A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries


Objective To quantify maternal, fetal and neonatal mortality in low- and middle-income countries, to identify when deaths occur and to identify relationships between maternal deaths and stillbirths and neonatal deaths.

Methods A prospective study of pregnancy outcomes was performed in 106 communities at seven sites in Argentina, Guatemala, India, Kenya, Pakistan and Zambia. Pregnant women were enrolled and followed until six weeks postpartum.

Findings Between 2010 and 2012, 214,070 of 220,235 enrolled women (97.2%) completed follow-up. The maternal mortality ratio was 168 per 100,000 live births, ranging from 69 per 100,000 in Argentina to 316 per 100,000 in Pakistan. Overall, 29% (98/336) of maternal deaths occurred around the time of delivery: most were attributed to haemorrhage (86/336), pre-eclampsia or eclampsia (55/336) or sepsis (39/336). Around 70% (4349/6213) of stillbirths were probably intrapartum; 34% (1804/5230) of neonates died on the day of delivery and 14% (755/5230) died the day after. Stillbirths were more common in women who died than in those alive six weeks postpartum (risk ratio, RR: 9.48; 95% confidence interval, CI: 7.97–11.27), as were perinatal deaths (RR: 4.30; 95% CI: 3.26–5.67) and 7-day (RR: 3.94; 95% CI: 2.74–5.65) and 28-day neonatal deaths (RR: 7.36; 95% CI: 5.54–9.77).

Conclusion Most maternal, fetal and neonatal deaths occurred at or around delivery and were attributed to preventable causes. Maternal death increased the risk of perinatal and neonatal death. Improving obstetric and neonatal care around the time of birth offers the greatest chance of reducing mortality.

Introduction

An estimated 340,000 maternal deaths, 2.7 million stillbirths and 3.1 million neonatal deaths occur worldwide each year – almost all in low-income countries. In some parts of sub-Saharan Africa, a woman’s lifetime risk of dying in childbirth is as high as one in seven. Although women may die at any time during pregnancy and up to six weeks postpartum, the majority die during the last trimester or within the first week following birth. Similarly, it has been estimated that, in low-income countries almost half of stillbirths occur during or around the time of delivery and nearly three quarters of neonatal deaths take place within the first few days following birth. Thus, the period around delivery is thought to be the time when the woman and her fetus or infant are at the highest risk of dying. Although the timing of the mother’s death will, in itself, have a substantial influence on the risk of a fetal or neonatal death, the conditions that cause maternal death will also contribute to the risk. For example, pre-eclampsia and eclampsia are important causes of maternal death and major contributors to fetal and neonatal mortality because of their association with asphyxia and preterm birth. Haemorrhage and obstructed labour increase the risk of both stillbirth and early neonatal death associated with birth asphyxia. In addition, intrapartum stillbirth is usually attributed to obstetric...
Prospective, maternal newborn health

Between 2010 to 2012, as part of a prospective, maternal newborn health study of all pregnancies, we documented maternal, fetal and neonatal deaths that occurred up to six weeks postpartum. The study was done in 106 communities at six sites in five low-income countries (Chimaltenango, Guatemala; Nagpur District and Karnataka District, India; Western Province, Kenya; Thatta District, Pakistan; and Lusaka, Zambia) and at one site in a middle-income country (Corrientes, Argentina). These seven sites were selected by the Eunice Kennedy Shriver National Institute of Child Health and Human Development in the United States of America (USA), which supports the Global Network for Women’s and Children’s Health Research, to represent rural or semi-urban geographical areas served by government health services. Each site included between six and 24 distinct communities. In general, each community represented the catchment area of a primary health-care centre and, in each, 300 to 500 births took place annually. Beginning in 2009, the study investigators at each site initiated an ongoing, prospective maternal and newborn health registry of pregnant women for each community. The objective was to enrol pregnant women by 20 weeks’ gestation and to obtain data on pregnancy outcomes for all deliveries that took place in the community. Each community employed a registry administrator who identified and tracked pregnancies and their outcomes in coordination with community elders, birth attendants and other health-care workers.

All pregnant women resident in study communities were eligible for inclusion. Women were enrolled during pregnancy and data on pregnancy outcomes were collected by the trained registry administrators – usually nurses or health workers – who were supervised by study site investigators. At each site, efforts were made to verify that all pregnant women residing in the study communities were included in the registry and that data on all outcomes had been obtained. The study coordinators, who were generally nurses or physicians, monitored enrolment and follow-up to ensure that the data collected were consistent, complete and of a high quality. For hospital births, registry administrators reviewed hospital birth records routinely to identify deliveries to women from the study communities. In addition, culturally appropriate strategies were used at each site to ensure that all outcomes were reported. For example, elders or chiefs in one village used mobile phones to send text messages when women enrolled in the study gave birth. Such strategies increased the likelihood that we were able to identify all pregnancies and maternal and fetal outcomes.

