

Review

Global and regional estimates of preeclampsia and eclampsia: a systematic review



Edgardo Abalos^{a,*}, Cristina Cuesta^a, Ana L. Grosso^a, Doris Chou^b, Lale Say^b

^a Centro Rosarino de Estudios Perinatales, Moreno 878, P6, 2000 Rosario, Argentina

^b World Health Organization (WHO) Department of Reproductive Health and Research, Geneva, Switzerland

ARTICLE INFO

Article history:

Received 15 February 2013

Received in revised form 18 April 2013

Accepted 6 May 2013

Keywords:

Pregnancy
Hypertensive disorders
Preeclampsia
Eclampsia
Incidence
Epidemiology

ABSTRACT

Reduction of maternal mortality is a target within the Millennium Development Goals. Data on the incidence of preeclampsia and eclampsia, one of the main causes of maternal deaths, are required at both national and regional levels to inform policies. We conducted a systematic review of the incidence of hypertensive disorders of pregnancy (HDP) with the objective of evaluating its magnitude globally and in different regions and settings. We selected studies using pre-specified criteria, recorded database characteristics and assessed methodological quality of the eligible studies reporting incidence of any HDP during the period 2002–2010. A logistic model was then developed to estimate the global and regional incidence of HDP using pre-specified predictor variables where empiric data were not available. We found 129 studies meeting the inclusion criteria, from which 74 reports with 78 datasets reporting HDP were analysed. This represents nearly 39 million women from 40 countries. When the model was applied, the overall estimates are 4.6% (95% uncertainty range 2.7–8.2), and 1.4% (95% uncertainty range 1.0–2.0) of all deliveries for preeclampsia and eclampsia respectively, with a wide variation across regions. The figures we obtained give a general idea of the magnitude of the problem and suggest that some regional variations might exist. The absence of data in many countries is of concern, however, and efforts should be made to implement data collection and reporting for substantial statistics. The implementation of large scale surveys conducted during a short period of time could provide more reliable and up-to-date estimations to inform policy.

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* Corresponding author. Tel.: +54 341 4483887; fax: +54 341 4483887.

E-mail addresses: edgardoabalos@crep.org.ar, crep@crep.org.ar (E. Abalos).

1. Introduction

Hypertensive disorders of pregnancy (HDP) are important causes of maternal mortality. They account for nearly 18% of all maternal deaths worldwide, with an estimated 62,000 to 77,000 deaths per year [1]. As there are about 127 million births annually in the world [2], the risk of maternal death from HDP is approximately one in 1700 to one in 2100 deliveries globally. There is, however, a wide variation across regions in the lifetime risk of a woman dying from maternal causes (from 1 in 3800 in developed countries to 1 in 39 in Sub-Saharan Africa) [3], as well as in the contribution of HDP to the total maternal mortality. In Latin America and the Caribbean HDP represent the highest cause of death, being the second cause in developed countries [1].

There are broad categories for the classification of HDP. These are gestational hypertension, or pregnancy-induced hypertension, which is hypertension without proteinuria; preeclampsia, which is hypertension with proteinuria; and chronic hypertension, or essential hypertension, which is pre-existing hypertension with or without superimposed preeclampsia [4]. Most of the morbidity is concentrated among pregnancies complicated by preeclampsia or eclampsia (when convulsions occur in a woman with preeclampsia), and for every woman who dies, approximately 20 others suffer severe morbidity [5].

Regional, country and provincial variations on the above-mentioned global figures are likely to exist but are not currently known. There is therefore a need to establish the magnitude and the regional distribution of HDP around the world to adequately inform reproductive health policies and programmes. We conducted a systematic review of the incidence of HDP with the objective of evaluating the magnitude of the problem globally and in different regions and settings.

2. Methods

We used the World Health Organization (WHO) Systematic Review of Maternal Mortality and Morbidity Project Protocol as a template [1,6], considering the same criteria for screening, identification and selection of studies to all potentially eligible papers published during the period 2002–2010.

2.1. Search strategy: screening and selection of studies

Medline and Embase databases for the period 2002–2010 were scanned for all potentially eligible studies using the following search terms: preeclampsia, preeclampsia, eclampsia, hypertension, pregnancy-induced, HELLP syndrome, incidence, prevalence, treatment, therapeutics, tertiary prevention, secondary prevention, primary prevention, diagnosis, epidemiology with variations in the terms commonly used (Table 1). Reference lists of identified reports were scanned for related articles. No language restrictions were applied. Two reviewers (EA and ALG) independently screened the citations identified by the searches on the basis of their titles and abstracts. The full text of the report was obtained if both reviewers considered a citation as potentially eligible. A second round of screening of the full papers was undertaken in the same manner. Studies were also assessed and checked by these two reviewers (EA and ALG), who independently completed an ad hoc form. Disagreements were resolved by discussion.

