Institution:
UNIVERSITY OF LIVERPOOL

Unit of Assessment:
UOA2 - Public Health, Health Services and Primary Care

Title of case study:
Making Pregnancy Safer in Low Resource Settings Through the Development of Safe Misoprostol Use

1. Summary of the impact

This University of Liverpool (UoL) research programme has provided the first international guidance on pregnancy dosage regimes for the drug misoprostol. Although commonly used, its use in pregnancy is off-label. This has led to a wide variety of different dosage regimens. Professors Weeks, Alfirevic and Neilson (all UoL) have been at the forefront of research into its correct use since 1998. In 2007 they initiated a WHO expert conference to conduct dosage reviews, thus establishing an international consensus. These regimens were adopted by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, and updated in 2012. Examples of resulting guidelines with social marketing are provided.

2. Underpinning research

Misoprostol research has been undertaken in the UoL Department of Women's and Children's Health since 1998. The Cochrane Pregnancy and Childbirth Group is based in the department with Profs Neilson and Alfirevic as co-ordinating editors. Prof Weeks joined the Department in 2003.

Misoprostol was originally developed for the prevention of stomach ulcers, but is used world-wide in pregnancy off-label for miscarriage management, labour induction and bleeding after childbirth. The sensitivity of the uterus to misoprostol increases markedly through pregnancy. In early pregnancy 800mcg is often needed, whilst in late pregnancy the as little as 50 mcg may be too high dose. Thus the use of the correct dose, route and frequency of administration is very important. However, the lack of a mainstream licensed product for reproductive health use and its wide availability on the black market mean that it is commonly used at inappropriate or dangerous dosages (Deole & Weeks, *Int J Gynecol Obstet* 2010;109:71). The use of excessive doses has been responsible for many maternal deaths from ruptured uterus in South Africa (see 5th report into Confidential Enquiries in Maternal Deaths in South Africa). A review in 2005 reported that in 1998 over 700,000 pregnancies were induced with misoprostol in the USA despite causing uterine rupture, maternal and fetal deaths, and brain damage in newborn infants.

For many indications, the appropriate dosage remained unknown. This prompted the UoL to conduct randomised trials to find the optimal regimens in terms of efficacy and safety for incomplete miscarriage (Uganda, 2001-5) [1] and three more to define the optimal dosage and route for labour induction (multicentre 2003-6 [2] and 2006-8 [3], Libya 2009-11 [4]). These studies have clarified that low doses of oral and vaginal misoprostol (20-25mcg) are not only effective for labour induction, but reduce the rate of uterine over-contraction and fetal heart rate abnormalities.

These trials feed into Cochrane reviews that address misoprostol use, including those on oral misoprostol for induction of labour (Alfirevic & Weeks, 2006, under active revision in 2013), medical treatment for early fetal death (Neilson et al, 2006) and medical treatments for incomplete miscarriage (Neilson et al 2013). Other systematic reviews have also been conducted by the UoL on misoprostol for the induction of labour [5,8] and on the effect of dosage variation on misoprostol side effects [6].

In 2007, Prof Weeks set up and chaired an international expert conference to develop consensus guidelines on misoprostol dosages jointly funded by the World Health Organisation and Rockefeller Foundation. Key international researchers from 13 countries undertook data synthesis and held a joint meeting to produce robust and high quality evidence. This research and resulting policy papers drew heavily on primary research and systematic reviews generated by Alfirevic, Nielson and Weeks. The proceedings of the 'Bellagio meeting' with dosage recommendations were published with Prof Weeks as editor; Profs Alfirevic and Weeks were authors on 5 of the 10 policy papers [7].

Current work includes randomised trial of self-administered oral misoprostol versus placebo in rural Uganda (funded by Bill and Melinda Gates Foundation / Gynuity Health Projects) and a randomised trial of oral misoprostol versus Foley catheter for labour induction (MRC/DFID/Wellcome).

3. References to the research

1. **Weeks A**, Alia G, Blum J, Winikoff B, Ekwaru P, Durocher J, Mirembe F. A randomized trial of misoprostol compared with manual vacuum aspiration for incomplete abortion. Obstet Gynecol 2005;106:540-7 Citations: 40 Impact Factor: 4.798

2. Ewert K, Powers B, Robertson S, **Alfirevic Z.** Controlled-release misoprostol vaginal insert in parous women for labor induction: a randomized controlled trial. Obstet Gynecol 2006;108:1130.DOI: 10.1097/01.AOG.0000239100.16166.5a Citations: 8 Impact Factor: 4.798

