Hemostatic Agents

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
Hemostatic Agents

Summary

Hemostatic agents are medical substances that induce blood clotting and stop harmful blood loss. There is growing evidence to support the use of hemostatic agents to manage postpartum hemorrhage. They are administered in the uterus and act quickly to stop or control excessive bleeding when medications fail or are unavailable.

Statement of Need

Obstetric hemorrhage is estimated to cause 25% of all maternal deaths and is the leading direct cause of maternal mortality worldwide. Postpartum hemorrhage (PPH), defined as vaginal bleeding in excess of 500 ml after delivery, is generally considered to account for a majority of the cases of obstetric hemorrhage, occurs in over 10% of all births, and is associated with a 1% case fatality rate.

Although active management of the third stage of labor (AMTSL) can prevent up to 60% of PPH cases, PPH continues to have a devastating impact on women in resource-poor settings where home births are common and hospitals or health facilities are often inaccessible. Obstetric hemorrhage accounts for 34% of maternal deaths in Africa, 31% in Asia, and 21% in Latin America and the Caribbean, while only 13% of maternal deaths in developed countries are due to hemorrhage. Additionally, if women do survive PPH, approximately 12% will have severe anemia, and if women survive severe PPH (greater than 1,000 ml of blood loss) (“near misses”), they are significantly more likely to die in the year following the PPH.

AMTSL is recommended by the World Health Organization (WHO) and endorsed by the International Federation of Obstetricians and Gynecologists and the International Congress of Midwives for the prevention of PPH. The three components of AMTSL are prophylactic uterotonics, controlled cord traction, and uterine massage. While its effectiveness has been well documented, AMTSL poses some challenges and limitations for use in low-resource settings. Even when performed exactly, AMTSL prevents only 40% to 50% of PPH from uterine atony. In severe cases of intractable uterine atony, bleeding will not respond to the administration of uterotonics.

Definitive treatment of PPH-related shock and PPH unresponsive to uterotonics can only occur in a comprehensive emergency obstetric care (EmOC) facility. In cases where other treatment options are unsuccessful or practitioners are not sufficiently skilled, the last resort is to perform an emergency hysterectomy, leaving the woman unable to have more children.

In low-resource settings where many women do not have access to EmOC facilities, there is a compelling need for new, innovative, and easy-to-use nonsurgical PPH treatment methods that can stop the bleeding and keep women alive when surgery is unavailable. Hemostatic agents could act quickly to stop PPH and require no special equipment. The biggest technical challenge to adoption of this technology in low-
resource settings is that no single hemostatic product has been packaged with a delivery technology that facilitates easy uterine administration by minimally trained health workers and traditional birth attendants in low-resource communities.

Technology Solutions Landscape

As noted by Achneck et al. in their comprehensive review of topical hemostatic agents, “In the last decade, the number of effective hemostatic agents has increased dramatically.”

New technologies have been designed specifically for use in arresting bleeding in areas of difficult accessibility and have gained widespread use for pelvic surgery in the last few years. Certain hemostatic agents that excel at high-pressure bleeding and arterial spurting are particularly well suited to control oozing from raw surfaces such as the uterine wall. Some gelatin hemostatic products will swell and induce a tamponade-like effect upon contact with blood.

There is growing evidence to support the use of hemostatic agents for PPH management as an adjunct to conventional methods. Documented use of hemostatic agents for PPH includes the following:

- **Placenta previa**: Recently, Law et al. reported on the successful use of a hemostatic agent for placenta previa and indicated that “hemostatic gel provides quick and effective control in the lower segment where surgical intervention may be difficult.” One hemostatic gel, Floseal™, is a collagen sealant and coagulation promoter that controls bleeding ranging from capillary ooze to arterial spurting. It is considered to be easily applicable and provide quick and effective hemostatic control in the lower segment where surgical intervention may be difficult.

