bias may affect rates in both directions; women who use facilities may have higher risk leading to upward reporting/overestimation bias, or may be of higher economic status, being able to afford care, and in turn have lower risk, leading to underestimation bias. It is difficult to judge the direction of bias from the data, although multi-site studies may reduce selection bias by representing a greater mix of the population. Facility-based studies could theoretically provide more accurate estimates of hypertensive disorders if more detailed information is available about signs and symptoms, blood pressure measurement and screening test. Most of the data presented in Table 5 are drawn from medical records, but they, nevertheless, raise concerns about the quality and completeness of these records, particularly reporting of conditions and information that correctly differentiates chronic HTN, gestational HTN and PE.

Summary of the Current WHO Recommendations

In the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*, the WHO (2011) identified two groups of pregnant women for whom antihypertensive medication should be considered: 1) women with mild to moderate HTN, and 2) women with severe HTN. The WHO defined mild to moderate HTN as diastolic blood pressure greater than or equal to 90 mmHg but not exceeding 110 mmHg. Severe HTN included women with diastolic blood pressure consistently greater than 100 mmHg. This distinction between mild to moderate and severe HTN is appropriate based on the research literature, although the cut-off of 100 mmHg may not be a standard criterion across all practice guidelines.

In most published studies, the goal of antihypertensive treatment is different for women with mild to moderate HTN than for women with severe HTN. With mild to moderate HTN, the goal of most studies is prevention of poor pregnancy outcomes such as PE, growth restriction, severe HTN, eclampsia and stillbirth. For severe HTN, the treatment goal measured in most studies is morbidity and mortality, as measured by continued severe HTN, maternal stroke, maternal death, preterm birth, growth restriction and fetal or neonatal death. Accordingly, the literature for these two groups is updated separately below.

Mild to Moderate Hypertension

Based on the literature reviewed in the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia*, women with mild to moderate HTN on antihypertensive medications had no statistically significant differences in outcomes when compared to women on placebo (WHO 2011). Specifically, there was no difference between treatment and placebo with regard to PE (based on 22 trials), eclampsia (five trials), HELLP syndrome (one trial) or maternal death (four trials). The lack of benefit with treatment was consistent across both gestational HTN and chronic HTN. As a result of these findings, the WHO 2011 report did not recommend treatment for mild to moderate HTN.

Severe Hypertension

In contrast, the WHO strongly recommended treatment for severe HTN, but acknowledged that this recommendation was based on low-quality evidence. When comparing different

There are limited data to guide medication selection, but trials suggest that calcium channel blockers were associated with less persistently elevated blood pressure compared with hydralazine.

treatment regimens, the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* (WHO 2011) cited a Cochrane review of five studies in which calcium channel blockers were associated with a significant reduction in the odds of persistently severe high blood pressure compared to hydralazine but no significant differences were noted in the frequency of PE. The WHO report also highlighted that there were no differences in outcomes between hydralazine and labetalol or calcium channel blockers and labetalol. As a result, the WHO recommendations allowed for the drug and route of administration to be based on clinician preference, although they noted that diuretics should be avoided.

Summary of the Literature since the 2011 WHO Recommendations

Update Regarding Antihypertensive Medication for Mild to Moderate Hypertension

Several Cochrane reviews cited in the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* have been updated since its 2011 release. Abalos et al. (2010) published a revision to the 2007 "Antihypertensive drug therapy for mild to moderate hypertension in pregnancy." The Cochrane review included 46 randomized trials involving the treatment of pregnant women with maternal blood pressures of 140–169 mmHg systolic and 90–109 mmHg diastolic; 28 trials compared treatment to placebo and 19 trials compared different antihypertensive medications. This review reported two significant findings that were not included in the 2011 WHO recommendations. First, the review found that treatment with antihypertensive medications compared to placebo was associated with a significant decrease in the risk of developing severe HTN (RR 0.5, 95% CI 0.41-0.61), and suggested that the number needed to treat to prevent one severe hypertensive patient was 10. Second, it showed no statistically significant difference between treatment and placebo for PE or stillbirth when all treatments were considered together. When the medication subgroups were examined separately, however, beta blockers compared to placebo showed a statistically significant decrease in PE (RR 0.73, 95% CI 0.57-0.94); beta blockers also were associated with greater

Women with mild to moderate hypertension on antihypertensive medications had no statistically significant differences in outcomes when compared to women on placebo.

prevention of severe HTN than methyldopa (RR 0.79, 95% CI 0.63-0.99) (Abalos et al. 2010).

These findings were echoed by another updated Cochrane review released in 2012 by Magee and Duley, "Oral beta blockers for mild to moderate HTN during pregnancy." This review found that beta blockers were associated with a significant reduction in women with severe HTN during pregnancy (RR 0.37, 95% CI 0.26-0.53) compared to placebo. Beta blockers, however, were also associated with an increased risk of small for gestational age neonates (RR 1.36, 95% CI 1.02-1.82) compared to placebo. When compared to other antihypertensive medications, beta blockers were associated with a reduced risk of small for gestational age neonates (RR 0.69, 95% CI 0.48-0.99). Only four studies in this review examined neonatal respiratory distress syndrome (RDS) but beta blockers were favorably linked to lower percentages of newborns with RDS. Like the other Cochrane review, this review found no difference in the risk of proteinuria with or without beta blockers (Magee and Duley 2012).

Two recent randomized controlled trials were identified that focus on mild to moderate HTN and were not included in the Cochrane reviews mentioned above. Molvi et al. (2012) performed a prospective non-blinded randomized controlled trial in Kashmir, India, of 150 patients with mild to moderate gestational HTN. The women, diagnosed by two blood pressures more than six hours apart with a systolic of 140–159 mmHg or a diastolic 90–109 mmHg, were randomized, using sealed envelopes with treatment enclosed, to labetalol, methyldopa or standard care (no medications). Patients with proteinuria or chronic HTN were excluded. The authors found that treatment was associated with lower odds of severe HTN, proteinuria, antenatal hospitalization, preterm birth and neonatal intensive care unit admission. Labetalol was associated with lower rates of severe HTN and antenatal hospitalization than methyldopa but otherwise there was no significant difference between the medication groups (using a $p<0.05$ to define significance) (Molvi et al. 2012).

The second randomized controlled trial was conducted in Egypt. El-Guindy and Nabhan (2008) identified 125 women with mild to moderate chronic or gestational HTN defined as two blood pressures more than four hours apart with a systolic blood pressure of 140–159 mmHg or a diastolic of 90–99 mmHg. Each woman was randomized using a computer generated 1:1 treatment protocol to either "less tight" control (goal blood pressure 130–139/80-89 mmHg) or "tight" control (goal blood pressure less than 130/80 mmHg). Methyldopa was used to maintain blood pressure control. The groups did not differ with regard to PE, proteinuria or HELLP syndrome. The "tight" control group showed significantly less severe HTN and antenatal hospitalizations (El-Guindy and Nabhan 2008).

Since 2011, there has been one additional study addressing the possible association between antihypertensive medication and small for gestational age birth weight. Su et al. (2013) performed a retrospective cohort study using birth certificate data in Taiwan. They found an association between both beta blockers and calcium channel blockers and small for gestational age neonates. This study, however, was a retrospective cohort study using birth certificate data, and the authors did not control for degree of HTN. Their findings may be explained by the fact that more severely hypertensive women (those requiring medication) are likely to have more severely affected neonates (Su et al. 2013); PE has been shown to be strongly related to growth restriction in a number of studies (Xiao et al. 2003; Allen et al. 2004; Buchbinder et al. 2002; Odegard et al. 2000; Xiong et al. 1999).

Updates Regarding Antihypertensive Medication for Severe Hypertension

It is widely accepted that severe HTN cannot be tolerated due to concern for end organ damage including an increased risk of maternal cerebral hemorrhage or infarct. There are limited data, however, to guide medication selection. Even the American College of Obstetricians and Gynecologists does not specify which medication is best to treat severe HTN. Since the 2011 WHO report, Ronsmans and Campbell (2011) reviewed all studies related to mortality reduction using interventions associated with

hypertensive disorders in pregnancy. They identified five trials that examined the optimal medication for treatment of severe HTN. As described in the WHO recommendations, calcium channel blockers, such as nifedipine, were associated with less persistently elevated blood pressure (higher than 160/100 mmHg) compared with hydralazine (RR 0.33, 95% CI 0.15-0.7).

