Research

Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries

Nhu Thi Nguyen Ngoc, Mario Merialdi, Hany Abdel-Aleem, Guillermo Carrol, Manorama Purwar, Nelly Zavaleta, Liana Campódonico, Mohamed M Ali, G Justus Hofmeyr, Matthews Mathai, Ornella Lincetto, & José Villar

Objective To report stillbirth and early neonatal mortality and to quantify the relative importance of different primary obstetric causes of perinatal mortality in 171 perinatal deaths from 7993 pregnancies that ended after 28 weeks in nulliparous women.

Methods A review of all stillbirths and early newborn deaths reported in the WHO calcium supplementation trial for the prevention of pre-eclampsia conducted at seven WHO collaborating centres in Argentina, Egypt, India, Peru, South Africa and Viet Nam. We used the Baird–Pattinson system to assign primary obstetric causes of death and classified causes of early neonatal death using the International classification of diseases and related health problems, Tenth revision (ICD-10).

Findings Stillbirth rate was 12.5 per 1000 births and early neonatal mortality rate was 9.0 per 1000 live births. Spontaneous preterm delivery and hypertensive disorders were the most common obstetric events leading to perinatal deaths (28.7% and 23.6%, respectively). Prematurity was the main cause of early neonatal deaths (62%).

Conclusions Advancements in the care of premature infants and prevention of spontaneous preterm labour and hypertensive disorders of pregnancy could lead to a substantial decrease in perinatal mortality in hospital settings in developing countries.

Introduction

A two-thirds reduction of mortality in children less than 5 years old by 2015 is one of the UN Millennium Development Goals. Despite a decline in mortality in children in this age group in the last few decades, neonatal mortality numbers have not changed substantially. While infant mortality rates are expected to decrease as a result of the widespread implementation of effective interventions such as vaccines and oral rehydration therapy, the proportion of neonatal deaths is likely to increase.

One of the most striking examples of inequity between countries is in the area of newborn health. Of the 4 million neonatal deaths that occur every year, 98% are in the poorest countries of the world. This figure seems even more catastrophic when seen in the light of the estimate that for every neonatal death there is one stillbirth. Perinatal deaths are responsible for about 7% of the total global burden of disease. This percentage exceeds that caused by vaccine-preventable diseases and malaria together. The disparity between high-income and low-income countries in neonatal mortality is unacceptably large and continues to increase. Knowledge of the relative importance of the different causes of stillbirth and neonatal deaths in developing countries is still lacking. Preterm birth, infection and birth asphyxia are thought to be the main causes of death in newborn babies worldwide. However, Kulmala et al. report that the importance of causes of death may vary according to whether the birth setting was a hospital or in the community. In hospital-based surveys, women who are at high risk of negative outcomes (e.g. referred cases) might be over-represented, while community based studies may be less reliable with respect to accurate diagnosis of the causes of deaths. Additionally, surveys — both hospital and community based — may not provide information on pregnancy

1 Hung Vuong Hospital, 128 Hungvuong Street, Q5, Ho Chi Minh City, Viet Nam. Correspondence to Dr Ngoc (email: ngockiet@hcm.vnn.vn).
3 Department of Obstetrics and Gynaecology, Assiut University Hospital, Assiut, Egypt.
4 Centro Rosarino de Estudios Perinatales (CREP), Rosario, Argentina.
5 Department of Obstetrics and Gynaecology, Government Medical College and Hospital, Nagpur, India.
6 Instituto de Investigación Nutricional, Lima, Peru.
7 Department of Obstetrics and Gynaecology, East London Hospital Complex, East London, South Africa.
8 Christian Medical College, Vellore, India.
9 Department of Making Pregnancy Safer, World Health Organization, Geneva, Switzerland.

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complications or events prior to delivery that may have influenced the risk of death for the fetus or the newborn child. From an obstetric and neonatal care perspective, such information is crucial if the primary events that started the pathological process leading to the death of the fetus or the newborn child are to be understood.

Here, we report primary obstetric causes of death and rates of early neonatal death (until 7 days postpartum) and stillbirth (fetal death after 28 weeks’ gestation) in 7993 pregnancies of nulliparous women enrolled in a trial of calcium supplementation for the prevention of pre-eclampsia conducted in six developing countries. Additionally, final neonatal causes of death are reported and we assess differences in mortality by centre and gestational age at delivery.

Methods

Study population

Between 2001 and 2004 WHO conducted a multicentre, randomized, placebo-controlled, double-blind trial of calcium supplementation for the prevention of pre-eclampsia in women with low calcium intake. Seven centres in six countries participated in the trial: Rosario (Argentina), Assiut (Egypt), Nagpur and Vellore (India), Lima (Peru), East London (South Africa) and Ho Chi Minh City (Viet Nam).