Demographic and medical data were obtained for each woman by either the registry administrator or the study coordinator. All deaths that occurred during pregnancy or in the six weeks postpartum were reported using World Health Organization (WHO) classifications. The cause of each maternal death was assigned by the registry administrator on the basis of clinical and other information provided by the birth attendant and the woman’s family. All death reports were reviewed by the supervising physician at the study site. For deaths for which a definite cause could not be established, we undertook a secondary investigation to identify contributing factors, such as haemorrhage, pre-eclampsia, eclampsia or obstructed labour, and classified the cause accordingly. Details of this procedure have been described elsewhere.

Study data were entered onto Microsoft Access computer files (Microsoft, Redmond, USA) at each study site and data were edited before transmission to the central data centre at RTI International in the United States, where additional data edits were performed and the data were analysed using SAS version 9.2 (SAS Institute, Cary, USA). The study findings were reported using descriptive statistics and risk ratios were calculated for maternal, fetal and neonatal outcomes. Generalized estimation equations were used to adjust for the characteristics of each site and for clustering.

The study was approved by university review boards at each local site, by partner universities in the United States and by RTI International and was registered as trial NCT01073475 at the ClinicalTrials.gov registry (United States National Library of Medicine, Bethesda, USA). All women provided informed consent before enrolment.

Results

Between 2010 and 2012, 224 234 pregnant women were considered for enrolment in the study and 220 365 were regarded as eligible. Of these, 220 235 were enrolled since 130 refused
### Table 1. Details of births in six countries, by study site, 2010–2012

<table>
<thead>
<tr>
<th>Study site</th>
<th>No. of women enrolled</th>
<th>No. (%) of births by attendant</th>
<th>No. (%) of births by place</th>
<th>No. (%) of caesarean sections performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Physician</td>
<td>Nurse</td>
<td>Traditional birth attendant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Argentina</td>
<td>8 861</td>
<td>2 140 (27.3)</td>
<td>6 381 (72.2)</td>
<td></td>
</tr>
<tr>
<td>Guatemala</td>
<td>19 725</td>
<td>3 747 (19.1)</td>
<td>15 606 (78.9)</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>65 810</td>
<td>10 072 (15.3)</td>
<td>54 638 (83.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 518 (57.0)</td>
<td>10 654 (28.6)</td>
<td>22 864 (61.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 656 (6.9)</td>
<td>9 800 (21.4)</td>
<td>37 262 (80.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 008</td>
<td>5 193 (22.5)</td>
<td>18 905 (80.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>214 070</td>
<td>79 255 (37.1)</td>
<td>67 791 (31.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Delivery occurred during transit to a health-care facility or information was not available.*

### Table 2. Maternal, fetal and neonatal deaths in six countries, by study site, 2010–2012

<table>
<thead>
<tr>
<th>Study site</th>
<th>No. of women enrolled</th>
<th>No. of maternal deaths</th>
<th>Maternal mortality ratio, deaths per 100 000 live births (95% CI)</th>
<th>Stillbirths</th>
<th>Mortality rate, deaths per 1000 live births (95% CI)</th>
<th>Perinatal deaths</th>
<th>Mortality rate, deaths per 1000 births (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>8 861</td>
<td>6</td>
<td>69 (4-153)</td>
<td>126</td>
<td>141 (117-166)</td>
<td>398</td>
<td>200 (181-220)</td>
</tr>
<tr>
<td>Guatemala</td>
<td>19 725</td>
<td>21</td>
<td>109 (63-156)</td>
<td>302</td>
<td>204 (181-220)</td>
<td>302</td>
<td>200 (181-220)</td>
</tr>
<tr>
<td>India</td>
<td>65 810</td>
<td>139 (109-168)</td>
<td>10 072 (15.3)</td>
<td>1 607</td>
<td>257 (244-269)</td>
<td>1 178</td>
<td>193 (182-204)</td>
</tr>
<tr>
<td></td>
<td>30 838</td>
<td>84</td>
<td>131 (63-193)</td>
<td>1 178</td>
<td>257 (244-269)</td>
<td>1 178</td>
<td>193 (182-204)</td>
</tr>
<tr>
<td></td>
<td>30 838</td>
<td>84</td>
<td>131 (63-193)</td>
<td>1 178</td>
<td>257 (244-269)</td>
<td>1 178</td>
<td>193 (182-204)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>40 656</td>
<td>116</td>
<td>136 (63-193)</td>
<td>1 178</td>
<td>257 (244-269)</td>
<td>1 178</td>
<td>193 (182-204)</td>
</tr>
<tr>
<td>Zambia</td>
<td>21 008</td>
<td>29</td>
<td>144 (97-197)</td>
<td>440</td>
<td>210 (193-230)</td>
<td>300</td>
<td>210 (193-230)</td>
</tr>
<tr>
<td>Total</td>
<td>214 070</td>
<td>336</td>
<td>161 (59-186)</td>
<td>623</td>
<td>297 (280-304)</td>
<td>2 408</td>
<td>209 (202-215)</td>
</tr>
</tbody>
</table>

