Update on Maternal Mortality in the Developed World

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Abstract Over the last three decades, maternal mortality in developed countries has increased. Deaths are now less related to pregnancy and more related to pre-existing and co-morbid conditions that complicate pregnancy, such as increased maternal age, obesity, hypertension and diabetes. This article reviews new literature and updates since late 2011, including detailed information on causes of death in the developed world including: cardiovascular disease, hemorrhage, hypertensive disorders, sepsis, thromboembolic events, amniotic fluid embolism and anesthetic complications. Up to 50 % of maternal deaths in the developed world are preventable by identifying best practices, reducing variability in care and eliminating recurrent errors in the management of a few common diagnoses.

Keywords Maternal mortality · Cardiovascular disease · Postpartum hemorrhage · Hypertensive disorders of pregnancy · Sepsis · Venous thromboembolism

Introduction

In 2000, the United Nations agreed to eight Millennium Development Goals (MDGs) to be achieved by 2015. Among

them, MDG 5—Improving Maternal Health—set out to reduce worldwide maternal mortality by 75 %. The maternal mortality ratio or MMR (the number of maternal deaths per 100,000 live births) varies broadly across the globe, from 14/100,000 in the developed world to 640/100,000 in Sub-Saharan Africa [1•].

A 2012 systematic review of maternal mortality in developed countries (1980–2007) found an overall MMR of 12.90/100,000 [2]. Direct maternal deaths result from obstetric complications of the pregnant state (pregnancy, delivery, and postpartum); or from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above [3]. Indirect maternal deaths result from previous existing disease, or diseases that developed during pregnancy, and which were not due to direct obstetric causes but aggravated by physiological effects of pregnancy [3]. The most frequent direct causes of death include hemorrhage (2.03/100,000), hypertensive disorders (1.82/100,000), sepsis (1.41/100,000), thromboembolic events (1.34/100,000), and amniotic fluid embolism (AFE) (0.92/100,000). Anesthetic complications are a rare cause of direct maternal mortality (0.17/100,000). The most frequent indirect causes of death include cardiovascular disease (1.28/100,000), central nervous system complications (0.66/100,000) and sepsis (0.05/100,000).

Despite broad healthcare availability, advanced technologies and greater health care spending per capita than any other country in the world [4] the MMR in the United States (U.S.) has increased from 7.2/100,000 in 1987 to 15.5/100,000 in 2008—the latest year for which data is available [5]. In the last decade, the MMR increased from 12.0/100,000 in 1998 to 15.2/100,000 in 2008 [6, 7]. The most frequent direct causes of maternal death are identical to those previously noted, including obstetric hemorrhage (1.81/100,000), hypertensive disorders of pregnancy (1.79/

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100,000), infection (1.55/100,000), venous thromboembolism (1.48/100,000), AFE (1.09/100,000) and, rarely, anesthetic complications (0.17/100,000). Interestingly, the highest cause-specific MMR for the U.S. is indirect—cardiovascular disease (3.48/100,000).

The U.S. currently has no nationwide system for tracking maternal deaths. Since 1952, however, the United Kingdom (U.K) has reported and reviewed maternal mortality, with the Centre for Maternal and Child Enquiries (CMACE) publishing “Saving Mother’s Lives” every three years—a detailed analysis of all maternal deaths in the U.K. [8]. CMACE reports are referred to extensively in this review.

Etiology of Increased Maternal Mortality

Multiple etiologies have been theorized as contributing to the increasing maternal mortality in the developed world, including: better case identification, increasing maternal age [9•, 10], increasing obesity and associated chronic medical conditions [10], inequities in medical care secondary to race, class and various social determinants of health [9•] and increasing cesarean delivery (CD) rates [10, 11].

Case identification

Changes in how deaths are classified affect maternal mortality rates and impact trends and comparisons. The World Health Organization (WHO), the *International Classification of Diseases*, Tenth Revision (ICD-10) and the Centers for Disease Control and Prevention (CDC) all currently define “maternal death” as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes [3]. In 1999, implementation of ICD-10 in the U.S. resulted in a 13 % increase in the number of maternal deaths identified [12]. The identified rate increased again in 2003 after pregnancy status became a required item on the U.S. Standard Certificate of Death [12].