Studies identified through the literature search were included if they reported data on HDP subsequent to 2002. Those studies containing only data prior to 2002 or those, which could not be disaggregated by year that included data from before 1990 were excluded, as they were considered elsewhere [6].

Priority was given to primary papers. For reviews and systematic reviews, only the primary studies complying with

Table 1

Search strategy.

| | |
|--|--|
| MEDLINE^a | |
| 1. Exp hypertension, pregnancy-induced/or exp eclampsia/or exp hellp syndrome/or exp preeclampsia/2. preeclampsia.mp. | |
| 3. Preeclampsia.mp. | |
| 4. 1 or 2 or 3 | |
| 5. Limit 4 to yr="2002–2010" | |
| 6. Incidence.mp. or exp Incidence/ | |
| 7. Prevalence.mp. or exp Prevalence/ | |
| 8. Treatment.mp. or exp Therapeutics/ | |
| 9. Exp Tertiary Prevention/or exp Secondary Prevention/or exp Primary Prevention/or prevention.mp. | |
| 10. Diagnosis.mp. or exp Diagnosis/ | |
| 11. 6 or 7 or 8 or 9 or 10 | |
| 12. Limit 5 to humans | |
| 13. Exp Epidemiology/or epidemiology.mp. | |
| 14. 11 or 13 | |
| 15. 12 and 14 | |
| EMBASE^a | |
| 1. Exp PREECLAMPsia/or exp "ECLAMPsia AND PREECLAMPsia"/or preeclampsia.mp. | |
| 2. Exp ECLAMPsia/or eclampsia.mp. | |
| 3. Pregnancy induced hypertension.mp. or exp maternal hypertension/4. hellp syndrome.mp. or exp HELLP syndrome/5. 1 or 2 or 3 or 4 6. exp EPIDEMIOLOGY/or epidemiology.mp. | |
| 7. Prevalence.mp. or exp PREVALENCE/ | |
| 8. exp INCIDENCE/or incidence.mp. | |
| 9. Treatment.mp. or exp MATERNAL TREATMENT/10. exp SECONDARY PREVENTION/or exp PREVENTION/or prevention.mp. or exp PREVENTION STUDY/or exp PRIMARY PREVENTION/11. exp DIAGNOSIS/or diagnosis.mp. | |
| 12. 6 or 7 or 8 or 9 or 10 or 11 | |
| 13. 5 and 12 | |
| 14. Limit 13 to human | |
| 15. Limit 14 to yr="2002–2010" | |

^a Date of search: March 11th, 2011.

eligibility criteria were extracted and included. For papers publishing data from the same database or dataset, priority was given to those adjusting more with the eligibility criteria (time period, population, etc.). When possible, multiple datasets were created from a single paper if data on country/region, time periods, interventions, special populations, etc. could be disaggregated. Both clinical trials and observational studies (cross-sectional,

Table 2

Quality control definitions.

| | |
|----------------------------------|---|
| Outcome: | 1: if a definition of the outcome was specified 0: if a definition of the outcome was not specified |
| Study design: | 1: for studies that are not controlled trials 0: for controlled trials |
| Population: | |
| Population coverage: | 1: national 0: not national (province/city/hospital) |
| Size of the study [*] : | Preeclampsia/Gestational Hypertension 1: $N \geq 500$ 0: $N < 500$ Eclampsia/Chronic Hypertension 1: $N \geq 1000$ 0: $N < 1000$ |

Quality was established for each outcome.

"1" indicates good quality.

The sum of all items gives an overall assessment of the quality of the study, ranging from 0 (worst quality) to 4 (best quality). At the end, the percentages of articles with general quality ≥ 2 were estimated.

^{*} The size of the study was set to ensure a confidence interval to estimate the incidence of the outcome with a significance level of 0.05 and:

Expected incidence of approximately 4% and precision of 1.7% for Preeclampsia.

Expected incidence of approximately 5% and precision of 1.9% for Gestational Hypertension.

Expected incidence of approximately 1% and precision of 0.6% for Eclampsia.

Expected incidence of approximately 1.5% and precision of 0.75% for Chronic Hypertension.

incidence/prevalence surveys) were considered for inclusion. The intervention and control arms of controlled trials were treated separately and different datasets were created according to the number of groups (i.e.: two datasets for a two-arm trial, one for the intervention group, one for the control group, three datasets for a 3-arm trial, etc.). In the analysis, only the control arm was considered, for external validity. We excluded studies and reports from countries where national data were available for this time window. Articles were also excluded if dates for the data-collection period were not specified or if sample sizes were less than 200 women.

2.2. Outcomes

The four main outcomes analysed as HDP were preeclampsia, eclampsia, pregnancy-induced hypertension and chronic hypertension.