3. Bricker L, Peden H, Tomlinson AJ, Al-Hussaini TK, Idama T, Candelier C, Luckas M, Furniss H, Davies A, Kumar B, Roberts J, **Alfirevic Z**. Titrated low-dose vaginal and/or oral misoprostol to induce labour for prelabour membrane rupture: a randomised trial. BJOG. 2008 Nov;115(12):1503-11. doi: 10.1111/j.1471-0528.2008.01890.x Citations: 3 Impact Factor: 3.760

4. Elati A, Elmahaishi M, Elmahaishi M, Elsraiti O, **Weeks A**. The effect of misoprostol on postpartum contractions: a randomised comparison of three sublingual doses. BJOG 2011;118(4):466-73. doi: 10.1111/j.1471-0528.2010.02821.x Citations: 3 Impact Factor: 3.760

5. Kundodyiwa T, **Alfirevic Z** and **Weeks AD**. Low Dose Oral Misoprostol for Induction of Labor: A Systematic Review. Obstetrics and Gynecology 2009;113(2):374-383.doi: 10.1097/AOG.0b013e3181945859 Citations: 14 Impact Factor: 4.798

6. Elati A, **Weeks AD.** Risk of fever after Misoprostol for the prevention of postpartum hemorrhage: a meta-analysis. Obstetrics and Gynaecology 2012;120(5):1140-8. doi: 10.1097/AOG.0b013e3182707341 Citations: 0 Impact Factor: 4.798

7. Weeks A and Faundes A. Misoprostol in obstetrics and gynecology. *International Journal of Gynecology and Obstetrics*, 2007;99(2):S156-9. Doi: http://dx.doi.org/10.1016/j.ijgo.2007.09.003 Citations: 23 Impact Factor: 3.760

8. Hofmeyr GJ, Gülmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review. Br J Obstet Gynaecol. 1999 Aug;106(8):798-803. http://www.ncbi.nlm.nih.gov/pubmed/10453829 Citations: 95 Impact Factor: 3.760

Key Research Grants

2011 – 2016. **DFID/MRC/Wellcome Trust** Joint Global Health Trial Grant. Induction of labour in pre-eclamptic women: a randomised trial comparing balloon catheter with oral misoprostol, £699,651. **PI AD Weeks**.

2010 – 2013. Gynuity Health Projects. MamaMiso: a pilot study of self- administered misoprostol to prevent bleeding after childbirth. $ 238,986, **PI AD Weeks**. UoL (funds supplied by Bill & Melinda Gates Foundation)

2013 – 2014. **NIHR HTA**. Which method is best for the induction of labour: A network meta-analysis and cost effectiveness review, £141,759, PI **Alfirevic Z**.

4. Details of the impact

The team not only conducted high quality research on misoprostol, but have also provided practitioners worldwide with high-quality, evidence-based guidelines to ensure effective and safe misoprostol use in pregnancy.

National and International Guidelines

The 'Bellagio guidelines' that came out of the UoL led expert reviews in 2007 were the first international guidelines to address the appropriate dosages of misoprostol in pregnancy. A recognition of their importance led to their adoption by the International Federation of Gynecology and Obstetrics (FIGO) in 2009. This is the only organisation that brings together professional societies of obstetricians and gynaecologists on a global basis. The adopted guidelines were disseminated at the 2009 FIGO World Congress in South Africa at a special session chaired by Prof Weeks. The congress was attended by 6,400 delegates from 158 countries, and misoprostol dosage packs, produced for the event, were placed in the delegates' conference bags. Each of the 10,000 packs contained a gestational calendar, credit card sized memory aid and an A4 sticker [9] with the FIGO misoprostol doses printed on them. Those remaining were distributed to regional conferences in Africa and South Asia. Although funded by FIGO, the summary graph on misoprostol dosage and marketing packs was designed by Prof Weeks and produced by a local printer in Liverpool. The FIGO misoprostol dosage guidelines were subsequently updated and presented at a special session at the FIGO World Congress in Rome in 2012 (8,000 delegates from 170 countries). This time 13,000 updated marketing packs in English, French and Spanish were produced for distribution in delegate packs. Those remaining were distributed at regional conferences. These findings have also been used by many international organisations including Gynuity Health Projects (www.gynuity.org), the Postabortion Care Consortium (www.pac-consortium.org), and PATH (www.path.org).

The UoL team has also used their expertise on misoprostol to impact on national and international guideline development groups. Prof Alfirevic was on the expert group that developed the 2008 *NICE Guidelines for Induction of Labour* [10] (and his work referenced in the final report), Prof Weeks was on the committee that developed the *WHO recommendations for induction of labour* [11] (3 of his publications are referenced in the final report), and Prof Neilson chaired the expert group that developed the *WHO Recommendations for the prevention of postpartum haemorrhage* (WHO 2006, updated in 2012 [12]). The team's work has also been heavily cited in the successful application to place misoprostol on the core list of the 18th WHO Model List of Essential Medicines for use in postpartum haemorrhage. Profs Weeks or Alfirevic were cited 4 times in the original application [13], and 6 times in the formal safety review commissioned by WHO [14].