Raheem et al. (2012) performed a small but well-executed double blinded randomized controlled trial to compare treatment options in women who were 24 gestational weeks or more with severe HTN. Fifty Malaysian women who presented to one hospital with two blood pressures higher than 160 mmHg systolic or 110 mmHg diastolic more than four hours apart were randomized to receive either oral nifedipine or intravenous labetalol. There was no significant difference between the two treatment groups regarding the primary endpoint of median time to achieve a blood pressure less than 150/100 mmHg. There also was no difference in side effects, intensive care unit admissions or mode of delivery. The findings are particularly significant because nifedipine was administered orally.

The only other study of severe HTN in pregnancy of relevance to this review since the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* is a prospective observational trial in Egypt (Abdel-Hady et al. 2010). This study focused on expectant management of women diagnosed with severe PE between 24 and 34 weeks. More than 200 women were expectantly managed with methyldopa as a first-line antihypertensive and labetalol as a second line agent. Delivery was undertaken when eclampsia, HELLP, non-reassuring fetal testing or growth restriction occurred. The median length of expectant management was 12 days (SD: six days). As expected, neonatal survival rates were significantly better the later the onset of severe PE (19.7% if less than 28 weeks, 45.5% 28–32 weeks and 79.8% 32–34 weeks). When delivery was needed before 28 weeks, no neonate survived. Maternal morbidity was also significantly greater in the women who developed PE prior to 28 weeks. Worldwide there is a growing trend toward expectantly managing severe PE to prolong gestation. This study, while small, suggests that in developing countries, the benefit to the neonate of

expectant management when severe PE develops before 28 weeks may come at a cost of significant maternal morbidity (Abdel-Hady et al. 2010).

Limitations and Future Studies

Since the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* were reported, there have been limited new data evaluating the benefits of blood pressure control as a preventive treatment for PE. We performed an extensive search of PubMed and then bibliographic review of selected references but were able to find few studies performed since 2010 when the WHO report concluded its literature search. The lack of new data may be due to the following reasons:

- Variability in how disease is classified and subdivided (chronic, gestational, mild, moderate and severe PE).
- Evaluation of the prevalence of complications requires a large-scale study.
- Randomization and blinding are often difficult in obstetrics.

The Control of Hypertension in Pregnancy Study (CHIPS) Trial, which concluded in 2014, was a multi-center randomized controlled trial in which women with a viable fetus between 14 and 33+6 weeks gestation with mild-moderate chronic or gestational HTN (diastolic blood pressure 90–105 mmHg unmedicated or 85–105 mmHg with medication) were randomized to tight control with a diastolic goal of less than 85 mmHg or loose control with a diastolic goal of less than 100 mmHg. Exclusion criteria include systolic blood pressure greater than or equal to 160 mmHg at randomization, proteinuria defined as greater than or equal to 0.3 grams/day by 24 hour urine collection, use of an angiotensis converting enzyme inhibitor at or after 14 weeks, major fetal anomaly, multiple gestation, a plan to terminate or prior participation in the CHIPS study. The primary outcome is pregnancy loss or neonatal intensive care admission, but planned secondary outcomes include maternal complications such as PE, severe HTN and eclampsia. This study likely will help to further clarify whether blood pressure control decreases the risk of PE.

Summary of Recommendations

Since the *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* were released in 2011, several Cochrane reviews have been updated and a few new studies have been reported. Based on the most recent literature, we suggest the following recommendations with regard to antihypertensive medication in low-resource settings:

- Consider treatment of moderate hypertensive disease (due to gestational HTN or chronic HTN) in pregnancy, particularly in the late second and early third trimester. This recommendation is made with a goal of reducing the risk of life-threatening, severe HTN and with the acknowledgment that there is no antihypertensive regimen that prevents PE.
- Although there is no clear first-line agent for the treatment of mild to moderate HTN in pregnancy, beta blockers have been found to have some advantages over methyldopa.
- It is important for maternal health that all women with severe HTN be treated with an antihypertensive medication. Oral calcium channel blockers, IV beta blockers and IV hydralazine are all acceptable options for treatment. Oral calcium channel blockers have the advantage of not requiring vascular access and thus have significant advantages in some settings.

The WHO strongly recommended treatment for severe hypertension but acknowledged that this recommendation was based on low-quality evidence.

Unmet Need for Antihypertensive Medications

In addition to assessing estimates of the prevalence of chronic HTN and hypertensive disorders in pregnancy, we also attempted to evaluate unmet need for antihypertensive medication in middle- and low-resource settings. Unmet need for antihypertensive medications in pregnancy can be calculated as the number of pregnant women with hypertensive disorders who are not on antihypertensive medication divided by the number of all pregnant women with hypertensive disorders within a specified time period. No studies were found in low-resource countries of population-based estimates of the proportion of pregnant women with hypertensive disorders who are on antihypertensive medication (or conversely, not on antihypertensive medication). We alternatively searched for studies identifying factors that influence unmet need for these medications in pregnancy. The factors include: 1) procurement of antihypertensive medications in-country; 2) availability of medications in the public and private sectors; 3) accessibility of medications to consumers, including cost and purchasing power; and 4) provision of medications to women with PE and eclampsia in health care facilities.

WHO lists six antihypertensive medications on its Essential Medicine List (17th edition, March 2011), including four that may be recommended for pregnant women. They are:

- Amlodipine (calcium channel blockers): Tablet: 5 mg (as maleat, mesylate or besylate)
- Bisoprolol (beta blockers, including labetalol): Tablet: 1.25 mg; 5 mg (includes metroprolol and carvedilol as alternatives)
- Hydralazine: Powder for injection: 20 mg (hydrochloride in ampoule); Tablet: 25 mg; 5 mg (hydrochloride)
- Methyldopa: Tablet: 250 mg

We searched for procurement, availability, accessibility and provision studies that included the above antihypertensive medications. We identified seven studies described below.

National Procurement

Many developing countries have a national essential medicine list (NEML). Although not all medications found on this list may be procured in practice, the list indicates the country's official

policy on drug procurement. In a study comparing compliance of NEMLs in 13 countries with the WHO Essential Medicines List (WHO/EML) in 2007, one country included amlodipine, four included hydralazine and all 13 included methyldopa (Twagirumukiza et al. 2010; see Table 6). Note that bisoprolol was not on included in the 2007 WHO/EML.

Table 6: Antihypertensive Drugs on the National Essential Medicine Lists (NEML)

Medicine	Benin	Burundi	Cameroon	Congo	DRC	Ivory Coast	Kenya	Mozambique	Niger	Rwanda	Senegal	Tanzania	Uganda	Countries with Medicine on NEML	
														N	%
Amlodopine, 5 gm							Y							1	8
Hydralazine	Y		Y						Y		Y			4	31
Methyldopa	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13	100

In Madagascar, hydralazine, nifedipine and methyldopa were on the NEMLs as of 2011 (MCHIP Report, 2013).

In at least in one country, Bahrain, the procurement of antihypertensive medications for pregnant women decreased, but the procurement of all hypertensive medications increased between 1995 and 2004. The Bahrain Directorate of Material Management/ Procurement Management section increased its spending from $626,152 ($1.068 per capita expenditure) in 1995 to $3,220,812 ($4.55 per capita expenditure) in 2004 for all antihypertensive medications. Among all antihypertensive medications, however, the proportion procured of methyldopa and hydralazine (used in pregnancy only) decreased between these years. In 1995, 18.7% and 1.5% of all antihypertensive medications procured were methyldopa and hydralazine, respectively; in 2004, the respective figures decreased to 3.1% and 0.2% (Al Khaja et al. 2012).

Drug Availability in the Public and Private Sectors

Antihypertensive medications for pregnancy generally are available to consumers in low- or middle-resource countries more frequently in the private sector than in the public sector. According to one study analyzing data collected from 36 countries in 2003, the lowest priced generic of nifedipine was available in 46–82% of private sector facilities, but it was available in only 20–35% of public sector facilities. Excluding upper-middle income countries, the lowest-priced generic of nifedipine was available in up to 75%

of the private and 25% of the public sector. Availability of the lowest-priced generics was higher than originator brand products (Van Mourik et al. 2010; see Table 7).