Maternal Age

Between 1993 and 2005 the percentage of deliveries to women aged 35 years and older increased from 10.4 % [13] to 14.4 % [14]. By 2011, the birth rate for women aged 40–44 was the highest since 1967 and the only age-specific rate that showed a steady increase over the last decade. The number of births to women over 50 has also increased every year since

1997 [15]. Berg et al. [16] compared the rates of preexisting medical conditions for women admitted to labor and delivery between two time periods: 1993–1997 and 2001–2005. The incidence of many co-morbidities was increased including chronic hypertension (RR = 1.24, 1.09–1.41), cardiac disease (RR = 1.13, 1.00–1.27), asthma (RR = 1.95, 1.69–2.25) and diabetes (RR = 1.23, 1.05–1.45). In total, preexisting medical conditions increased 20 % (RR = 1.20, 1.10–1.30). The highest MMR for developed countries is observed in women over 45 years old (163.73/100,000) [2].

Obesity

Obesity rates worldwide have doubled since 1980 [17] and rates in pregnant women are at all-time highs. Of 30,000 Irish women who delivered between 2004 and 2011, only 52.5 % were normal weight, with 27.8 % overweight and 16.8 % obese [18]. Obesity contributes to increased maternal mortality [19, 20]. Compared to normal weight women, overweight and obese women have a two- to six-fold increased risk of hypertensive disorders of pregnancy, two- to six-fold increased risk of gestational diabetes, 1.4 to 1.9-fold increased risk of CD, and 1.4 fold increased risk of postpartum hemorrhage [18, 21].

Inequities in Maternity Care

From 1993 to 2006, minority women accounted for 40.7 % of live births in the U.S. but 61.8 % of maternal deaths. Although causes and timing of maternal deaths are similar [22], the MMR is 11.7/100,000 for white women, 9.6/100,000 for Hispanic women and 39.2/100,000 for non-Hispanic black women [23]. Black women have no higher prevalence of preeclampsia/eclampsia, postpartum hemorrhage, placenta previa or placental abruption; however, they have the worst maternal mortality in the U.S., with risk of death 3–5 times higher than white women [6, 22, 24, 25]. Beyond broad inequities secondary to social determinants of health, Hispanic and black women more often suffer from co-morbidities that complicate pregnancy such as hypertension [26] and diabetes [27].

Rising CD rates and abnormal placentation

The CD rate for singleton births in the U.S. increased nearly 60 % between 1996 and 2009 (from 19.7 % to 31.3 %) and remained stable at this rate through 2011 [15]. For a woman with two prior CDs, there is a 2 % incidence of placenta previa with almost half of these cases having placenta accreta [28]. Up to 9 % of women undergoing multiple CD suffer from major complications with 1 % requiring hysterectomy, most commonly as a result of abnormal placentation [29]. One decision-analysis warned

of increasing postpartum hemorrhage and peripartum hysterectomy secondary to increasing CD rates and showed that by 2020 the CD could be as high as 56.2 %, resulting in an additional 6,236 placenta previas, 4,504 placenta accretas, and 130 maternal deaths annually [30].

Cardiovascular Disease

Cardiovascular disease is now the leading cause of maternal mortality in both the U.S. (3.48/100,000) [31] and the U.K. (2.31/100,000) [19]. This increasing mortality is a result of an increased rate of acquired heart disease as the pregnant population becomes older, more obese and more hypertensive [19, 32]. The population of pregnant congenital heart disease (CHD) patients has increased, as more women with complex CHD survive to adulthood. This population, however, contributed only 6 % of the total cardiovascular maternal mortality in the U.K. [19].

A prospective assessment of maternal deaths from cardiovascular disease in the Netherlands [33•] found an MMR of 3.0/100,000, similar to that of the U.S. and the U.K. While the most common cause of severe cardiac morbidity was cardiomyopathy (peripartum, 27 %), the most common cause of cardiac death was aortic dissection, with a case fatality rate of 83 %. Interestingly, 47 % of women who experienced cardiac arrest in pregnancy survived in this cohort, emphasizing the importance of resuscitation efforts in pregnant women.

Women with known congenital or acquired heart disease should be under the care of a cardiologist who establishes baseline cardiovascular function prior to pregnancy and follows the patient's cardiovascular response to the physiologic changes of pregnancy. [19, 34, 35•] A delivery plan involving cardiology, obstetrics, anesthesiology, neonatology and nursing is important with specific plans detailing the anticipated delivery, labor analgesia or surgical anesthesia, appropriate labor or surgical monitoring and appropriate uterotonic agents in the case of hemorrhage. If the patient undergoes labor, ECG monitoring may be warranted if the patient has a history of arrhythmia, and a predetermined plan for emergent surgical anesthesia is imperative.

