(Draft, Do not quote)

Magnesium sulfate use for the treatment of severe preeclampsia and eclampsia among cases of related maternal deaths: A three-year review of maternal deaths in Mexico City

Author and co-authors:

1. Sandra G. García, ScD; Senior Associate and Director; Population Council, Mexico Office; Morelos #21, Colonia Del Carmen, Delegación Coyoacán, Mexico DF, 04100; Mexico
2. Marieke G. van Dijk, MD, MA; Regional Associate; Population Council, Mexico Office; Morelos #21, Colonia Del Carmen, Delegación Coyoacán, Mexico DF, 04100; Mexico
3. Jorge A. Valencia, MSc; Consultant for the Population Council, Mexico Office; Morelos #21, Colonia Del Carmen, Delegación Coyoacán, Mexico DF, 04100; Mexico
4. Patricio Sanhueza Smith, MD; Coordinator of the Reproductive Health Program of the Ministry of Health of Mexico City; Altadena #23, Colonia Nápoles, Delegación Benito Juárez; México DF, 03810; Mexico.

Corresponding author:

Marieke G. van Dijk¸ Population Council, Mexico Office; Morelos #21, Colonia Del Carmen, Delegación Coyoacán, Mexico DF, 04100; Mexico; Mexico DF, 04100; Mexico. Tel: (+52-55) 5999 -8630 and - 8656; E-mail: mvandijk@popcouncil.org

Word count: 5.828 words

Abstract

To better understand whether magnesium sulfate is used for women with severe preeclampsia or eclampsia in Mexico City hospitals, we conducted a maternal mortality medical file review of women who died of (pre)eclampsia in Mexico City in 2005, 2006 and 2007. We excluded the files not containing clinical information, bringing us to 91 files over the three years. Sixty-four women (70.3%) had gone through a trajectory of visits to more than one health care facility (up to five facilities). In the total of these clinical visits (n=189), women were diagnosed 54 times with severe preeclampsia. In 12 cases (22.2%) they were given anticonvulsant treatment with magnesium sulfate alone (not combined with other anticonvulsant drugs), and in 7 cases (13.0%), magnesium sulfate was given combined with other anticonvulsant drugs. In 15 cases (27.8%), women were not given anticonvulsant treatment at all. Women were diagnosed 61 times with eclampsia and given magnesium sulfate alone in 5 cases (8.2%), and magnesium sulfate combined in 28 cases (46.0%). Six women with eclampsia (9.8%) did not receive anticonvulsant treatment. Despite clear evidence that magnesium sulfate is indicated in severe preeclampsia and eclampsia, the drug is not used routinely in Mexico City.

Introduction

For more than two decades, reducing maternal mortality has been an international development priority.[1] Despite years of research documenting the effectiveness of relatively simple, affordable measures that can significantly reduce maternal mortality, in many developing countries complications from pregnancy and childbirth continue to be a leading cause of death among women of reproductive age. Of the 529,000 maternal deaths that occur each year, 99% take place in developing countries.[2] The vast majority could be prevented with the adoption of evidence-based clinical practices that have been proven to reduce maternal mortality.

The gestational hypertension disorders of preeclampsia and eclampsia are leading causes of maternal mortality that continue to plague developing countries, despite ample evidence on how to effectively manage and treat these conditions. A multisystem disorder of unknown cause, preeclampsia is characterized by high blood pressure and excess protein in the urine after 20 weeks of gestation. In healthy nulliparous women, preeclampsia prevalence ranges from 2% to 7% and generally poses negligible risk to the pregnancy. However, frequency and severity are higher in women with associated risk factors, namely multifetal gestation, chronic hypertension, previous preeclampsia, pregestational diabetes mellitus, and preexisting thrombophilias.[3] If not managed appropriately, preeclampsia can lead to eclampsia, a serious and life-threatening complication described as preeclampsia with convulsions. Eclampsia can permanently damage vital organs and if left untreated can cause coma, brain damage, or death to the mother and/or baby. Globally, preeclampsia and eclampsia account for more than 50,000 maternal deaths per year, nearly all of which occur in developing countries.[4]

