Changing perspectives of infectious causes of maternal mortality

Ajay Halder1,2, Reeta Vijayselvi1, Ruby Jose1

1Department of Obstetrics and Gynecology, Christian Medical College, Vellore, India
2Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Bhopal, India

Abstract

Objective: Infections significantly contribute to maternal mortality. There is a perceived change in the spectrum of such infections. This study aims to estimate the contribution of various types of infections to maternal mortality.

Material and Methods: We retrospectively reviewed records of maternal death cases that took place between 2003 and 2012 in the Christian Medical College, Vellore, India. The International Classification of Diseases-Maternal Mortality was used to classify the causes of deaths and World Health Organization near-miss criteria were used to identify organ dysfunction that occurred before death. Infections during pregnancy were divided into three groups, i.e., pregnancy-related infections, pregnancy-unrelated infections, and nosocomial infections.

Results: In this study, 32.53% of maternal deaths were because of some type of infection as the primary cause. The contribution of pregnancy-related infections was comparable with that of pregnancy-unrelated infections (16.03% vs. 16.50%). Metritis with pelvic cellulitis, septic abortions, tuberculosis, malaria, scrub typhus, and H1N1 influenza (influenza A virus subtype) were among the most commonly encountered causes of maternal death due to infections. Another 7.07% of cases developed severe systemic infection during the course of illness as nosocomial infection. A significant majority of mothers were below 30 years of age, were primiparae, had advanced gestational age, and had operative delivery. Cardiovascular and respiratory system dysfunctions were the most common organ dysfunctions encountered.

Conclusion: The contribution of pregnancy-unrelated infections to maternal deaths is significant. Control of these diverse community-acquired infections holds the key to a reduction in maternal mortality along with the promotion of clean birthing practices. Nosocomial infections should not be underestimated as a contributor to maternal mortality. (J Turk Ger Gynecol Assoc 2015; 16: 208-13)

Keywords: Infections, maternal mortality, organ dysfunction

Received: 03 July, 2015 Accepted: 14 October, 2015

Introduction

Puerperal sepsis was the most common cause of maternal death in the 19th century, accounting for up to 50% of all maternal deaths (1). The introduction of hand hygiene and sterilization practices, followed by the use of antibiotics, resulted in a sharp fall in the incidence of sepsis. However, puerperal infections are still reported as one of the major causes of maternal death, accounting for up to 15% of deaths (2-4). Puerperal sepsis is a polymicrobial infection of the genital tract caused by bacteria that normally inhabit the birth canal (5). In contrast, the term puerperal infection is used for genital tract infection along with other generalized infections that are incidental to pregnancy, such as tuberculosis, malaria, H1N1 influenza, and other endemic infections, including scrub typhus and dengue hemorrhagic fever (5). With the growing awareness and better availability of antiseptics and antibiotics, followed by control of bacterial genital sepsis, incidental systemic infections contributing to maternal death have increased. For example, in the sub-Saharan Africa, tuberculosis, pneumonia and meningitis, which are infections related to human immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS), have become major contributors to maternal mortality (6, 7). Poor sanitation, lack of proper housing, and poor vector control measures are the reasons for most of these vector-borne diseases.

Another important group is nosocomial infections, the contribution of which has gone unnoticed until now. With the control of delivery-associated and community-acquired infections in the Western world, hospital-acquired infections caused by resistant organisms are increasing. Although prospective studies on genital sepsis associated with childbirth are available, there is a dearth of information regarding infections that are unrelated to pregnancy (community acquired). Nosocomial infections, which are acquired after admission to a hospital, remain largely unquantified in the south Indian population. This study aims to define the spectrum of infectious diseases that directly or indirectly contribute to maternal death in a hospital setting.
Material and Methods

