Management of Postpartum Hemorrhage - Findings from a survey with 69 FIGO Member Associations

Background

Since 1990 reducing deaths from complications of pregnancy and childbirth has been high on the international agenda, spearheaded through Millennium Development Goal 5 which had the aim of reducing maternal mortality by 3 quarters by 2015. While the global number of maternal deaths was reduced by 43% during this period, some countries made little progress and the overall number of maternal death remains unacceptably high[1]. With the introduction of the Sustainable Development Agenda which will cover the period 2016-2030, the international community has been set a new target - to reduce the global maternal mortality ratio to less than 70 per 100 000 live births, with no country having a maternal mortality rate of more than twice the global average.

Postpartum hemorrhage (PPH) is still the leading direct cause of maternal mortality and morbidity globally[2] (see chart to the right). International recommendations point national maternal health programs to a set of key components to successfully reduce maternal morbidity and mortality. These include ensuring that key medicines such as oxytocin and misoprostol are on international and national essential medicines lists (EML) in correct dosages[3], that policy and service delivery guidelines exist that support the provision of such uterotonics[4], and that such evidence-based guidelines are fully utilized - serving as the basis for pre-service education as well as in-service training[5,6].

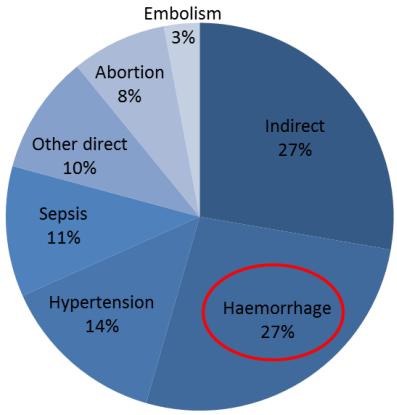


Chart showing causes of maternal death

Since 2010, FIGO has partnered with Gynuity Health Projects in an initiative to advocate for, and disseminate, evidence-based information on the management of PPH in low-resource countries by acting as a guiding organization for advocacy among the medical community and clinical policymakers. With reference to the international recommendations discussed above, this Initiative has supported the successful application for misoprostol to be included on the list of Essential Medicines for its prevention of PPH indication; has provided guidelines, protocols and other training materials on misoprostol use for PPH prevention and treatment (www.figo.org/figo-project-publications); conducted more than 35 expert panel sessions providing new evidence on management of PPH at national regional and global ob/gyn and women's health conferences; and otherwise disseminated evidence on interventions to reduce maternal mortality and morbidity from PPH.

Aim

To find out about countries' national guidelines for PPH, and inclusion of key PPH medicines on national EMLs as well as any challenges to implementing evidence-based practice in order to further support national FIGO Member Associations in their work towards their maternal health goals.

Methods

A web-based survey was developed and sent out by email to 130 FIGO Member Associations. Three email reminders were sent before the survey was closed. The survey was composed of 18 questions, some of which were single response questions, others permitted multiple responses. The broad question areas covered were:

Guidelines and content: Whether there are standard national clinical guidelines on the management of PPH. If so, if they recommend the use of misoprostol to prevent and treat PPH and if so, what is the recommended regimen and conditions under which it is recommended?

Creation of guidelines: What year the current edition of the standard clinical guidelines were published, when the next full review is due and whether minor revisions can be made between full reviews. Which agencies took the lead in developing the guidelines and which international/regional/national guidelines are used as principal referencing guidelines when drafting national guidelines.

EML and challenges to implementation: What the main challenges of implementing guidelines that include use of misoprostol for PPH management are. Whether misoprostol is included on national Essential Medicines Lists (or equivalent list of priority medicines), and if so, for what indications is it listed?

It was decided to ask questions specifically about misoprostol for two reasons. Firstly, that misoprostol represents a key medicine in the fight against maternal mortality and morbidity from PPH. While oxytocin remains the first choice of treatment, in many low-resource settings it is either not available or not feasible to use because it requires refrigeration and injection. Misoprostol may be more practicable as it is a readily-available and inexpensive drug which comes in tablet form, is stable at room temperature, and does not require any special skills, equipment, or facilities for its use. Recent evidence shows that when oxytocin is not available or feasible, misoprostol is effective for prevention and treatment of PPH[7,8]. These factors make it an important component of an integrated package of PPH interventions, especially in resource-poor and community settings. Secondly, that misoprostol, as a newer technology and supported by new science, can be used as an indicator for how quickly guidelines respond to latest evidence in PPH management. A number of international organizations have produced guidelines which include misoprostol (e.g. FIGO and WHO produced guidelines for misoprostol use for prevention and treatment of PPH in 2012) thus it can serve as an interesting point of comparison for both international and national recommendations.