Obstetric hemorrhage

In the most recent triennium (2006–2008), CMACE reported a decrease in maternal deaths from hemorrhage [8]. A recent study from Ireland, however, found the overall postpartum hemorrhage (PPH) rate increased three-fold between 1999 and 2009, from 1.5 % to 4.1 % (RR = 3.03, CI 2.76–3.34) [36]. PPH secondary to uterine atony rose from 1 % to 3.4 % and the rate of blood transfusion

increased from 4.7/1,000 deliveries to 12.9/1,000. This increase in PPH requiring blood transfusion suggests an increase in hemorrhage severity. Increases were observed across all modes of delivery – vaginal, instrumented and elective and emergency cesarean.

The reason(s) for increasing PPH is unknown. Changes in maternal characteristics (including BMI) do not explain the recent increases [37]. Although concern has been expressed that more liberal use of oxytocin is a risk factor for atony secondary to desensitization of uterine oxytocin receptors [38], neither labor induction nor oxytocin augmentation was associated with increase in atonic PPH risk when studied [37].

A Danish study evaluated the differences between vaginal delivery (VD) and CD on hemorrhage and transfusion risk. After adjusting for age, BMI, birth weight, smoking, parity, multiple gestation and previous CD, red cell transfusion risk was lower with a planned first CD than a planned first VD (OR = 0.82, CI 0.73–0.92) [39]. Women planning a CD for their second delivery, however, had a higher red cell transfusion risk with prior CD compared with a prior VD (OR = 1.37, CI 1.07–1.76; $P < 0.05$) [39]. Furthermore, those women intending a VD after a prior CD had a three-fold higher red cell transfusion risk compared with the intended VD after a prior VD group (OR = 3.29, CI 2.95–3.68; $P < 0.001$) [39].

CMACE found frequent substandard care in the management of hemorrhage, with major errors in 44 % of cases and minor management errors in 22 % [8]. Early recognition of life-threatening hemorrhage may be assisted by a modified early obstetric warning system (MEOWS) [40]. MEOWS purports that physiologic changes precede critical illness, so when vital signs reach predetermined thresholds, a bedside nurse is mandated to alert a clinician. Recently validated, MEOWS alerts clinicians to hemorrhage (43 %), preeclampsia (31 %), infection (20 %), anesthetic morbidity (4 %) and acute asthma (2 %) [41••]. This recent validation study found MEOWS to be a well-designed tool, with a sensitivity of 89 % (CI 81–95 %), specificity of 79 % (CI 76–82 %), positive predictive value of 39 % (CI 32–46 %), and negative predictive value of 98 % (CI 96–99 %) [41••]. This simple tool can help assure that critically ill obstetric patients, regardless of underlying diagnosis, are recognized and receive early intervention.

Hypertensive Disorders of Pregnancy

Deaths from pre-eclampsia/eclampsia in CMACE reports have remained relatively stable over the past 6 triennia [8]. The primary cause of death in these patients remains neurologic events including intracranial hemorrhage (9 of 14) and anoxia following cardiac arrest in association with

eclamptic seizures (5 of 14). Additional causes of death include liver complications (necrosis, subcapsular hemorrhage, complications of acute fatty liver), multi-system organ failure and intra-abdominal hemorrhage. A sudden increase in eclamptic deaths (5 in this triennium) is totally unexpected; it is the first report with any eclamptic deaths since 1997 [42]. These deaths occurred in the setting of a 50 % reduction in eclampsia cases since 1992, concurrent with the increased use of magnesium for anticonvulsant prophylaxis. Combining the CMACE and UK Obstetric Surveillance System (UKOSS) data the case fatality rate from eclampsia is 3.1 % [8].

In the Netherlands, marked differences were noted in pre-eclampsia/eclampsia related maternal mortality by region [43]. Substandard care, especially in the use of magnesium for seizure prophylaxis, was involved. A French study found the risk of death from hypertensive disorders and hemorrhage was as much as 6.5 times higher in certain regions of the country compared to others and identified that as many as 64.8 % of women in these areas received non-optimum care [44]. CMACE identified failure to adequately control blood pressure to be the single most common failure in treatment of the preeclamptic patient [8]. Disparities in care and treatment failures stress the importance of protocols, checklists, and alert systems such as MEOWS.

Infection/Sepsis

Case fatality rates for septic shock in pregnancy were once as high as 28 % [45, 46] but rates decreased significantly in the early 2000s [47]. Unfortunately, the 2006–2008 CMACE reported an increasing trend in sepsis-related maternal deaths, with mortality rising from 0.85/100,000 (2003–2005) to 1.13/100,000 (2006–2008) [19, 42, 50]. Group A *Streptococcus* was the leading microbe involved [19] and was also found to be the culprit (43 %) in maternal sepsis deaths in one representative country, the Netherlands [47].