This study is a retrospective review of maternal death cases that occurred in the Christian Medical College, Vellore, India between January 2003 and December 2012. This tertiary-level teaching hospital caters to the large local population of Vellore and adjoining districts. A considerable number of women with high-risk pregnancy are referred to this center for advanced care during pregnancy and delivery from the whole of southern India and beyond. It is a privately owned faith-based institute where mostly lower-middle-class population is treated and a fair proportion (20%–30%) of patients is treated without cost for charity. The busy labor room has approximately eight beds for high-risk patients and 28 for low-risk patients, and there are eight beds in a high-dependency unit attached to the labor room complex. An operating room and blood bank facilities are available to support our high-output labor room, which is run by four to five postgraduate-level doctors with a proportionate number of junior doctors and staff nurses round the clock. Antenatal outpatient visits and admission and labor records are diligently maintained by on-duty staff and preserved by the medical records department. An online record of outpatient visit proceedings, investigations, and a detailed discharge summary is maintained against the patient's registration number. For this study, we identified and completed information regarding maternal death cases through a review of records from the labor room, intensive-care units, and outpatient database and discharge summaries. Maternal deaths were defined and classified according to International Classification of Diseases-Maternal Mortality (ICD-MM) (8). Deaths due to infections as the primary cause were classified into pregnancy-related infection or puerperal sepsis (endometritis, peritonitis, pelvic abscess, surgical site infection, and necrotizing fasciitis) and non-pregnancy-related or incidental infections, such as malaria, tuberculosis, and pneumonia (9). Deaths were considered to be associated with hospital-acquired infection when after a primary non-infectious cause, women developed signs of severe systemic infection later during the course of illness before death (9).

Twenty-five World Health Organization (WHO) near-miss criteria (10) were used to identify organ dysfunction that occurred during the period preceding maternal death. These 25 criteria belong to three categories, namely clinical criteria, laboratory criteria, and intervention-related criteria. Each system dysfunction is identified by the presence of at least one WHO near-miss criterion specific to that system (11). Information was collected in an Epi Info™ (CDC; Atlanta, USA) database using the WHO near-miss tool (11), and statistical analysis was performed on an Excel spreadsheet (Microsoft; Washington, USA). This study was approved by the Institutional Ethics Committee and a waiver for informed consent was provided because of the retrospective nature of the study. This study was not funded.

Results

During the 10 years of the study period, there were 212 registered maternal deaths in the institute with 98,139 total births and 95,384 live births between 2003 and 2012. During this period, there were 28,788 cesarean deliveries with an average cesarean section rate of 29.33%. The average perinatal mortality rate was 35.391 per 1000 live births. Only in 154 out of the 212 cases were the details provided in the records sufficient enough to extract useful information in addition to the final diagnosis. There were 84 maternal death cases that revealed severe systemic infection either as the primary cause of death or acquired during the course of illness. Table 1 shows the causes of maternal deaths that had signs of severe systemic infection. In 16.03% of maternal death cases, pregnancy-related infections were found to be the primary cause, which includes deaths due to sepsis following abortions. Metritis with pelvic cellulitis (11.79%) was the single most important cause of pregnancy-related infection. Septic abortions were observed in 3.37% of cases. Pregnancy-unrelated infections as a group were observed in 16.47% as the primary cause. Tuberculosis (4.7%), which included pulmonary tuberculosis (eight cases) and tubercular meningitis (two cases), was the most common incidental or pregnancy-unrelated infection associated with maternal mortality. This was closely followed by malaria, H1N1 influenza, and scrub typhus with six cases (2.8%) each. Only one mother died of AIDS-associated pneumonia. Nosocomial infections significantly contributed (7.07%) to the morbidity of mothers as a secondary cause, all of which were defined as ventilator-acquired pneumonia.

The mean age of the women who died of infections was 23.98±4.15 years, with more than 95% of the mothers below 30 years of age (Table 2). Approximately 60% of the women who died were pregnant for the first time, with fewer women (15.78%) having two or more prior deliveries. Over 83% of women who died were in their third trimester of pregnancy, with more than 53.94% of women beyond 36 weeks of pregnancy. On comparing mothers with severe infection with those without

<table>
<thead>
<tr>
<th>Table 1. Infectious causes of maternal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-related infection</td>
</tr>
<tr>
<td>Metritis with pelvic cellulitis</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Septic abortion</td>
</tr>
<tr>
<td>Pregnancy-unrelated/Incidental infection</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>H1N1 influenza</td>
</tr>
<tr>
<td>Scrub typhus</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Dengue hemorrhagic fever</td>
</tr>
<tr>
<td>Typhoid</td>
</tr>
<tr>
<td>Herpes zoster</td>
</tr>
<tr>
<td>HIV with Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td>Orbital cellulitis</td>
</tr>
<tr>
<td>Hospital-acquired infection</td>
</tr>
<tr>
<td>Ventilator-acquired pneumonia</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
blood transfusion during their stay in the hospital. The average duration (median) of hospital stay was 8 days, with 4 and 14 days as the 25th and 75th percentiles, respectively, whereas the average duration from delivery to death was also 8 days, with 6 and 13 days as the 25th and 75th percentiles, respectively.