2.3. Quality assessment

To check internal validity, the methodological quality of all datasets was assessed using the following criteria (Table 2):

- Outcomes: whether or not the definition of preeclampsia, eclampsia, gestational hypertension and/or chronic hypertension was specified.
- Study design: whether the data come from observational incidence/prevalence studies, or from randomised controlled trials.

- Population coverage: whether the study reports on national or not national (province/city/hospital) incidence of HDP.
- Sample size (if sample size was >500 or not for preeclampsia and gestational hypertension, and >1000 or not for eclampsia and chronic hypertension): to ensure a narrow confidence interval to estimate the incidence (with a significance level equal to 0.05, an expected incidence of approximately 4% and precision of 1.7% for preeclampsia, and of 5% and 1.9% for gestational hypertension, of 1% and 0.6% for eclampsia and of 1.5% and 0.75% for chronic hypertension, respectively).

2.4. Statistical procedures

2.4.1. Crude estimates

For each study, we computed crude incidences of HDP. The pooled incidence for the different WHO regions was calculated by weighting the sample size of individual studies. The Cochran Q test and the I^2 statistic were used to explore the degree of heterogeneity between and within WHO regions. When I^2 was greater than 75%, the incidences within a region were considered very heterogeneous.

2.4.2. Model-based estimates

For countries without national data, a logistic model was developed to estimate the incidence of HDP using country macroeconomic indicators, variables related to health care, and variables related to population characteristics. Percentage of estimated births attended by skilled health personnel; adolescent

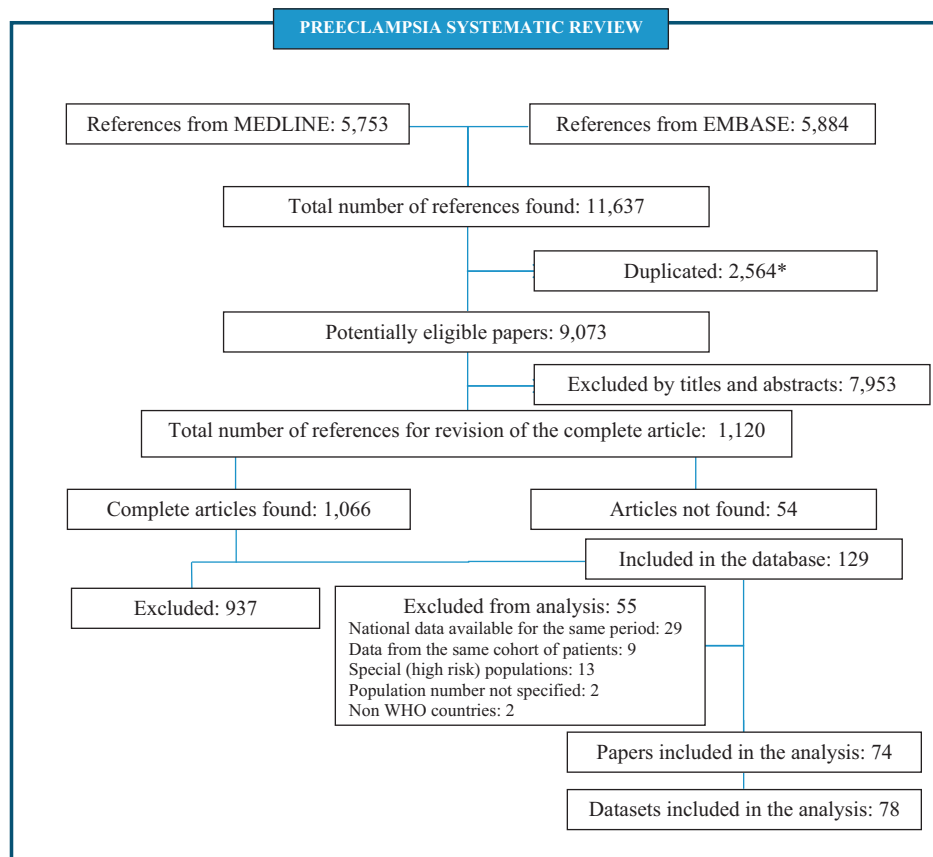


Fig. 1. Flowchart for identification and selection of studies × Database overlap: Of the 4800 journals indexed in EMBASE, 1800 are not indexed in MEDLINE. Similarly, of the 5200 journals indexed in MEDLINE, 1800 are not indexed in EMBASE. www.info.embase.com/embase_suite/about/brochures/embase_fs.pdf. The actual degree of reference overlap varies widely according to the topic but studies comparing searches of the two databases have generally concluded that a comprehensive search requires that both databases be searched (Suarez-Almazor 2000). Although MEDLINE and EMBASE searches tend not to identify the same sets of references, they have been found to return similar numbers of relevant references.

birth-rate per 1000 women; female mortality rate (probability of dying between 15 and 49 years per 1000 population); percentage of the population in urban area; maternal mortality ratio (per 100,000 live births); per capita government expenditure on health; general government expenditure on health as a percentage of total government expenditure; gross domestic product at purchasing power parity per capita; and general fertility rate were chosen as data were available for most countries. Two important predictor variables, use of magnesium sulphate and level of education of women, could not be used in the model as the frequency of missing values was greater than 70%. The WHO region was also considered as a factor variable in the model.

