One in Five Maternal Deaths in Bangladesh Associated with Acute Jaundice: Results from a National Maternal Mortality Survey

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Abstract. We estimated the proportion of maternal deaths in Bangladesh associated with acute onset of jaundice. We used verbal autopsy data from a nationally representative maternal mortality survey to calculate the proportion of maternal deaths associated with jaundice and compared it to previously published estimates. Of all maternal deaths between 2008 and 2010, 23% were associated with jaundice, compared with 19% from 1998 to 2001. Approximately one of five maternal deaths was preceded by jaundice, unchanged in 10 years. Our findings highlight the need to better understand the etiology of these maternal deaths in Bangladesh.

INTRODUCTION

Hepatitis E virus (HEV) is the most frequent cause of acute infectious hepatitis in Africa and Asia and is responsible for large water-borne outbreaks.^{1,2} An estimated 3.4 million people residing in Africa and Asia became ill from hepatitis E infection in 2005, though none of the countries in these regions have functional public health surveillance systems from which to estimate disease incidence.^{1,2}

Although most people with acute hepatitis E recover completely from the illness (> 99%), the case-fatality ratio among pregnant women with HEV can be as high as 25% during outbreaks and in clinical case series in Africa and Asia,¹ with the risk of mortality increasing during each trimester.³ Pregnant women with hepatitis E can succumb to fulminant hepatic failure as well as obstetric complications such as hemorrhage^{3,4}; the exact biological mechanism for these deaths is not known but assumed to be related to the immunological changes of pregnancy and, possibly, to micronutrient deficiencies during pregnancy.⁵ Limited hospital-based studies have shown that vertical transmission to the unborn fetus is nearly 100%, and HEV infection in pregnant women increases the risk of miscarriage, stillbirth, and premature birth.^{3–5} Vertically transmitted HEV infection in neonates can result in complications such as icteric hepatitis, anicteric hepatitis, or hyperbilirubinemia⁶; neonatal hypothermia and hypoglycemia are also common.⁶

The increased risk of mortality among pregnant women and their fetuses and newborns during HEV infection has been well described, yet there are no population-based studies to estimate the number of deaths due to hepatitis E. In the majority of HEV-endemic countries of Africa and Asia, population-based estimates of causes of death rely on the use of verbal autopsy methods.⁷ Verbal autopsy is carried out using a structured questionnaire administered to surviving family members or caregivers that captures reported signs, symptoms, medical history of illness, and circumstances that preceded death.⁷ The questionnaires are reviewed by physicians or coded based on algorithms to diagnose the most common direct and indirect causes of death. These methods have been useful in distinguishing between maternal and non-maternal deaths and track-

ing the decrease in maternal mortality in populations lacking routine death registration.

Although verbal autopsy surveys have many limitations in diagnosing infectious causes of death, they can provide information on signs and symptoms of illness consistent with certain infectious etiologies, such as acute onset of jaundice, which would be consistent with hepatitis E infection. An analysis using data from the Bangladesh Maternal Mortality and Health Care Survey 2001 (BMMS 2001) and the Matlab Health and Demographic Surveillance System 2003–2005 showed that 19–27% of maternal deaths were associated with acute onset of jaundice, and the estimated maternal mortality ratio associated with jaundice was 54 per 100,000 live births from 1998 to 2001 and 55 per 100,000 live births from 2003 to 2005.⁸ Similarly, an analysis of maternal mortality data from a tertiary hospital in Nepal also found that 16–28% of maternal deaths were associated with acute hepatitis.⁹

Herein, we report population-based estimates of maternal mortality associated with jaundice using the BMMS 2010 and compare it with the BMMS 2001 estimates.

METHODS

Detailed methods of the BMMS 2010 survey are described elsewhere.¹⁰ In brief, 175,000 sampled households were asked to recall all deaths among women aged 13–49 years that occurred during the 3 years before the date of the survey. A detailed verbal autopsy questionnaire using an adapted version of the World Health Organization structured questionnaire for adults to identify the cause of death was used to collect data. The questionnaires were administered by trained data collectors with at least 12 years of formal education, but without medical training. Cause of death was assigned by an independent review of the verbal autopsy data by two physicians using the International Classification of Diseases, 10th revision (ICD-10). In case of disagreement, a third physician reviewed the verbal autopsy questionnaire. Maternal deaths were defined as those that occurred during pregnancy or within 42 days of termination of pregnancy following a live birth, still birth, or abortion/miscarriage. Acute onset of jaundice was defined as the yellowing of eyes during the pregnant woman's most recent illness episode. It was measured by asking family members if the woman's sclera had turned yellow during the last illness associated with her death.

We calculated the proportion of maternal deaths and the maternal mortality ratio associated with acute onset of jaundice,

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similar to the study that used data from the BMMS 2001,¹¹ taking into account the cluster sampling weights. We tabulated the assigned cause of death for these women based on the verbal autopsy coding methods. The BMMS survey protocol was approved by the icddr's Ethical Review Committee, and all respondents interviewed provided informed consent before participation.¹⁰ All data used for this analysis were de-linked with personal identifiable information.