The principal strategy for preventing eclamptic convulsions and controlling acute convulsions is the use of anticonvulsant medication. Several large randomized controlled trials have demonstrated that the use of magnesium sulfate is associated with a significantly reduced rate of

recurrent seizures and maternal death compared to other anticonvulsants such as diazepam, phenytoin or a lytic coctail.[3,5,6] The largest trial to date, known as the Magpie Trial, enrolled 10,141 women with preeclampsia and found that use of magnesium sulfate led to a 58 percent lower risk of eclampsia compared to a placebo. Maternal mortality was also lower among women allocated to receive magnesium sulfate.[4] Evidence from later studies showed that the benefit-to-risk ratio of magnesium sulfate prophylaxis does not support routine use in cases of mild preclampsia.[7,8] There is now international consensus, however, that magnesium sulfate use is the standard of care among women with *severe* preeclampsia or eclampsia, particularly due to its relatively low cost at less than US $5 per patient.[9] However in spite of this safe, effective, and inexpensive drug, magnesium sulfate still is not widely used to manage preeclampsia and eclampsia in developing countries.[10,11]

In Mexico, a high percentage of pregnant women receive prenatal care and are attended by skilled health care providers – over 90% in 2006.[12] However nationally, in 2007 1,157 women still died during pregnancy, labor, within 42 days postpartum or due to late pregnancy-related complications.[13] These deaths translate into a maternal mortality ratio of 57.4 maternal deaths per 100,000 live births (see Table 1). Severe preeclampsia and eclampsia are the leading causes of maternal mortality in Mexico, with 24.1% of maternal deaths associated with these disorders. Paradoxically, the maternal mortality ratio in the national capitol Mexico City was higher than the national statistic (70.3 deaths per 100,000 live births in 2007). The proportion of hypertensive disorders of Mexico City, which is a state in itself (a "Federal District"), was 18.1% (17 of the total deaths). [13]

In an effort to improve the use of prophylactic magnesium sulfate in patients with severe preeclampsia and eclampsia, the Federal Ministry of Health (MOH) in Mexico recently (2006) updated its national clinical guidelines on prevention, diagnosis and treatment of preeclampsia/eclampsia. The guidelines stipulate that magnesium sulfate is the drug of choice to

prevent and treat convulsions in preeclampsia and eclampsia.[14] The drug is also included on the National Essential Drug List, and is being distributed country-wide at all levels of care (including primary level). When magnesium sulfate is not available, the guidelines recommend the use of either phenytoin or phenobarbital. Despite these efforts, experts on the issue indicate that magnesium sulfate use remains low.

Lumbiganon and coauthors conducted a study on the use of magnesium sulfate in Mexico City between 2000 and 2002 in 22 public sector hospitals in Mexico City, including MOH and social security hospitals (such as IMSS – in English: Mexican Institute of Social Security, or ISSSTE – Institute for Social Security and Services of State Employees).[15] The study was part of a trial to evaluate the improvement in obstetric practices using an active dissemination strategy to promote uptake of the recommendations contained in *The WHO Reproductive Health Library*. The study team collected data on the occurrences of pre-eclampsia and eclampsia and the use of anticonvulsants as part of measuring the rate of evidence-based practices in the main trial. They collected data from 1,000 women or for six months, whichever was first reached in each unit. The overall prevalence of pre-eclampsia and eclampsia in Mexico was found to be 5.5% and 0.6%, respectively. They found that in 8 out of 22 hospitals, magnesium sulfate was used for women with preeclampsia, and the rate of use ranged from 0.8% to 8.5%. Magnesium sulfate was used in 11 hospitals for women with eclampsia, and the rates of use ranged from 9.1% to 60.0%. Phenytoin was more commonly used than magnesium sulfate; diazepam was not used at all. The authors of the study found the very low rate of magnesium use alarming, and urged for immediate actions to ensure wider use of this effective and inexpensive drug for these conditions.

Compelled by the findings and recommendations by Lumbiganon and colleagues, we conducted a detailed review of maternal mortality medical files of women who died from hypertensive disorders in Mexico City in three consecutive years: 2005, 2006 and 2007 in order to

(1) describe the type and quality of information available from the medical files and death records of women who died due to these hypertensive disorders; (2) document whether or not magnesium sulfate was used when indicated, and (3) assess, quantify and attempt to qualify how often and how well magnesium sulfate was used.

DATA AND METHODS

Ethical review and data sources

In accordance with the guidelines set for by the Population Council's Institutional Review Board (IRB), this study was exempt from full committee review, because the study involved only secondary data analysis with blinded patient identifiers. Nevertheless, investigators were required to fully describe the procedures used for ensuring confidentiality and privacy of the information contained in the medical records. These procedures were shared with and approved by the Mexico City Ministry of Health.

