Editorial

The expanding role of tranexamic acid in the management of obstetric hemorrhage

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Reducing mortality and morbidity in obstetric patients presents challenges at each end of the coagulation spectrum. The greatest cause of maternal mortality worldwide is from hemorrhage, and yet women also die in large numbers from peripartum pulmonary embolism (1). Pharmacologic manipulation of the coagulation cascade, including the use of the antifbrinolytic tranexamic acid, has become an important part of reducing hemorrhage risk in cardiac, trauma, and orthopedic patients (2), and will now likely become a more common practice in obstetric management with the recent publication of the World Maternal Antifibrinolytic (WOMAN) trial (3).

Until the publication of the results of the WOMAN trial, the principal concern about using pro-clotting pharmacologic agents to treat obstetric hemorrhage has been safety. Pregnancy represents a hypercoagulable physiologic state with a several-fold increased incidence of thromboembolic complications including pulmonary embolism as compared with non-pregnant patients (RR =4.29; 95% CI, 3.49–5.22) (4). The incidence of thromboembolic complications related to pregnancy in the United States is 1.72 per 1,000 deliveries with 1.1 maternal deaths from pulmonary embolism per 100,000 deliveries (5). Hemorrhage is the leading cause of maternal death worldwide, but in high resource environments, death from hemorrhage and thromboembolism are approximately equal in proportion. In the United States for example, 11.4% of maternal deaths result from hemorrhage, and 9.3% thromboembolism (the greatest proportion of maternal deaths (32.6%) now results from cardiovascular complications) (6). Strategic initiatives aimed at reducing deaths on each extreme of the coagulation spectrum (from hemorrhage or thromboembolism) must not come at the cost of increasing deaths from the other.

The clinical advantages of using tranexamic acid to treat hemorrhage have taken time to become realized. This antifibrinolytic lysine analog was first synthesized in 1962 for use in the treatment of postpartum hemorrhage (7). It serves as a competitive inhibitor of plasminogen activation and has been shown to be effective when employed as a prophylactic hemorrhage reduction strategy in numerous randomized, controlled trials, specifically in reductions of estimated blood loss and administration of red cell transfusions during cardiac bypass, orthopedic joint replacement, among other clinical circumstances, without demonstrable evidence of increased thrombotic complications including stroke and myocardial infarction (8). Administration of tranexamic acid has also been reported to be an effective therapeutic strategy in trauma in reducing death from hemorrhage, again without an increase in thrombotic complications (9).

However, obstetric hemorrhage has unique features that have limited the generalizability of pharmacologic management strategies from non-obstetric settings. On one hand, the higher baseline prevalence of thromboembolism made the use of tranexamic acid unattractive in obstetric patients, but conversely, the disproportional coagulopathy observed relative to total blood loss when compared with surgical or traumatic hemorrhage (10) made it appear to perhaps be a welcome intervention. The excessive or rapid

development of coagulopathy in obstetric hemorrhage is likely multifactorial and not completely understood, but is believed to result from high consumption of clotting factors related to placental separation from the uterus (11). Increased fibrinolysis and platelet activation are observed, as well as a substantial release of tissue factor into the maternal blood stream, which may also activate consumption of procoagulant factors (12). Tranexamic acid administration has been shown to stabilize fibrinolysis and D-dimer liberation in obstetric hemorrhage and may be well-suited to counter some aspects of the disproportional coagulopathy (13). Prior to publication of the WOMAN trial, several small, randomized trials were conducted on the prophylactic use of tranexamic acid in the setting of cesarean delivery at low-risk for hemorrhage. Some of the trials had methodological and qualitative problems that limited interpretation in meta-analysis, but generally the use of tranexamic acid in low-risk parturients was associated with only a small reduction in estimated blood loss [78 mL (95% CI, 58–98 mL)] (14), and this effect size did not seem to warrant routine use of tranexamic acid given the uncertainty regarding thromboembolic safety.

The recently published WOMAN trial was conducted in 193 centers in 21 countries and represented a herculean effort by the research team at the London School of Hygiene. Parturients were enrolled in mostly low-resource environments, with the largest recruitment occurring in Nigeria, Pakistan and Uganda. Approximately 20,000 women with postpartum hemorrhage, defined by what are widely accepted thresholds of pathologic hemorrhage (greater than 500 mL in vaginal delivery, 1,000 mL in cesarean delivery), were randomized to receive either tranexamic acid (1 gram load with option to redose once if no response was observed in 30 minutes) or placebo. The primary outcome of the trial, death from hemorrhage, was reduced by approximately one third (1.5% treatment group; 1.9% placebo; RR =0.81; 95% CI, 0.65–1.00; P=0.045) (3). These results paralleled those from the CRASH-2 trial conducted by the same institution that showed a similar reduction in death from hemorrhage in trauma patients with tranexamic acid (9).