### Discussion

South Asia, including India, has observed a 63% fall in maternal mortality over the last 20 years (12). Even with this positive trend, India has contributed an estimated 50,000 maternal deaths, which is approximately 72% of maternal deaths in South Asia in the year 2013. Direct causes of maternal death remain the most important causes, constituting approximately 50% of all maternal deaths (13). Obstetric hemorrhage, hypertensive disorders of pregnancy, puerperal sepsis, and abortion-related deaths are the most important direct causes (14). All direct causes of maternal mortality are considered preventable; however, pregnancy-related infections (puerperal sepsis) have the highest case fatality ratio among them (15). There are three major groups into which infections in pregnancy have been traditionally classified, namely pregnancy-related infection, pregnancy-unrelated or incidental infection, and nosocomial infection (9). We found that 16.07% (34/212) of maternal deaths were due to pregnancy-related infections in our study, which includes 3.37% deaths due to septic abortions. Being mainly related to the cleanliness of the birthing environment, a reduction in pregnancy-related infection could be achieved after the introduction of antisepsis and antibiotics. In a large multicenter study (12) of 7065 sites and 188 countries that evaluated the causes of maternal deaths from 1990 to 2013, there was a reduction in maternal deaths due to sepsis from 12% to 9%. The clean birthing practices campaign, (16) training programs for skilled birth attendants, and promotion of institutionalized deliveries (Janani Suraksha Yojana) are some of the measures in India that played a pivotal role in bringing the puerperal sepsis rate down (17). Having said that, several large-scale multicenter studies have revealed that there is as much as a 50-fold difference in puerperal sepsis rates across centers in Africa and Asia (18). This is because of the lack of a standard definition and under reporting of sepsis cases (19, 20). Most of the studies from low- and middle-income countries are hospital based, which is not a true representation of the community. There is further under reporting because of the fact that early discharge of patients occurs as a result of a shortage of hospital beds and because puerperal fever typically only occurs 24–72 h after delivery, when women have already been discharged.

Chuang et al. (21), in their study of 220 cases of puerperal sepsis, found bacteremia associated with Group A streptococcus (GAS) to be the most common clinical presentation, followed by endometritis, peritonitis, necrotizing fasciitis, and toxic shock syndrome, in that order. Bacteremia with GAS organisms without any foci was not encountered in our cases of maternal deaths because it is amenable to treatment by potent antibiotics, and thus, is not fatal. The proportion of other clinical presentations of genital sepsis is similar to that of Chuang et al. (21). Studies (5, 22, 23) have identified several obstetric risk factors for puerperal sepsis, such as pre-labor rupture of membranes, prolonged

---

### Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Parity</th>
<th>Total=76 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>46 (60.52)</td>
</tr>
<tr>
<td>1</td>
<td>18 (23.68)</td>
</tr>
<tr>
<td>2 or more</td>
<td>12 (15.78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age at delivery</th>
<th>Total=76 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 weeks or less</td>
<td>8 (10.52)</td>
</tr>
<tr>
<td>21–28 weeks</td>
<td>5 (6.57)</td>
</tr>
<tr>
<td>&gt;28–36 weeks</td>
<td>22 (28.94)</td>
</tr>
<tr>
<td>More than 36 weeks</td>
<td>41 (53.94)</td>
</tr>
</tbody>
</table>