In 2008, the Mexico City Ministry of Health authorized us to review the maternal mortality medical files over three years (2005, 2006 and 2007). These medical files represent all the maternal deaths that took place in Mexico City over these years, including those women who died in a hospital, at home or elsewhere (for example, in a taxi on the way to a hospital). Women were treated at different levels of care (primary care and public health centers, private practices, secondary and tertiary care hospitals) and at different types of public sector institutions: the medical facilities of the MOH public healthcare system (accessible for all people without formal employment); the social security systems for governmental and non-governmental employees (includes IMSS facilities, ISSSTE facilities, Mexican Petroleum – PEMEX – facilities and others); private medical facilities and traditional healers or midwives.

Following the guidelines of Mexico's national AIDeM group (Inmediate Attention to Maternal Deaths, in English) – a committee of experts appointed by and reporting to, the federal MOH – maternal mortality medical files should all contain a death certificate, a clinical summary of the case and a series of other documents, which are filled out after the death has occurred[a]. In some cases, the files include the complete patient chart; however, beginning in 2007, the federal MOH decided that the inclusion of the patient chart would no longer be compulsory. The clinical summary alone was considered sufficient.[16] The maternal mortality medical files we reviewed for this study, had already passed through the thorough review and investigation of each individual death, from hospital- and county-level to federal information system level, to explore whether and how the death could have been prevented[b].

For our study, we were mostly interested in the use of magnesium sulfate in the facility at which the maternal deaths took place; as such, we selected the charts of maternal deaths according to *place of death* (Mexico City), in contrast to place of residency of the patient. Over one third of the women (37.4%) who were treated and died in Mexico City facilities were residents of other states of Mexico (mainly from the neighboring "Estado de México").

[a] Other documents may include: "critical links" (an innovative method to evaluate medical performance at every level of care, and provide recommendations for improvement), county-level and hospital-level reviews, confidential questionnaire to physician, verbal autopsy to family members and the autopsy report.

[b] In Mexico, when a maternal death occurs, the complete file (including the patient chart) is evaluated at the hospital level, and afterwards at the "county" level. The file (without patient chart) is sent to the Ministry of Health at the state level, and the death certificate to the INEGI (National Institute of Statistics and Geography) at federal level. At the state level, the files are evaluated by a maternal mortality committee and a team epidemiologists of the department of Health Information (DGIS). All the deaths are submitted to the RAMOS methodology (Reproductive Age Mortality Studies), which enables to identify and investigate the causes of all deaths of women in reproductive age. In case doubts arise concerning the accurateness of the death certificate or the summary, the patient chart is requested from the hospital for a more in-depth review. The cases are then classified according to the ICD-10 system (International Statistical Classification of Diseases and Related Health Problems. At the same time, the INEGI does an independent ICD-10 classification of the case. Once per year, both classifications are compared, contradictory cases are reviewed together, after which a final decision is made on the cause of death to be registered.

Sample determination

From the total cases of maternal deaths, we first selected those in which "hypertensive disorder" was indicated as the cause of death (ICD-10 codes O10-O16). We then discarded some of these cases – those in which the death certificate indicated hypertensive disorder as cause of death, but while studying the file, we could not find any clinical diagnoses made to confirm the stated cause of death ("false-positives"). In addition, we also excluded the cases in which the file's clinical notes clearly indicated a hypertensive disorder-related death, but in which the death certificate failed to classify the death as such, either as the direct cause of death, or as the indirect cause of death ("false-negatives"). Finally, we also discarded cases of late maternal deaths (taking place more than 42 days after delivery) or sequelae of direct obstetric causes (events which took place one year after delivery).

We were obliged to make a few assumptions in order to classify the available information. For example, when physicians diagnosed these maternal deaths as cases of HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) in the patient charts without mentioning diagnosis of preeclampsia or eclampsia, we classified these cases as severe preeclampsia. As the medical files were often incomplete for purposes of this analysis, we decided to include those files that contained either a clinical summary (prepared by the attending physician), or a patient chart, or both, independent of all the other sections that may be included in the file. This procedure led us to the final sample described in Table 2.

Table 2 notes the number of Mexico City maternal mortality medical files we reviewed for the three years of interest (2005 – 2007), that indicated hypertensive disorder as cause of death according to the death certificate. As described above, after excluding certain cases, we were left with a total sample size of 91 maternal deaths of interest across the three-year period. It is important to note, however, that there is a discrepancy between the number of hypertensive disorder-related

deaths reported by the official MOH information system (DGIS in Spanish), when compared to the total number of maternal mortality medical files we reviewed in our analysis (see Tables 1 and 2). In the years 2005 and 2007, the official DGIS data by place of death compared to the number of deaths we included in our analysis are: 49 vs. 60 in 2005 and 29 vs. 36 in 2007. This discrepancy could be explained by a different interpretation of the cause of death, or more likely, because in DGIS deaths are registered in the year they are reported, which does not always coincide with the year in which the death took place. Serious underreporting of maternal deaths is very unlikely in the urban context of Mexico City. Table 3 shows the patient files analyzed in the present study (for each year and total), by the information source.