*CI: confidence interval.

*Maternal mortality ratio includes deaths within 42 days of delivery.*
to give consent. Data on outcomes up to six weeks after delivery were available for 214 070 of the 220 235 women (97.2%). The proportion of deliveries conducted by a physician ranged from 1.9% (503/27 072) in Kenya to 72.2% (6381/8861) in Argentina (Table 1). Deliveries by traditional birth attendants were rarely reported in Argentina, whereas 62.2% (12 276/19 724) of births in Guatemala were conducted by such attendants. The proportion of deliveries that took place in a hospital ranged from 7.7% (1609/21 008) in Zambia to 98.9% (8757/8861) in Argentina. Across all study sites, 44.0% (94 094/214 070) of deliveries took place in a hospital, compared with 30.4% (65 152/214 070) at home and 24.9% (53 233/214 070) in a health clinic. The caesarean section rate ranged from 34.4% (3048/8861) in Argentina to 1.1% (231/21 008) in Zambia.

In total, 336 maternal deaths occurred among the 214 070 women, which corresponded to an overall maternal mortality ratio of 168 per 100 000 live births. The ratio ranged from 69 per 100 000 live births in Argentina to 316 per 100 000 in Pakistan (Table 2). Around 21% (72/336) of pregnant women who died did so before delivery, whereas 29% (98/336) died during or immediately following delivery and an additional 9% (31/336) died on the day after delivery. Maternal deaths were due to: haemorrhage in 86/336 women (26%); pre-eclampsia or eclampsia in 55/336 (16%); sepsis in 39/336 (12%); suicide or accident in 23/336 (6.8%); anaemia in 22/336 (6.5%); infection with, for example, malaria or HIV in 21/336 (6.3%); heart disease in 16/336 (4.8%); obstructed labour in 12 (3.6%); other medical causes such as gestational diabetes or cancer in 5/336 (1.5%); and an unknown cause in 57/336 (17%).

Overall there were 6213 stillbirths, which corresponded to a rate of 29.7 per 1000 births; the figure ranged from 14.1 per 1000 births in Argentina to 56.1 per 1000 in Pakistan (Table 2). There were 4208 7-day neonatal deaths, which corresponded to a rate of 20.9 per 1000 live births; the figure ranged from 8.2 per 1000 live births in Argentina to 40.6 per 1000 in Pakistan. Altogether, there were more than 10 000 perinatal deaths (i.e. stillbirths and neonatal deaths up to 7 days after delivery) and the overall perinatal mortality rate was 50.1 per 1000 births; the figure ranged from 22.3 per 1000 births in Argentina to 95.3 per 1000 in Pakistan. In total, 34% (1804/5230) of neonatal deaths occurred on the day of delivery, 14% (755/5230) occurred on the following day and an additional 28% (1464/5230) occurred during the remainder of the first week of life. We assumed that fetal death occurred before labour in the 30% (1864/6213) of stillbirths that were macerated. The remaining 70% (4349/6213) probably occurred close to delivery or while the woman was in labour. While approximately 64% (137, 404/214 070) of deliveries took place at Asian sites, between 73% (244/336) and 75% (7858/10 421) of maternal, fetal and neonatal deaths occurred in this region.

We examined the association between perinatal and neonatal outcomes and the death of the mother. A total of 345 fetuses or neonates were recorded for the 336 women who died. Among those born to women who died, 110 were stillborn, 42 died by day 28 and 154 survived for more than 28 days (Table 3). In addition, there were 28 miscarriages or medically terminated pregnancies and the status of 11 fetuses or neonates was unknown. In total, 152 of 336 maternal deaths (45%) were associated with a stillbirth or a neonatal death. Among women who died, the stillbirth rate was 241 per 1000 births compared with 29 per 1000 in women who were still alive after six weeks. Moreover, the 7-day neonatal mortality rate was 159 per 1000 live births in women who died compared with 26 per 1000 in those who were still alive after six weeks. Finally, we calculated the association between the mother’s death and the risk of stillbirth and neonatal death (Table 3). The risk of a stillbirth was significantly higher in women who died than in those who were still alive after six weeks (risk ratio, RR: 9.48; 95% confidence interval, CI: 7.97–11.27), as were the risks of perinatal death (RR: 4.30; CI: 3.26–5.67), neonatal death within 7 days (RR: 3.94; CI: 2.74–5.65) and neonatal death within 28 days (RR: 7.36; CI: 5.54–9.77).