Results

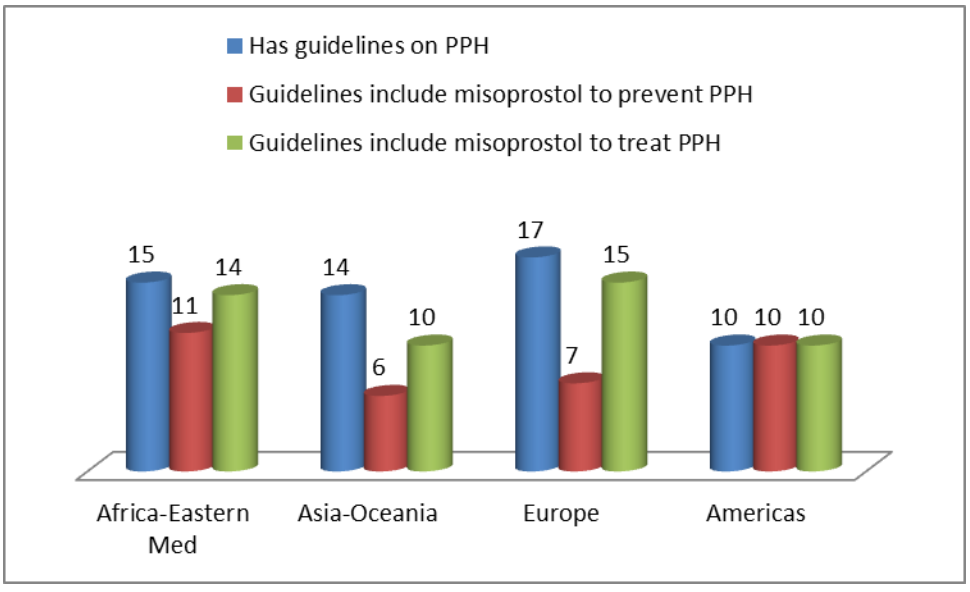
One hundred and thirty FIGO Member Associations (MAs) were contacted, of which complete surveys were received from 69 (53%) (see Table 1).

Table 1: Responders by FIGO Region

FIGO Region	Total number of MAs	Number to respond	Proportion
African-Eastern Mediterranean	37	17	46%
Asia-Oceania	26	17	65%
Europe	44	24	55%
Latin America	20	9	45%
North America	3	2	67%
Total	130	69	53%

Of those responding, 56 (81%) reported that their country has national guidelines on PPH management. Of this number, 34 (61%) included recommendations for misoprostol for prevention of PPH, and 49 (88%) included recommendations for misoprostol for treatment of PPH, with 33 (59%) having recommendations for both indications (see Chart below for breakdown by region).

Chart showing existence and content of guidelines by region



Regimens and conditions under which misoprostol was recommended varied greatly in national guidelines on PPH management. Seven different regimens were noted for prevention and 13 for treatment (see Table 2). Conditions under which misoprostol is recommended for prevention of PPH included: for every birth in any facility, for "high risk" births, for births outside facilities, when oxytocin is not available, when unskilled birth attendant is present at the delivery, and some did not specify conditions for use. The same conditions were given in the case of misoprostol for treatment of PPH with the additional condition 'after failure of first line treatment with other agents.'