Data extraction

We reviewed a total of 91 patient files (sample described above and Table 2), and extracted relevant information/variables in an Microsoft Excel spreadsheet (version 2007). We began registering relevant information from the *first* moment in which a woman's file indicates that she began presenting symptoms indicative of hypertensive disease. After recording basic socio-demographical and reproductive history data, we followed the chronology of every woman's pathway through (often) several visits to different medical units prior to her death, and noted whether or not treatment with magnesium sulfate or other drugs was initiated. For every medical visit a woman made, we registered the type of healthcare institution at which she received care, the level of such care (primary, secondary or tertiary level of care), and the type of provider who attended to her. We also extracted information on two objective symptoms of hypertensive disease: clinical hypertension and proteinuria, and classified them according to the Mexican clinical guidelines on prevention, diagnosis and treatment of preeclampsia/eclampsia.[14] In addition, per medical visit we registered clinical diagnosis, anticonvulsant treatment(s), referrals, treatment at Intensive Care Units

(ICU) , and presence/management of side-effects of magnesium sulfate. We analysed the data using the software for statistical analysis SPSS (version 14.0, 2005).

RESULTS

Women's characteristics

We extracted basic socio-demographical and reproductive history characteristics from the patient files of the women included in our study, over the three years (see Table 4). Nearly half (48.3%) of the women died between the ages of 25 to 34 years, and more than half (68.2%) had had at least one prior pregnancy. For over one-third of this sample (37.4 %) we have no data on whether these women received antenatal care, and of close to 20% of the women, patient files reported they had minimal antenatal visits (1 or 2 times) or no visits at all. Antenatal care is almost always provided by a physician (although these may be *pasantes* – interns in their last year of medical studies who are carrying out their mandatory year of volunteer social service). We tried to register the risk factors for preeclampsia, as they are mentioned in the Mexican clinical guidelines: preeclampsia in previous pregnancies, intergenesic period of more than 10 years, chronical hypertention, renal disease, diabetes mellitus, trombofilias, Body Mass Index (BMI) of more than 30 kg/m^2, age more than 40 years, and others; however, these were very seldom registered in the files. The only risk factor we could identify was the percentage of women above 40 years (9.9%).

Pathway through, and experiences at multiple health care facilities

We documented and analysized the pathway of women once they began having hypertensive disorder-related symptoms that eventually lead to their death, such as hypertension, proteinuria, and subjective symptoms such as bad headaches, edema, blurred vision or flashing lights before the eyes (see Table 5). Table 5 provides a break-down of each clinical visit made by the 91 women in our

sample, and the column labeled "final clinical visit" describes what occurred at the health care facility where the women died or where they were treated for the last time, after which they may have died at home or during transfer. This table specifyies the type of healthcare institution and level of facility, as well as clinical data on these women per each clinical visit – bloodpressure when arriving at the facility, levels of proteinuria, main diagnosis made by attending clinician, type of health care provider and anticonvulsant treatment received. To complement this table, Figure 1 provides a visual pathway through the different clinical visits made by the women. Women were both referred from a antenatal care visit or sought help on their own because they began feeling badly.

Of all 91 women, nearly one-third (n = 27) made one single ("final") visit at which they died, and 64 women had visited at least one additional healthcare facility prior to the final clinical visit. Our study team is currently analyzing the particular characteristics of the 27 women who made only one visit, to see if there are any associations with having made one visit. Four women had made four prior clinical visits, after which they died during the fifth and final clinical visit. Twenty-four women (37.5%) went to the primary-care level first (MOH or social security health centers, or private physicians), the others went directly to a hospital. Some may have gone to the primary-care level at later visits. At the last visit, all medical units were of a secondary (35.2%) or tertiary level care (64.8%), in the large majority from the Ministry of Health at state level (63.7%). Almost all women, at all clinical visits, were diagnosed and treated by a physician (including *pasantes* at the primary level, and residents).

The lack of explicit data on levels of proteinuria (89.1% missing at the first visit prior to final visit, and 67.0% missing at the only/final visit), is alarming. Even when taking into account that we did not always have access to complete patient charts, the data seem to suggest that simple diagnostic

tests as urine dipsticks are either not being used routinely, or that dipsticks are being used but the results are not recorded in patients' files routinely.