Due to the inability to disaggregate some study and report level data to annual figures, and the lack of time-matched data for the majority of predictor variables, all data were grouped at country level and across the time period of 2002–2010. In order to have one value for each predictor variable for the period 2002–2010 for each country, we averaged the data for each country and imputed missing values where necessary.

An iterative bootstrap procedure was performed to derive a mean and uncertainty interval [7]. A bootstrap sample from the full input dataset, with equal probability of selection and with replacement, was drawn. This sample was used to adjust a logistic model, employing the predictor variables covariates and weighting each observation by the square root of the number of cases in the dataset. The bootstrap sample, model adjustment and estimation steps were repeated 1000 times.

Final estimates for each country were then obtained either directly from national data if available, or from the model results. To obtain regional and global point estimates and uncertainty ranges of the distribution of HDP a weighted average using the number of live births by country [8] was calculated. The mean of

the resulting bootstrap distribution was the point estimate, and the 2.5th and 97.5th percentile were the lower and upper boundaries of the uncertainty interval, respectively.

3. Results

3.1. Study selection for modelling and direct estimations

Fig. 1 summarises the identification and selection of the articles and datasets for incorporation into the analysis. For the period 2002–2010, of the 11,637 citations screened, there were 129 studies from 44 countries meeting the inclusion criteria. The final number of reports analysed for this period was 74, with 78 datasets having HDP as an endpoint for 40 countries (Fig. 2). Overall, 78 datasets were included in the final analysis: 52 of these reported preeclampsia, 42 reported eclampsia, 20 reported gestational hypertension and 15 reported chronic hypertension. Seven datasets reported non-specified hypertension. Due to the paucity of data on the latter three conditions, we concentrated the analysis for preeclampsia and eclampsia. Data on severe preeclampsia were not considered for the analysis if total preeclampsia cases could not be obtained.

The overall quality of the reports was average to good. The summary measure for the pre-specified items assessing methodological quality was adequate in 75.0% of datasets reporting preeclampsia and in 52.4% of those reporting eclampsia. In relation to outcome definition, the quality was adequate in 82.7% and 54.8% for preeclampsia and eclampsia, respectively. For study design, it was good in 94.2% for preeclampsia and 95.2% for eclampsia. Only 9.6% of the datasets reporting preeclampsia and 9.5% of those reporting eclampsia showed national data. The sample size was deemed adequate for 92.3% of the preeclampsia and 95.2% of the eclampsia datasets (Fig. 3).

