

ANALYSIS



Rethinking our approach to postpartum haemorrhage and uterotonics

Andrew Weeks and **James Neilson** suggest that we have inappropriately generalised evidence on the use of uterotonics from uncomplicated births to all births. They call for stronger focus on women with complex births to reduce deaths from postpartum haemorrhage

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Postpartum haemorrhage (defined as a bleed >500 mL) is estimated to affect 1-15% of vaginal births, depending on the definition used, the method of assessing blood loss, the setting, and the population studied. Risk factors include Asian ethnicity, obesity, previous postpartum haemorrhage, multiple pregnancy, anaemia, large baby, age over 40, induction of labour, prolonged labour, placental abruption, and caesarean delivery.¹

Although global mortality from postpartum haemorrhage is falling, its incidence is increasing in high resource settings, the reasons for which are unclear.²⁻⁴ Many of those who survive have severe anaemia, renal failure, or psychological trauma, and the offspring may have difficulties in breast feeding and bonding.

Current best practice globally is for all pregnant women to receive a uterotonic drug at the time of childbirth to prevent postpartum haemorrhage. This recommendation has been in place since the 1980s when randomised trials showed that routine prophylaxis with oxytocin based uterotonic drugs reduced the rate of postpartum haemorrhage.⁵ The assumption that this would translate into fewer maternal deaths—based on the understanding that atony was the most common cause of haemorrhage related deaths—led to the promotion of active management of the third stage of labour, which comprises a prophylactic uterotonic drug, early cord clamping, and controlled cord traction.

Here we discuss the problems with generalising data from spontaneous vaginal (“normal”) births to complex births, and call for a change in global strategy on postpartum haemorrhage.

Rationale for universal prophylaxis

Atonic uterus is the failure of the uterine muscle to contract adequately to stop blood flow to the placental bed after detachment of the placenta in the third stage of labour. The reported rate of atonic uterus in women with postpartum haemorrhage in high resource settings varies widely, from 30% to 79%.⁴⁻⁶ This is partially because the diagnosis of atony is

often subjective and used in the absence of retained placental tissue or obvious trauma.

Atony is also difficult to assess at the time of caesarean section, when the assessment is made on palpation of uterine tone rather than on vaginal blood loss, which is largely hidden under surgical drapes. In practice the diagnosis is given in a wide range of clinical situations, from a woman with a small bleed after spontaneous vaginal birth to a woman bleeding heavily after emergency caesarean for obstructed labour.

Uterotonic agents such as oxytocin, ergometrine, and misoprostol stimulate uterine contractions, and numerous high quality randomised controlled trials have shown that they reduce the rate of postpartum haemorrhage when given prophylactically.⁷ For example, a meta-analysis of oxytocin prophylaxis trials shows an overall reduction in severe postpartum haemorrhage (defined as >1000 mL) of 38% compared with placebo (risk ratio 0.62, 95% confidence interval 0.44 to 0.87).⁸ Similarly, active management of labour as a package reduces the rate of severe postpartum haemorrhage by 66% compared with physiological care (0.34, 0.14 to 0.87).⁷

For the treatment of postpartum haemorrhage, there are studies that compare different oxytocics but understandably very few trials with an arm that receives no treatment or placebo. Observational studies suggest that widespread availability of uterotonics for the management of postpartum haemorrhage may reduce deaths.⁹⁻¹⁰ But there is little evidence of an effect on maternal deaths from randomised trial data, at least for misoprostol.¹¹

Given that oxytocin and misoprostol are relatively free from adverse effects, global evidence based efforts have focused on promoting the use of uterotonics for all births.¹² However, the problem with generalising the available evidence to all births is that trials tend to exclude women who have complicated births, and yet they are the births most likely to end in maternal death.