Perhaps the most import finding of the WOMAN trial was the reassurance that using low doses of tranexamic acid in obstetric patients appears safe with regard to thromboembolic risk. Low but equal numbers of arterial and venous thromboembolic complications were observed in both the treatment and placebo arms of the study. Specifically there were 17 (0.2%) reported pulmonary embolism cases in the tranexamic group compared with 20 (0.2%) in the placebo group (RR =0.85; 95% CI, 0.43–1.61; P=0.611) (3). In addition, there were similar rates for stroke, myocardial infarction and deep venous thrombosis in both groups. One could hypothesize underreporting of complications in a trial conducted in low resource environments; however, these rates of embolic complications are equivalent to those previously reported in pregnant patients (4).

As practitioners around the world are now considering how to apply the results from the WOMAN trial to their patients, it is important to consider the external validity of its results, particularly when applying them to high resource practice environments. The *de facto* primary outcome of the trial was death from hemorrhage. It was changed mid recruitment from a composite of maternal death or hysterectomy, to death alone, when it was observed that patients were being enrolled concurrently with a decision to perform an emergent hysterectomy. Patients were recruited from almost entirely low resource settings, and the results, particularly the reduction in maternal death from hemorrhage, may not apply elsewhere, due to differences in practices. For context, the maternal death rate in this hemorrhaging population was a staggering 2.6% in the trial (1 in 38 women). This is substantially higher than the death rate from hemorrhage seen in high resource environments (estimated to be less than 0.1% among women who experience severe hemorrhage in the United States) (6,15). Given the low absolute rate of hemorrhagic death in high resource settings, it would be difficult to demonstrate a reduction in maternal death from hemorrhage using a similar therapeutic tranexamic acid administration strategy much less a prophylactic one. For example the calculated number needed to treat to prevent maternal death from hemorrhage in the WOMAN trial was 274 but had a 95% confidence interval of 137 to over 17,000. The number needed to treat to prevent maternal death in settings with lower mortality rates would naturally be much higher, so the expected benefit of using tranexamic acid would more likely be reduction in maternal morbidity. This would include reductions in estimated blood loss and transfusion administration, and intensive care admissions, which are still meaningful outcomes for obstetric patients. A current trial conducted by the Maternal Fetal Medicine Unit Network in North American is enrolling patients at high risk for hemorrhage (scheduled cesarean delivery for placental invasion disorder) to receive prophylactic tranexamic acid or placebo with the primary outcome of estimated blood loss (16).

Several safety considerations have become evident related to tranexamic acid administration recently that were not necessarily apparent in the WOMAN trial. First, there have been reported serious thromboembolic events related to its administration that warrant attention. A case cluster of 18 parturients developed renal cortical thrombosis in France following tranexamic acid administration that involved continuous infusion (17). For context, this is a complication that is extremely rare in pregnancy, and all of these previously young healthy women suffered permanent kidney damage with eight requiring dialysis six months postpartum. This complication may be related to cumulative dose (mean loading dose in these cases was 1.8±0.9 g and mean infusion was 0.5–1 g/h for 5.3 h), which perhaps only differed substantively from the WOMAN trial by the addition of several-hour-long infusions (the WOMAN trial was 1–2 bolus doses of 1 g only). A second safety concern has manifest in highly consequential drug substitution errors. There have been several reported cases of maternal death following the intrathecal administration of tranexamic acid in obstetrics (18). Unfortunately, some 2 mL (500 mg) vials of tranexamic acid are remarkably similar to vials of bupivacaine that are administered for spinal anesthesia for cesarean delivery. There are few drug substitution errors that have been as uniformly lethal as injecting one half of a gram of tranexamic acid into the cerebrospinal fluid. Perhaps the most important element of increasing use of tranexamic acid would be to ensure that systems are in place for safe administration to avoid such similar tragedies. A third known complication of tranexamic acid is seizure activity. Tranexamic acid is a competitive antagonist of gamma-aminobutyric acid (GABA), which reduces the inhibition of neurotransmission thus increases excitability in neural networks. Dose dependent seizure activity has been reported with an incidence of 0.9–2.5% in non-obstetric patients, but this effect has generally not been observed with to the same degree in pregnant patients for unclear reasons (19).

In conclusion, we are likely to see a substantial increase in the worldwide use of tranexamic acid in obstetric management following the publication of the WOMAN trial. The results of this important clinical investigation provide hope in the effort to reduce the global burden of death from maternal hemorrhage. However, caution is warranted with any paradigm shift in clinical medicine, particularly one related to manipulation of the finely-balanced coagulation cascade. Thoughtful expansion of the use of tranexamic acid in pregnant patients should adhere to the universal maxim in medicine of first ensuring that we are not unintentionally harming patients. The limited complications reported in the WOMAN trial are a reason to be optimistic at least with regard to the risk of thromboembolism from low doses of tranexamic acid in pregnant patients. However, there are important safety considerations related to both dosage and systems of administration, as well as appropriate healthcare resource utilization in general, that require our focus now as we apply the results of the WOMAN trial beyond a setting of high maternal mortality.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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