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REVIEW ARTICLE

What's New in Obstetric Anesthesia: a focus on maternal morbidity and mortality

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ABSTRACT
The Ostheimer lecture is given each year at the annual meeting of the Society for Obstetric Anesthesia and Perinatology. It summarizes "What's New in Obstetric Anesthesia" based on a systematic evaluation of the relevant literature published in the previous calendar year. In this review I consider studies published in 2016 focused on the prevalence of, and risk factors for, maternal morbidity and mortality. I also discuss novel therapeutic approaches to the prevention and treatment of major sources of maternal morbidity and mortality.

Keywords: Maternal morbidity; Maternal mortality; Anesthesia; Postpartum hemorrhage; Preeclampsia; Health services research

Disclosure

The material presented here is based on the Ostheimer lecture given on May 13, 2017 at the annual meeting of the Society for Obstetric Anesthesia and Perinatology. The Ostheimer lecture summarizes "What's New in Obstetric Anesthesia" from the previous calendar year, in this case 2016. The lecture was prepared based on a systematic review of the highest impact anesthesia, obstetric, pediatric, and general medical journals. A syllabus summarizing 126 articles identified as being of special interest is available at www.soap.org. An article highlighting the main themes from the lecture is published separately in the journal *Anesthesia and Analgesia*. Here, I will focus on articles concerning maternal morbidity and mortality that are of relevance to obstetric anesthesiologists.

Maternal mortality

Effectively measuring the causes and frequency of maternal mortality allows the development of strategies to reduce the rate of maternal death. The Global Burden of Disease (GBD) Study is conducted by the Institute for Health Metrics and Evaluation in Seattle and engages researchers from around the world. It aggregates all available data sources and applies advanced statistical methods to generate comprehensive and accurate estimates of the rates of disability and death worldwide. In 2016, the GBD published a study to characterize maternal deaths from 1990 to 2015 in 195 countries.[1] It showed that the maternal mortality ratio (MMR, defined as number of maternal deaths per 100 000 livebirths) worldwide rose slightly from 282 in 1990 to 288 in 2000.[1] However, over the next decade and a half, the MMR fell by about 30% to a ratio of 196 in 2015, likely due to a combination of more deliveries occurring in medical facilities, lower rates of adolescent pregnancy, and improvement in the healthcare infrastructure in some low resource settings. While this decrease represents tremendous progress, it is sobering that in 2015 there were still an estimated 275 288 maternal deaths, a tragic figure considering that the vast majority of these deaths are preventable.

The GBD study documented large disparities in the frequency of maternal mortality amongst countries. In 2015, there was a thousand-fold variation between the country with the lowest MMR (Iceland, 0.8) and the highest MMR (Central African Republic, 1074).[1] Overall, 49 countries had MMRs of less than 15, while at the other end of the spectrum, eight countries had MMRs in excess of 600. High MMRs were closely tied to measures of economic development, with countries in the two lowest quintiles of socio-demographic index (SDI) account-

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ing for about 80% of maternal deaths; data from these countries demonstrated high adolescent fertility and high mortality rates among adolescents.

Overall, direct obstetric death accounted for an estimated 86% of maternal mortalities, with hemorrhage and hypertensive disorders the leading specific causes of death.[1] About half of worldwide maternal deaths result from these two complications, which speaks to the need to develop more effective preventative interventions and therapies to address preeclampsia and bleeding in low-resource settings. The report noted that, in 2015, the United States (US) had a high MMR for a high-income country (26.4) and that it was one of the few countries where the MMR had increased during the study period.[1] It suggested that the US should "consider implementing regular, comprehensive confidential enquiries into drivers of maternal mortality."