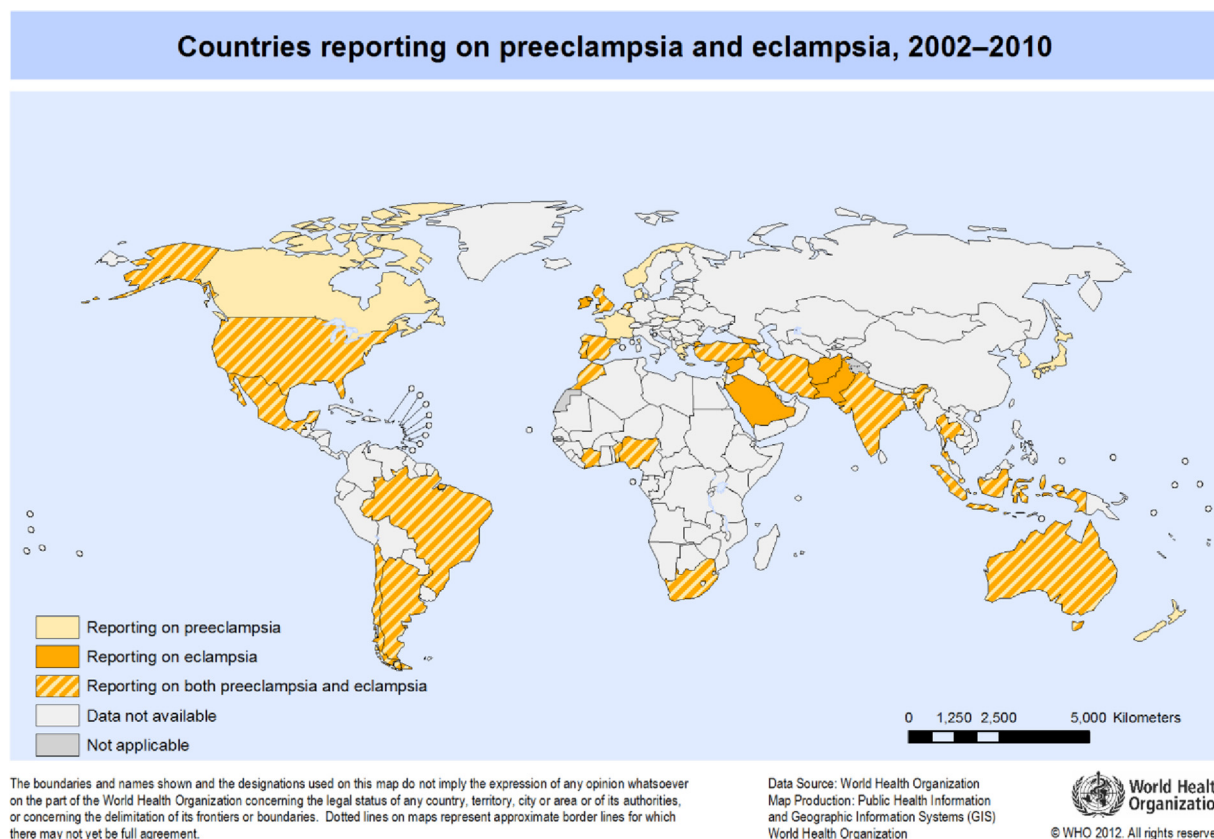


Fig. 2. Countries reporting preeclampsia/eclampsia.

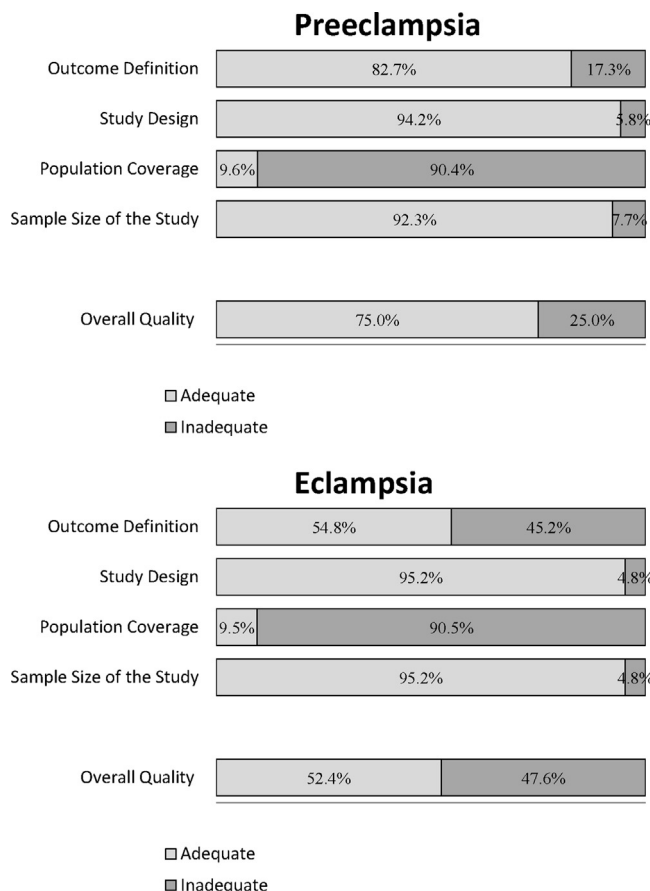


Fig. 3. Quality assessment of selected studies.

National data on preeclampsia and/or eclampsia were available for only seven countries (Denmark, Kuwait, Norway, Portugal, The Netherlands, United States of America, and United Kingdom). We counted with subnational data (i.e. regional or hospital estimates) for 33 countries. Estimates were obtained from the model for all countries with no national data and with predictor variables. These were available for 193 countries [1].

3.2. Preeclampsia

The crude incidence of preeclampsia was 2.3%, ranging from 1.2% to 4.2% across regions (Table 3). Five articles reported multi-country data, where it was not possible to discriminate the incidence of preeclampsia by country, and the summary of 4.5% reported by them was considered in the global, but not in the regional, estimates.

When the model was applied, the results showed a moderate increase in the incidence of preeclampsia overall and in some regions with wide uncertainty ranges (Table 3). The overall estimate is 4.6% (95% uncertainty range 2.7–8.2), ranging from 1.0% in the Eastern Mediterranean (EMRO) Region to 5.6% in the African (AFRO) Region. The adjustment of the model was moderately satisfactory [area under receiving operating curve (ROC) = 0.60]. Interestingly, the overall incidence is close to that informed by the multi-country studies.

3.3. Eclampsia

The crude incidence of eclampsia was 1.1%, from 0.1% to 2.7% in the different regions (Table 4). Two articles reported multi-country data, with a summary incidence of 0.5%. As stated above, heterogeneity is too high to draw conclusions about regions taking into account the crude estimates.