Evidence based on uncomplicated births

Two landmark multicentre studies conducted in low resource settings in 2005-08 puzzled researchers with their low rates of large postpartum haemorrhages (defined as >1700 mL). These bleeds were experienced by just eight of 9348 women (0.09%) who had a vaginal birth without oxytocin prophylaxis,¹³ and 14 of 31 055 of those (0.05%) who did receive prophylaxis.¹⁴ This compares to rates of around 0.5-1% for postpartum bleeds of 2000-2500 mL with prophylaxis in high resource populations (table 1).¹⁵

Similarly, a systematic review in 2013 found only eight deaths in 36 283 women (0.02%) who participated in trials of misoprostol prophylaxis in low and middle income countries.¹¹ This is lower than the 0.1% of deaths due to postpartum haemorrhage that would be expected, based on the assumption that 27% of maternal deaths are due to postpartum haemorrhage,¹⁶ in settings where the maternal mortality rates are around 400 per 100 000 live births.

One likely contributor to such low rates is the difficulty of recruiting patients to clinical trials of postpartum haemorrhage. Logistical and consent difficulties mean that trials generally only include low risk women with uncomplicated, spontaneous vaginal births, in whom postpartum haemorrhage is relatively uncommon. Consequently the trials exclude those who have caesarean sections or instrumental births or who develop intrapartum complications such as placental abruption or dysfunctional labour.⁷ For example, only 10 of the 1881 women in the Cochrane review of treatments for postpartum haemorrhage had caesarean sections despite this being a major risk factor for postpartum haemorrhage.⁹

This inclusion bias is a problem. Excessive blood loss is well recognised to be far more common in women who have complicated births.¹⁷⁻¹⁹ In data from Liverpool Women's Hospital, the 14% of women who had emergency caesarean sections made up nearly 40% of postpartum haemorrhages of >2000 mL (fig 1). Conversely, only 0.3% of the 28% of women who were low risk and gave birth on the midwife led unit had massive postpartum haemorrhages, representing 8% of all massive postpartum haemorrhages in the hospital. And this is despite an increasing number of women opting for a physiological third stage of labour without the use of oxytocin prophylaxis.

Uterotonics are not always effective

Uterotonics might not be as effective as we think for the prevention of deaths from major postpartum haemorrhage. This could be for two reasons—if atony isn't the cause or if women are not responsive to them. Although clinical trials demonstrate the efficacy of uterotonics for reducing the rate of smaller, largely atonic bleeds, these types of bleeds rarely lead to maternal death. For example, in the inquiry into maternal deaths in South Africa uterine atony accounted for just 6% of maternal deaths from postpartum haemorrhage—even though many women gave birth in areas with limited access to uterotonics. Instead, most deaths occurred in women who had caesarean sections (26%), uterine rupture (18%), abruptio placentae (16%), or retained placenta (9%).²⁰

Postpartum haemorrhage has several natural histories. Some postpartum bleeds are very difficult to deal with clinically, for example after a massive abruption and intrauterine death or placenta praevia, and frequently require surgical intervention before they cease. Women who give birth after prolonged oxytocin use are also at risk of haemorrhage and seem to be less

responsive to oxytocin. Laboratory studies show that repeated exposure to oxytocin reduces myometrial contractility,²¹ and this is likely to reduce the efficacy of uterotonics in those who have already received oxytocin. It is unsurprising therefore that complicated and surgical births are over-represented in those women having massive bleeds. By contrast, postpartum haemorrhages after normal births and uncomplicated labours are typically much easier to manage and have better outcomes.^{13 14}

Guidelines focus on normal births

Of 529 trial reports on techniques to prevent postpartum haemorrhage in the Cochrane Pregnancy and Childbirth Trials Register, 422 (80%) are on uterotonic drugs to prevent atony, and most relate to normal births.

The WHO guidelines reflect the underlying focus of randomised controlled trials on normal births. In their 2012 guidelines, for example, 10 of their 12 recommendations on the prevention of postpartum bleeds are related to normal birth, and 11 of 20 recommendations on treatment are related to uterotonics or treatment of the atonic uterus.¹² The use of evidence based medicine has led to the guidelines focusing on randomised trials—and thus on women with low risk pregnancies.