Table 7: Availability of Nifedipine by World Bank Income Group Countries

World Bank Income Group*	Public Sector Percentage Availability		Private Sector Percentage Availability	
	Lowest Priced Generic, % (N)	Originator Brand, % (N)	Lowest Priced Generic, % (N)	Originator Brand, % (N)
Low income	24.5 (19)	0.2 (19)	74.8 (21)	13.0 (21)
Lower-middle income	20.4 (8)	21.5 (8)	45.6 (9)	38.6 (9)
Upper-middle income	35.0 (3)	0.0 (3)	82.1 (3)	36.9 (3)

*Low-income: Chad, Ethiopia, Ghana, India, Kenya, Kyrgyzstan, Mali, Mongolia, Nigeria, Pakistan, Sudan, Tajikistan, Tanzania, Uganda, Uzbekistan, Yemen.
Lower-middle income: Armenia, Cameroon, China, El-Salvador, Fiji, Indonesia, Jordan, Morocco, Peru, Philippines, Sri Lanka, Syria, Tunisia.
Upper-middle income: Brazil, Kazakhstan, Lebanon, Malaysia, South Africa.

USAID's Maternal and Child Health Integrated Program

Under USAID's Maternal and Child Health Integrated Program (MCHIP), a number of Quality of Care (QoC) surveys have recently been conducted to assess the quality of and access to maternal and newborn care at health facilities. These surveys, which collect primary data from multiple sources and analyze them together, have been carried out in Ethiopia, Madagascar, Mozambique, Rwanda and Tanzania. In Madagascar, a QoC survey was conducted in 36 facilities in 15 regions of the country. The 36 facilities included all 33 health facilities (both hospitals and health centers), which had an average caseload of two or more deliveries per day, plus three additional facilities in MCHIP demonstration districts. Antihypertensive medications were available in 50% of facilities. Women with PE or eclampsia were observed in seven facilities, but antihypertensive medication was available in only two of these facilities. In the first facility, only methyldopa was available, and in the second, hydralazine, nifedipine, methyldopa and labetalol were all available (Rasolofomanana et al. 2011).

In Mozambique, a Quality and Humanization of Care Assessment (similar to the QoC surveys) was implemented in 46 health facilities, with observations of 525 deliveries and 303 antenatal care consults. Antihypertensives were found to be almost

universally stocked in the facilities (MCHIP Report 2013). In Tanzania, the sample in the QoC survey consisted of 52 health facilities in 12 regions (12 regional hospitals, 29 health centers and 11 dispensaries). Hydralazine or apresoline was available in 10 of the 12 regional hospital pharmacies, nifedipine in eight and labetalol in one. Additionally, hydralazine or apresoline was present in six of 38 health center pharmacies, nifedipine in 10, and labetalol was not present in any of the pharmacies (Plotkin et al. 2011).

Cost and Purchasing Power

The high cost of antihypertensive drugs in developing countries is likely a major barrier for medication compliance among pregnant women. Patient prices for cardiovascular drugs, including nifedipine, are high compared to international reference prices (the median price of high-quality, multisource medicines offered to developing and middle-income countries by different suppliers) (Van Mourik et al. 2010; see Table 7). Based on 34 low-income, lower-middle income, and upper-middle income countries, one month of treatment for chronic high blood pressure costs an average of 1.8 to 8.3 days' wages. Although drugs sold in the public sector are less costly than those sold in the private sector, Van Mourik et al. (2010) found that drugs are available less frequently in the public sector (see Table 8 for cost of nifedipine).

Table 8: Cost of Nifedipine by World Bank Income Group Countries

World Bank Income Group	Public Sector Median Price Ration* CPI and PPP Adjusted)		Private Sector Median Price* Ration (CPI and PPP Adjusted)	
	Lowest Priced Generic, % (N)	Originator Brand, % (N)	Lowest Priced Generic, % (N)	Originator Brand, % (N)
Low income	9.8 (6)	Missing	74.8 (21)	13.0 (21)
Lower-middle income	9.5 (2)	20.4 (1)	45.6 (9)	38.6 (9)
Upper-middle income	9.5 (1)	Missing	82.1 (3)	36.9 (3)

*Median price ration = Median local price/International reference price.
CPI: Consumer price index; PPP: Purchasing power parity.

According to one study in Mexico, the price of methyldopa and hydralazine was high in 1996, and the costs had risen, but purchasing power had fallen since 1990 (Calvo-Vargas et al. 1998,

Table 9). Both the high cost in the mid-1990s and the steep rise in cost from only six years prior are important barriers to medication compliance. It is likely the cost of these drugs is higher today, while the Mexican population's purchasing power is lower.

Table 9: Cost (US Dollars) and Purchasing Power of Methyldopa and Hydralazine

	Daily Dosage (Mg)	Monthly Cost (1990)	Monthly Cost (1996)	Annual Cost (1990)	Annual Cost (1996)	% Of Min. Wage Necessary For Purchase (1990)	% Of Min. Wage Necessary For Purchase (1996)
Methyldopa (Aldomet)	1500	11.07	23.36	132.84	280.32	11.0	28.1
Hydralazine (Apresolina)	150	11.41	12.66	136.92	151.92	11.4	15.5

The results of a 2001–2002 study of 128 Ghanaian men and women with high blood pressure showed that 93% (119) of patients did not comply with their HTN medications; 96% (114) of non-compliant patients cited unaffordable drug prices as the main reason they did not stay on their medication (Buabeng et al. 2004). The price (US Dollars) per month for nifedipine (40 mg) was $8.80; only 2 of 36 patients on this therapy were compliant. The price per month of nifedipine (40 mg) + methyldopa (1 g) was $19.00; none of the 11 patients on this therapy were compliant.

Finally, the findings of a 2007 study of multiple African countries show considerable variation in the cost and purchasing power of medications across countries (Twagirumukiza et al. 2010; see Tables 10 and 11). Medication prices were highest in the Ivory Coast and lowest in Uganda, with amlodopine being most costly and hydralazine least costly.

Table 10: Price per Tablet in Public and Private Sector per Country (Median medicine prices per tablet in US Dollars using national official exchange rate of July 2007)

Countries	Outlets	Methyldopa, 250 Mg	Amlodipine, 5 Mg	Hydralazine, 25 Mg
Benin	Public	4.2	28.0	2.4
	Private	5.2	39.5	3.6
Burundi	Public	4.0	25.5	2.6
	Private	4.7	33.9	5.0
Cameroon	Public	4.0	10.0	2.5
	Private	4.2	19.8	3.9
Congo	Public	3.4	16.5	2.0
	Private	3.5	23.0	2.0
Democratic Republic of Congo	Public	4.1	11.0	2.4
	Private	5.9	21.1	3.6
Ivory Coast	Public	7.2	108.5	3.4
	Private	9.8	197.5	4.8
Kenya	Public	1.2	20.0	2.9
	Private	1.1	37.2	3.1
Mozambique	Public	1.6	18.4	1.9
	Private	2.5	29.8	1.9
Niger	Public	4.3	12.5	4.1
	Private	6.9	21.8	6.1
Rwanda	Public	0.8	18.5	3.7
	Private	0.9	26.1	5.1
Senegal	Public	1.6	40.0	2.9
	Private	2.5	59.5	4.6
Tanzania	Public	1.0	10.0	2.3
	Private	1.4	19.8	3.2
Uganda	Public	0.5	10.0	3.9
	Private	0.8	18.8	8.0
Overall median price	Public	3.4	18.4	2.6
	Private	3.5	26.1	3.9
IDPI		3.2	13.3	2.1

IDPI: Median price advocated by the International Drug Price Indicator Guide.

