



*“Postpartum haemorrhage: new insights
from published trials and the
development of novel management
options”*

**Thesis submitted in accordance with the requirements of
the University of Liverpool for the degree of Doctor in**

Philosophy

by

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Declaration

I declare that the studies and reviews presented in this thesis are the result of my own independent work, unless otherwise acknowledged.

The content of this thesis has not and is not being currently submitted for candidature for any other degree.

Nasreen Aflaifel

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Thesis contribution

This thesis contributes to the area of postpartum haemorrhage. Specifically, it introduces novel thinking and techniques to the fields of prevention and early management.

The work in this thesis, including the publications, is collaboration between me and my supervisors. I designed the introduction and undertook the literature review. I wrote the first draft of the protocols for all of the included studies that my PhD thesis is based upon. I also located and collected all editions of the 'Ten Teachers' book, summarised the topic on postpartum haemorrhage, and extracted the illustrated tables and figures.

I searched for and contacted the corresponding authors for the studies included in the histogram study described in Chapter 3. I worked on the original data from the studies, further analysed the data to meet the scope of the chapter, extracted the figures and wrote the initial discussion points.

The systematic review in this thesis was completed under the supervision of Professor Zarko Alfirevic. The search strategy used in the systematic review was designed with assistance from Miss Lynne Hampson, Cochrane Search Coordinator. I conducted the search process in all databases, removed the duplicate articles via EndNote and then made an independent decision upon inclusion and exclusion of founded studies, designed data extraction sheet and undertook the data extraction, summarised the findings in form of tables, and wrote the discussion with valuable guidance from the supervisor.

The original idea to undertake studies involving the PPH Butterfly was that of Professor Andrew Weeks, but I undertook all of the work for the studies, beginning with writing the protocol, and then running the studies and the subsequent data collection and analysis. However, a pressure system used in the mannequin study was supplied and calibrated by Mr John Porter. Although Mr Peter Watt undertook the designing and production of prototypes of the PPH Butterfly, I was involved in development of the device from the very early stages, and provided ideas and some utensil that contributed to the design of the device.

I also wrote the first draft of the published papers included in the thesis. I have gone through the process of submitting papers to relevant journals. I have also responded to reviewers' comments and approved the final version of papers for publication. I have prepared all the presentations listed in the thesis and this included all posters and oral presentations.

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Medical research is rarely an individual effort, and so it is with this thesis. At every stage over the last 3 years I have been advised and assisted by many people and without them this project could not have been completed.

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List of published papers

A. Papers published in peer-reviewed journals

1. **Aflaifel, N.**, and Weeks, A. 2012. Active management of the third stage of labour. *British Medical Journal*, 345, e4546.
2. **Aflaifel, N.**, and Weeks, A. 2012. Push, pull, squeeze, clamp: 100 years of changes in the management of the third stage of labour as described by Ten Teachers. *British Medical Journal*, 345, e8270.

B. Manuscript submitted to peer-reviewed journal

3. **Aflaifel, N.**, Chandhiok, N., Fawole, B., Geller, S. and Weeks, A. The use of histograms to assess the efficacy of uterotonic treatment for postpartum haemorrhage: a feasibility study. 2015 (submitted to *Maternal and Child Health Journal*).

C. Manuscript under preparation

4. **Aflaifel, N.**, Meher S., and Alfirevic, Z. 2015. Clinical outcomes in PPH trials.
5. Weeks, A., