Best Practice & Research Clinical Obstetrics and Gynaecology
Vol. 22, No. 6, pp. 1025–1041, 2008
doi:10.1016/j.bpobgyn.2008.08.005
available online at http://www.sciencedirect.com

3

Misoprostol for the prevention and treatment of postpartum haemorrhage

Prof G. Justus Hofmeyr* MRCOG
Effective Care Research Unit, University of the Witwatersrand/University of Fort Hare/East London Hospital Complex, South Africa

Dr A. Metin Gülmezoglu MD
UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), World Health Organization, Geneva, Switzerland

Postpartum haemorrhage (PPH) causes preventable maternal deaths, mainly in low-income countries. Misoprostol has powerful uterotonic effects and, because it is well absorbed orally and sublingually, has the potential to be used more widely than would be possible with injectable uterotonics alone. Misoprostol is clearly less effective than oxytocin. Placebo-controlled studies have had variable results, although two recent trials in low-income communities have shown promising results. The main recognized side effects have been dose-related pyrexia and shivering, including occasional hyperpyrexia. In the randomized trials reported to date, there has been a trend to more deaths with misoprostol than with the control groups. The dose that has been most commonly used in clinical trials for preventing PPH is 600 μg orally. Meta-analysis of direct and adjusted indirect comparisons between 600 and 400 μg showed very similar effectiveness. To date, there is very limited evidence for the effectiveness of misoprostol, the lowest effective dose and the magnitude of adverse effects, both direct and indirect. The need for further research is a matter of great urgency.

Key words: maternal death; misoprostol; postpartum haemorrhage; prostaglandin; uterotonic.

INTRODUCTION

Misoprostol for postpartum haemorrhage: a global issue

The use of misoprostol for preventing or treating postpartum haemorrhage (PPH) has become a high-profile issue globally. Apart form the usual clinical and public health

* Corresponding author. Dept of Obstetrics and Gynaecology, East London Hospital Complex, PB X9047, East London 5201, South Africa, Tel.: +27 0 43 709 2483; Fax: +866929822.
E-mail address: gjh@global.co.za (G.J. Hofmeyr).

considerations, the subject has been complicated by sensitivities surrounding the off-label use of misoprostol during pregnancy, dissociation of the original patent-holding company from the drug evaluation process and the global imperative to reduce maternal mortality as a matter of urgency.[1] This chapter presents an overview of the topic, addressing all these issues.

Postpartum haemorrhage: pathopysiology

Placental bed haemostasis following childbirth is a remarkable physiological process. During pregnancy, trophoblast invasion of the maternal spiral arterioles creates wide-diameter, non-contractile vessels, ensuring a high volume blood flow to the placenta. After the birth of the baby, the placenta separates from the uterine wall and the severed placental blood vessel lumina are compressed by extrinsic pressure from the surrounding mesh of myometrial fibres. Central to this process is the efficient and sustained contraction of the myometrium, under the influence of endogenous uterotonic hormones.

This physiological process is imperfect. Under the relatively ideal circumstances of low-risk women enrolled in randomized clinical trials of active versus expectant management of the third stage of labour, in the 'physiological' (natural third stage) group estimated blood loss in excess of 1000 mL occurred in 83 of 3158 women (2.6%).[2] With routine clinical intervention, including administration of a uterotonic drug and controlled traction on the clamped umbilical cord, this number was reduced to 27 of 3126 women (0.9%) [relative risk (RR) 0.33, 95% confidence interval (CI) 0.21 to 0.51]. Clinical estimation has been found to underestimate blood loss by at least 50%.

Uterotonic drugs

Effective uterotonic drugs have existed for many years. Systematic review of randomized trials found that prophylactic administration of oxytocin reduced severe PPH from 83/1136 (7%) to 48/1107 (4.3%) (RR 0.61, 95% CI 0.44 to 0.87).[3] Prophylactic use of intravenous ergot alkaloids reduced severe PPH from 11/724 (1.5%) to 1/705 (0.14%) (RR 0.09, 95% CI 0.01 to 0.72).[4] In randomized trials comparing oxytocin–ergometrine with oxytocin alone, oxytocin–ergometrine was marginally more effective than oxytocin alone but with more side-effects.[5]

Postpartum haemorrhage: disease burden

The disease burden associated with imperfect postpartum haemostasis is immense.[6] PPH is a major cause of maternal mortality in low-income countries. Rates as high as 40 maternal deaths per 100,000 births in parts of sub-Saharan Africa[7] are in stark contrast to the approximately 1 in 100,000 births in the United Kingdom. The potential to save mothers' lives with medical interventions for haemorrhage is thus considerable.[8] No significant reduction in rates of PPH has been reported by industrialized countries in recent times.[9]

In contrast to the considerable body of randomized trials of preventive measures, there is remarkably little information from randomized trials concerning the treatment of PPH. Uterotonics are generally used empirically for treatment, extrapolating from their demonstrated effectiveness in reducing blood loss when used prophylactically.

Although PPH can be caused by factors such as genital tract injury, infection, retained products of conception and coagulopathy, the most important cause is uterine