### Table 3. Obstetric and perinatal outcomes

<table>
<thead>
<tr>
<th>Mode of termination of pregnancy</th>
<th>Total=82 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>40 (48.78)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>29 (35.36)</td>
</tr>
<tr>
<td>Surgical abortion</td>
<td>3 (3.65)</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>2 (2.43)</td>
</tr>
<tr>
<td>Medicated abortion</td>
<td>2 (2.43)</td>
</tr>
<tr>
<td>Died pregnant</td>
<td>5 (6.09)</td>
</tr>
<tr>
<td>Neonatal outcome</td>
<td>Total=75 (100%)</td>
</tr>
<tr>
<td>Live birth</td>
<td>48 (62)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>27 (36)</td>
</tr>
<tr>
<td>Early neonatal death</td>
<td>18 (25)</td>
</tr>
</tbody>
</table>
labor, multiple vaginal examinations (more than five), obstetri-
cal maneuvers, anemia, primiparity, and poor nutrition. How-
ever, the single most important factor associated with infection
is operative delivery. In this study, the cesarean section rate in
maternal mortality cases with infection was 42% compared with
29.33% in cases without infection. It was further found by Smaill
et al. (23) that endometritis is associated more with emergency
cesarean section than with elective surgery. Rising trends in
obesity and gestational diabetes are increasingly contributing to
puerperal sepsis in the form of surgical site infections (24).
Infections unrelated to pregnancy are community-acquired in-
fecions, such as pulmonary tuberculosis, malaria, HIV-AIDS,
H1N1 influenza, and other endemic infections, such as dengue
hemorrhagic fever and scrub typhus. Estimates of the contri-
bution of these infections to indirect causes or indeterminate
causes remain largely unknown (25). Unrelated infections as a
group were found to have claimed 16.47% (35/212) lives in this
study, which is similar to pregnancy-related infections. Among
all these incidental causes, tuberculosis remains the most im-
portant cause of death in the Indian subcontinent. In an esti-
mate from 1999 (26), death due to tuberculosis was observed
in more women in their reproductive age group (15–45 years)
than all causes of maternal mortality put together. If diagnosed
early and treated with multi-drug antitubercular treatment, the
outcome in infected women is as good as in women without
the disease. In contrast, with late treatment or no treatment,
there is a high incidence of fetal growth restriction, preterm
labour, and perinatal loss, along with increased maternal mor-
tality and morbidity (27, 28). After tuberculosis, malaria is the
second most common infection resulting in pregnant women
dying worldwide. In sub-Saharan Africa, almost 25% of maternal
deaths can be attributed to malaria or malaria complicated by
HIV-AIDS (29). Pregnant women are three times more likely to
suffer from a severe disease and have a 50% increase in mortal-
ity associated with it (30, 31). Primiparae are more likely to suf-
fer from adverse maternal outcomes due to severe anemia and
cardiac failure during labor, whereas multiparous women have
milder maternal symptoms but suffer from disproportionately
high perinatal morbidity and mortality due to innate immunity
and placental sequestration of malarial parasites (30, 32).
This institution witnessed six clustered cases of maternal deaths
with polymerase chain reaction-positive H1N1 influenza during
the pandemic, which started in 2009 and peaked in 2011. In
India, the largest numbers of deaths were reported during the
same period (33). Pregnant women are at an increased risk of
severe respiratory morbidity and mortality and adverse perina-
tal outcomes (34-36). Late recognition, delay in initiating antivi-
ral treatment, and the presence of comorbid conditions, such

Table 4. Organ dysfunction in maternal mortality cases (infected versus non-infected group)

<table>
<thead>
<tr>
<th>WHO Organ Dysfunction Criteria</th>
<th>Incidence of organ dysfunction</th>
<th>Infected group (t=84) versus non-infected group (t=68)</th>
<th>Total incidence (% with 95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular dysfunction</td>
<td>70.23</td>
<td>82.35</td>
<td>70.23 (60.45–80.01)</td>
<td>0.083</td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>90.47</td>
<td>76.47</td>
<td>90.47 (85.2–95.74)</td>
<td>0.009</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>33.33</td>
<td>41.17</td>
<td>33.33 (24.87–41.79)</td>
<td>0.159</td>
</tr>
<tr>
<td>Coagulation dysfunction</td>
<td>52.38</td>
<td>50</td>
<td>52.38 (43.42–61.34)</td>
<td>0.385</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>38.09</td>
<td>19.11</td>
<td>38.09 (29.37–46.81)</td>
<td>0.005</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
<td>23.81</td>
<td>20.58</td>
<td>23.81 (16.17–31.45)</td>
<td>0.317</td>
</tr>
<tr>
<td>Uterine dysfunction</td>
<td>7.14</td>
<td>11.16</td>
<td>7.14 (2.52–11.76)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

PaO₂: partial pressure of oxygen in artery; FiO₂: fraction of inspired oxygen; CI: confidence interval
as asthma and diabetes, were found to increase morbidity and mortality (37). Scrub typhus is a zoonosis that is endemic to the Asia-Pacific region (38). It is poorly studied in the Indian subcontinent and its contribution to maternal death remains unmeasured. In a case series by Mahajan (39), five pregnant women diagnosed with scrub typhus were studied. One woman died of multi-organ failure. In this study, there were six maternal deaths attributable to scrub typhus during the 10-year period. The disease mainly presents as rash, fever, myalgia, and lymphadenopathy. Complications that develop after a week include jaundice, septic shock, pneumonitis, myocarditis, and meningoencephalitis (39).

