The WOMAN Trial: Clinical and Contextual Factors Surrounding the Deaths of 483 Women Following Post-Partum Hemorrhage in Developing Countries

Roberto Picetti, Lori Miller, Haleema Shakur-Still, Tracey Pepple, Danielle Beaumont, Eni Balogun, Etienne Asonganyi, Rizwana Chaudhri, Mohamed El-Sheikh, Bellington Vwalika, Sabaratnam Arulkumaran, and Ian Roberts, on behalf of the WOMAN Trial Collaborators

Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, United Kingdom (R.P., L.M., H.S.-S., T.P., D.B., I.R.); Maternity Unit, Kumba District Hospital, Kumba, Southwest Province, Cameroon (E.A.); Holy Family Hospital, Gynecology & Obstetrics Unit 1, Rawalpindi, Pakistan (R.C.); Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan (M.E.-S.); Department of Obstetrics and Gynaecology, School of Medicine, University of Zambia, Lusaka, Zambia (B.V.); and St George’s University of London, London, United Kingdom (S.A.)

ABSTRACT

The etiology of maternal mortality is postpartum hemorrhage in approximately 8.0% of cases in developed countries and 19.7% in developing countries. As a leading cause of maternal death, its prevention and early treatment are a priority. As part of the WOMAN Trial, a randomized trial of tranexamic acid to treat postpartum hemorrhage, information on the causes of maternal death was recorded. The aim of this study was to review the circumstances of maternal death in more than 20,000 women in 21 countries.

The WOMAN Trial demonstrated that tranexamic acid reduced maternal death in women with postpartum hemorrhage. The study took place between 2010 and 2016 in 193 hospitals in 21 countries and recruited 20,060 women who were 16 years or older and were diagnosed with postpartum hemorrhage following vaginal or cesarean deliveries. In cases of maternal death, obstetricians were asked to record the cause of death and provide a brief narrative of the circumstances surrounding the death.

Of the 20,060 women recruited for the trial, 12,343 were from Africa, 6030 from Asia, and 1049 from Europe. A total of 483 deaths were recorded, with case fatality rates of 3.0% (n = 375) in Africa and 1.7% (n = 105) in Asia; there were no deaths in the European cohort. Narratives were obtained for 52% of the recorded deaths.

The odds of maternal death were 5 times higher in cases involving stillbirths versus live births (odds ratio = 5.26, 95% confidence interval = 4.34–6.39). The risk of death was also associated with more than 1000 mL of blood loss, a systolic blood pressure of <90 mm Hg, and hemodynamic instability. Among the 483 deaths, 13.3% were women who died within 3 hours of delivery and 59.8% who died between 3 and 24 hours after delivery.

Women who gave birth outside of a participating hospital were 3 times more likely to die than those who gave birth at a participating hospital (odds ratio = 3.12, 95% confidence interval = 2.55–3.81). Based on the narratives, women who gave birth elsewhere were often in critical condition upon their arrival at a participating hospital.

Bleeding was the most common cause of death for 346 women (72%). Bleeding was the cause of death for 91% of women who died within 3 hours of delivery and 83% of those who died within 24 hours of delivery. The primary cause of bleeding was uterine atony (53.2%). On average, women who died lost 2.1 L of blood (SD = 0.9 L, median = 2 L, interquartile range = 1.5–2.5 L) versus 1.2 L of blood for women who lived (SD = 0.6 L, median = 1 L, interquartile range = 0.8–1.5 L). More women who died received blood transfusions than those who lived (92.1% vs 53.8%). The narratives noted that blood was often unavailable for transfusion because of blood shortages or the family's inability to purchase blood.

In this study, blood loss was observed to be the leading cause of death in women from Africa and Asia. Achieving mortality rates in developing countries similar to those in developed countries will require attention to issues such as late presentation due to births outside of hospitals and the lack of blood for transfusion.

EDITORIAL COMMENT

(Postpartum hemorrhage is one of the leading causes of maternal morbidity and mortality worldwide. In the developing world, the risk of mortality from postpartum hemorrhage is higher...
than in other settings. However, even in the United States, reduction of postpartum hemorrhage and mitigation of its downstream effects have been components of major obstetric quality improvement projects. For example, aggressive efforts by perinatal quality collaboratives to reduce the impact of postpartum hemorrhage have commonly utilized a team-based care approach such as that developed by the California Maternal Quality Care Collaborative (MCN Am J Matern Child Nurs 2011;36:297–304).