Table 11: Defined Daily Dose (DDD) Prices and Purchasing Power Parity (PP)-Based Gross Domestic Product (GDP) per Capita, Adjusted DDD Prices in US Dollars*

Countries	2007 PPP-GNI per Capita	Medicines	Methyldopa (Aldomet) 1000 Mg	Amlodipine 5 Mg	Hydralazine Tablets 100 Mg
Benin	1310	DDD Price Adjusted Price	16.8 3.7	28.0 6.2	9.6 2.1
Burundi	330	DDD Price Adjusted Price	16.0 14.1	25.5 22.4	10.4 9.1
Cameroon	2120	DDD Price Adjusted Price	16.0 2.2	10.0 1.4	10.0 1.4
Congo	2750	DDD Price Adjusted Price	13.6 1.4	16.5 1.7	8.0 0.8
Democratic Republic of Congo	290	DDD Price Adjusted Price	16.4 16.4	11.0 11.0	9.6 9.6
Ivory Coast	1590	DDD Price Adjusted Price	28.8 5.3	108.5 19.8	13.6 2.5
Kenya	1540	DDD Price Adjusted Price	4.4 0.8	20.0 3.8	11.6 2.2
Mozambique	690	DDD Price Adjusted Price	6.4 2.7	18.4 7.7	7.6 3.2
Niger	630	DDD Price Adjusted Price	22.4 7.9	17.2 5.8	20.4 7.5
Rwanda	860	DDD Price Adjusted Price	3.2 1.1	18.5 6.2	14.8 5.0
Senegal	1640	DDD Price Adjusted Price	6.4 1.1	40.0 7.1	11.6 2.1
Tanzania	1200	DDD Price Adjusted Price	4.0 1.0	10.0 2.4	9.2 2.2
Uganda	920	DDD Price Adjusted Price	2.0 0.6	10.0 3.2	15.6 4.9

*Income adjusted price = DDD price in the country x Lowest PPP-based GDP per Capita in sampled countries (DRC) PPP-based GDP per Capita Country.

Facility-Based Provision of Medication to Women with Pre-Eclampsia and Eclampsia

Provision of appropriate antihypertensive medication for women presenting at health care facilities with PE and eclampsia is part of WHO/IMPAC standards for definitive treatment for these conditions in developing countries. In one study assessing the timeliness of care for severe PE and eclampsia in Benin, Ecuador and Jamaica, only 77% of women received treatment with antihypertensive medications (see Table 12). Health facilities in Jamaica provided medication to more than 80% of women

presenting at health care facilities with PE and eclampsia and those in Ecuador to about 80% of its patients, but facilities in Benin provided medication to less than 40% of pre-eclamptic and less than 80% of eclamptic patients. Of the nine cases in the study where antihypertensive medication was not given, four had a delayed/missed diagnosis, and one did not buy the medication. Reasons for lack of provision of antihypertensive medication were unclear for the remaining four women (Edson et al. 2007).

Table 12: Provision of Antihypertensive Medication to Patients Presenting with Severe Pre-Eclampsia and Eclampsia in Benin, Ecuador and Jamaica

	N	Yes, % (N)	No, % (N)	Missing (N)
Severe PE	49	71.4 (35)	12.2 (6)	16.3 (8)
Eclampsia	42	83.3 (35)	7.1 (3)	9.5 (4)
All	91	76.9 (70)	9.8 (9)	13.2 (12)

Based on a quality of care study in three hospitals in Mexico City (Perez-Cuevas et al. 2007), women presenting with PE fare better than their counterparts in Benin, Ecuador and Jamaica. About 87% of women with mild PE received antihypertensive medications, and 96% of women with severe PE received medication at the time of delivery.

According to the MCHIP QoC surveys, antihypertensive medications were administered to at least two of nine suspected PE/E cases in Madagascar. In at least one case, medication was not administered to a woman who was a candidate for them even though the medications were available in the facility (Rasolofomanana et al. 2011). In Mozambique, antihypertensive medications were provided to seven of eight cases of PE/E (MCHIP Report 2013). Finally, in Tanzania, only two of eight PE/E cases were treated with appropriate antihypertensive medications, and medication was provided inappropriately in three cases (Plotkin et al. 2011).

Conclusions of Unmet Need

At least 15 countries include antihypertensive drugs appropriate in pregnancy on their NEML. However, none of the NEMLs were in complete alignment with the WHO/EML, and most NEMLs did not include amlodipine or hydralazine. Studies in low-income countries suggest that reasons for non-compliance with WHO/EML include lack of political will, insufficient

human and financial resources, and conflicts of interest. Although listing medicines on NEMLs does not mean they are more often prescribed by physicians, NEML drugs are cheaper, and their listing on NEML may lead to price reduction through reduced taxes and custom fees, choice of less expensive suppliers and government subsidies.

Although antihypertensive drugs are available in a larger portion of the private than public sector, the cost of drugs is higher in the private sector. Medications are generally cost-inhibitive and an important factor in non-compliance among individuals with hypertensive disorders. Listing antihypertensive medications appropriate in pregnancy on NEMLs may increase their use.

Finally, although the absence of antihypertensive medications in some health care facilities may be one factor in the lack of provision to pregnant women with HTN or PE/E, missed and delayed diagnoses are an additional important factor, especially in poorer countries. In these countries, staff require adequate training to diagnose and treat HTN among pregnant women, as well as PE and eclampsia. Other reasons for lack of provider compliance in providing medication as noted in MCHIP are not reported.

Appendix: Studies of Hypertension in Pregnancy: Population-Based and Clinic- and Facility-Based Studies

Population-Based Studies

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country or Region	Study Sample and Source of Data	Measures of Hypertensive Disorders	Prevalence Estimates, % (n)
Allen VM, Joseph K, Murphy KE, Magee LA, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population-based study. *BMC Pregnancy Childbirth.* 2004; 4: 17.	Nova Scotia, Canada	135,466 singleton births to residents of Nova Scotia, Canada, between 1988 and 2000 at least 20 weeks of pregnancy and birth weight 500 grams or more with no known major fetal anomalies. Data were obtained from the Nova Scotia Atlee Perinatal Database, which contained several hundred variables including maternal diagnoses and morbidity for all pregnancies and births in Nova Scotia hospitals and residents since 1988. The database included diagnoses of hypertensive disorders in pregnancy occurring during the antepartum and postpartum periods.	Medical records: Mild PIH: physician diagnosis if transient HTN or diastolic BP over 90 mm Hg on two or more occasions in 24 hours. Severe PIH: physician diagnosis if diastolic BP 110mm or over on two or more occasions in six hours, magnesium sulfate administered for seizure prophylaxis, if 2=proteinuria, low platelets or elevated liver enzymes; HELLP and eclampsia also measured. Chronic HTN: History when not pregnant or before 20 weeks; PIH superimposed on chronic HTN as well.	Mild PIH: 7.7 (10,460) Severe PIH: 1.3 (1,770) HELLP: 0.15 (202) Eclampsia: 0.002 (32) Chronic HTN, without PIH: 0.6 (767) Chronic HTN, with PIH: 0.4 (475) Total Chronic HTN: 0.9 (1,242) ANY HTN disorder: 10.1 (13,760)
Alves E, Correia S, Barros H, Azevedo A. Prevalence of self-reported cardiovascular risk factors in Portuguese women: a survey after delivery. *Int J Public Health.* 2012; 57: 837–847.	Porto, Portugal	8,182 mothers consecutively invited after delivery using the birth cohort Geracao XXI. Recruitment between April 2005 and September 2006 at all five public maternity units in six municipalities of the metropolitan area of Porto, Portugal. All maternities, except one, are included in a general hospital, with a variety of medical and surgical specialties; all correspond to level III maternity units, with differentiated perinatal support.	Data collected by questionnaire and abstracted from medical records for a history of HTN.	HTN: 1.7
Bateman BT, Shaw KM, Kuklina EV, Cllaghan WM, Seely EW, Hernandez-Diaz S. Hypertension in women of reproductive age in the United States: NHANES 1999–2008. *PLoS One.* 2012; 7: e36171.	US	56,494,634 deliveries from 1995–2008 in the Nationwide Inpatient Sample (NIS; part of Healthcare Cost & Utilization Project (HCUP), a federal-state-industry partnership funded by the Agency for Healthcare Research & Quality (AHRQ). NIS is a 20% stratified sample of all nonfederal, short-term, general and specialty hospitals open to the public, as defined by the American Hospital Association. NIS hospitals selected on number of beds, rural/urban location, region, teaching status and ownership. NIS includes all discharges from sampled hospitals.	HTN in pregnancy based on ICD-9-CM codes collected for billing using following non-mutually exclusive categories: chronic HTN, primary HTN and secondary HTN (chronic HTN in association with conditions that cause HTN through vascular or endocrine mechanisms).	Chronic HTN: 1.3 (731,694) Secondary HTN: 1.2 (649,899) Primary HTN: 0.1 (81,795)