It is important that obstetric providers recognize the risk of death as a result of group A *Streptococcus* infection in the peripartum population [42, 48–51] since maternal death from sepsis is often preventable with early intervention. Experts have called for practice improvements that include earlier recognition and treatment, and multidisciplinary care with protocols such as the “*Surviving sepsis resuscitation bundle*” [42, 48]. Early recognition can be difficult because physiologic changes of pregnancy may mask or attenuate initial signs and symptoms of infection [19, 48, 50].

Understanding which women are at risk for sepsis may assist the clinician in recognition. Risk factors include history of pelvic infection, current group B streptococcal

infection, recent group A streptococcus infection in close contacts, impaired immunity, impaired glucose tolerance, obesity, prolonged rupture of membranes, obstetric interventions, vaginal trauma, assisted reproduction and multiple gestation [19, 48, 52, 53]. Demographic risk factors include low socioeconomic status, age >35 years, or minority ethnicity [19, 48, 52, 53].

Thromboembolic Disorders

The incidence of venous thromboembolic events (VTE) is increased in pregnancy and is a major cause of mortality with an MMR that ranges from 1.34/100,000 [2] to 1.48/100,000 [6]. Risk of VTE during the third trimester is six times higher than non-pregnancy (incidence rate ratio = 6.1; CI 4.7–7.9) [54] and the postpartum period is especially risky, with the first six weeks conferring a 22-fold increase in risk [54]. VTE in pregnancy is increasing, with a 1.62 (CI 1.48–1.78) fold increased risk for 2006–2009 compared to 1994–1997 [55•]. Between 1994 and 2009, there was a 14 % increase in any VTE-associated pregnancy hospitalizations, with antepartum hospitalizations up by 17 % and postpartum hospitalizations up by 47 % [55•]. The prevalence of hypertension and obesity among VTE-associated pregnancy hospitalizations doubled between 1994–1997 and 2006–2009 with significant increases in diabetes and heart disease also noted [55•]. Increasing maternal age is also a VTE risk factor and pregnant women over age 35 have a 70 % increased risk for postpartum VTE compared to 25–34 year olds [54].

After reviewing all maternal deaths from 2000 to 2006 among the almost 1.5 million deliveries in their large healthcare organization in the U.S., Clark and colleagues reported, “Some maternal deaths can clearly be prevented by better individual care. However, given the categories of death observed and the diversity of conditions within broad categories such as cardiac death or infection, it would appear that a systematic reduction in maternal mortality rate in the U.S. can be achieved only through...a reduction in pulmonary embolism deaths” [56]. They recommend following U.K. guidelines of universal VTE prophylaxis for all women having CD, including postpartum thromboprophylaxis for seven days with low molecular weight heparin (LMWH) for all emergency CD and thromboprophylaxis for seven days with LMWH for all elective CD in women with one or more additional risk factors (such as age over 35 years or BMI >30) [57]. This policy would reduce the mortality rate to 0.9 per 100,000, or approximately nine deaths annually in the U.S. [56]. Given the potential for bleeding complications with anticoagulation and the widespread use of neuraxial anesthesia for CD, pneumatic compression device use is recommended for all CD regardless of emergency status or risk factors.

Amniotic Fluid Embolism

In the most recent CMACE report, AFE was a more common direct cause of maternal death than problems of early pregnancy, hemorrhage, or anesthesia-related mortality [8]. AFE has features suggesting an anaphylactic reaction and recent theories have focused on immunological mechanisms, including complement activation. An AFE is not necessarily a fatal event if it occurs in a labor center with immediate high-quality response available. Survival of both mother and infant are possible, though neurologic injury of either mother and/or infant occurs frequently [58].

Recent studies have found maternal case fatality rates from AFE of 11, 20 and 27 % [58–60]. 25 % of women required hysterectomy for hemorrhage and coagulopathy was seen in >60 % of cases [19]. AFE is unpredictable and unpreventable, despite some associated risk factors. Although Kramer et al. [60] were unable to find significant trends in AFE despite an increase in labor induction, CD rates and maternal age, another study of 60 women with AFE, did find significant associations with induction of labor, multiple gestation, increasing maternal age and ethnicity. In addition, postnatal AFE was associated with CD [58]. These common conditions, however, are not necessarily predictive of this rare event.

Anesthetic Complications

Anesthesia-related maternal mortality is a rare cause of maternal death in the U.S. (0.17/100,000) [6] and the developed world overall (0.17/100,000) [2]. In a comparison of maternal deaths from 1979–1990 to 1991–2002, anesthetic complications accounted for only 1.6 % of total maternal deaths, representing a 59 % decrease over the 2 decades [61].