Pregnant women receiving antenatal care between November 2001 and July 2003 at the participating centres were eligible for the trial if gestational age was less than 20 weeks, they were nulliparous and willing and able to give informed consent. Gestational age at trial entry was established with use of the “best obstetric estimate”, including ultrasound examination (if required) by the attending obstetrician. Women were deemed ineligible if they had history of urolithiasis or symptoms suggestive of urolithiasis or any renal disease. Other exclusion criteria were: parathyroid disease; blood pressure \( \geq 140 \text{ mmHg systolic and/or } \geq 90 \text{ mmHg diastolic; treatment with antihypertensives, diuretics, digoxin, phenytoin or tetracyclines; and a history of hypertension. Women who were planning to deliver in a health facility outside the study area were also excluded.}

Participants were randomly allocated either a supplement of 1500 mg per day of elemental calcium as calcium carbonate or a placebo from the time of enrolment until delivery or initiation of any magnesium sulfate treatment or the clinical suspicion of urolithiasis. After enrolment, women were examined at monthly intervals or more often by study personnel who completed specific data collection forms at each antenatal visit and hospital admission, and at delivery. More details of the study design and results of maternal and neonatal outcomes by supplement type are presented elsewhere.

Calculating mortality and stillbirth

Early neonatal mortality and stillbirths were calculated, overall and by gestational age intervals, as the number of early neonatal deaths and stillbirths per 1000 live births and all births, respectively. To allow for comparisons to be made between centres and other studies, the numerator and the denominator of all rate calculations included only fetuses and infants of at least 28 weeks’ gestation, as indicated by ICD-10.

The risk and cumulative probability of stillbirth and early neonatal mortality (per 1000 births and live births, respectively) by gestational age were calculated using Kaplan-Meier survival analysis methods.

Assigning cause of death

One author (MM), who was unaware of treatment allocation, assigned primary causes of deaths on the basis of information extracted from the data-collection forms completed during pregnancy and during labour and delivery. Only one cause per case was assigned.

Cause of death assignment was made in accordance with a modified version of the classification system proposed by Baird et al. in 1954 to determine primary obstetric causes for fetal and neonatal deaths. Pattinson et al. adapted the system for use in developing country settings allowing for the identification of the following primary obstetrics causes of death: spontaneous preterm labour (<37 weeks), infections, antepartum haemorrhage, intrauterine growth restriction, hypertension, fetal abnormality, trauma and intrapartum asphyxia, maternal disease, other, unexplained intrauterine death and multiple pregnancy.

Research teams at each centre assigned final neonatal causes of death using information extracted from hospital records. Causes of death were coded in parentheses.
The 7993 pregnancies included in this study were among the 8325 women enrolled in the WHO calcium supplementation trial for the prevention of pre-eclampsia. 4151 women were randomly assigned to receive calcium supplementation while 4161 received a placebo. There were 30 multiple pregnancies in the calcium group and 36 in the placebo group. Delivery information was not available for 3.4% and 3.7% of the recruited women in the calcium and placebo group, respectively.

We recorded 100 stillbirths and 71 early neonatal deaths during the study period. There were 12.5 stillbirths per 1000 births and early neonatal mortality was 9.0 per 1000 live births. Of the 171 pregnancies that ended with a perinatal death, 107 terminated before term — 87 by spontaneous delivery and 30 by indicated preterm delivery.

Table 1 shows the trends in early neonatal mortality, stillbirths, early neonatal mortality risk and stillbirth risk over gestational time. While early neonatal mortality and stillbirth rates decreased with advancing gestational age, the risk of stillbirth and early neonatal death remained high throughout gestation. This was expected because the stillbirth risk quantifies the hazard of stillbirth and is calculated by including in the denominator the number of undelivered fetuses, which decreases with gestational time.

The most common primary obstetric causes of perinatal death were spontaneous preterm delivery and hypertensive disorders (28.7% and 26.3%, respectively; Table 1). The relative importance of these two primary obstetric causes of death is reflected in the causes of 71 early neonatal deaths, 60.5% of which were attributable to prematurity (Table 2). An assessment of numbers of death by supplement type showed that hypertensive disorders were less common in the calcium group (P = 0.04).

Table 3 shows the relative importance of various causes of death in newborns at different intervals of gestational age at delivery, overall and by supplement type. Prematurity remained the most important cause of death even when gestational ages approached term.