Table 2: Regimens and conditions recommended for misoprostol use (multiple responses possible)

Misoprostol for PPH prevention (N=34) Regimen	%	Misoprostol for PPH treatment (N=49) Regimen	%
400 µg oral	8.8%	400 µg oral	6.1%
400 µg rectal/sublingual	2.9%	400 µg sublingual/rectal	2.0%
600 µg oral	55.8%	400-600 µg rectal	2.0%
600 µg rectal	11.8%	600 µg oral	14.3%
800 µg sublingual	20.6%	600 µg rectal	10.2%
800 µg rectal	11.8%	600 µg sublingual/rectal	2.0%
1000 µg rectal	11.8%	800 µg rectal	2.0%
Not specified	8.8%	600-800 µg sublingual/rectal	2.0%
		800 µg sublingual	34.7%
		800 µg rectal	10.2%
		800-1000 µg rectal/oral/sublingual	2.0%
		800-1000 µg rectal	2.0%
		1000 µg rectal	36.7%
		Not specified	2.0%

FIGO and WHO recommendations are highlighted in this Table.

Of the countries with national guidelines (n=56), the obstetrics and gynecology association and Ministry of Health were most often cited as the lead agencies involved in the creation of national guidelines (66% and 61% involved respectively). The most current versions of the guidelines had been published between 2006 and 2016; 20 had a year scheduled for their review (ranging from 2016 to 2010), 10 were reported as 'currently underway', and 26 had no review planned or the timescale for review was not known. 94% reported that their Association would be involved in the next review of the guidelines and 80% said minor revisions to the guidelines were possible between reviews.

In response to the question about which international, regional or other guidelines were used as principle referencing guidelines when drafting national guidelines, the majority of those who had national guidelines (75%) indicated using the WHO *Recommendations for the prevention and treatment of postpartum haemorrhage* from 2012; 63% used the FIGO *Prevention and Treatment of Post-Partum Hemorrhage in Low Resource Settings* from 2012; 45% used the RCOG *Postpartum Haemorrhage, Prevention and Management* Green-top Guidelines from 2009; 41% used the ACOG *Clinical Management Guidelines on Postpartum Hemorrhage* reaffirmed in 2013; and 14% used the FLASOG *Consenso Latinoamericano sobre usos del Misoprostol en Obstetricia y Ginecología* from 2012. See Table 3.

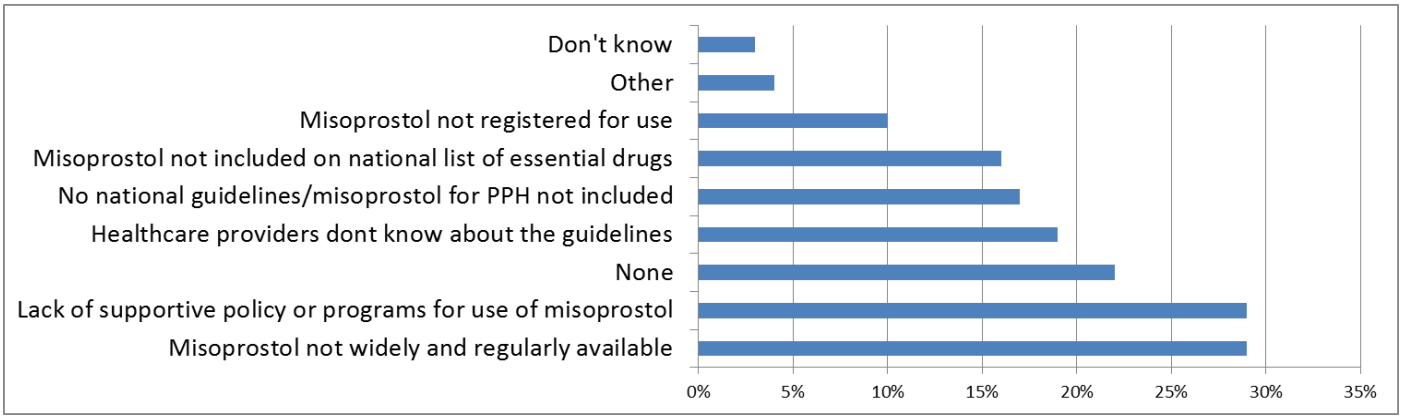
Table 3: Principle referencing guidelines used to develop national guidelines and their recommendations