When the model was applied, most incidences are slightly modified but again show a wide uncertainty range (Table 4). Overall eclampsia is estimated in 1.4% of all deliveries (95% uncertainty range 1.0–2.0). The lowest figures were estimated in the EURO and WPRO regions (0.1%), and the highest for the AFRO region (2.9%). The adjustment of the model is also moderate (area under ROC = 0.61).

4. Discussion

4.1. Summary of main findings, strengths and limitations

This study is the first systematic analysis providing estimates of the global distribution of incidence of preeclampsia and eclampsia. From our datasets, the model-based incidence of preeclampsia and eclampsia are approximately 4.6% and 1.4% of all deliveries, with a wide variation across the different regions of the world. Although this could represent different risks of developing preeclampsia in some regions or different management of preeclampsia cases to prevent eclampsia in others, the literature is scarce in terms of datasets describing HDP as the main outcome for incidence. The limitations inherent in our approach are largely imposed by the nature of the available data, as the quality of the results and conclusions from a systematic review are only as accurate as the data provided by the primary datasets.

Data on the incidence of preeclampsia and eclampsia between 2002 and 2010 were available from only 40 countries, of which only seven had a national coverage. Most of the articles involved in this review correspond to North America and some countries in Europe. In terms of the number of women included, 94.6% of them are from USA, with little contribution from other regions (Table 5). This bias in regional representation makes it very difficult to estimate accurately the incidence of preeclampsia and eclampsia for different regions. To overcome some of the limitations of data

Table 3
Crude and model-based incidences of preeclampsia.

| Preeclampsia | | | | |
|--------------|--|--------------------|------------------|---|
| WHO Region | Number of datasets (number of women included) | I^2 ^a | Crude incidences | Model-based incidences (95% uncertainty range) |
| AFRO | 7 (51,038) | 81 | 4.0 | 5.6 (3.6–11.3) |
| AMRO | 9 (36,667,754) | 66 | 2.3 | 3.0 (1.5–5.2) |
| EMRO | 3 (41,320) | 0 | 1.2 | 1.0 (0.1–2.6) |
| EURO | 19 (448,410) | 46 | 3.8 | 5.3 (1.8–9.3) |
| SEARO | 4 (42,630) | 48 | 2.7 | 5.1 (1.9–10.9) |
| WPRO | 5 (361,402) | 0 | 4.2 | 3.9 (1.8–9.2) |
| Overall | 52 (37,652,006) | 48 | 2.3 | 4.6 (2.7–8.2) |

^a 0%: homogeneity; 25%: low heterogeneity; 50%: moderate heterogeneity; 75%: high heterogeneity.

Table 4

Crude and model-based incidences of eclampsia.

| Eclampsia | | | | |
|------------|--|--------------------|------------------|---|
| WHO Region | Number of datasets (number of women included) | I^2 ^a | Crude incidences | Model-based incidences (95% uncertainty range) |
| AFRO | 11 (89,743) | 85 | 2.7 | 2.9 (1.4–7.4) |
| AMRO | 5 (36,606,264) | 97 | 1.1 | 0.7 (0.4–0.9) |
| EMRO | 10 (148,909) | 95 | 0.5 | 1.9 (0.7–2.9) |
| EURO | 7 (656,889) | 100 | 0.1 | 0.1 (0.0–0.4) |
| SEARO | 5 (202,499) | 95 | 1.3 | 1.1 (1.0–1.3) |
| WPRO | 2 (310,636) | 100 | 0.1 | 0.1 (0.0–0.1) |
| Overall | 42 (38,006,992) | 96 | 0.5 | 1.4 (1.0–2.0) |

^a 0%: homogeneity; 25%: low heterogeneity; 50%: moderate heterogeneity; 75%: high heterogeneity.**Table 5**

Regional distributions of datasets reporting preeclampsia/eclampsia.