### Table 1. Primary obstetric causes of perinatal deaths

<table>
<thead>
<tr>
<th>Primary obstetric cause</th>
<th>Total* (n = 171)</th>
<th>Calcium group* (n = 78)</th>
<th>Placebo group* (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Singleton pregnancy</td>
<td>Multiple pregnancy</td>
<td>Singleton pregnancy</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Unexplained intrauterine fetal death</td>
<td>14 (8.2)</td>
<td>4 (2.3)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Spontaneous preterm labour</td>
<td>35 (20.5)</td>
<td>20 (11.7)</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>Intrapartum-related</td>
<td>13 (7.6)</td>
<td>7 (4.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (2.9)</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fetal abnormalities</td>
<td>20 (11.7)</td>
<td>9 (5.3)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>44 (25.7)</td>
<td>19 (11.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>4 (2.3)</td>
<td>2 (1.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>8 (4.7)</td>
<td>3 (1.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (4.0)</td>
<td>2 (1.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>152 (88.8)</strong></td>
<td><strong>68 (39.8)</strong></td>
<td><strong>10 (5.9)</strong></td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages; denominator is numbers of perinatal deaths, overall and by supplement group.

### Table 2. Causes of early neonatal deaths

<table>
<thead>
<tr>
<th>Primary obstetric cause</th>
<th>Total*</th>
<th>Calcium group*</th>
<th>Placebo group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Singleton pregnancy</td>
<td>Multiple pregnancy</td>
<td>Singleton pregnancy</td>
</tr>
<tr>
<td>Prematurity-related</td>
<td>30 (42.2)</td>
<td>13 (18.3)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Asphyxia and birth trauma</td>
<td>16 (22.5)</td>
<td>0 (0)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>9 (12.7)</td>
<td>0 (0)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>58 (81.6)</strong></td>
<td><strong>13 (18.3)</strong></td>
<td><strong>26 (83.9)</strong></td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages; denominator is numbers of early neonatal deaths, overall and by supplement group.
Discussion

Our analysis indicates that hypertensive disorders and spontaneous preterm delivery were the main primary obstetric events that led to fetal or newborn deaths in pregnancies included in the WHO multinational calcium supplementation trial.7 Stratified analysis by supplement type showed that calcium supplementation was associated with an important reduction in deaths attributable to hypertensive disorders of pregnancy. This observation suggests that simple and affordable interventions such as nutritional supplementation might contribute to a decrease in mortality even at secondary and tertiary care health facilities.7

The most important causes of early neonatal deaths were prematurity, asphyxia and congenital anomalies. Prematurity was the single most important cause of death in infants born before 37 weeks. This finding is noteworthy since in developed countries, where intensive neonatal care is available, only very preterm babies are at risk of dying. Prematurity, however, has devastating effects in developing countries where mortality is high even at late gestational ages.

Although the study was conducted in hospitals that had neonatal intensive care units or where referral to tertiary care was possible, the high numbers of early neonatal deaths and stillbirths that we observed were larger than those reported in developed countries.9,10 This difference suggests that improvement in health system performance, particularly in the prevention and treatment of obstetric and neonatal complications, could lead to important decreases in perinatal mortality in developing countries even in populations with access to secondary and tertiary care facilities.

Although our analysis showed differences in the relative importance of primary obstetric causes between study sites, results of stratified analysis by centre showed that spontaneous delivery and/or hypertension tended to persist as the most important causes at all centres. However, these results should be interpreted with caution since sample sizes were small when analysis was done by individual centres. Differences by centre may be attributable to chance but could also reflect variations in the availability of specific forms of care—i.e. corticosteroid use and/or exposure to different diseases, such as syphilis or malaria. However, since our data is derived from the trial data-collection forms rather than from medical records we are not able to speculate on this issue. While the collection of data by standardized procedures in the context of a clinical trial assures the uniformity and quality of data examined, it inevitably limits the amount of information available.

We also observed differences between singleton and multiple pregnancies with respect to primary causes of death; however, we think the number of multiple pregnancies is too small to allow for a meaningful interpretation of this observation. Interestingly, we noted a reduced percentage of stillbirths related to infection when compared with data from other published work.11,12 This finding might be explained by the fact that we assigned only one cause of death and that in this context hypertensive disorders and preterm delivery might frequently have been rated as the primary diagnosis rather than infection, especially if access to confirmatory laboratory analysis was limited.

The design of the clinical trial combined the characteristics of community and hospital based studies because women were recruited in general antenatal care clinics before 20 weeks’ gestation and were followed up until delivery and hospital discharge, thus avoiding the bias of over-representation of hospital referral cases. In addition, most deliveries happened in hospital settings under medical supervision, and medical staff could ascertain causes of death. Our study, therefore, offers a reliable picture of the relative importance of different determinants of stillbirth and newborn mortality in populations of nulliparous pregnant women in several developing countries and could be defined as set in mixed, community and hospital, settings. However, in interpreting the data one must consider that the study population received antenatal care regularly and in the context of a research project. Furthermore, the study inclusion criteria targeted women at high risk of pre-eclampsia (those with a low calcium intake and nulliparous).7,13 Recruitment to the study before 20 weeks’ gestation

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</thead>
<tbody>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>4</td>
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</tr>
<tr>
<td>Calcium group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prematurity</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Congenital malformations</td>
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<td>0</td>
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<td>4</td>
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<tr>
<td>Total</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>8</td>
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<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Overall</td>
<td>17</td>
<td>11</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 3. Cause of neonatal death by intervals of gestational age at delivery
was a requirement to allow for the effect of calcium supplementation. While these features of the study design could limit the external validity of the study, we think the results are informative when applied to populations of women who receive regular antenatal care and who give birth in health facilities.