Guidelines	Used	Prevention		Treatment	
		Regimen	When	Regimen	When
WHO 2012	75% (42)	600 µg oral	In settings where oxytocin is unavailable	800 µg sl	If oxytocin is un-available or if the bleeding does not respond to oxytocin
FIGO 2012	63% (35)	600 µg oral	In settings where oxytocin is unavailable	800 µg sl	In settings where oxytocin is unavailable
RCOG 2012	45% (25)	600 µg oral	In situations where no oxytocin is available or birth attendants' facilities are limited (e.g. a home birth)	1000 µg rectal	Where parenteral prostaglandins are not available or where there are contra-indications to prostaglandin F2
ACOG 2012	41% (23)	Not included	-	800–1000 µg rectal	Not specified
FLASOG 2012	14% (8)	Not included	-	800 µg rectal	Not specified

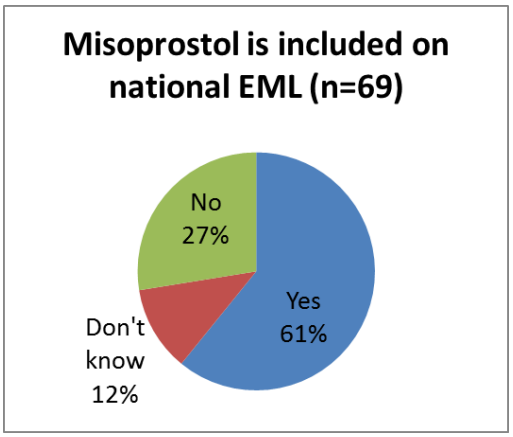
**Used = listed in the survey as one of the principle referencing guidelines when drafting national guidelines*

One question asked responders for their opinion on potential challenges to implementing guidelines that include use of misoprostol for PPH. The most common responses were: lack of supportive policy or programs for use of misoprostol; misoprostol not widely and regularly available; misoprostol not included on national EML; healthcare providers not knowing about the guidelines; lack of national guidelines/misoprostol not included in national guidelines; and misoprostol not being registered for use (not one of the listed potential challenges but entered by responders under the option 'other'). Of the 69 responders, 15 (22%) reported no challenges (see Figure 1).

Figure 1: Challenges in implementing guidelines that include use of misoprostol for PPH (N=69, multiple answers possible)



Regarding national essential medicines lists, 42 (61%) reported that misoprostol was included on their country's EML. Of these, 55% reported it was listed for prevention of PPH; 74% reported it was listed for treatment of PPH; 69% reported it was listed for indications other than postpartum hemorrhage (such as induction of labor, management of incomplete abortion/miscarriage, medical abortion); and 10% reported that indications for use were not specified on their EML for misoprostol.



Discussion

Lack of complete, up-to-date, evidence based national guidelines

19% of associations reported that their country do not have national guidelines on PPH management. Of countries that do, guidance on misoprostol use is often absent (just 59% of reported guidelines include misoprostol for prevention and treatment of PPH). These findings support other evidence that many countries either do not have national guidelines on PPH or that their guidelines are not sufficiently up-to-date[9,10]. As national guidelines serve to guide training and best practice domestically, they are essential documents; not having this country-level tool is problematic for countries with high maternal mortality. Including key medicines like misoprostol in such guidelines is important in countries where a large number of women give birth in healthcare facilities in the community or at home, where access to oxytocin may be limited.

In FIGO's '*Prevention and treatment of postpartum hemorrhage in low-resource settings*' document published in 2012, FIGO calls professional associations to action - to work towards incorporation of recommendations into current guidelines, competencies, and curricula, and ensure that current best-evidence regimens are adopted[11]. FIGO reinforces this call to action and asks Member Associations without guidelines to initiate dialogue with the Ministry of Health in order to have them produced, and for Member Associations with guidelines that are not reflective of new best evidence, to advocate for timely revisions to be made.

Variance between guidelines and from international guidelines

A wide array of regimens for misoprostol are given in the different national guidelines, and national guidelines often do not align with international recommendations - findings previously reported elsewhere[8]. In this survey, despite many reporting to use WHO and/or FIGO guidelines as key referral documents, only about half then supported use of the same regimen. For prevention of PPH, 54% of responders who used WHO/FIGO guidelines as guiding documents recommended the same regimen of 600 mcg given orally, and two of these also listed other regimens as well. Similarly for treatment of PPH, 52% of responders who used WHO/FIGO guidelines as guiding documents recommended the same regimen of 800 mcg given sublingually, and five of these also listed alternative regimens as well.