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country or Region	Study Sample and Source of Data	Measures of Hypertensive Disorders	Prevalence Estimates, % (n)
Bombard JM, Dietz PM, Galavotti C, England LJ, Tong VT, Hayes DK, Morrow B. Chronic diseases and related risk factors among low-income mothers. *Matern Child Health J.* 2012; 16: 60–71.	Florida, Nebraska, New York (excluding New York City), Ohio, Washington, Vermont and South Carolina	14,990 women with a live birth in seven states (Florida, Nebraska, New York (excluding New York City), Ohio, South Carolina, Washington and Vermont) using Pregnancy Risk Assessment Monitoring System (PRAMS) data for 2005–2006 and linked birth certificate data for states with a 70% response rate in PRAMS and that implemented the 2003 revised birth certificate. (PRAMS data include maternal experiences and behaviors before, during and after pregnancy.)	Birth certificate included information on chronic HTN, and pregnancy-induced HTN (diagnosed first in pregnancy). Birth certificate data on HTN were not available in New York City.	Chronic HTN: 1.2 PIH: 4.7
Cheng D, Barra S. Hypertension during Pregnancy, Maryland PRAMS, Maryland Department of Health and Mental Hygiene, 2012.	Maryland	10,915 Maryland mothers who delivered live births in 2004–2010 and were surveyed 2–9 months after delivery, through PRAMS. Each month, sample of 200 Maryland women who recently delivered live-born infants is surveyed by mail or telephone, and responses are weighted to make the results representative of all Maryland births.	Identified HTN during pregnancy using maternal self-reports, not a clinical diagnosis.	HTN during pregnancy: 11.0
Hayes D, Shor R, Roberson E, Fuddy L. *Maternal High Blood Pressure and Pregnancy Fact Sheet.* Honolulu, HI: Hawaii Department of Health, Family Health Services Division; 2010.	Hawaii	Sample of live births to mothers from 2004–2008 in Hawaii, about 2,000 per year sampled for PRAMS; total number of births not given.	High blood pressure (HBP) reported on the birth certificate as chronic HTN, pregnancy-associated HTN, eclampsia, or seizures during labor or on PRAMS Survey as HBP, HTN, pregnancy-induced HTN, PE or toxemia.	HBP: 12.8% Chronic HBP: 2% Pregnancy-related HBP: 11%
Kuklina EV, Meikle SF, Jamieson DJ, Whiteman MK, Barfield WD, Hillis SD, Posner SF. Severe obstetric morbidity in the United States: 1998–2005. *Obstet Gynecol.* 2009; 113: 293–239.	US	7,605,289 hospitalizations during 1998–1999 and 8,409,938 hospitalizations during 2004–2005 were recorded using the NIS of the Healthcare Cost and Utilization Project (HCUP), a federal-state-industry partnership sponsored by AHRQ.	Identified HTN during pregnancy using ICD-9-CM; includes both gestational and pre-gestational HTN.	HTN 1998–99: 2.1 HTN 2004–05: 2.8
Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol.* 2009; 113: 1299–1306.	US	36,537,061 deliveries from 1998–2006 using the NIS of the HCUP. The NIS is the largest all-payer inpatient care database in the United States and uses discharges from the sampled hospitals to produce nationwide estimates.	Identified HTN in pregnancy using ICD-9-CM; classified in four mutually exclusive categories: eclampsia or severe pre-eclampsia (PE); mild PE, chronic HTN and gestational HTN.	Eclampsia/severe PE: 1.1 (394,596) Mild PE: 2.3 (824,604) Chronic HTN: 1.3 (489,153) Gestational HTN: 2.7 (996,092)

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country or Region	Study Sample and Source of Data	Measures of Hypertensive Disorders	Prevalence Estimates, % (n)
Lawler J, Osman M, Shelton JA, Yeh J. Population-based analysis of hypertensive disorders in pregnancy. *Hypertens Pregnancy*. 2007; 26: 67–76.	Western New York	77,358 women with singleton births from 1999–2003, included in the Western New York Perinatal Data System (PDS). PDS is a regionalized, perinatal data system based on the New York Electronic Birth Certificate for deliveries that occurred in the 17 hospitals with obstetrical services in the region.	The PDS and New York birth certificates separately classified in the following mutually exclusive categories: gestational HTN (PIH), PE, chronic HTN and eclampsia.	PIH: 2.3 (1,809) PE: 1.4 (1,103) Chronic HTN: 0.96 (741) Eclampsia: 0.09 (68)
Miranda ML, Swamy GK, Edwards S, Maxson P, Gelfand A, James S. Disparities in maternal hypertension and pregnancy outcomes: evidence from North Carolina, 1994–2003. *Public Health Rep*. 2010; 125: 579–587.	North Carolina	Study population: 350,717 singleton births to women 15–44 in North Carolina (NC) in 1994–2003 with no documented congenital anomalies. Excluded women with maternal complications besides HTN disorders. NC Detailed Birth Record provided data on maternal age, birth weight, clinical estimate of gestation, plurality, maternal complications, congenital abnormalities, maternal tobacco use and characteristics.	The NCDBR contains three medical history variables related to HTN: pregnancy-related HTN, chronic HTN and eclampsia. All three HTN designations were combined into a single category of "any HTN disorder."	HTN disorders: 8.18
Roberts CL, Algert CS, Morris JM, Ford JB, Henderson-Smart DJ. Hypertensive disorders in pregnancy: a population-based study. *Med J Aust*. 2005; 182: 332–335.	New South Wales (NSW), Australia	Linked birth and hospital records for 250,173 women from 2000–2002 (over 97% linkage) using data from the Midwives Data Collection (MDC) and the Inpatient Statistics Collection (ISC). ISC, a census of NSW inpatient hospitalizations, includes data from medical records coded according to ICD-10, while the MDC is a population-based surveillance system of all NSW births of at least 20 weeks' gestation or 400 grams or more.	Identified hypertension (HTN) during pregnancy in either dataset using 21 ICD-10; classified in mutually exclusive categories: chronic HTN; PE and eclampsia; chronic HTN with superimposed PE; and gestational HTN or HTN (unspecified).	Chronic HTN: 0.57 (1,411) PE: 4.15 (10,379) Chronic HTN with PE: 0.29 (731) Gestational HTN: 4.34 (10,864) Unspecified HTN: 0.45 (1,132) Eclampsia: 0.06 (161) HTN disorders: 9.80 (24,517)

