Summary of Evidence Base for Oxytocin in Uniject

Postpartum hemorrhage (PPH) is the world’s leading cause of maternal mortality. It is the most common type of obstetric hemorrhage and accounts for the majority of the 14 million cases of obstetric hemorrhage that occur each year, resulting in an estimated 150,000 maternal deaths annually. In the developed world, PPH is a largely preventable and manageable condition. In developing countries, however, mortality from PPH remains high despite international efforts. While data are limited, studies have shown that PPH causes approximately half of all maternal deaths in a number of developing countries. For example, PPH accounts for 59 percent of maternal deaths in Burkina Faso, 53 percent in the Philippines, and 43 percent in Indonesia. PPH also causes considerable suffering for women and their families and creates major demands on health systems.

PPH is defined as excessive vaginal bleeding (blood loss greater than 500 ml) within 24 hours after delivery. It is caused by a variety of conditions. Immediate PPH—heavy bleeding directly following childbirth or within the first 24 hours—is the most common type and can be caused by uterine atony (failure of the uterus to contract properly after delivery); retained placenta; inverted or ruptured uterus; or cervical, vaginal, or perineal lacerations. Uterine atony is the leading cause of immediate PPH. In the developing world, the main risk factors for PPH due to uterine atony include pre-eclampsia, prolonged labor, and high parity. Roughly two-thirds of women who suffer from PPH present no risk factors, however. Retained placenta, infection, and trophoblastic tumors can all produce delayed or “secondary” PPH, defined as hemorrhage after the first 24 hours postpartum.

The primary interventions shown to reduce the incidence of PPH are administration of a uterotonic drug or active management of the third stage of labor (AMTSL). Other preventive measures include reducing the incidence of prolonged labor (through the use of the partograph and timely intervention, when needed), minimizing the trauma associated with instrumental delivery, and possibly detecting and treating anemia during pregnancy. Studies performed in the late 1980s and 1990s (summarized in a 1996 meta-analysis by Prendiville) confirm that AMTSL is associated with reduced maternal blood loss, reduced postpartum anemia, and decreased need for blood transfusion. Active management is also associated with a reduced risk of prolonged third-stage of labor and reduced use of additional therapeutic uterotonic drugs. In hospital settings, AMTSL is associated with a reduction in PPH of about 62 percent. Researchers have not yet identified the most appropriate management of the third stage of labor in home delivery settings.

PPH due to uterine atony can generally be managed through a range of interventions that correspond to the timing, type, and severity of bleeding. Neither oxytocic drugs nor AMTSL are routinely used in developing countries, however. A recent international assessment of the use of AMTSL in developing countries revealed significant intracountry and intercountry variation in AMTSL practice. The same assessment found that routine prophylactic use of oxytocic drugs was far from the norm for most developing country women. Treatment of severe PPH requires access to obstetric emergency care, blood transfusion, and surgery—conditions that can be challenging in
developing countries, where most births occur in homes, community maternity centers, or district facilities. As a result, treatment is often unavailable for the majority of women.\textsuperscript{11} Thus, within the developing country context, routine prevention of PPH is the approach most likely to have a measurable impact on maternal deaths. In addition to saving women’s lives, preventing PPH can result in significant cost savings for health systems that would otherwise use their resources to treat PPH cases or the resulting morbidities. These savings can be reinvested in additional life-saving improvements.

WHO recently endorsed oxytocin as the most effective medicament for preventing PPH.\textsuperscript{12,13} Used prophylactically, oxytocin has been shown to reduce rates of PPH by approximately 50 percent.\textsuperscript{14} Based on a literature review and a large multicenter trial, WHO has identified the benefits that oxytocin holds over other oxytocic drugs.

- Because of their hypertensive effect in 10 to 15 percent of women, ergot-based drugs are contraindicated in women with high blood pressure or pre-eclampsia. They are also less heat stable than oxytocin.\textsuperscript{15}
- Misoprostol, a prostaglandin E\textsubscript{1} analogue, is estimated to be 30 percent less effective at reducing severe PPH than oxytocin.\textsuperscript{13} Studies in the Gambia\textsuperscript{16} and India\textsuperscript{17} are currently evaluating the prophylactic effect of misoprostol in home deliveries.
- Prostaglandin preparations such as prostaglandin F\textsubscript{2}-alpha are contraindicated in women with asthma due to potential bronchospasm. In addition, prostaglandins may be used alone or in conjunction with mifepristone as abortifacients. (Oxytocin cannot be used as an abortifacient, as its uterotonic effect depends on hormonal changes in the third trimester.)

To administer oxytocin at birth, health care providers currently use standard syringes requiring sterilization equipment. Single-use disposable or autodisable syringes can serve as an alternative, but these options require administration by a health provider with legal authority to provide injections and the skill to measure and inject a correct dose. PATH developed the Uniject injection device, a prefilled, single-use device that has already been used by thousands of health workers to administer tetanus, hepatitis B, and other vaccines. Uniject devices can also be filled with the proper dose of other medicaments, such as oxytocin. Oxytocin-filled devices can be stored at delivery sites outside the cold chain for at least two months (and possibly much longer). The oxytocin-filled devices are easily transported to home deliveries.

**Preliminary studies**

Several preliminary studies of oxytocin-filled Uniject devices provide initial information on acceptability, feasibility, and effectiveness in home, health center, and hospital settings. PATH, WHO, and the Indonesian Ministry of Health (MOH), for example, conducted a field trial in Indonesia. The results demonstrated that oxytocin-filled Uniject devices used as part of AMTSL were safe and acceptable to providers and mothers.\textsuperscript{18} Midwives attending home deliveries were interviewed about their use of oxytocin and syringes and about management of PPH before receiving oxytocin-filled Uniject devices. After attending a total of 2,220 deliveries in which oxytocin-filled Uniject devices were used, the same 140 midwives were interviewed again with a standardized questionnaire.
Midwives found oxytocin-filled Uniject devices much easier to use than ampoules and traditional syringes. They also found that the new technology virtually eliminated the common, unsafe practice of reusing nonsterile syringes.

PATH is currently conducting an evaluation of midwives’ use of oxytocin-filled Uniject devices in commune health centers in Vietnam including comparison of use of oxytocin via Uniject devices. Another component will compare the incidence of PPH in districts using Uniject as part of AMTSL with districts where it is not used. In addition, a hospital-based study undertaken by The Karolinska Institute in Angola found a dramatic reduction in PPH when oxytocin-filled Uniject devices were introduced. The results of this study are currently in press.

Status of Commercial Supply of Oxytocin in Uniject

Oxytocin-filled Uniject devices are not currently available commercially. As part of a current project, PATH is collaborating with a small generic drug company in India—Dolphin Laboratories Limited—to establish pilot-scale manufacturing of oxytocin-filled Uniject devices using filling and packaging equipment on loan from BD. Dolphin recently received approval from the Indian Drugs Controller to produce oxytocin-filled Uniject devices for research trial supply.

Dolphin Laboratories is well positioned to ensure a research supply of oxytocin-filled Uniject devices. In contrast, pharmaceutical producers new to oxytocin-filled Uniject devices would take two or more years to offer a comparable supply. While Dolphin does not have the operational capacity to serve as a global supplier of oxytocin-filled Uniject devices, they are reasonably well positioned to become a commercial supplier for needs in India and perhaps the South Asia region.

References


17. Derman R. The use of misoprostol to reduce the incidence of PPH in Karnataka, India. Presented at FIGO Bellagio Meeting, Nov. 2003; Santiago, Chile.


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