We recorded the diagnoses as they were mentioned in the patient files; we did not interpret diagnoses based on symptoms ourselves. The main diagnosis tends to worsen with every additional clinical visit (i.e. mild preeclampsias become severe and severe preeclampsias progress eclampsias and irreversible complications), and at the final visit, 40.7% of the women had severe preeclampsia and 44.0% of the women had eclampsia.

According to the clinical guidelines, women having mild or severe preeclampsia, or eclampsia, should be inmediately referred to a secondary- or tertiary-care level hospital. Of the 30 women who went to primary-level care (at the first or later visits), 70.0% were indeed referred (data not shown). Although not described in the clinical guidelines, 50.0% of patients were referred from the secondary level of care to other hospitals of secondary or tertiary level of care (often from private to public hospitals). The reason for these referrals may be that the patient began having complications and the health personnel felt they could not give adequate management, for example, because their hospital may not have had an Intensive Care Unit (ICU), but we cannot know from the data available.

Use of magnesium sulfate

We also recorded and analyzed information on use of magnesuim sulfate at each clinical visit (even if it may concern the same women) since each visit gives clinicians a new "opportunity" to diagnose and treat women correctly. The total of clinical visits made by the 91 women in our sample is 189.

The use of magnesium sulfate alone is very low at the first clinical visit prior to final visit (6.3%, see Table 5). This is partly explained because 37.5% of these women went to the primary

level of care. The clinical guidelines state that at this level of care all patients with (mild or) severe preeclampsia should be referred to a hospital urgently, rather than initiating treatment with magnesium sulfate, since these facilities do not usually have the capacity to manage complications of these cases. Magnesium sulfate should be used, however, when the patient is already presenting eclampsia, even if she first presents at a primary-level healthcare facility. Still, two-thirds of the 91 women did go to a hospital at the first visit and those who had severe preeclampsia or eclampsia should have received magnesium sulfate. For the 5 women who presented eclampsia at the primary level of care, magnesium sulfate also would have been indicated.

As seen in Table 5, at the final visit, magnesium sulfate alone, not combined with other anticonvulsants, was used in 13.2% of the cases. The use of magnesium sulfate in combination with other anticonvulsants is also higher (28.6%) at the final clinical visit.

Table 6 illustrates the use of anticonvulsants across all clinical visits according to the explicit medical diagnosis reported in the files. In 23.8% of all clinical visits (45 out of 189 cases), no data were recorded on the treatment regimen. Five cases of mild preeclampsia were observed, and in three cases, there was no mention of treatment given, but in the two cases where use of anticonvulsants was noted in the charts, these women were managed correctly (according to the Mexican clinical guidelines) since they were not given magnesium sulfate nor other anticonvulsants.

Of the 54 cases in which women were diagnosed with severe preeclampsia, magnesium sulfate alone was used to treat 22.2% of these cases. On seven occasions (13.0%) women were given magnesium sulfate combined with other anticonvulsant drugs, and on six occasions (11.2%) they were given other anticonvulsant drugs without magnesium sulfate. On 15 occasions in which women presented with severe preeclampsia (27.8%), women were not given any anticonvulsant treatment at all. In 25.9% of the cases of severe preeclampsia we did not find any registration of magnesium sulfate or other anticonvulsants, and we cannot assess whether the drugs were used or not. In the case

of unclassified preeclampsia – observed in 6 out of 189 clinical visits (3.2%) – we do not know whether the condition was mild or severe, so we cannot assess whether the anticonvulsant treatment was adequate.

In 61 out of 189 visits a diagnosis of eclampsia was made, and in only 5 of these 61 cases (8.2%) did women receive treatment of magnesium sulfate alone; in 8 out of 61 cases, the treatment was not recorded in the charts. In 28 cases (46.0%) magnesium was provided with other drugs, in 14 cases (22.9%) other drugs were given and in six cases (9.8%) women were not given any anticonvulsants.

As mentioned before, the clinical guidelines state that at the primary level of care magnesium sulfate should be only used when the patient is already presenting eclampsia. It is important to note that in Table 6 we have chosen to include all clinical visits made by the 91 women who died, even those visits to primary-level healthcare facilities. Strictly speaking, one could argue that we should have excluded the few cases of severe preeclampsia observed at the primary-level when evaluating the use of magnesium sulfate by clinical visit – doing so would certainly alter the percentages. But we chose to leave these cases in the table as they were so few in number. There were 5 out of 54 such cases among clinical visits with presentations of severe preeclampsia, and in only one of the five cases was the woman given magnesium sulfate when instead she should have been referred. The use of magnesium sulfate only at the hospital-level would be in 11 out of 49 cases (22.4%). The difference with our originally presented data (22.2%) is minimal.