| Region | Country | Number of women | Preeclampsia | | Eclampsia | |
|--------------|--|-----------------|--------------------|---------------------|--------------------|---------------------|
| | | | Number of datasets | Crude incidence (%) | Number of datasets | Crude incidence (%) |
| AFRO | Benin ⁴⁴ | 14,322 | 1 | 2.1 | 1 | 1.7 |
| | Cote d'Ivoire ⁴⁴ | 13,298 | 1 | 1.1 | 1 | 1.0 |
| | Nigeria ^{15,24,53,61,76,77,79,81,113} | 54,144 | 4 | 4.6 | 7 | 4.0 |
| | South Africa ^{54,55} | 11,849 | 1 | 9.3 | 2 | 1.6 |
| | Total | 93,613 | 7 | 4.0 | 11 | 2.7 |
| AMRO | Argentina ^{13,20} | 19,965 | 1 | 10.0 | 1 | 0.4 |
| | Brazil ^{101,103} | 14,511 | 1 | 1.5 | 1 | 0.6 |
| | Canada ^{110,117,118} | 72,743 | 3 | 0.8 | – | – |
| | Chile ^{41,42} | 7486 | 2 | 3.4 | 1 | 0.1 |
| | Mexico ⁶⁵ | 41,828 | 1 | 5.5 | 1 | 0.6 |
| | USA ⁶⁰ | 36,537,061 | 1 | 2.3 | 1 | 1.1 |
| | Total | 36,693,594 | 9 | 2.3 | 5 | 1.1 |
| EMRO | Afghanistan ¹⁰⁰ | 4317 | – | – | 1 | 1.7 |
| | Iran ¹²⁷ | 2300 | 1 | 1.1 | 1 | 0.1 |
| | Kuwait ⁸⁰ | 33,162 | 1 | 1.4 | 1 | 0.0 |
| | Morocco ^{44,70} | 43,325 | 1 | 0.7 | 2 | 0.9 |
| | Pakistan ^{1,4,74} | 5780 | – | – | 3 | 2.7 |
| | Saudi Arabic ¹⁰² | 32,000 | – | – | 1 | 0.1 |
| | Syrian Arabic ¹² | 28,025 | – | – | 1 | 0.2 |
| | Total | 148,909 | 3 | 1.2 | 10 | 0.5 |
| EURO | Denmark ²² | 70,924 | 1 | 3.0 | – | – |
| | France ^{36,121} | 5748 | 2 | 2.3 | – | – |
| | Georgia ⁵ | 18,554 | – | – | 1 | 0.1 |
| | Greece ⁸⁵ | 878 | 1 | 2.2 | – | – |
| | Ireland ⁷³ | 45,166 | – | – | 1 | 0.1 |
| | Israel ⁴⁹ | 1366 | 1 | 1.5 | – | – |
| | Netherlands ^{27,47,115,129} | 393,242 | 3 | 3.3 | 1 | 0.1 |
| | Norway ²⁹ | 317,688 | 1 | 4.0 | – | – |
| | Portugal ⁹¹ | 6726 | 1 | 1.4 | 1 | 0.1 |
| | Slovakia ³⁸ | 2263 | 1 | 8.0 | – | – |
| | Spain ²⁸ | 2546 | 1 | 0.9 | 1 | 0.0 |
| | Turkey ^{37,39} | 3581 | 2 | 15.6 | 1 | 1.2 |
| | United Kingdom ^{56,88,104,111} | 225,100 | 3 | 2.5 | 1 | 0.0 |
| | Total | 1,093,782 | 17 | 3.8 | 7 | 0.1 |
| SEARO | India ^{25,31,92} | 123,872 | 1 | 2.1 | 3 | 1.2 |
| | Indonesia ^{6,99} | 43,364 | 2 | 8.6 | 1 | 2.5 |
| | Thailand ⁶⁵ | 35,923 | 1 | 1.9 | 1 | 0.3 |
| | Total | 203,159 | 4 | 2.7 | 5 | 1.3 |
| WPRO | Australia ^{93,110} | 249,440 | 2 | 4.5 | 1 | 0.1 |
| | Japan ^{98,107} | 49,061 | 2 | 3.9 | – | – |
| | Korea, Republic ⁸⁴ | 1090 | 1 | 1.7 | – | – |
| | New Zealand ⁵² | 216 | 1 | 14.4 | – | – |
| | Singapore ¹⁰⁸ | 61,595 | 1 | 3.6 | 1 | 0.0 |
| | Total | 361,402 | 7 | 4.2 | 2 | 0.1 |
| Multicountry | Multicountry ^{69,83,114,122,123} | 39,452 | 5 | 4.5 | 2 | 0.5 |
| Total | | 38,633,911 | 52 | 2.3 | 42 | 0.5 |

availability, a logistic model was used to estimate the distribution of the incidence of preeclampsia and eclampsia in countries for which national data were not available. One of the advantages of considering the model is that the effect of single big studies is softened in the summary estimations. This approach also takes into account the total number of live-births by country, so that the regional estimates consider the burden of preeclampsia according to the population in a given region.

On the other hand, regional incidences are based on the data reported, which may not be representative of the whole region, nor reflect global proportions, due to lack of weighting.

There is a high degree of heterogeneity across studies between and within regions, so pooling the crude results in a single statistical summary estimate should be interpreted with caution.

Due to the paucity of data, all the figures for a country were aggregated over the nine-year period. Although this approach provides more stable estimates, there is an underlying assumption that the distribution of the incidence of preeclampsia and eclampsia remains stable over all years within a country. Whilst grouping of data over many years precludes year-matching of predictor variables, very few countries have complete time series for the significant predictors used in the modelling or have comparable data at a regional level for locality matching.