RESULTS

A total of 131 maternal deaths occurred in households sampled in the BMMS 2010. Of the identified 131 maternal deaths, 30 (23%) of these women had new onset of jaundice during their pregnancy before their deaths. The weighted maternal mortality ratio associated with jaundice from this survey was 45 per 100,000 live births (Table 1). Of the 30 maternal deaths with jaundice, 18 (60%) pregnancies resulted in live births of unknown outcome, six (20%) pregnancies ended in stillbirths, and three (10%) pregnancies ended in abortion or miscarriage; we do not have data on how many of the infants born alive survived. Of the 30 maternal deaths, 12 (40%) associated with jaundice in BMMS 2010 were coded as deaths from hemorrhage, and 36% were coded as either due to other indirect causes or were not classified at all suggesting that illnesses were not compatible with existing coding algorithms (Table 2).

There was no significant change in the proportion of maternal deaths associated with jaundice in the BMMS 2001 survey (19%) compared with the 2010 survey (23%, $P = 0.3$).

DISCUSSION

Approximately one in five maternal deaths in Bangladesh is associated with acute onset of jaundice, a figure that remained virtually unchanged in the past decade. The cause of these deaths is unknown, but available evidence suggests that hepatitis E may contribute significantly to these deaths.⁸ First, a review of hospital-based studies conducted in HEV-endemic countries of Africa and Asia showed that hepatitis E is the most common etiologic agent responsible for more than 50% of maternal deaths in women with acute liver disease or fulminant hepatitis.⁸ Second, the coded direct causes of death associated with jaundice were consistent with hepatitis E during pregnancy where women typically die of hemorrhage.^{3,4} Third, many of the deaths were not compatible with commonly recognized causes of deaths, and so were coded as "other" or not classified at all, which also suggests that hepatitis E could

TABLE 1

Number, proportion, and estimated rates of maternal deaths associated with maternal jaundice from the Bangladesh Maternal Mortality and Health Care Surveys, 2001 and 2010

	Bangladesh Maternal Mortality and Health Care Survey	
	2001 ⁸	2010
No. of maternal deaths	186	131
Maternal mortality ratio per 100,000 live births	322	194
Maternal deaths associated with jaundice,		
No. (%)	35 (19)	30 (23)
Mortality rate per 100,000 live births	54	45

TABLE 2

Coded direct causes of death assigned to maternal verbal autopsies associated with jaundice from the Bangladesh Maternal Mortality and Health Care Surveys, 2001 and 2010

Coded direct cause of death	Bangladesh Maternal Mortality and Health Care Survey	
	2001 ⁸ , n (%)	2010, n (%)
Hemorrhage	10 (29)	12 (40)
Eclampsia	8 (22)	2 (7)
Anemia	4 (11)	2 (7)
Abortion related	1 (3)	1 (3)
Cardiovascular disease	2 (6)	0
Respiratory disease	1 (3)	2 (7)
Puerperal sepsis	1 (3)	0
Other indirect	3 (9)	10 (33)
Not classified	5 (14)	1 (3)
Total	35 (100)	30 (100)

be the cause as there is currently no code for a maternal death due to hepatitis E.

The Maternal Mortality Estimation Inter-Agency Group, composed of several United Nations agencies, estimated that the maternal mortality ratio was 170 deaths per 100,000 live births in Bangladesh in 2013, which would mean that there were approximately 5,304 maternal deaths in Bangladesh in that year.¹² On the basis of our findings from the BMMS 2010, we estimate that 1,220 maternal deaths associated with jaundice occur each year in Bangladesh. If hepatitis E is indeed responsible for these deaths, a targeted hepatitis E immunization program could save thousands of lives. An effective hepatitis E vaccine (HEV 239 vaccine, Hecolin®, Haicang, Xiamen, China), produced and licensed in China, exists but is not recommended for general use in endemic countries, mainly because of lack of data on burden of disease.¹

There is precedent for the use of maternal vaccines to prevent maternal and neonatal mortality from infections. In the mid-1980s, before tetanus toxoid vaccination was widespread, Bangladesh had a high rate of maternal and neonatal tetanus. In 1996, an estimated 1,080 women died of pregnancy-related tetanus in Bangladesh each year, and mortality rates from neonatal tetanus were 6 cases per 1,000 live births in 1994.^{13,14} After implementation of intensified maternal tetanus vaccination campaigns between 1999 and 2015, maternal and neonatal mortality from tetanus has been successfully eliminated (defined as < 1 case neonatal tetanus per 1,000 live births) in Bangladesh.¹⁴ The number of reported cases of neonatal tetanus dropped from 1,265 cases in 1984 to 479 cases in 1999 and to 108 cases in 2013.¹⁴

An important limitation of our study was that it relied upon verbal autopsy data collected 1–3 years after the deaths occurred. In addition, our analysis assumes that a family report of yellowing of the sclera on verbal autopsy is a valid measurement of true jaundice, but to our knowledge this has never been validated. None of the women whose deaths we report here were tested for hepatitis E infection, which limits our ability to interpret these deaths as being caused by hepatitis E. However, they do suggest that better population-based studies to estimate the burden of diagnosed hepatitis E maternal deaths are urgently needed to determine if hepatitis E prevention could be a useful strategy to further reduce maternal mortality in Africa and Asia. Better estimates of the burden of hepatitis E in Bangladesh will be necessary to prioritize the use of scarce health-care resources for disease control or target the use of vaccines and other preventative measures for hepatitis E.

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