The approach to reducing the morbidity and mortality from postpartum hemorrhage includes both prevention and treatment efforts. Prevention efforts have generally focused on the use of active management of the third stage of labor. This involves uterotonic use upon delivery of the fetal shoulder. This can be accomplished by increasing the intravenous oxytocin, but it appears that a more reliable way is to administer 10 units of oxytocin IM (J Obstet Gynaecol Can 2009;31:980–993). The treatment of postpartum hemorrhage has been improved over recent years. Historically, the approach involved identification of the etiology and then specific treatments: repairing lacerations, removing residual products of conception, and uterotonics for atony. More recently, though, massive transfusion protocols have become incorporated into routine guidelines for postpartum hemorrhage management, and the use of intrauterine balloons for tamponade has become common (Obstet Gynecol Surv 2016;71:99–113). Even more recently, evidence from a large randomized trial of tranexamic acid versus placebo (the WOMAN study) in the setting of postpartum hemorrhage found a reduction in the risk of mortality (Lancet 2017;389(10084):2105–2116).

The WOMAN Trial was a study with the size and impact that usually lead to rapid change, and indeed, it has become much more common to use tranexamic acid in the setting of postpartum hemorrhage. However, one concern raised about the study was the clinical context in which it was conducted. Of the 20,000 women enrolled, the majority were in Africa, another 6,000 were from Asia, and only 1000 were from Europe.

In the current study abstracted above, the authors conducted a deeper dive into the mortalities that occurred in the WOMAN study. First, it was important to note that in this study, deaths in the majority of women were indeed due to obstetric hemorrhage (72%). Interestingly, women who had a stillbirth were 5 times more likely to die. By geographical region, the mortality rate in Africa was just above 3%; in Asia, it was 1.7%, and of the 1000 women in Europe, none of them died. Thus, cases that may potentially benefit from tranexamic acid would have been predominantly located in the developing world.

Despite the WOMAN study finding a difference predominantly in developed countries, the use of TXA in the setting of postpartum hemorrhage has expanded in the United States since its publication. One important consideration was that there were no obvious complications from TXA treatment, which likely lowered the threshold for consideration of its use. Furthermore, the current study demonstrates that women in the study did suffer high rates of mortality from hemorrhage, which was reduced by the TXA. One would think that while the mortality from hemorrhage is lower in the United States, there would still be a proportional reduction. Particular settings where TXA might receive even more attention and usage would be small community hospitals with more limited blood banks. In such settings, the risk from hemorrhage is likely higher, so it is probably a good idea to use TXA with postpartum hemorrhage in such settings.

The next step is to ascertain whether TXA should be used prophylactically. A systematic review of randomized controlled trials of tranexamic acid in nonobstetric surgery showed a reduction in the requirement of blood transfusion (Cochrane Database Syst Rev 2007;(4):CD001886). Further, there has been no evidence of an increased risk of thrombotic events in any of the clinical studies. Additionally, TXA has been studied in the setting of trauma and demonstrated reduction in mortality without an increase in complications (Lancet 2010;376:23–32). There are a handful of studies that have demonstrated that prophylactic tranexamic acid can reduce blood loss and rates of postpartum hemorrhage (Cochrane Database Syst Rev 2010;(7):CD007872). A recent prophylactic trial in the setting of vaginal delivery showed a modest reduction in postpartum hemorrhage, but the finding did not reach statistical significance (N Engl J Med 2018;379:731–742).
Additionally, none of the prophylaxis studies have demonstrated a reduction in blood transfusion or rates of more serious hemorrhage, primarily because of lack of power. Thus, I would continue to await large trials before adoption of prophylactic TXA. However, in the setting of postpartum hemorrhage, I think it is reasonable to use TXA, particularly if there is no response to first-line uterotonic agents. While some may wait for a large study powered for mortality in developed nations, it is unlikely that one will be completed any time soon.—ABC

Cervical Pessary to Prevent Preterm Birth in Asymptomatic High-Risk Women: A Systematic Review and Meta-analysis

Agustin Conde-Agudelo, Roberto Romero, and Kypros H. Nicolaides

Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, and Detroit, MI (A.C.-A., R.R.); Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit (A.C.-A.); Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor (R.R.); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing (R.R.); Center for Molecular Medicine and Genetics, Wayne State University (R.R.); Detroit Medical Center (R.R.), Detroit, MI; Department of Obstetrics and Gynecology, Florida International University, Miami, FL (R.R.); and Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK (K.H.N.)