As the updated clinical guidelines for treatment of preeclampsia and eclampsia were published in 2006, our study team is working on a more detailed analysis of the use of magnesium sulfate per year, to see whether the use of magnesium sulfate for the correct indications has increased over the years.

In only three cases of severe preeclampsia/eclampsia did the patient file mention the reason why magnesium sulfate was not used – (1) physicians decided to transfer the woman from the primary care level to a hospital; (2) the woman died at the moment after arrival, and (3) magnesium sulfate was not available.

We also tried to evaluate if in the cases that magnesium sulfate was used, it was applied correctly. However, these data were often not recorded, and if they were, the interpretation became very complex because of great variations in doses (both loading and maintenance, volume and type of solution, etc.). We did not find any cases in which monitoring was reported on the side-effects of magnesium sulfate (through measuring patellar reflex, respiratory frequency, uresis). In 16 out of a total of 57 cases in which magnesium sulfate was used (either alone or combined, see Table 6), use of calcium gluconate was registered. However, it was unclear from the patient files whether this drug was used for magnesium sulfate overdosage or for other indications.

Other relevant information in cases of preeclampsia and eclampsia

As shown in Table 7, from the charts of all 91 women, we also extracted some other relevant indicators at the healthcare facilities related to the treatment of preeclampsia and eclampsia, such as pregnancy and birth outcome, the timing of the delivery or cesarean section (in cases of severe preeclampsia or eclampsia, pregnancy should be terminated within six hours from diagnosis), and whether the women were treated at the ICU. The majority of the women (75.8%) delivered their baby through a cesarean section. More than half of the babies survived (56.0%). Among 26.4% of women, the termination of pregnancy was delayed over six hours (while the clinical guidelines stipulate that, in cases of severe preeclampsia and eclampsia, pregnancies should be terminated within a six hours period). Most women were treated at the ICU (73.6%) at some moment over the course of their illness.

DISCUSSION

Strengths and limitations

This study fills an important gap concerning the treatment and care received by Mexican women who suffered and died as a result of progressive preeclampsia and eclampsia. Our data are exhaustive for a major global metroplex (the Mexican capital city) over a recent three-year period (from 2005 to 2007), and for the first time, document detailed information regarding each particular woman's diagnoses, treatment regimen(s), and pathways to care – especially when multiple clinical visits were made by women. An important limitation, however, is that we confined our analysis to the patient charts (and medical death records) of those women who died from these hypertensive disorders. Since our sample did not include women who suffered yet survived these illnesses, we cannot make any conclusions about the survivors (in Mexico City, between 7,000 and 10,000 suffer from hypertensive disorders during pregnancy, per year [17]). It is possible, for example, that the use (and correct use) of magnesium sulfate in women who recovered from preeclampsia or eclampsia, may be higher than what we observed among the women in our sample. The research project done by Lumbiganon and colleagues[15] is interesting because their study team did an on-site review of the patient files of all preeclampsia and eclampsia cases of a sample of hospitals in Mexico City (including survivors), over time-period of six months. However, this study was somewhat limited as it focused only on the occurrence of preeclampsia and eclampsia, and the use of anticonvulsants. Our study strongly complements Lumbiganon's study with much more detailed information, such as the distinction between mild and severe preeclampsia, whether the use of magnesium was indicated per diagnosis (magnesium sulfate is not indicated for mild preeclampsia), the trajectory of women through prior hospitals, and other disease-related factors.

Incompleteness of medical maternal mortality medical files (*i.e.* the factors which determined which files we ultimately included in our study), as well as missing/non-recorded specific information from the files we analyzed is also a limitation of this study, but one that was outside the control of our research team. For example, some files contained only a death certificate, even if women were treated at hospitals, and others had other clinical documents but no death certificate. As noted in our methods section, we chose to analyze medical files in which a patient chart and/or a clinical summary provided somewhat more detailed medical information. Still, even patient charts (which were always photocopies), were at times hand-written and illegible. And clincial summaries differed in quality, too; some were quite thorough and complete, while others were too superficial to provide a clear picture of the case. Furthermore, even when we had the complete patient chart or summary, relevant information was not always registered, such as the drugs that were administered to the patient in the course of her disease, its dosages, monitoring of side-effects of magnesium sulfate, reasons for non-use of anticonvulsants, and whether or not women received on site diagnostic tests (i.e. blood pressure readings or dipstick tests for urine protein).