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country or Region	Study Sample and Source of Data	Measures of Hypertensive Disorders	Prevalence Estimates, % (n)
Roberts CL, Ford JB, Algert CS, Antonsen S, Chalmers J, Cnattingius S, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. *BMJ Open.* 2011; 1: e000101.	Australia (NSW and Western Australia), Alberta, Denmark, Norway, Scotland, Sweden and Massachusetts	Population health data (record-linked birth and hospital data, where available) for pregnancy HTN and PE in eight collaborating centers providing national or regional health data. Record-linked birth and hospital data used in Australia, Denmark and Massachusetts; Alberta, Canada (2002–07, 256,137) Australia: New South Wales, (1998–2006, 732,288) Western Australia, (2000–05,149,624) Denmark (1997–2006, 645,993) Norway (1999–2006, 456,353) Scotland (1997–2002, 531,622) Sweden (1997–2006, 913,779) Massachusetts (1998–2007, 762,723)	Coding of HTN based on ICD-9 or ICD-10 into mutually exclusive categories; pregnancy HTN PE, and early-onset PE (34 weeks or earlier).	Alberta, Canada: Chronic HTN: 0.4; PE:1.4, Any PIH: 6.0; All HTN: 6.4 New South Wales, Australia: Chronic HTN: 1.2; PE: 3.1; Any PIH: 8.8; All HTN:10.0 Western Australia: Chronic HTN: 1.1; PE: 2.9, Any PIH: 9.1; All HTN: 10.2 Denmark: Chronic HTN: 0.4; PE: 2.7; Any PIH: 3.6; All HTN: 4.0 Norway: Chronic HTN: 0.6; PE: 4.0; Any PIH: 5.8; All HTN: 6.4 Scotland: Chronic HTN: 0.3; PE: 2.2; Any PIH: 5.9; All HTN: 6.2 Sweden: Chronic HTN: 0.5; PE: 2.9; Any PIH: 3.9; All HTN: 4.4 Massachusetts: Chronic HTN: 1.6; PE: 3.3; Any PIH: 7.0 All HTN: 8.6
Su CY, Lin HC, Cheng HC, Yen AM, Chen YH, Kao S. Pregnancy outcomes of anti-hypertensives for women with chronic hypertension: a population-based study. *PLoS One* 2013; 8: e53844.	Taiwan	218,781 women with singleton live births in Taiwan during 2005. Data from two national databases, the National Health Insurance Research data set with comprehensive registration files and original claims data, and the birth certificate registry from the Taiwan Department of Health, with information about both infants and mothers.	Chronic HTN before pregnancy using outpatient or inpatient discharge diagnosis ICD-9-CM codes 401–405 for women eligible for cohort study (2,727) or who received Angiotensin II Receptor Blockers (ARBs) or ACE inhibitors (120) or more than one anti-HTN drug (722). PE defined by ICD-9CM codes 642.5 and 642.6 and gestational HTN by codes 642.	HTN: 1.63 (3,569) PE: 1.24 (2,721)
Tanaka M, Jaamaa G, Kaiser M, Hills E, Soim A, Zhu M, et al. Racial disparity in hypertensive disorders of pregnancy in New York State: a 10-year longitudinal population-based study. *Am J Public Health.* 2007; 97: 163–170.	New York	New York State discharge data for 2,571,069 women with delivery hospitalization from 1993–2002. The NYS hospital discharge database, Statewide Planning and Research Cooperative System (SPARCS), was formed in 1979 to monitor and fiscally manage inpatient and ambulatory hospitalization services in NYS.	Identified HTN in pregnancy recorded as discharge diagnoses using 10 ICD-9-CM; classified based on the most severe form: essential HTN; gestational HTN; PE; severe PE and eclampsia; PE superimposed on pre-existing HTN.	Essential HTN: 1.2 PIH: 1.5 PE: 2.4 PE superimposed on pre-existing HTN: 0.3 Severe PE and eclampsia: 0.8

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country or Region	Study Sample and Source of Data	Measures of Hypertensive Disorders	Prevalence Estimates, % (n)
Zetterström K, Lindeberg SN, Haglund B, Hanson U. Maternal complications in women with chronic hypertension: a population-based cohort study. *Acta Obstet Gynecol Scand.* 2005; 84: 419–424.	Sweden	Study population: 681,515 singleton births to Swedish women 15–44 years in 1992–98. Excluded women with diabetes, chronic renal disease or systemic lupus erythematosus (SLE). Data taken from the Swedish Medical Birth Register (SWBR, 99% of all births in Sweden). Starting at the first prenatal visit, demographic data, reproductive history and complications during pregnancy, delivery and neonatal period are prospectively collected for all hospital births and forwarded to SWBR through copies of standardized individual antenatal, obstetric and pediatric records.	Chronic HTN defined by either the ICD-9 or ICD-10 coding system or as HTN reported in a check-box. Diagnosis of PE in the Swedish version of ICD-9 and ICD-10 is based on a simplified version of the criteria proposed by Davey and MacGillivray.	Chronic HTN: 0.5 (3,374) PE: 2.78 (18,966)
Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy.* 2003; 22 (2): 203–212.	US	Study population includes 299,499 records representing 38,923,280 births; all sampled women who gave birth from 1988–1997, using the National Hospital Discharge Survey, a survey conducted by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC).	Identified HTN in pregnancy using 9 ICD-9-CM; classified in mutually exclusive categories: chronic HTN; transient HTN; mild PE, severe PE, eclampsia, PE or eclampsia superimposed on chronic HTN; unspecified HTN.	Chronic HTN: 0.61 (239,327) Transient HTN: 1.77 (689,756) Mild PE: 2.0 (780,042) Severe PE: 0.57 (223,461) Eclampsia: 0.1 (39,502) PE/E superimposed on HTN 0.18 (68,772) Unspecified HTN: 0.63 (244,331)

STUDIES OF **ONLY** SEVERE HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Ghana Statistical Service, Ghana Health Service, and Macro International. 2009. *Ghana Maternal Health Survey 2007.* Calverton, MD, US: Ghana Statistical Service, Ghana Health Service and Macro International.	Ghana	Subsample of households from 2007 Ghana Maternal Health Survey collected information from 10,370 pregnant women ages 15–49.	Self-reported edema.	Edema/PE: 2.0 (207)
Souza JP, de Sousa MH, Parpinelli MA, Amaral E, Cecatti JG. Self-reported maternal morbidity and associated factors among Brazilian women. *Rev Assoc Med Bras.* 2008; 54: 249–255.	Brazil	12,612 women ages 15–49 interviewed in the 1996 DHS for Brazil with pregnancies resulting in a maximum of six live births in the five preceding years.	Self-reported convulsions.	Convulsions: 2.7 (4,968)
Conde-Agudelo A, Belizan J. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *BJOG.* 2000; 107: 75–83.	LAC	Retrospective analysis of hospital records of all pregnancies (878,680) recorded from 1985–1997 in 19 countries in Perinatal Information System (a central system linking vital statistics with perinatal information) that ended in live births or stillbirths of at least 20 weeks' gestation or birth weight at least 500 g; depending on country, information was from many or all public health institutions.	PE or eclampsia as noted in perinatal records.	PE: 4.8 (42,530) Eclampsia: 0.2 (1,872)
Ashley D, McCaw-Binns A, Foster-Williams K. The perinatal morbidity and mortality survey of Jamaica 1986–1987. *Paediatric and Perinatal Epi.* 1988; 2: 138–147.	Jamaica	Prospective study of all pregnant women (10,310) in Jamaica who delivered a live birth or still birth of 500 g or more during a two-month period (September 1–October 31, 1986).	PE defined as HTN + proteinuria.	PE: 4.2 (HTN + proteinuria) Eclampsia: 0.7%
Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A; MOMS-B Group. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. *BJOG.* 2005; 112: 89–96.	Austria, Belgium, Finland, France, Hungary, Ireland, Italy, Norway and the UK	182,734 deliveries from 11 regions in nine European countries, during small time periods between January 1995 and February 1998. In most countries, data collection took place in one region; in France, three regions were included and the whole country for Finland. Data were collected on women who delivered after 24 completed weeks of gestation and who experienced one or more of the three conditions studied.	Diagnosis of severe PE was clinical, taken from the US National High Blood Pressure Education Program Working Group report on high blood pressure in pregnancy. The three blood criteria related to platelets, creatinine and hepatic enzymes were not used.	Severe PE: 0.4 (793)

STUDIES OF **ONLY** SEVERE HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Bouvier-Colle MH, Mohangoo AD, Gissler M, Novak-Antolic Z, Vutuc C, Szamotulska K, et al. What about the mothers? An analysis of maternal mortality and morbidity in perinatal health surveillance systems in Europe. *BJOG.* 2012; Jun; 119: 880–889.	25 countries in European Union and Norway	Data from the EURO-PERISTAT project, in which members of the EURO-PERISTAT Scientific Committee were responsible for organizing data collection in their country. They compiled data published by national organizations or provided the names of people to whom the data collection instruments should be sent. EURO-PERISTAT gathers population-based data at a national level. Regional data were accepted if they covered a geographically defined population. Only data from existing routine sources including vital registration systems, hospital administrative data, systems or regular surveys were used.	Identified eclampsia using ICD-10 codes.	Eclampsia rates (per 1,000): Czech Republic: 0.2 Denmark: 0.3 Estonia: 0.6 Finland: 0.2 France: 1.1 Germany-Bavaria: 0.7 Hungary 0.5 Italy: 1.6 Latvia: 0.4 Malta: 1.3 The Netherlands: 0.7 Poland: 0.2 Scotland only: 0.6 Slovenia: 1.1 Spain-Valencia: 0.3 United Kingdom: 0.67
Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. *Obstet Gynecol.* 2012; 120: 1029–1036.	United States	49,346,974 deliveries, 738,124 postpartum hospitalizations and 5,604 in-hospital mortalities in 1998–2009 from the Nationwide Inpatient Sample (NIS) of HCUP, a federal-state-industry partnership sponsored by AHRQ. NIS is the largest all-payer inpatient care database in US using discharges from sampled hospitals to produce nationwide estimates.	Identified eclampsia using ICD-9-CM.	Eclampsia: 3.5 (196)