While adaptations of international guidelines are acknowledged to be needed in order to make them locally-appropriate and better able to meet the specific needs of each country and health service, WHO notes that "(m)odifications to the recommendations, where necessary, should be limited to weak recommendations and justifications for any changes made in an explicit and transparent manner[4]." Given that modifications have been made to strong recommendations (i.e. those based on high quality evidence), and alternatives recommended are based on limited data and may be pharmacokinetically inferior[12], further work is needed to examine how international guidelines are used and what additional information determines regimens selected nationally.

The fact that international guidelines themselves often contain differing recommendations may also create an additional challenge for countries looking for international guidance when developing their protocols/guidelines. It may be possible in the future to ensure international organizations work together to synthesize evidence and potentially align their recommendations.

Moving guidelines into practice

In this survey, the most common challenge mentioned for implementing guidelines that include use of misoprostol for PPH was the lack of supportive policy and programs. Another key challenge frequently listed was that health care providers do not know about the guidelines. This supports other documentation of the fact that having national guidelines does not inevitably mean they will be clear and un-ambiguous, that they will be disseminated to healthcare workers, known about, or adhered to[13,14,15]. The survey findings further highlight the need to work towards translating evidence-based recommendations into practice at all levels. FIGO calls on Member Associations and partners to examine their country's knowledge-practice gap and work collaboratively and comprehensively to implement policies and practices that improve maternal outcomes.

Key Medicines on Essential Medicines Lists

A high number of countries do not have misoprostol on their essential medicines lists – a finding in conjunction with previous evidence showing that key medicines are frequently missing from essential medicines lists[16]. This is despite the fact that misoprostol has been listed for its prevention indication on the WHO Essential Medicines List since 2011 and for treatment indication since 2015. The WHO EML was established with the aim of helping countries prioritize medicines according to their health care needs but is only a blueprint - a medicine needs to be listed on national EML to ensure it can be procured and supplied domestically. In FIGO's 2012 '*Prevention and treatment of postpartum hemorrhage in low-resource settings*' document, one of the other specific calls to action from professional associations is to mobilize, to call upon national regulatory agencies and policy makers to approve misoprostol for PPH prevention and treatment, and to ensure that current best-evidence regimens are adopted[11]. FIGO reinforces this call to action given the need as evidenced from this survey.

Additionally, inclusion on national EML alone is insufficient without funding and functional supply chains for the medicine, as evidenced from the survey where the most common challenge mentioned for implementing guidelines on PPH was that misoprostol was not widely and regularly available. This supports evidence from a survey in 37 countries which showed that countries rarely had regular availability of misoprostol in their health facilities[7]. FIGO calls on Member Associations to include making improvements to national procurement systems, addressing logistics and supply chain issues, and removing regulations and policies which hamper supply efficiency to their advocacy work with Ministry of Health and other key stakeholders.

Conclusions

Having comprehensive, evidence-based guidelines on PPH and having misoprostol listed in national EMLs are key interventions which must be in place for a country to address the major cause of maternal mortality and morbidity. However, these alone will be ineffective unless there are also supportive policy and programs in place, broad dissemination and training of the guidelines, and full drug availability throughout all health facilities.

This survey was limited in that it did not ask about which healthcare providers were able to give key medicines, and was directed at the guidelines for obstetricians and gynecologists rather than other healthcare providers. It would also be interesting to examine guidelines provide for non-specialist providers such as midwives and others who often attend deliveries, to see whether they reflect the same gaps and needs. It is likely that this would highlight the need for more explicit discussion of task sharing within guidelines for by different cadres of healthcare providers.

It is hoped that findings presented here can be used in collaboration with partners to offer assistance to countries which do not have guidelines or are revising national guidelines to ensure they are comprehensive and evidence-based. Findings can also be used with partners to offer assistance to countries which do not have misoprostol listed on their EMLs. They could also be useful for discussion with partners when revising international guidelines to raise issues of conformity and dissemination. They will also be used to guide FIGOs work disseminating evidence useful on misoprostol and other promising technologies for the management of PPH in the future.

Many thanks to all of the Member Associations who took part in this survey.