In most cases, the absence of recorded/explicit information was analyzed as "not recorded;" in a few cases, however, we chose to make a modest assumption: in the cases where physicians mentioned in their notes that drugs were administered to the patient, but magnesium sulfate or other anticonvulsant drugs were not explicitly mentioned, we assumed that magnesium sulfate was not used and classified the case as such. When no drugs were listed at all in the charts, we reported the use of magnesium sulfate or other anticonvulsants as "not recorded." We are confident that this assumption can be made though, as preeclampsia and eclampsia are life-threatening conditions and it is unlikely that magnesium would have been used but not recorded. If our assumption is incorrect, then this too, would present a data-related limitation.

The lack of available information also challenged our task of interpretation. For example, in cases where we are confident that magnesium sulfate was not used, we do not know the reasons for non-use, including whether or not the drug was even available, and this in turn makes it impossible to draw major conclusions about barriers to magnesium sulfate use. According to the Mexican clinical guidelines, phenytoin (or phenobarbital) is the second choice anticonvulsant, which could explain the relatively common use of phenytoin in Mexico City. However, we believe that the availability of magnesium sulfate is not a major problem in Mexico City. Our study team is currently analyzing data from a complementary qualitative study in which we interviewed maternal health experts in Mexico City, and nearly all stated that magnesium sulfate is normally available, at least at the secondary and tertiary care hospitals. Interestingly, the present study also found a frequent use of diazepam, although diazepam is not mentioned in the Mexican clinical guidelines as an anticonvulsant. In our study, we assumed that diazepam was used as an anticonvulsant, but it is possible that the drug may have been used for sedation independently of convulsions.

An additional limitation of our study was that, especially at the final clinical visit, women already presented very severe complications such as cerebral hemorrhage, liver hematoma, or dissiminated intravascular coagulation. In these cases, magnesium sulfate may not have been indicated anymore at the final stages of the disease. We will take this factor into account in the continuation of our analysis of the data (as mentioned before, we also plan to analyze the characteristics of women who only visited one – the final- hospital, we will include an analysis of the tendency of use of magnesium sulfate over the three years of study, and we will do further analysis of the database).

We also did not analyze hypertensive treatment, or other general measures that should be taken with patients with hypertensive disorders during pregnancy.

Main conclusions and research/healthcare implications

Even though severe preeclampsia and eclampsia are the leading cause of maternal deaths in Mexico, effective evidence-based treatment has not been implemented as it should be. Many of our findings, including a generally low use of magnesium sulfate and a relatively high use of phenytoin, are consistent with those reported by Lumbiganon and colleagues (2000-2002) in their study of Mexico City hospitals.[15] And although our study focuses on more recent years, in which the Magpie trial results were already widely disseminated and, at least for the years 2006 and 2007, the Mexican clinical guidelines were already updated, the use of magnesium sulfate has not seemed to have improved much when compared to the study by Lumbignon and coauthors.

It is quite alarming, for example, that across the three years, in 27.8% of the cases in which women were diagnosed with severe preeclampsia and in 9.8% of the cases in which women were diagnosed with eclampsia, women were not administered any anticonvulsant treatment (Table 6). Reasons for the continued lack of adoption of the recommended practices may be that follow-up of clinical guidelines is not structurally monitored, and that no sanctions exist for health care providers that do not adhere to them. Lack of experience with or lack of knowledge on magnesium sulfate administration, including fear of side-effects, may be other barriers for the use of this anticonvulsant drug. Even so, representative surveys and in-depth qualitative studies are needed to document and understand reasons for clinicians non-use of magnesium sulfate.

In our sample, magnesium sulfate alone (not combined with other anticonvulsants), was used in only 22.2% of the total clinical visits in which women were diagnosed with severe preeclampsia, and in only 8.2% of the total clinical visits in which women were diagnosed with eclampsia (Table 6). As our analyses also showed, all too frequently women were administered other, less effective anticonvulsants, or they were administered magnesium sulfate in conjunction with other anticonvulsants – and in the latter case, we could find no studies to suggest whether or not the

benefits of magnesium sulfate are in some way attenuated or affected by such combinations. Research projects exploring the more common combinations of these drugs would no doubt be informative, however, given the clear evidence of the effectiveness of magnesium sulfate, a more ethical and beneficial research investment would be to carry out operations research interventions to study effective strategies for increasing physician uptake and proper use of this evidence-based treatment.