Discussion

We had three primary goals. The first was to determine maternal, fetal and neonatal mortality rates across the seven study sites. The two extremes were Argentina and Pakistan, where Pakistan had generally 4-fold to 5-fold higher mortality than Argentina. The second goal was to establish when maternal, fetal and neonatal deaths occurred. We found that nearly 20% of maternal deaths occurred before the day of delivery and another 30% occurred on the day of delivery. Thereafter, the number of maternal deaths decreased slowly throughout the following six weeks. The timing is consistent with our observation that the main causes of maternal death were haemorrhage, pre-eclampsia and eclampsia. Approximately two thirds of stillbirths were regarded as occurring around the time of delivery since these fetuses showed no signs of maceration. Moreover, approximately one third of neonatal deaths occurred on the day of delivery and another 25% occurred in the two days following delivery. Our third goal was to identify relationships between maternal deaths and stillbirths and neonatal deaths. Overall, if the mother died during pregnancy or in the six weeks after delivery, about half of their fetuses or neonates also died. However, it is important to note that half of their neonates survived the neonatal period. Previous research has suggested that infants who have lost their mothers have significantly higher risks of death and disease well into childhood and that maternal death also has an adverse effect on other siblings and on the extended family.13,24–30,32,35

Our study is a prospective, international, population-based research to assess the relationship between maternal and perinatal deaths. This study has several strengths. First, we prospectively registered all pregnant women in defined geographical catchment areas and the follow-up rate was high. In addition, the study was population-based and took place in areas where a substantial proportion of births occurred at home. Thus data from this study are likely to be more representative of these areas than many hospital-based studies of maternal mortality. Moreover, we employed trained coordinators to help ensure that the quality of the data collected on fetal, newborn and maternal outcomes was high. The follow-up rate to 28 days postpartum was very high (97%), which means that very few neonatal deaths were missed. Although maternal deaths are rare, we were able to calculate ma-
ternal mortality ratios and to assess the timing of maternal death and its association with perinatal or neonatal death because our study included more than 200 000 pregnant women.

One of the study’s limitations was that, since enrolment began at 16 weeks gestation, we may have missed some maternal deaths that occurred early in gestation, before the pregnancy had been recognized. Therefore, we may have underestimated maternal death rates, especially among women with early pregnancy losses, including those due to abortion. Additionally, although we asked each site to use WHO criteria to assign the cause of death, no specific methods were provided and thus each site probably interpreted the criteria slightly differently. Nevertheless, our study is one of the few that has prospectively registered pregnant women in low-income areas and followed them through to six weeks postpartum, thereby enabling maternal mortality to be estimated in the whole population. We did not analyse the relationship between maternal death and perinatal outcomes by country because the number of maternal deaths was small. However, we recognize that regional differences are an important area for future research.

Although maternal mortality has decreased significantly worldwide for several decades, the maternal mortality ratio remains high, especially in low-income countries, and is particularly high in sub-Saharan Africa and south Asia. These areas also have some of the highest rates and some of the highest absolute numbers of stillbirths and neonatal deaths. Our findings have important implications for the timing of interventions. We found, in agreement with other researchers, that the period of highest risk for both the mother and her fetus or neonate is around the time of delivery.3–6 Additionally, we also found that the majority of maternal deaths were attributed to causes associated with labour or delivery, such as haemorrhage, pre-eclampsia, eclampsia and sepsis.7–9 In 2011, other studies showed that maternal, fetal and newborn deaths are often due to the same causes and that interventions that reduce stillbirth and early neonatal mortality also reduce maternal mortality.2,4,5 Since then, others have described the possible connection between maternal and perinatal outcomes in greater detail.4,8,9,10

Our study confirms that the mother’s death has important implications for the risk that her fetus or neonate will also die. Since most deaths occurred near to delivery and because most obstetric complications are not recognized in advance, the intervention most likely, by far, to reduce mortality is the provision of high-quality emergency obstetric and neonatal care in hospitals capable of carrying out deliveries by caesarean section, blood transfusion and neonatal resuscitation in addition to other key elements of obstetric care, such as uterine evacuation of the retained products of conception, manual removal of the placenta, assisted vaginal delivery by forceps or vacuum and the administration of oxytocin, anticonvulsants and antibiotics. Although the provision of health-care services in homes and clinics is an important component of the overall system of obstetric and newborn care, programmes that focus on improving obstetric and neonatal care close to the time of birth appear to have the greatest chance of reducing all three types of pregnancy-related mortality: maternal, fetal and neonatal.