From 1979 to 1990, failed intubation at the *induction* of anesthesia was the leading cause of anesthesia-related maternal mortality [62]. Most recently, however, the most common time to lose the airway is postoperatively, either at emergence, in recovery, or in the immediate postpartum period [20, 63]. Decompressing the stomach, waiting for full emergence before extubation and following the guidelines of the Anesthesia Patient Safety Foundation and the American Society of Anesthesiologists for monitoring for drug-induced postoperative respiratory depression will keep deaths from postoperative airway loss rare [64]. As some of the maternal deaths occurred in recovery, on the labor ward and on the postpartum floor, systems must be in place to afford the same degree of monitoring and support as for any other postoperative patient.

Deaths related to regional anesthesia are rare and infection is typically the cause. In the 2006–2008 CMACE report,

a single woman died multiple days after a spinal anesthetic for CD with acute hemorrhagic disseminated leukoencephalitis secondary to an empyema [40, 42]. In 2010, the CDC published a series of five postpartum women who developed bacterial meningitis after spinal anesthesia [65]. Four of the five cases involved the bacteria *Streptococcus salivarius*. These cases emphasize the importance of following the American Society of Anesthesiology's recommendations for sterility during regional anesthesia techniques including removal of jewelry, washing hands with an alcohol-based preparation, sterile gloves and a face mask [66].

Conclusion

Some life-threatening maternal events are likely not preventable, such as AFE [67]. Between 20 and 50 % of maternal deaths in the U.S., however, have been deemed preventable. A North Carolina review found that 46 % of African American maternal deaths and 33 % of white maternal deaths could likely be prevented with improved quality of care, especially those deaths secondary to hemorrhage and chronic disease [67]. After individual review of every maternal death in California, 40 % were deemed preventable [9•]. The most common types of preventable events include inadequate diagnosis or recognition of high-risk diagnosis (54.4 %), treatment failures (38.0 %), and documentation/hand-off errors (30.7 %) [9•, 68]. Table 1 outlines pearls to assist clinicians in preventing maternal mortality.

The Hospital Corporation of America recently reported a maternal death rate of 6.5 per 100,000 pregnancies—less than half of the reported maternal deaths for the U.S. overall [56]. Obstetrics safety champion Dr. Steven Clark has recommended reduction of variability in the provision of care through the use of standard protocols, reliance on checklists instead of memory for critical processes, and an approach to peer review that emphasizes systems change over individual error. In addition, he stresses that eliminating repetitive errors in the management of a few common diagnoses—hypertension, postpartum hemorrhage, pulmonary embolism, and cardiac disease—could contribute significantly to a reduction in maternal mortality (see Table 1).

In 2011, the American Congress of Obstetricians and Gynecologists, under the direction of President Dr. James N. Martin, Jr, established a “Hypertension in Pregnancy Guidelines Task Force” to attempt to identify evidence-based best practices and to standardize national management. There is a call for national management guidelines for six life-threatening maternal conditions in the U.S: hypertensive disorders in pregnancy, postpartum hemorrhage, prevention of venous thromboembolism in

Table 1 Ten Clinical Diamonds for Preventing Maternal Death. From Clark and Hankins [69], with permission from Wolters Kluwer Health

- (1) A pregnant patient reporting acute chest pain always should undergo an immediate computed tomography angiogram
- (2) A patient with preeclampsia reporting shortness of breath should undergo a chest X-ray immediately
- (3) Any hospitalized patient with preeclampsia experiencing either a systolic blood pressure of 160 or a diastolic pressure of 110 should receive an intravenous antihypertensive agent within 15 min
- (4) Angiographic embolization is not meant to be used for acute, massive postpartum hemorrhage
- (5) Any patient with identified structural or functional cardiac disease gets a Maternal–Fetal Medicine consultation
- (6) If more than a single dose of medication is necessary to treat uterine atony, go to the patient's bedside until the atony has resolved
- (7) Never treat "postpartum hemorrhage" without simultaneously pursuing an actual clinical diagnosis
- (8) In the postpartum patient who is bleeding or who recently has stopped bleeding and is oliguric, furosemide is not the answer
- (9) Any woman with placental previa and one or more cesarean deliveries should be evaluated and delivered in a tertiary care medical center
- (10) If your Labor and Delivery unit does not have a recently updated massive transfusion protocol based on established trauma protocols, get one today

pregnancy and postpartum, diagnosis and management of placenta accreta, management of the obese obstetrical patient and management of cardiac disease in pregnancy [10]. Through the use of such guidelines, protocols, checklists, and alert systems, we can work to avert preventable maternal mortality.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer A. Tessmer-Tuck, Katherine W. Arendt, and Paula A. Craig declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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