This is in contrast to the non-evidence based recommendations that arise from audits of maternal deaths, which focus on those with the worst outcomes. For example the inquiry into maternal deaths in South Africa examined 4867 maternal deaths in 2008-12. They made 10 recommendations on postpartum haemorrhage: two on community detection of postpartum haemorrhage and transport to health facilities, two on staff training, three on effective assessment and monitoring of women with postpartum haemorrhage, two on clinical care for abruption and labour induction, and just one on the use of uterotonics (specifically, the use of stronger oxytocics in caesarean section).²⁰ In the United Kingdom the 2014 confidential inquiry into maternal deaths made six recommendations on postpartum haemorrhage: two relate to improving antenatal and intrapartum care, and four to improving the quality of care of postpartum haemorrhage in coagulopathy, monitoring, and early hysterectomy.²²

Call for clearer thinking on postpartum haemorrhage

Women who have a postpartum haemorrhage exist on a spectrum ranging from those with uncomplicated pregnancies in whom major bleeds are rare to women with placental abruption or praevia or second stage caesarean section in whom major bleeds are common and difficult to control. Many women exist between these extremes with minor risk factors, such as instrumental deliveries and induced labour. The risk of haemorrhage is raised in these women but if it occurs it is usually easier to control. The number of low risk women whose pregnancies have been uncomplicated up to the time of birth is difficult to quantify, but is estimated at 43% in the UK.²³ The separation of women into groups according to their risk of haemorrhage provides a useful model with wide implications and potential benefits (fig 2).

Firstly, it helps to reconcile the longstanding difference in views of many midwives and obstetricians. Advocates of physiological management of the third stage of labour (including many midwives) may be right not to focus on the dangers of haemorrhage for women with low risk pregnancies, uncomplicated labour, and minimal risk factors. Conversely,

those who advocate active third stage management for all (a policy largely driven by obstetricians) correctly see the high risk of postpartum haemorrhage in women with complex births. Both professions are correct with respect to the group of women that they predominantly deal with. The only danger comes in the belief that their own perception of risk applies to all births. This can lead to an overly relaxed attitude towards high risk women or the unnecessary medicalisation of low risk women.

Secondly, an understanding of the differences in postpartum haemorrhage after normal and complicated births could help explain temporal changes in its incidence. The underlying reasons for the slowly rising rates of postpartum bleeds in well resourced settings may be explained by rising rates of birth intervention and risk factors. It also provides a hypothesis for the major fall in deaths from postpartum haemorrhage in the UK before the development of effective uterotonics in the 1930s.²⁴ The arrival of interventions such as labour induction, digital diagnosis of placenta praevia in theatre, and safe caesarean section may have done much to reduce the rates of bleeding from abruption, placenta praevia and obstructed labour, respectively. All these interventions will have moved women out of the highest risk group and given them a lower risk profile.

Thirdly, it shows how the recruitment of largely low risk women to clinical trials has distorted the evidence base for the prevention and treatment of postpartum haemorrhage. This has led researchers and policy makers to unintentionally focus on normal births. Future guidelines should broaden their scope and give more weight to studies of postpartum bleeds after complex births, even if they provide lower quality evidence. Data from community based observational studies, audits, and confidential inquiries may be essential.

Finally, this understanding has implications for global maternal health. A focus on universal uterotonics may be effective for the reduction of postnatal anaemia by reducing the average blood loss at the time of birth. However, it is probably not the most important or cost effective intervention globally to prevent deaths from postpartum haemorrhage. This does not mean a move away from the use of uterotonics for high risk births in which atony may still be a contributing factor, but accepting that they may be only a small part of the solution. It may prove more important to provide good surgical facilities and technique, haemodynamic support, and blood transfusion.

Further trials in those with complex risk factors will be crucial to provide evidence to guide care for those with complex births. The time has come to concentrate on those at the highest risk both nationally and internationally.