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中东收入国家孕产妇、胎儿和新生儿死亡率的前瞻性研究

目的：量化中东收入国家孕产妇、胎儿和新生儿死亡率，确定发生死亡的时间以及孕产妇死亡、死产和新生儿死亡之间的关系。

方法：在阿联酋、卡塔尔、印度、肯尼亚、巴基斯坦和赞比亚的七个地点 106 个社区进行妊娠结局的前瞻性研究。招募孕妇并随访至产后六周。

结果：在 2010 和 2012 年间，对纳入研究的 220235 名女性中，214070 名（97.2%）完成随访。死产死亡率为每 10 万例活产 168 例死亡，范围从阿联酋的每 10 万例 69 例到巴基斯坦的每 10 万例 336 例不等。整体而言，29%（98/336）的孕妇孕产妇死亡发生在分娩前；大多数是因为出血（86/336）、子痫前期或子痫（55/336）或败血性感染（39/336），大约 70%（4349/6213）的死亡可能发生在分娩期：34%（1804/5230）的新生儿死亡发生在分娩当天，14%（755/5230）在第二天。与产后六周之后仍存活的女性相比，死产在死亡女性中更加普遍（风险比：RR：9.48；95% 置信区间，CI：7.97 – 11.27），死产死亡率（RR：4.30；95% CI：3.26 – 5.67）和 7 天（RR：3.94；95% CI：2.74 – 5.65）和 28 天新生儿死亡率（RR：7.36；95% CI：5.54 – 9.77）的情况也是如此。

结论：大多数孕产妇、胎儿和新生儿死亡发生在分娩或分娩前，且都归因于可预防的原因。孕产妇死亡增加孕产期和新生儿死亡的风险。改善分娩前后产科和儿科护理是降低死亡率的最大机会。

Резюме

Une étude prospective de la mortalité maternelle, foetale et néonatale dans les pays à revenus faible et intermédiaire

Objectif Quantifier la mortalité maternelle, foetale et néonatale dans les pays à revenus faible et intermédiaire pour identifier à quel moment survient le décès et pour analyser les relations entre les décès maternels et les mortinaisances/décès néonatals.

Méthodes Une étude prospective sur des grossesses a été effectuée dans 106 collectivités sur 7 sites: Argentine, Guatemala, Inde, Kenya, Pakistan et Zambie. Les femmes enceintes ont été inscrites et suivies jusqu'à 6 semaines après leur accouchement.

Résultats Entre 2010 et 2012, 214 070 femmes inscrites sur 220 235 (97.2%) ont participé au suivi. Le taux de mortalité maternelle était de 168 pour 100 000 naissances d'enfants vivants, allant de 69 pour 100 000 en Argentine à 316 pour 100 000 au Pakistan. Dans l'ensemble, 29% (98/336) des décès maternels ont eu lieu au moment de la naissance: la plupart des décès ont été dus à une hémorragie (86/336), une prééclampsie ou une éclampsie (55/336), ou encore une septicémie (39/336). Environ 70% (4349/6213) des enfants sont morts dans l'année suivant l'accouchement, 34% (1804/5230) des nouveau-nés morts sont nés le jour de leur naissance et 14% (755/5230) le lendemain. Les mortinaisances...
Pregnancy-related mortality in low- and middle-income countries

La mayoría de las muertes maternas, prenatales y neonatales se produjeron en las primeras 24 horas del parto, las hemorragias (86/336) y la preeclampsia (55/336). Alrededor del 70% (4349/6213) de los fallecimientos pudieron haber sido evitables. La mortalidad materna aumentó el riesgo de muerte perinatal y neonatal. La mejor atención obstétrica y neonatal en el momento del nacimiento ofrece las mayores posibilidades para reducir la mortalidad.

Conclusión
La mayoría de las muertes perinatales y neonatales ocurrieron en o en torno al parto y se atribuyeron a causas evitables. La muerte materna aumentó el riesgo de muerte perinatal y neonatal. Mejorar la atención obstétrica y neonatal en el momento del nacimiento ofrece las mayores posibilidades para reducir la mortalidad.