Compared with other studies conducted in community and/or hospital settings, our results could provide an indication on how future trends in stillbirth and neonatal mortality may develop. Global estimates of neonatal mortality published in 2005 show that, worldwide, 27% of deaths in newborns are attributable to prematurity; infection and asphyxia account for about one third of deaths each. Those estimates are consistent with the results of a large community study from Bangladesh reporting on almost 4000 deliveries, which have shown that intrapartum conditions and preterm delivery were the most important determinants of perinatal death.

The relative importance of causes of deaths is likely to change when moving from community to hospital settings, as shown by a very large study from South Africa which included data from more than 300 000 deliveries in hospitals and health facilities located in metropolitan, city and rural areas. Results showed that hypertensive disorders were the most important cause of perinatal death, followed by preterm delivery and intrapartum conditions.

Conclusion

The conclusion that can be drawn from the comparisons of the results of these large studies is that preterm delivery and intrapartum-related causes are the maternal complications most likely to contribute to the risk of perinatal death in poor and disadvantaged populations, especially for deliveries occurring outside hospitals or health-care facilities. However, it is likely that their relative importance will change in the future. Making effective obstetric and newborn care practices widely available and ensuring adequate and timely access to care, especially for disadvantaged populations with no hospital care, could reduce the risk associated with both preterm delivery and intrapartum complications. If these improvements are implemented, it is plausible to expect a reduction in the proportion of perinatal mortality attributed to intrapartum complications and an increase in the relative importance of preterm delivery and hypertensive disorders of pregnancy. This possible scenario is lent support by our results from almost 8000 pregnancies. Therefore, research efforts to identify the causes of preterm delivery and hypertensive disorders of pregnancy should be encouraged. The ultimate objective should be to translate new knowledge into the development of effective screening, preventive and therapeutic interventions that are currently lacking and which could save millions of newborn lives and reduce health care costs and morbidity and disability. However, to effectively contribute to the prevention of newborn mortality and morbidity, research should not be focused solely on the determinants of specific conditions responsible for large numbers of newborn deaths. Importantly, research is also needed to assess how to implement interventions within the health systems, especially those that would reach populations in most need.

Despite their limitations, our results do show that, even for babies who are born in hospitals with access to tertiary care, there could be room for improvement in newborn health outcomes that would close the equity gap between rich and poor countries in maternal and newborn health.

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South Africa: N Fiti, B Gaxela, Z Sobe-kwa and ZB Ntet, East London Hospital Complex.

Viet Nam: NT Hieu, T Hanh Le and staff at the antenatal clinic of Hungvuong Hospital.

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Causas de mortalidad neonatal precoz: datos de 7993 embarazos en seis países en desarrollo

Objetivo Informar sobre la mortalidad y la mortalidad neonatal precoz y cuantificar la importancia relativa de diferentes causas obstétricas primarias de mortalidad perinatal en 171 defunciones perinatales correspondientes a 7993 embarazos de más de 28 semanas en mujeres nulíparas.

Métodos Se examinaron todos los casos de mortalidad neonatal y defunción precoz de recién nacidos notificados en un ensayo OMS de administración de suplementos de calcio para la prevención de la preeclampsia menado en siete centros colaboradores de la OMS en la Argentina, Egipto, la India, el Perú, Sudáfrica y Vietnam. Usamos el sistema de Baird-Pattinson para asignar causas obstétricas primarias de muerte y causas clasificadas de mortalidad neonatal precoz mediante la Clasificación Estadística Internacional de Enfermedades y Problemas de Salud Conexas, décima revisión (CIE-10).

Resultados La tasa de mortalidad neonatal fue del 12,5 por 1000 nacimientos, y la tasa de mortalidad neonatal precoz, de 9,0 por 1000 nacidos vivos. El parto pretermín espontáneo y los trastornos hipertensivos fueron los casos obstétricos más comunes asociados a las defunciones perinatales (28,7% y 23,6%, respectivamente). La prematuridad fue la causa principal de las defunciones neonatales precoz (62%).

Conclusiones Los progresos en el trabajo en prevención y la prevención del parto pretermín espontáneo y de los trastornos hipertensivos del embarazo podrían propiciar una disminución sustancial de la mortalidad perinatal en los entornos hospitalarios en los países en desarrollo.
References