To understand better the factors that contribute to the high rate of maternal mortality in the US, Moaddab et al. used data from 2005 to 2014 from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics database and the Detailed Mortality Underlying Cause of Death database (CDC WONDER).[2] They examined the correlation amongst MMRs and state-level measures of demographics, lifestyle, health status, and healthcare utilization, and found an approximately seven-fold variation in the rate of MMR between states.[2] The state-specific characteristics that were independently associated with a higher MMR included the proportion of deliveries to non-Hispanic blacks, unintended pregnancies, four or fewer prenatal visits, unmarried mothers, and cesarean deliveries. The data show that non-Hispanic blacks in the US account for a markedly disproportionate share of maternal mortality. To improve the MMR in the US, efforts should be directed at improving access to, and utilization of, obstetric care in underserved minority communities.

The GBD study showed that the MMR in the United Kingdom (UK) was 9.2, approximately three-fold lower than that of the US.[1] Part of this difference may be explained by the fact that maternal deaths in the UK have long been audited and catalogued as part of the Confidential Enquiry into Maternal Deaths program. These audits are reviewed and summarized, to derive lessons that can help improve maternal safety. Using data from the Confidential Enquiry, 383 maternal deaths that occurred between 2009 and 2013 were identified.[3] In order to perform a case-control study to define risk factors for maternal death, these were matched to 1516 women who did not have any life-threatening complications during pregnancy, obtained from the UK Obstetric Surveillance System.

Seven risk factors were identified as independently associated with the risk of maternal death. These included pre-existing medical comorbidity (adjusted odds ratio (aOR) 8.7), anemia during pregnancy (aOR 3.6), previous pregnancy problems (aOR 1.9), inadequate antenatal care (aOR 46.9), substance misuse (aOR 12.2), unemployment (aOR 1.8) and higher maternal age (aOR 1.06 per year).[3] Importantly, the population-attributable fraction of age, which estimates the proportion of maternal deaths that would be eliminated if these factors were not present in the population, was 87%. These data demonstrate factors that elevate the risk of maternal death in the UK, and about which action can be planned. Strategies proposed include developing systems to ensure appropriate care for women with pre-existing conditions, prior pregnancy complications, substance use disorders, or advanced maternal age.[3] Of particular note, the strong association with anemia may point to opportunities to improve outcomes through more aggressive use of iron supplementation.

The past few decades have seen a marked reduction in the rate of maternal mortality attributable to anesthesia in the US and other developed countries. In the US, the most recent estimates from the CDC suggested that anesthesia accounted for 0.2% of all maternal deaths from 2011 to 2013 (down from 2.5% in 1987 to 1990).[4] However, relatively little is known about anesthesia-related mortality in low- and middle-income countries. Sobhy et al. therefore conducted a systematic review and meta-analysis to identify all relevant studies from low- or middle-income countries that reported the risk of death associated with anesthesia for an obstetric procedure or that described rates of anesthesia-attributed deaths.[5]

They identified 44 articles, that included approximately 600 000 pregnancies, which reported the risks of death associated with anesthesia; and 95 articles, including approximately 32 million pregnancies, which reported data on anesthesia-related deaths as a proportion of total death.[5] The composite frequency of death from anesthesia was 1.2 per 1000 obstetric procedures, which is remarkably high given the known safety of anesthesia in high-resource settings. Overall, anesthesia accounted for an estimated 3.5% of direct maternal deaths, but this proportion was much higher (13.8%) in pregnancies ending in cesarean delivery. Risk factors for maternal death included the use of general versus regional anesthesia (relative risk (RR) ~3) and anesthesia provided by a non-physician anesthetist (RR ~ 2). Rates of maternal mortality from anesthesia were about 10-fold higher in rural compared to urban settings. The cause of anesthesia-related death was reported for 124 patients, and of these 45% were due to airway complications such as failed tracheal intubation, 31% due to aspiration, 27% from causes attributed to staff competency, intraoperative monitoring, and equipment failure, and 6% due to high spinal anesthesia.

These data importantly highlight the need for quality and safety improvements in anesthetic practice in low-

resource settings. They also underscore the need for additional research to define optimal systems for the provision of safe care in low-resource settings, and for providers in high-resource settings to support provider education and training in low- and middle-income countries.