HYPERTENSION IN WOMEN OF CHILDBEARING AGE				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Chowa PE, Lin C, Goma F, South-Paul J. Prevalence of Hypertension Among Women of Child Bearing Age in Zambia. *Medical Journal of Zambia. 2011; 38:3-8.*	Zambia	Study sample included 150 women during their regularly scheduled gynecological visits at the Department of Gynecology at the University Teaching Hospital, Lusaka City, and 104 women at the Liteta Hospital, Chibombo District. Women were between the ages of 18 and 45 years and came to one of the two hospitals for a routine gynecological visit.	HTN was defined as 140/90 mmHg or greater.	HTN: 18.6 (Urban) HTN: 6.7 (Rural)
Robitaille C, Dai S, Waters C, Loukine L, Bancej C, Quach S, et al. Diagnosed hypertension in Canada: incidence, prevalence and as associated mortality. *CMAJ*. 2012; 184: E49–E56.	Canada	Retrospective, population-based cohort study of more than 26 million Canadian men and women 20 years and older from 1998/99 to 2007/08. Excluded women ages 20–54 with suspected pregnancy-induced HTN (diagnosis code for HTN 120 days before or 180 days after any pregnancy-related visit). Data obtained from linked health administrative databases, including the Canadian Chronic Disease Surveillance System, a collaborative network of provincial and territorial surveillance systems collecting information on diabetes and other chronic conditions; health insurance registries; the physician billing database; and the Canadian Institute for Health Information's Discharge Abstract Database, which includes all patients discharged from a hospital. Denominator for incidence and prevalence was the total number of people eligible for health insurance in a province or territory; includes results only from women ages 20–44.	Insured individuals had diagnosed HTN if they met the following criteria: Either two or more physician claims for HTN within two years, or one recording of HTN in the hospital discharge abstract. ICD codes were used to identify HTN cases (ICD-9-CM: 401.x, 402.x, 403.x, 404.x, 405.x; OCD-10-CA: I10.x, I11.x, I12.x, I13.x or I15.x). Cases were deemed incident in the first year in which they met the case definition. Prevalence cases while patients were alive and resided in province or territory and health insurance number was valid.	Prevalence (%); Incidence, per 100 per year Women only: 20–24 years: Pr=0.5; In=0.2 25–29 years: Pr=1.6; In=0.3 30–34 years: Pr=3.2; In=0.4 35–39 years: Pr=5.2; In=0.7 40–44 years: Pr=8.7; In=1.2
Bateman, BT, Shaw KM, Kuklina EV, Cllaghan WM, Seely EW, Hernandez-Diaz S. Hypertension in women of reproductive age in the United States: NHANES 1999–2008. *PLoS One*. 2012; 7: e36171.	US	Identified 5,521 women aged 20–44 years old from 1999–2008 NHANES, a nationally representative, cross-sectional survey (with physician examination) designed to assess the health and nutritional status of the US civilian, non-institutionalized population. Data were analyzed from five survey periods. Overall examination survey response rates ranged from 75–80%.	HTN defined as having an average BP $\geq$140/90 mmHg (as measured by physician using an appropriately sized cuff); or those who self-reported taking anti-HTN medications.	HTN % (95% CI) by survey cycle: 1999–2000: 8.0 (6.3–10.1) 2001–2002: 7.3 (5.5–9.6) 2003–2004: 7.3 (5.7–9.1) 2005–2006: 6.0 (4.6–7.8) 2007–2008: 9.3 (7.5–11.4) Overall: 7.7 (6.9–8.5)

HYPERTENSION IN WOMEN OF CHILDBEARING AGE				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Hayes DK, Fan AZ, Smith RA, Bombard JM. Trends in selected chronic conditions and behavioral risk factors among women of reproductive age, Behavioral Risk Factor Surveillance System, 2001–2009. *Prev Chronic Dis.* 2011; 8: A120.	US	Data for 327,917 women aged 18–44 from 2001–2009 Behavioral Risk Factor Surveillance System, state-based telephone survey of health behavior in US adults. Analysis restricted to 2003–2009 due to a substantially different question about blood pressure in the 2001 survey. Excluded women pregnant at time of survey and women with missing data on any risk factor, chronic condition or covariates in specific analyses. Missing data ranged from 0.05–6.4%.	High blood pressure was considered present if the woman reported she had ever been told by a doctor or other health professional that she had the condition.	Chronic high blood pressure by survey year; % (95% CI) 2003: 9.0 (8.6–9.4) 2005: 9.2 (8.8–9.6) 2007: 9.8 (9.4–10.2) 2009: 10.1 (9.7–10.5)

Hospital- and Clinic-Based Studies

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Gaio DS, Schmidt MI, Duncan BB, Nucci LB, Matos MC, Branchtein L. Hypertensive disorders in pregnancy: Frequency and associated factors in a cohort of Brazilian women. *Hypertens Pregnancy*. 2001; 20: 269–281.	Brazil	Cohort study of 4,892 women aged 20 years or older without a history of previous non-pregnancy-related diabetes mellitus who presented at selected centers of the Brazilian National Health System from 1991–1995 in six Brazilian state capitals (based on Brazilian Study of Gestational Diabetes).	Chronic HTN, PE, eclampsia, superimposed PE/eclampsia as noted in medical records.	PE/eclampsia: 2.3 (113) Chronic HTN: 4.0 (198) Superimposed PE/eclampsia: 0.5 (24) Transitory HTN: 0.7 (32) Total HTN: 7.5 (367)
Vigil-De Gracia P, Montufar-Rueda C, Smith A. Pregnancy and severe chronic hypertension: maternal outcome. *Hypertens Pregnancy*. 2004; 23: 285–293.	Panama City	Medical records from 26,825 women delivered between July 1996 and June 2001 at the Complejo Hospitalario "Arnulfo Arias Madrid" de la Caja de Seguro Social in Panama City, which serves as a hospital of tertiary care facility and reference for all the Republic of Panama.	Mutually exclusive categories: chronic HTN and severe chronic HTN (severe if maximum systolic at least 160 or maximum diastolic at least 110 on two occasions more than four hours apart after receiving first dose of antihypertensive drugs only in second half of pregnancy).	Chronic HTN: 2.2 (591) Severe HTN: 0.6 (154)
Póvoa AM, Costa F, Rodrigues T, Patrício B, Cardoso F. Prevalence of hypertension during pregnancy in Portugal. *Hypertens Pregnancy*. 2008; 27: 279–284.	Portugal	National Survey of HTN in 85% of public maternity wards in Portugal in November 2005, where 90% of deliveries occur; obstetricians completed questionnaires and medical records obtained at time of discharge for 6,723 pregnancies of at least 24 weeks' gestation; estimated to be 82% of deliveries in Portugal.	Chronic HTN: BP at least 140/90 mmHg before pregnancy or before 20 weeks gestation; Gestational HTN: BP at least 140/90 mmHg first noted in pregnancy; PE BP at least 140/90 mmHg after 30 weeks with proteinuria 300 mg protein, or 1+ dipstick, also with gestational HTN or HELLP syndrome.	Chronic HTN: 1.5 (1.2; 1.8) (99) Gestational HTN: 2.5 (2.1; 2.9) (166) PE: 1.4, (1.1;1.7) (91); 2.0 (122) Any HTN: 6.0 (5.4; 6.6)
Yucesoy G, Ozkan S, Bodur H, Tan T, Caliskan E, Vural B, et al. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. *Arch Gynecol Obstet.* 2005; 273: 43–49.	Kocaeli, Turkey	5,155 deliveries found using the medical records of gravid women managed at Kocaeli University, School of Medicine, Department of Obstetrics and Gynecology, between June 1997 and June 2004.	Diagnosis of HTN in pregnancy based on criteria defined by the National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy.	HTN in pregnancy: 8.49 (438)

