6.16 Postpartum haemorrhage

See Background Paper 6.16 (BP6_16PPH.pdf)

Background

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths.[1] These deaths have a major impact on the lives and health of the families affected. Between 1990 and 2010, there was a global reduction in maternal deaths and the maternal mortality ratio (MMR) from 543 000 and 400 per 100 000 live births to 287 000 and 210 per 100 000 live births respectively. However, developing countries continue to experience higher numbers of maternal deaths compared to developed countries.[2] In 2010, the MMR in developing countries was 240 per 100 000 live births (284 000 maternal deaths) compared to 16 (2 200 maternal deaths) in developed countries. Thirty-five countries have been identified as either making insufficient or no progress towards achieving the Fifth Millennium Development Goal (MDG5), which aims to reduce the global maternal mortality rate by 75% from 2000 to 2015.[2]

Every year about 14 million women around the world suffer from PPH.[3] The risk of maternal mortality from haemorrhage is 1 in 1 000 deliveries in developing countries (100 per 100 000 live births). Most deaths (about 99%) from PPH occur in low- and middle-income countries compared with only 1% in industrialized nations.[4] However, recent studies have shown an increase in the incidence of PPH in developed countries as well.[5] Therefore, in order to reduce the MMR and achieve MDG5, it is essential to achieve a major reduction in the incidence of PPH.

The WHO and professional bodies recommend active management of the third stage of labour (AMTSL) for all vaginal births in order to prevent PPH.[6] This involves prophylactic administration of uterotonic medicines before delivery of the placenta in addition to other non-pharmacological interventions, such as late cord clamping and controlled cord traction of the umbilical cord (in settings where skilled birth attendants are available). Although AMTSL reduces postpartum blood loss, about 3% to 16.5% of women will still go on to experience PPH and will require treatment.

Oxytocin injection is the recommended first line uterotonic medicine for preventing and treating PPH because it is more effective than ergometrine and other uterotonics and has relatively fewer side-effects. However, oxytocin is unstable at room temperature and requires special temperature storage conditions to remain effective.[7] The cold chain storage required to transport and store oxytocin is unreliable in resource-constrained countries. In addition, the fact that oxytocin must be administered parenterally requires the involvement of skilled health personnel.

Developments since 2004

Following the 2004 Report, in an effort to address the barriers to the use of oxytocin, the TI Pharma Hot Medicines Consortium has initiated studies to develop heat-stable oxytocin formulations.[8] Although progress has been made in improving the stability of oxytocin in the laboratory, a heat-stable oxytocin formulation is not yet available for therapeutic use.

The Program for Appropriate Technology in Health (PATH) has also developed the oxytocin Uniject, a device to ensure safer, accurate and easy dosage of oxytocin, especially in settings where skilled health workers are not available. Recent studies have supported the effectiveness of the oxytocin Uniject when used by trained birth attendants.[9,10] PATH has also incorporated a temperature-time-indicator (TTI) into the Uniject device to monitor the quality of the product in transit and storage.[11] Despite these advances, the oxytocin Uniject is yet to be deployed for use on a large scale.

Based on evidence, the WHO 2012 guidelines for managing PPH advise the use of misoprostol in situations where the use of oxytocin is not possible.[12] Misoprostol is inexpensive (less than US$ 1 per dose), can be given orally, is relatively stable at room temperature (no need for refrigeration) and has a long shelf life, all of which are major advantages over oxytocin.[13] The slightly lower potency of misoprostol is partly offset by these advantages.[14] However, misoprostol is sensitive to moisture and may degrade in areas of high humidity.[15] It also has side-effects which include transient fever, shivering, nausea, vomiting and diarrhoea. An additional practical problem is that misoprostol can be (mis)used for carrying out abortions and is therefore not marketed or approved in many countries.

The 2012 WHO guidelines also recommend the use of tranexamic acid - an antifibrinolytic agent used in surgery to reduce blood loss - as an alternative treatment for PPH when other uterotonics are unavailable or where the bleeding may be partly due to trauma.[2,12]

Remaining challenges

While substantial progress has been made towards improving on the existing interventions for managing PPH, the burden of PPH still persists because there is no "silver bullet" for either the prevention or treatment of PPH. The current interventions are inadequate. Efforts to address the following research opportunities will help meet the PPH prevention and treatment needs in most populations.

Research needs

Further research is needed to support the development of heat-stable oxytocin. When developed, the thermostable oxytocin should be packaged in Unijects to provide it with the additional advantage of ease of use in low-resource settings. The use of the currently available oxytocin Uniject with the TTI should be scaled up in low-resource settings in tandem with adequate post-marketing pharmacovigilance.