Website

In 2002 Prof Weeks set up a website (www.misoprostol.org) to disseminate information related to misoprostol in pregnancy. The University of Liverpool has subsequently funded multiple revisions and updates. It now contains 169 documents and 58 pages and includes the FIGO guidelines, an extensive bibliography of over 1800 references, and information on availability, dangers and protocols. Dosage posters are also available for download and the main pages are translated into Dutch, Spanish and Russian.

The website is used extensively throughout the world. It currently receives around 16,500 visits per month (an increase of 45% from 2011) and tops the Google search for misoprostol. Visitors to the site come from all over the world: for example in September 2013 the top 15 countries were India, Mexico, Australia, Brazil, Germany, Canada, UK, South Africa, Czech Republic, Turkey, Indonesia, United Arab Emirates, Poland, Columbia and Kenya. Most visitors are directed from search engines, but 10% directly type 'www.misoprostol.org'. 74% of the visits are to the home page or main dosage page. The website is also referenced in guidelines including the Royal College of Obstetricians and Gynaecologists guideline on Late Intrauterine Fetal Death and Stillbirth [15].

Leading opinion change amongst practitioners

The guidelines have also been spread to practitioners through the production of highly cited articles. Prof Weeks has authored important BMJ editorials on the topic of misoprostol use (Elati & Weeks *BMJ* 2011;342:d2877; Aflaifel & Weeks *BMJ* 2012;345:e4546; together accessed from www.bmj.com 22,031 times) and has written influential reviews on the subject. His review in BJOG was one of the 10 most downloaded articles of 2009 (Elati & Weeks *BJOG* 2009;116(supp1):61). The team's work on misoprostol is frequently referenced in textbooks including the Oxford Handbook of Clinical Specialities [16], Williams Obstetrics (22nd edition), Dewhurst's Textbook of

Obstetrics and Gynaecology, Obstetrics: Normal and Problem Pregnancies, Protocols for High-Risk Pregnancies, and Oxford Desk Reference: Obstetrics and Gynaecology.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4.

9. **Prof Weeks's** design of the A4 sticker was first published in a review article (BJOG 2009;116(supp1):61) and subsequently used at the FIGO congresses in 2009 and 2012. The latest version is downloadable from the FIGO website (http://www.figo.org/files/figo-corp/Misoprostol_Recommended%20Dosages%202012.pdf

10. National Institute for Health and Clinical Excellence. Clinical guideline no. 70: Induction of labour. London: National Institute for Health and Clinical Excellence; 2008

11. World Health Organization. WHO recommendations for induction of labour. Geneva: WHO Press; 2011

12. World Health Organization. WHO Recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: WHO Press; 2012

13. Blum J, Durocher J & Abbas D (on behalf of Gynuity Health Projects, NY). Proposal for the inclusion of misoprostol in the WHO Model List of Essential Medicines (2010). Available at: http://www.who.int/selection_medicines/committees/expert/18/applications/Misoprostol_application.pdf

14. Wannmacher L. Safety profile of misoprostol for obstetrical indications. Commissioned report for the 18th WHO Expert Committee on the Selection and use of Essential Medicines (March 2011). Report available at: http://www.who.int/selection_medicines/committees/expert/18/applications/Misoprostol_safety_review.pdf

15. Collier J, Longmore M, Turmezei T, Mafi A. Oxford Handbook of Clinical Specialities (8th Edition). OUP Oxford, 2009, pp62. The reference list can be accessed at http://www.oup.co.uk/academic/series/oxhmed/links/ohcs8weblinks/ch1/

16. Royal College of Obstetricians and Gynaecologists. Green-Top Guideline no 55. Late Intrauterine Fetal Death and Stillbirth. 2010. Available at http://www.rcog.org.uk/files/rcog-corp/GTG 55 31072013.pdf

Key individuals able to verify the information provided above:

Contact:, Karolinska Institutet, Stockholm, Sweden. Collaborator on the Bellagio review panel and co-author of several published guidelines.

Contact: FIGO; and Department of Obstetrics & Gynaecology, University of British Columbia, Canada.

Contact: Department of Reproductive Health and Research, World Health Organization, Geneva.

Contact: NICE Guideline Development Group for Induction of Labour, Simpson Centre for Reproductive Health, University of Edinburgh, Scotland.

Contact: Royal College of Obstetricians and Gynaecologists; FIGO; and St George's, University of London, UK.