There were four HIV-positive women who died during these 10 years in our hospital, but only one death could be attributed to an HIV-AIDS-related complication (Table 1). For Tamil Nadu (a southern state in India), which is considered to have a high prevalence of HIV, this finding appears biased (40). A possible explanation is that being a privately owned institute, there are fewer HIV-positive women registered in our hospital because the Indian government provides antiretroviral therapy and all delivery services to these mothers free of cost in public-sector hospitals. After the increase in coverage of antiretroviral therapy, there is reduced HIV-related mortality among pregnant women (41).

The concept of near miss has led to the appreciation of all events that follow the primary cause leading to severe maternal outcomes. In this context, we could focus on the fact that many patients who have obstetric hemorrhage or pregnancy-induced hypertension as the primary cause end up in an intensive-care unit for a long time and may develop a nosocomial infection. Ventilator-associated infections are the most serious among these, others being urinary tract infections, bedsores, etc. The contribution of hospital-acquired infections to morbidity and mortality specific to pregnancy is largely unknown. This study estimated that 7.07% (15/212) of women developed a nosocomial infection before they died. All of these had ventilator-associated pneumonia as a nosocomial infection in this study. With the increase in hospital deliveries, increasing use of antibiotics, and widespread availability of intensive-care unit facilities, nosocomial infections are on the rise and will continue adversely affecting outcomes unless kept in check.

Organ dysfunction criteria are used to access the severity of the maternal disease and prevent severe maternal outcomes (42). Cardiovascular and respiratory dysfunctions are the most commonly encountered organ dysfunctions: 70.23% and 90.47%, respectively, in mothers who died of severe infection. The organ dysfunctions that were significantly different from the non-infected group are respiratory dysfunction (90.47% vs. 76.47% p<0.009) and hepatic dysfunction (38.09% vs. 19.11% p<0.005). The first finding may be because of many infections specific to the respiratory system, such as tuberculosis and H1N1 influenza, whereas the second observation is because of more chances of multi-organ dysfunction in the puerperal infection group.

In conclusion, infections during pregnancy continue to be a major contributor to maternal mortality, although the proportions of causes are changing. Pregnancy-unrelated or incidental infections are as important, if not more so, as a contributor to maternal mortality compared with genital sepsis. Along with clean birthing practices and the use of prophylactic and therapeutic antibiotics, the fight has to be continued against tuberculosis and vector-borne diseases to avert these preventable maternal deaths. Awareness, primary prevention, early diagnosis, and treatment are required to control seasonal and epidemic diseases, such as malaria, H1N1 influenza, and dengue. Education, prevention of anemia, food fortification, and a midday meal program in schools will pay sustained dividends by ensuring that girls become stronger mothers of tomorrow.

Limitations of the study, records were deficient in being able to provide complete data. The diseases were diagnosed with methods that were available at the time and at times, on the clinical decision of the treating physician. Therefore, the classification of deaths according to a specific causative agent is less than accurate.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Christian Medical College Vellore, India.

**Informed Consent:** Exemption from informed consent was received from Ethics committee as it was a retrospective review of death records which took place over a decade.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - A.H., R.J.; Design - A.H., R.J.; Supervision - A.H., R.J., R.V.; Resource - A.H., R.V.; Materials - A.H., R.J., R.V.; Data Collection and/or Processing - A.H., R.J., R.V.; Analysis and/or Interpretation - A.H., R.J., A.H., R.V.; Writing - A.H., R.J.; Critical Reviews - A.H., R.J., R.V.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**References**

8. The WHO Application of ICD-10 to deaths during pregnancy, child-birth and the puerperium: ICD-MM. Available from:
17. Shiffman J, Ved R. The state of political priority for safe motherhood in India. BJOG 2007; 114: 785-90. [CrossRef]
23. Smalld FM, Gyte GML. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev 2010; CD007482. [CrossRef]
36. Rasmussen SA, Jamieson DJ, Breesee JS. Pandemic influenza and pregnant women. Emerg Infect Dis 2008; 14: 95-100. [CrossRef]
42. Cecalti JG, Souza JP, Oliveira Neto AF, Farpinelli MA, Sousa MH, Say L, Pattinson RC. Pre-validation of the WHO organ dysfunction based criteria for identification of maternal near miss. Reproductive Health 2011; 8: 22. [CrossRef]