There is some evidence that sublingual misoprostol is beneficial in the treatment of PPH, especially where there is no access to oxytocin. Research studies are therefore needed to establish a standard safe and effective dose of misoprostol for treating PPH. Evidence is also currently limited on the effectiveness of the use of misoprostol by less skilled or lay caregivers at the community level.[15,16] There is a need for operational research to determine if the benefits of advanced community distribution of misoprostol to pregnant women and to lower cadre health workers at the community level outweigh the potential disadvantages. This study would also inform decisions about the lifting of regulatory barriers that prevent lower cadre health workers from administering oxytocin or misoprostol, especially in low-resource settings.

The potential of tranexamic acid in treating PPH should also be explored. Trials comparing the safety and efficacy of tranexamic acid and tranexamic acid in addition to existing uterotonics would be helpful in understanding the possible benefits of tranexamic acid in managing PPH. Finally, research is needed to discover new, patient-friendly and easy-to-use medicines for preventing and treating PPH.

References

[1] *Countdown to 2015: Maternal, Newborn and Child Survival* [Internet]. WHO and UNICEF, 2012. Available at: http://www.countdown2015mnch.org/documents/2012Report/2012-Complete.pdf. Last accessed 1 September 2012.

[2] *Trends in Maternal Mortality: 1990 to 2010. WHO, UNICEF, UNFPA and The World Bank estimates*. Geneva, WHO, 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241503631_eng.pdf. Last accessed 1 September 2012.

[3] Miller S, Lester F, Hensleigh P. Central European University. Prevention and Treatment of Postpartum Hemorrhage: New Advances for Low-Resource Settings. *The Journal of Midwifery & Women's Health*, 2004, 49(4):283–92.

[4] Haeri S, Dildy III GA. Maternal Mortality From Hemorrhage. *Seminars in Perinatology*, 2012, 36(1):48–55.

[5] Knight M et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy and Childbirth*, 2009, 9(1):55.

[6] PATH. Postpartum hemorrhage prevention and treatment website. 2011. Available at: http://www.pphprevention.org/pph.php. Last accessed 18 September 2012.

[7] De Groot AN, Vree TB, Walker GJA. Stability of oral oxytocics in tropical climates: Results of simulation studies on oral ergometrine, oral methylergometrine, buccal oxytocin and buccal desamino-oxytocin. Geneva, WHO, 1994. Available at: http://apps.who.int/medicinedocs/pdf/s2231e/s2231e.pdf. Last accessed 14 November 2012.

[8] Avanti C et al. A new strategy to stabilize oxytocin in aqueous solutions: II. Suppression of cysteine-mediated intermolecular reactions by a combination of divalent metal ions and citrate. *Mol. Pharm*, 2012, 9(3):554–62.

[9] POPPHI. *Pilot use of oxytocin in a Uniject device for AMTSL in Mali. Evaluation of the safety and feasibility of a new delivery technology*. PATH, 2008. Available at: http://www.pphprevention.org/files/UnijectReport_Mali_FINAL.pdf. Last accessed 10 October 2012.

[10] Stanton CK et al. Impact on postpartum hemorrhage of prophylactic administration of oxytocin 10 IU via Uniject™ by peripheral health care providers at home births: design of a community-based cluster-randomized trial. *BMC Pregnancy Childbirth*, 2012, 12:42.

[11] PATH. Newsflash: Oxytocin can take the heat... More storage flexibility with a TTI. Available at: http://www.pphprevention.org/files/TTIWebAnnouncement_001.pdf. Last accessed 10 October 2012.

[12] *WHO recommendations for the prevention and treatment of postpartum haemorrhage*. Geneva, World Health Organization, 2012. Available at: http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf. Last accessed 14 January 2013.

[13] Derman R et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. *Lancet*, 2006, 368:1248–53.

[14] Church C, Smith J. How stable are medicines moved from original packs into compliance aids? *Pharmaceutical Journal*, 2006, 276(7384):75–81.

[15] Oladapo OT. Misoprostol for preventing and treating postpartum hemorrhage in the community: A closer look at the evidence. *Int J Gynaecol Obstet*, 2012, 119(2):105–10.

[16] Raghavan S, Abbas D, Winikoff B. Misoprostol for prevention and treatment of postpartum hemorrhage: What do we know? What is next? *Int J Gynaecol Obstet.* 2012, 119 Suppl 1:S35–38.