STUDIES OF HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Zareian Z. Hypertensive disorders of pregnancy. *Int J Gynaecol Obstet.* 2004; 87:194–198.	Iran	Retrospective analysis of medical records of all pregnant patients (2,300) referred for delivery to Shahid Mottahari Clinic of Jahrom (SW Iran) from September 23, 2002 to September 22, 2003.	Disorders as noted in medical records using WHO definition to determine PE.	Chronic HTN: 2.7% HTN disorders: 3.3% (75; 32% with PE, 60% with transient HTN of pregnancy, 4% eclampsia) PE superimposed on chronic HTN: 1.3%
Urasa DP, Nystrom L, Carlstedt A, Msamanga GI, Lindmark G. Management of hypertension in pregnancy as a quality indicator of antenatal care in rural Tanzania. *African J Reprod Health.* 2003; 7: 69–76.	Tanzania	Prospective study of clinic-based sample of 379 pregnant women receiving antenatal care in 30% of Rufiji District clinics providing antenatal care at the dispensary, health center and hospital levels (35% of women not screened for hypertension).	Measured by research observer with newly purchased aneroid sphygmomanometer.	Elevated blood pressure: 3.2 (12)
Perez A, Bacallao J, Alcina S, Gomez Y. Severe maternal morbidity in the intensive care unit of a Havana teaching hospital, 1998 to 2004. *MEDICC Rev.* 2008; 10: 17–23.	Havana, Cuba	312 obstetric patients admitted to ICU 1998–2004 at Enrique Cabrera General Teaching Hospital in Havana, Cuba, with length of stay over 24 hours and whose family members provided informed consent. Data collected daily and updated from patients' charts and daily case discussions by medical team in charge of critically ill obstetric patients. Discharge diagnosis for 109 women.	HTN was recorded as a pre-existing illness or the patient ICU discharge status.	HTN: 10.1 (11)

STUDIES OF ONLY SEVERE HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Minkauskiene M, Nadisauskiene RJ, Padaiga Z. Severe and acute maternal morbidity: Lithuanian experience and review. *Int J Fertil Womens Med.* 2006; 51: 39–46.	Lithuania	All deliveries (13,399) in seven primary, secondary or tertiary maternity care units from different regions of Lithuania. Study sample represented 45.3% of the Lithuanian maternity population. The number of deliveries was used as the denominator to calculate incidence of every SAMM condition.	Severe PE: BP over 170/110 mmHg on two occasions after six months; BP over 160/100 plus $\geq$0.3 g proteinuria in 24 hours or $>$0.3 g in urinalysis; or BP of 140/90 mmHg plus proteinuria with: visual disturbances, liguria, vomiting, severe headache, epigastric or right upper quadrant pain, thrombocytopenia or increased aspartate amino-transferase. Eclampsia: pre-natal convulsions or first 10 days postpartum and features in 24 hours after convulsions (2): HTN, proteinuria, in-creased aspartate aminotransferase, thrombocytopenia. HELLP syndrome: three criteria present: hemolysis, raised liver enzyme activity and low platelets.	Severe PE: 0.425 (57) Eclampsia: 0.022 (2) HELLP: 0.007 (1)
Chen CL, Cheng Y, Wang PH, Juang CM, Chiu LM, Yang MJ, Hung CS, Yang ML. Review of pre-eclampsia in Taiwan: a multi-institutional study. Zhonghua Yi Xue Sa Zhi (Taipei) 2000; 63:869-875.	Taiwan	All cases of PE and eclampsia in 14 medical centers and regional hospitals among 206,551 deliveries in Taiwan from 1993–1999. Patients' charts were reviewed by using a defined data collection form, which included age, parity, gestational age and month at onset of PE, and maternal symptoms and signs.	PE defined as PIH (systolic blood pressure $>$140 mmHg or diastolic blood pressure $>$90 mmHg) with proteinuria and independent part edema. Complications included eclampsia.	PE and eclampsia: 2.0 (4,193)
Ghandi MN, Welz T, Ronsmans C. Severe acute maternal morbidity in rural South Africa. *Int J Gynaecol Obstet.* 2004; 87: 180–187.	South Africa	5728 deliveries over a nine-month period in all four primary hospitals in the rural Jozini Health District of KwaZulu Natal. Included 31 cases of SAMM, defined as "a women who, at any time in pregnancy until six weeks postpartum, suffered acute, severe organ dysfunction that could have resulted in maternal death had it not been for appropriate medical treatment."	Identified SAMM cases as eclampsia by the local team and external specialist.	Eclampsia: 0.2% (12; 39% of SAMM cases)

STUDIES OF ONLY SEVERE HYPERTENSION IN PREGNANCY				
Reference	Country	Study Sample and Source of Data	Measures of HTN Disorders	Prevalence Estimates, % (n)
Ghazal-Aswad S, Badrinath P, Sidky I, Safi TH, Gargash H, Abdul-Razak Y, Mirghani H. Severe acute maternal morbidity in a high-income developing multiethnic country. *Matern Child Health J.* 2013;17: 399–404.	Abu Dhabi, UAE	122,705 deliveries in four maternal units in the Emirate of Abu Dhabi between 1998 and 2003. A total of 926 cases with severe maternal morbidity were identified.	All relevant information was collected and recorded by the principal investigator and the lead clinician in the birth units in a pre-defined format. Eclampsia, HELLP and severe PE were based on clinical criteria.	PE 0.37: (459) Eclampsia: 0.057 (71) HELLP: 0.02 (23)
Chantry AA, Deneux-Tharaux C, Cans C, Ego A, Quantin C, Bouvier-Colle MH, et al. Hospital discharge data can be used for monitoring procedures and intensive care related to severe maternal morbidity. *J Clin Epidemiol.* 2011; 64: 1014–1022.	France	30,614 deliveries identified using computerized medical records from four French hospitals (Caen, Cochin [AP-HP, Paris], Grenoble and Lille university hospitals) and selected according to hospitalizations of women of reproductive age with at least one code for pregnancy, delivery or postpartum, and who were discharged between January 2006 and December 2007. Medical record, considered the gold standard, was compared with discharge data from the Programme of Medicalization of Information System (PMSI), established in 1991 and extended in 1997 to all French health care facilities.	Identified by PMSI ICD 10 code: O15.	Among 64,061 abstracts: eclampsia: 0.14% (89) (PMSI) Among 30,614 deliveries: eclampsia: 0.065% (20) (Medical Records)
Tukur J, Umar BA, Rabi'u A. *Ann Afr Med.* 2007; 6: 164–167.	Nigeria	Retrospective analysis of medical records of all women (2,197) who delivered at the Federal Medical Centre (tertiary hospital in rural northern Nigeria) between 2002 and 2005. Eclamptics were generally managed by sedation with intravenous diazepam, treatment of severe HTN with intravenous hydralazine and delivering the baby through the safest and fastest means.	Eclampsia as noted in medical record. Diagnostic measure not articulated.	Eclampsia: 9.42 (207)
Moodley J, Daya P. Eclampsia: a continuing problem in developing countries. *Int J Gynaecol Obstet.* 1994; 44: 9–14.	South Africa	Retrospective analysis of hospital records of all hospital deliveries at King Edward VIII Hospital in 1980 (16,276) and 1990 (14,268).	Eclampsia as noted in hospital record. Diagnostic measure not articulated.	Eclampsia in 1980: 0.3 Eclampsia in 1990: 0.6
Siddiqui SA, Soomro N, Shabih-ul-Hasnain F. Severe obstetric morbidity and its outcome in patients presenting in a tertiary care hospital in Karachi. *J Pak Med Assoc.* 2012;62:226–231.	Karachi, Pakistan	1,508 deliveries at the Obstetric Unit-II of Civil Hospital, Karachi, Pakistan, during April to September 2010, from which 130 patients met the inclusion criteria.	Disease specific criteria, as described by Waterstone et al., used to classify HTN disorders: included both eclampsia and severe PE.	Eclampsia: 1.3 (20) Severe PE: 0.7 (11)

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