- **Lacerations**: Regarding use for complicated obstetric lacerations, Whiteside et al. report a case where prompt hemostasis was achieved with application of a fibrin sealant and conclude that hemostatic agents may be useful for homeostasis when traditional techniques fail in complicated lacerations of the vulva and vagina associated with obstetric delivery. The fibrin sealant TISSEEL™ is noted as being well-suited to controlling oozing from raw surfaces and was administered in this case of traumatic bleeding: “…after suturing, vaginal packing, and IV tranexamic acid, and 3,500 ml blood loss and received 4 U transfusion, TISSEEL™ was used as a thin layer on vaginal wall and bleeding settled. When the tissues are very oedematous, it can be difficult to insert sutures. We tried this innovative option with very effective results. The absence of long-term complications is reassuring and we recommend its use in similarly extreme situations.”

- **Uterine atony**: There is growing evidence for hemostatic use for massive obstetric hemorrhage caused by uterine atony. Moriarty et al. report that hemostasis was achieved instantaneously in a case of uterine atony when Floseal™ was delivered to the oozing area through a single syringe.
With regards to uterine packing, some of the commercially available hemostatic agent formats (such as QuickClot®, a kaolin-infused gauze*) lend themselves to uterine packing. These gauze bandages have the advantage of providing an absorptive matrix, potentially a tamponade effect, and have the advantage of being impregnated with hemostatic agents. It is important to note that uterine packing (prior to hemostatic agent impregnation of gauze) fell out of favor in the 1950s without review of evidence—concerns were infection and hemorrhage masking. However, a 1993 paper showed high success rates with uterine packing.¹⁰

**Gap Analysis**

The advantages of hemostatics are that they act quickly and require no special equipment, thus they are particularly appropriate for lower-level settings or settings without surgical capacity. The biggest challenge to immediate testing and adoption of this technology in low-resource settings is that no hemostatic products have been packaged with a delivery technology that facilitates easy uterine administration by minimally trained health workers and traditional birth attendants in low-resource communities. There is a need to develop an appropriate hemostatic agent delivery technology from a list of candidate solutions that include dual-syringe delivery mechanisms, thermo-gels, absorbable gelatin sponges, sprays, or foaming gels.

Additionally, currently approved hemostatic technologies are very expensive. Further research needs to be conducted to improve product use and reduce cost. Current challenges include ease of mixing, having the form factor specifically designed for uterine application, an appropriate delivery method, and premeasured-dose packaging.

Finally, hemostatic agents do not address the root cause of uterine atony (i.e., does not cause the uterus to contract) so additional treatment options will be required. Hemostatics would be used only after uterotonics have failed. In this situation, there is evidence that the agents will stop bleeding and buy time for the patient to receive treatment at a comprehensive EmOC facility.

**Investment Opportunity**

Acceptability of hemostatic agents for PPH management could be advanced through investment in developing an appropriate, low-cost, and easy-to-use hemostatic delivery technology for intrauterine use. Appropriate delivery of novel hemostatic clotting agents will enable birth attendants in low-resource communities to provide lifesaving treatment for PPH.

*There are currently no independent studies.*
The following activities describe critical steps toward developing an affordable hemostatic product for use by birth attendants for the control of PPH:

- Develop an understanding of the cost and pricing structure of current hemostatic products with the intent of developing a reasonable approximation of the lowest prices that could be expected for use in low-resource settings.
- Conduct a landscape of all potential delivery technologies and identify functional gaps, misuse modes, hazards, and overall acceptability for each approach.
- Develop prototypes of several leading delivery concepts using the constraints and requirements previously identified.
- Evaluate the viability of these conceptual prototypes in the field where health care workers will first be trained then observed in simulated use scenarios.
- Disseminate findings and invite collaborative involvement in the development process by convening a workshop that includes attendance by a committee of leading PPH management experts.
- Develop a collaboration of key hemostatic agent manufacturers.
- Identify the necessary provisions for global access to hemostatic agents and delivery technologies.
- Conduct anticipated animal safety studies.
- Conduct a randomized controlled trial to demonstrate effectiveness.

If the above steps lead to a positive outcome:

- Establish manufacturing capacity and requirements to achieve market penetration in poor countries.
- Initiate critical steps to advance policy and programmatic plans to accelerate market penetration and uptake, ensure commercial sustainability, ensure low-resource setting affordability, and ensure global access to the technology.
- Advocate promoting inclusion in the WHO guidelines for PPH management, manufacturing scale-up, and global and in-country regulatory approvals.
References