Maternal morbidity and its determinants

Maternal mortality, while clearly a devastating outcome, accounts for only a small fraction of the adverse maternal outcomes that occur during pregnancy. While the MMR in the US is 26.4 per 100 000 livebirths, the frequency of severe maternal morbidity in the US is approximately 1000 per 100 000 livebirths.[6] Several studies published in 2016 provided insights into the health systems and hospital characteristics that are important determinants of the risk of severe maternal morbidity.

As previously discussed, there are major disparities in the risk of maternal mortality associated with race, with non-Hispanic black women having a much higher rate of maternal mortality than white women in the US. A critical question, which is important in ultimately defining interventions to eliminate it, is the extent to which the disparity is caused by higher rates of co-morbidity in black women versus the characteristics and quality of health systems and hospitals where black women deliver.

This question was taken up in a study by Howell et al. using the Nationwide Inpatient Sample from 2010 and 2011, a database designed to be maximally representative of all US hospital admissions.[7] Using this database, hospitals were ranked by their proportion of deliveries of black women and this identified the top 5% of hospitals as high-black serving, the top 5–25% as medium-black serving, and the rest as low-black serving.[7] Nearly three-quarters of deliveries among black women occurred at high- or medium-black serving hospitals, and notably the rates of severe maternal morbidity were higher in high- or medium black-serving hospitals than in low-black serving hospitals, even after adjusting for patient characteristics (17.3 and 16.5 versus 13.5 per 1000 deliveries). Black women who delivered at low-black serving hospitals had better outcomes than high-black serving hospitals. Likewise, white women who delivered at high-black serving hospitals had worse outcomes than those who delivered at low black-serving hospitals.

These patterns suggest that "black serving" hospitals may have lower quality and safety standards than other hospitals in the US. This same group observed similar results in an analysis of New York City hospitals,[8] as did an analysis from the CDC using the obstetric data from seven states.[9] Part of the explanation for the extreme disparities in maternal mortality and morbidity may therefore be inequalities in the standard of care provided to black patients. Addressing these disparities will require a societal commitment to allocating resources to improve antenatal and peri-delivery care in hospitals serving minority communities.[7]

Just as the hospital where delivery occurs is an important determinant of the quality and safety of obstetric care, new data suggest the skill of the obstetrician contributes to the likelihood of a good outcome. There is a large body of literature demonstrating an association between surgeons' annual volume and morbidity and mortality from certain high-risk procedures.[10] This association had not been previously evaluated in cesarean delivery, and Drukker et al. sought to define the association between an obstetrician's annual volume and short-term outcomes following cesarean delivery.[11] The investigators used data from a single, high-volume delivery center in Israel from 2006 to 2013: this included 11 954 cesarean deliveries. The median annual volume of cesarean deliveries that obstetricians supervised or performed was 48. The investigators dichotomized providers into low- or high-volume surgeons, based on this median. They found that, after adjusting for confounding factors, those treated by a high-volume surgeon had a 17% lower risk of the primary study outcome, a composite of adverse outcomes that are related to the surgery (aOR 0.83, 95% confidence interval (CI) 0.74 to 0.93). Individual adverse maternal outcomes that were significantly less common in those treated by high-volume obstetricians included urinary and gastrointestinal tract injuries, hemoglobin decrease >3 g/dL, and prolonged maternal hospitalization. To determine whether there was a threshold number of cesarean deliveries performed at which outcome rates would stabilize, they reclassified the obstetricians into quartiles based on annual cesarean delivery volume. They found no observable threshold effect, rather an inverse relationship between volume quartile and the frequency of the primary adverse outcome. A limitation of the study is that it was performed at a single center, so future studies will need to establish whether these results can be generalized to other settings. Another limitation is the potential for residual confounding by case-mix. However, it is likely that more complex surgical cases were triaged to high-volume providers suggesting that, if anything, the benefits of being treated by higher volume obstetricians may be underestimated in the risk estimates.