We also recognise the limitations due to the particular issue of misclassification or underreporting of HDP. Data from RCTs, where it would be expected that blood pressure and proteinuria were measured carefully, were downgraded as low quality for external validity, and only account for 3.8% of the datasets, so a stratified analysis for this subgroup was not performed. On the other hand, many of the cross-sectional studies reporting incidence of HDP were research papers testing diagnostic or predictor tests for preeclampsia so we assume that diagnosis of preeclampsia and eclampsia was somehow standardised. Even though there were some variations in the way authors defined preeclampsia, for our quality assessment we only took into consideration whether the definition was explicit or not and no subgroup analysis was conducted in this regard.

Magnesium sulphate more than halves the risk of developing eclampsia in women with preeclampsia [9]. One of the original objectives of this study was to gain insight into existing programmes to provide treatment strategies such as magnesium sulphate for the prevention or treatment of eclampsia. Although magnesium sulphate is considered by WHO an “essential drug” [10], it is difficult to obtain reliable data regarding its availability and use in most countries. As stated earlier, it could not be used in the model as the global proportion of missing values is 77%. On the other hand, 22% of the papers selected for this study mentioned the use (or not use) of magnesium sulphate for prevention or treatment of eclampsia. Barriers described to the use of magnesium sulphate include drug licensing and availability; inadequate and poorly implemented clinical guidelines; and lack of political support for policy change [11].

Only 16 of the 42 datasets with cases of eclampsia reported maternal deaths related to this condition. Overall, the case fatality rate due to eclampsia in this population was 8.3%.

This study highlights the lack of high quality data on the incidence of preeclampsia and eclampsia, one of the leading causes of maternal mortality globally. The absence of data in many countries is of concern, and efforts should be made to implement data collection and reporting for substantial statistics, rather than filling blank spaces with data provided by models. The figures we obtained give a rough idea of the magnitude of the problem and

suggest that some regional variations might exist. However, to have a reliable picture of preeclampsia and eclampsia worldwide – of its magnitude, distribution and consequences – a global survey tackling this condition is mandatory.

Contributors

LS, EA and DC conceived the review. All authors developed the methodology. ALG performed the literature search and prepared the vital registration data. ALG and EA considered studies for inclusion and extracted the data. CC performed the statistical analysis. EA, CC, LS and DC drafted the text and tables. All authors reviewed and approved the manuscript.

Conflict of interest statement

The authors declare that they have no conflicts of interest. Two WHO staff members are part of the team who conducted the study. The findings in this paper represent the conclusions of the authors.

Funding

The Department of Reproductive Health and Research, WHO through the Special Programme of Research, Development, and Research Training in Human Reproduction and the US Fund for UNICEF through a grant from the Bill and Melinda Gates Foundation to CHERG.

Acknowledgements

Special thanks to Ann Beth Moller for her contribution with translations of original papers published in other languages, to Daniel Giordano, Hugo Gamero and Fernando Burgueño from Centro Rosarino de Estudios Perinatales (CREP) for the design of the database and data entry.

References

- [1] Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–74.
- [2] World Fertility Data. United Nation Population Division/DESA. Fertility and Family Planning Section; (accessed 16.07.2012) http://www.un.org/esa/population/publications/WFD%202008/WFP_WFD_2008/Data.html.
- [3] World Health Organization. Trends in maternal mortality: 1990–2010 WHO, UNICEF, UNFPA and The World Bank estimates. Geneva, Switzerland.: WHO Press; 2012. © World Health Organization.
- [4] Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183(1):S1–22.
- [5] Health Canada. Special Report on Maternal Mortality and Severe Morbidity in Canada – Enhanced Surveillance: the Path to Prevention. Ottawa: Minister of Public Works and Government Services Canada; 2004.
- [6] Gulmezoglu AM, Say L, Betran AP, Villar J, Piaggio G. WHO systematic review of maternal mortality and morbidity: methodological issues and challenges. *BMC Med Res Methodol* 2004;4:16.
- [7] Efron B, Tibshirani R. An Introduction to the Bootstrap. New York: Chapman & Hall/CRC; 1993.
- [8] United Nations, Department of Economic And Social Affairs, Population Division. World Population Prospects: the 2010 revision. CD-ROM edition; 2011.
- [9] Duley L, Gülmezoglu AM, Henderson-Smith DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010;11:CD000025. <http://dx.doi.org/10.1002/14651858.CD000025.pub2>.
- [10] World Health Organization. WHO Model List of Essential Medicines. 17th Edition. Geneva, Switzerland: WHO Press; 2011. © World Health Organization.
- [11] Aaserud M, Lewin S, Innvaer S, et al. Translating research into policy and practice in developing countries: a case study of magnesium sulphate for pre-eclampsia. *BMC Health Serv Res* 2005;5:68.