Am J Obstet Gynecol 2020;223:42–65.e2

ABSTRACT

Preterm birth is associated with a multitude of short-term complications in infants compared with term delivery. These short-term complications include respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, intraventricular hemorrhage, periventricular leukomalacia, and retinopathy of prematurity. Preterm birth can also be associated with complications that arise later in life such as diabetes mellitus, lung function impairment, venous thromboembolism, sleep-disordered breathing, ischemic heart disease, and chronic kidney disease. Preterm birth has also been associated with increased mortality from birth to 45 years of age. Several interventions, including progestogens (17α-hydroxyprogesterone caproate, vaginal progesterone, and oral progesterone), omega-3 long-chain polyunsaturated fatty acids supplementation, cervical cerclage, and cervical pessary, have been proposed in order to prevent preterm birth in asymptomatic, high-risk women. Vaginal progesterone and cervical cerclage have been shown to prevent or reduce the risk of preterm birth, whereas 17α-hydroxyprogesterone caproate, oral progesterone, and omega-3 long-chain polyunsaturated fatty acid supplementation have had inconclusive results. Studies of the efficacy of cervical pessary in preventing preterm birth have also shown conflicting results. These authors performed a systematic review and meta-analysis to evaluate whether cervical pessary aids in the prevention of preterm birth and perinatal morbidity and mortality in asymptomatic high-risk women.

Articles relevant to the study were identified through searches in MEDLINE, EMBASE, POPLINE, LILACS, CINAHL, the Cochrane Central Register of Controlled Trials, clinical trial registries, and Google Scholar. Terms used to search the articles were cervical pessary and preterm birth. Articles were included if they were randomized controlled trials comparing asymptomatic women at high risk of preterm birth with and without a pessary in place, as well as other interventions (such as vaginal progesterone or cervical cerclage). Articles were excluded if they were quasi-randomized, analyzed cervical pessary in women with arrested preterm labor or placenta previa, or did not contain reported clinical outcomes. The primary outcome was spontaneous preterm birth at less than 34 weeks' gestation, and the secondary outcomes were adverse pregnancy and maternal and perinatal outcomes. Pooled relative risks were calculated with 95% confidence intervals (CIs), and the quality of evidence was determined using the GRADE methodology, which breaks down the levels of certainty into 4 categories: high, moderate, low, and very low.

Overall, 12 studies were included in the analyses. These 12 studies included 4687 women and 7167 fetuses/infants. Eight articles assessed pessary versus no pessary in women with a short cervix, 2 articles evaluated pessary versus no pessary in unselected multiple gestations, and 2 articles compared the pessary versus vaginal progesterone in women with a short cervix. Ten trials were designed to evaluate cervical pessaries in women with a short cervix (defined as cervical length $\leq 25$, $<25$, $\leq 30$, $<30$, $\leq 50$, $<50$, $\leq 75$, $<75$, $\leq 100$, $<100$, $\leq 125$, $<125$, $\leq 150$, $<150$, $\leq 175$, $<175$, $\leq 200$, $<200$, $\leq 225$, $<225$, $\leq 250$, $<250$, $\leq 275$, $<275$, $\leq 300$, $<300$, $\leq 325$, $<325$, $\leq 350$, $<350$, $\leq 375$, $<375$, $\leq 400$, $<400$, $\leq 425$, $<425$, $\leq 450$, $<450$, $\leq 475$, $<475$, $\leq 500$, $<500$, $\leq 525$, $<525$, $\leq 550$, $<550$, $\leq 575$, $<575$, $\leq 600$, $<600$, $\leq 625$, $<625$, $\leq 650$, $<650$, $\leq 675$, $<675$, $\leq 700$, $<700$, $\leq 725$)}