References

[1] WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division 2015. Trends in maternal mortality: 1990 to 2015 http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2015/en/

[2] Lale Say, Doris Chou, Alison Gemmill, et al. 2014. Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health.* Volume 2, Issue 6, June, Pages e323–e333. http://www.sciencedirect.com/science/article/pii/S2214109X1470227X

[3] Jane Hutchings, Keith Neroutsos, Kathleen Donnelly 2010. *International Perspectives On Sexual And Reproductive Health* Volume 36, Issue 4 December. Pages 205 – 208 https://www.guttmacher.org/about/journals/ipsrh/2010/12/making-list-role-essential-medicines-lists-reproductive-health

[4] WHO 2012 WHO recommendations for the prevention and treatment of postpartum haemorrhage http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/

[5] University Research Co 2013. A Global Improvement Framework for Health Worker in Service Training https://www.usaidassist.org/sites/assist/files/inservicetraining_july2013.11x17spreads.pdf

[6] Jhpiego 2012 The health impacts of pre-service education: An Integrative Review and Evidence-Based Conceptual Model. https://www.k4health.org/sites/default/files/PSETechnical%20ReportFinal.pdf

[7] Gynuity Health Projects 2015 Instructions for Use: Misoprostol for Prevention of Postpartum Hemorrhage. http://gynuity.org/downloads/clinguide_ifu_pphprevention_en.pdf

[8] Gynuity Health Projects 2012 Instructions for Use: Misoprostol for Treatment of Postpartum Hemorrhage. http://gynuity.org/downloads/clinguide_ifupphtreatment_en.pdf

[9] Jeffrey Michael Smith, Sheena Currie, Tirza Cannon et al. 2014. Are national policies and programs for prevention and management of postpartum hemorrhage and preeclampsia adequate? A key informant survey in 37 countries. *Glob Health Sci Pract* August 1, vol. 2 no. 3 p. 275-284. http://www.ncbi.nlm.nih.gov/pubmed/25276587

[10] Joshua D Dahlk, Hector Mendez-Figueroa, Lindsay Maggio et al. 2015. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *American Journal of Obstetrics & Gynecology*, Volume 213 , Issue 1 , 76.e1 - 76.e10. http://www.ncbi.nlm.nih.gov/pubmed/25731692

[11] André Lalonde 2012. Prevention and treatment of postpartum hemorrhage in low-resource settings. *International Journal of Gynecology & Obstetrics.* Volume 117, Issue 2, May 2012, Pages 108–118 http://www.sciencedirect.com/science/article/pii/S0020729212000951

[12] Tang, O.S. Gemzell-Danielsson K, Ho PC 2007. Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. *International Journal of Gynecology and Obstetrics*, Volume 99 , S160 - S167. http://www.ncbi.nlm.nih.gov/pubmed/17963768

[13] Ann Starrs, Beverly Winikoff, 2012. Misoprostol for postpartum hemorrhage: Moving from evidence to practice *International Journal of Gynecology & Obstetrics* Volume 116, Issue 1, January, Pages 1–3doi:10.1016/j.ijgo.2011.10.005 http://www.ncbi.nlm.nih.gov/pubmed/22078140

[14] Sydney A Spangler, Abebe Gebramariam Gobezayehu, Tewodros Getachew et al. 2014. Interpretation of national policy regarding community-based use of misoprostol for postpartum hemorrhage prevention in Ethiopia: a tale of two regions. J *Midwifery Womens Health.* 2014 Jan;59 Suppl 1:S83-90. doi: 10.1111/jmwh.12154. http://www.ncbi.nlm.nih.gov/pubmed/24588920

[15] Louise Braddick, Victoria Tuckey, Zan Abbas et al. 2016. A mixed-methods study of barriers and facilitators to the implementation of postpartum hemorrhage guidelines in Uganda *International Journal of Gynecology & Obstetrics* Volume 132, Issue 1, January, Pages 89–93 http://www.ncbi.nlm.nih.gov/pubmed/26475077

[16] Suzanne Hill, Annie Yang, Lisa Bero 2012 Priority Medicines for Maternal and Child Health: A Global Survey of National Essential Medicines Lists *PLoS ONE* 7(5): e38055. doi:10.1371/journal.pone.0038055 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0038055