An important implication of the generally poor quality and incompleteness of the maternal mortality medical files we reviewed, is that a lack of general information may have affected the quality of care given to the 91 women who died as a result of these hypertensive disorders. Illegible notes, lack of information on treatment and lack of registration of the follow-up of treatment, may plausibly affect the quality of care in the hospitals, especially when women make multiple visits, because a clinician may not know what a woman may or may not have received before s/he attends to her. At the time of the maternal death audits at hospital, "county" and state levels, charts may be so confusing, full of gaps or even contain contradictory information, that no proper healthcare recommendations can be made to healthcare facilities or to clinicians. Mexico's Federal Ministry of Health, as well as state-level Ministries of Health should design and implement mechanisms to ensure that medical charts contain correct, legible and complete information.

In closing, an adequate implemention of magnesium sulfate treatment can have an important impact on the maternal mortality and morbidity due to severe preeclampsia and eclampsia in Mexico City. Research is needed urgently to design and evaluate innovative approaches to improve magnesium sulfate use and other evidence-based practices, and Mexican health officials and decision-makers should reinforce monitoring and supervision over their correct implementation.

Acknowledgements

This project was made possible by the generous support of the John D. and Catherine T. MacArthur Foundation. We kindly thank Mexico City Minister of Health, Dr. Armando Ahued, and the institution he represents, for a fruitful collaboration and for authorization to review the maternal death records used in this study. We are also grateful to Population Council researcher, Katherine Wilson and Council consultant, Xipatl Contreras, for their support in data collection and preliminary analysis, as well as Council consultant, Karla Berdichevsky, for her help in piloting an early version of this study protocol. Finally, we thank expert colleauges whose early technical advice was helpful to the design of this study: Drs. Leila Duley, Stephen Kennedy, and Ana Langer.

REFERENCES

1. United Nations. *The Millennium Development Goals Report 2006.* New York: United Nations, 2006.
2. WHO, UNICEF, UNFPA. *Maternal Mortality in 2000: Estimates developed by WHO, UNICEF, UNFPA.* WHO, 2004.
3. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *The Lancet* 2005;365:785-799.
4. The Magpie Trial Collaborative Group. Do women with preeclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: A randomised placebo-controlled trial. *The Lancet* 2002;359:1877-1890.
5. Duley L, Gülmezoglu AM. Magnesium sulfate versus lytic cocktail for eclampsia (Cochrane review). *The Reproductive Health Library*, Issue 9, 2006.
6. Duley L, Gülmezoglu AM, Henderson-Smart DJ. Magnesium sulfate and other anticonvulsants for women with pre-eclampsia (Cochrane review). *The Reproductive Health Librar*y, Issue 9, 2006.
7. Sibai BH. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *American Journal of Obstetrics and Gynecology* 2004; 190: 1520-1526.
8. Sibai BH. Magnesium sulfate prophylaxis in preeclampsia:Evidence From Randomized Trials. *Clinical Obstetrics and Gynecology* 2005;48(2):478-488.
9. Sheth SS, Chalmers I. Magnesium for preventing and treating eclampsia: Time for international action. *The Lancet* 2002;359:1872-1873.
10. Aaserud M, Lewin S, Innvaer S, Paulsen E J, Dahlgren A T, Trommald M, et al. Translating research into policy and practice in developing countries: a case study of magnesium sulfate for pre-eclampsia. *BMC Health Services Research* 2005,5:68.

11. Langer A, Villar J, Tell K, Kim T, Kennedy S. Reducing eclampsia-related deaths – a call to action. *The Lancet* 2008;371:705-706.

12. CNEGySR, Federal MOH; *Salud Materna en México. 2007-2012. Avances y Retos.* Powerpoint presentation for the meeting with the Mac-Arthur Foundation, Nov. 2007

13. Dirección General de Información en Salud (DGIS), Sistema Nacional de Información en Salud; Cube of Maternal Deaths 2002-2007. Mexico, 2009.

14. MOH Mexico; *Prevención, Diagnósticoy Manejo de la Preeclampsia/Eclampsia. Lineamiento técnico*. Centro Nacional de Equidad de Género y Salud Reproductiva. Mexico D.F. Cuarta edición, abril 2007.

15. Lumbiganon P, Gülmezoglu A M, Piaggio G, Grimshaw J; Magnesium sulfate is not used for pre-eclampsia and eclampsia in Mexico and Thailand as much as it should be. *Bull World Health Organ.* 2007 Oct;85(10):763-7.

16. Dr. Patricio Sanhueza, Coordinator of the Reproductive Health Program, Ministry of Health of Mexico City, Personal communication, 9 February 2009.

17. Dr. Patricio Sanhueza, Coordinator of the Reproductive Health Program, Ministry of Health of Mexico City, Personal communication, 7 April 2009.

Figure 1. Women's pathway through different health care facilities visited prior to their death due to preeclampsia and eclampsia in Mexico City (2005-2007)