The frequency of peripartum hysterectomy has been increasing in the US, largely owing to the increase in the cesarean delivery rate.[12] Prior studies have demonstrated that maternal morbidity and mortality following peripartum hysterectomy is lower when performed in high-volume settings[13] and experts recommend that patients with placenta accreta should be treated in centers with multidisciplinary expertise in the care of this condition.[14,15] Govindappagari et al. sought to describe

the hospitals where women at high risk of peripartum hysterectomy (defined by the presence of placenta previa and prior cesarean delivery) deliver in the US, and how that has changed over time.[15]

The investigators used data from the Perspective database, which contains hospitalization data for 500 hospitals in the US, from 2006 to 2014. In this sample, the prevalence of peripartum hysterectomy increased from 81.4 per 100 000 deliveries in 2006 to 98.4 per 100 000 deliveries in 2014. There was evidence in this sample of these cases being concentrated in high-volume delivery and high-volume peripartum hysterectomy centers. The prevalence of hysterectomy decreased from the periods of 2006–2008 to 2012–2014 in hospitals in the lowest quintile for delivery volume, and increased to the largest degree in hospitals in the top quintile for delivery volume. Similarly, the hysterectomy prevalence increased most in hospitals performing more than five peripartum hysterectomies annually. Although the finding that such high-risk cases are being triaged to the centers most equipped to deal with them is encouraging, the pattern of concentration in high-volume centers lagged in the South and Midwest (compared to the Northeast) and in rural locations.

Novel approaches to important causes of maternal morbidity and mortality

Hemorrhage and hypertensive disorders, including preeclampsia, are the leading causes of maternal death worldwide, and consequently there is an urgent need to develop inexpensive, effective interventions that can be used in low-resource settings where maternal mortality rates are the highest. In this regard, two papers published in 2016 describe novel approaches to addressing hemorrhage and hypertensive disorders.

In the first, Purwosunu et al. describe the development and testing of a device to control postpartum hemorrhage.[16] Traditionally, in low-resource settings postpartum hemorrhage is managed with uterine packing, but this approach is both incompletely effective and conceals ongoing bleeding. The investigators created a device that generates negative pressure within the uterine cavity, causing the potential space of the uterine cavity to be obliterated and so tamponade bleeding due to uterine atony (this contrasts with the commonly used Bakri balloon which inflates to generate positive pressure on the uterine wall). It consists of four parts, a distal loop with pores that is inserted into the uterus, an occlusion balloon that sits in front of the cervix, a valve for inflating the occlusion balloon, and a vacuum port. The investigators conducted a prospective proof of concept evaluation in 10 women who failed first-line therapies for hemorrhage; bleeding stopped in all of the patients. While larger studies demonstrating its safety and effectiveness will be needed, the device offers a promising low-cost intervention that could be used in low-resource settings.

The second study examined a novel approach for the prevention of preeclampsia. Endothelial dysfunction is an important component in the pathogenesis of preeclampsia. Statins are known to promote endothelial function via their pleotropic effects. In animal models of preeclampsia, statins have been shown to restore endothelial function. Constantine et al. conducted a pilot, multicenter, double-blind randomized controlled clinical trial in which 20 pregnant women with a history of severe preeclampsia who had previously delivered at less than 34 weeks-of-gestation (a very high-risk group for recurrence) were randomized between 12 and 16 weeks-of-gestation to pravastatin 10 mg or placebo.[17] No safety concerns were associated with treatment with pravastatin. Maternal cholesterol levels were lower in the pravastatin arm, as expected, but there was no impact on infant birth weight or umbilical cord cholesterol concentrations. In the placebo arm, four of the 10 patients developed preeclampsia, including three with severe features. In contrast, in the statin arm, none of the patients developed preeclampsia. These very promising results favor the conduct of large-scale studies. A highly effective therapy to prevent preeclampsia would have an extraordinary impact in decreasing maternal and neonatal morbidity and mortality.

Studies published in 2016 played an important role in advancing our understanding of patterns of, and risk factors for, maternal morbidity and mortality; and in charting new directions for interventions that may reduce the occurrence of these outcomes. The challenge that lies ahead is to use these data to inform the development of practices and systems-based changes that produce meaningful reductions in the occurrence of these tragic outcomes. In our role as peri-delivery physicians, obstetric anesthesiologists should lead the way.[18,19]

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