Contributors and sources: ADW is professor of international maternal health with an interest in the third stage of labour and the prevention of maternal deaths in low resource settings. He has collaborated on research projects with Gynuity Health Projects, FIGO, and WHO and these ideas have come out of ongoing research projects by and with them. JPN is professor of obstetrics and gynaecology and has a longstanding interest in global maternal health. He is a coordinating editor of the Cochrane Pregnancy and Childbirth Group. He chaired the WHO guideline development committee that produced the postpartum haemorrhage guidelines in 2007 and now chairs the WHO carbetocin

trial steering committee. ADW had the original idea for the paper and wrote the first draft after discussion with JPN, who edited the manuscript and added discussion points. ADW is the guarantor.

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Key messages

Randomised controlled trials have shown uterotonics to be safe and effective for prophylaxis and management of postpartum haemorrhage

But evidence on uterotonics was gathered predominantly from low risk women with normal births and may not apply to complex births, where the risk of haemorrhage is higher

Because many guidelines are based on randomised trial evidence, they concentrate on normal births and largely ignore those most at risk

In low resource settings efforts to reduce postpartum haemorrhage deaths may be better focused on those with complicated pregnancies and births rather than on improving the access to routine uterotonics for lower risk women

Table**Table 1| Table Postpartum haemorrhage at Liverpool Women's Hospital 2009-13 inclusive**

	Total births (n)	Postpartum bleed \geq 2000 ml (n)	Risk of postpartum haemorrhage (%)	Proportion of all postpartum haemorrhage (%)
Spontaneous vaginal birth (midwife led unit)	10 916	34	0.3	8*
Induced or high risk normal birth (consultant led unit)	12 997	86	0.7	17.6
Operative vaginal birth	5586	87	1.6	20.6
Elective caesarean section	4368	53	1.2	12.5
Emergency caesarean section	5404	163	3.0	38.5
Total	39 271	423	1.1	

*38% of these were associated with need for manual removal of the placenta

Figures

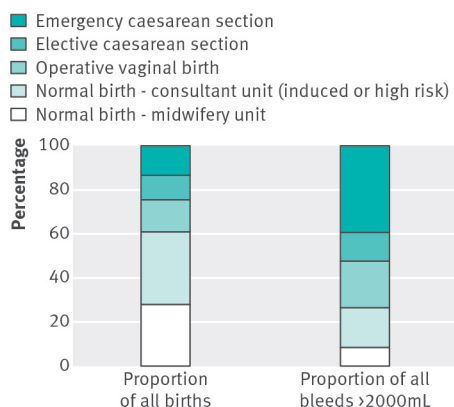


Fig 1 Births at Liverpool Women’s Hospital 2009-13. The graph on the left shows the types of birth among all women. The graph on the right shows the types of birth for those who had bleeds >2000 mL

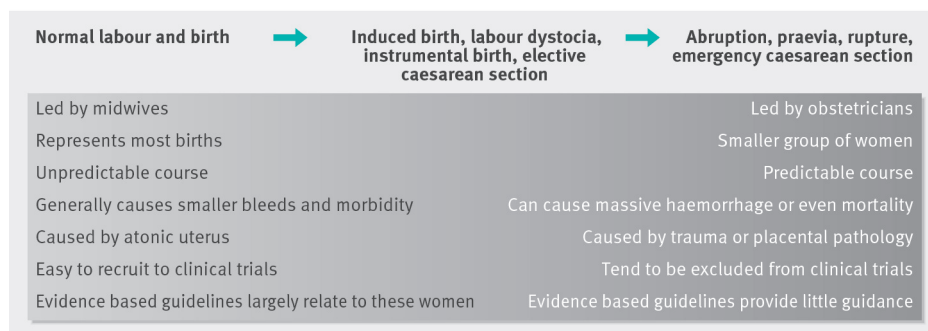


Fig 2 Spectrum of risk of postpartum haemorrhage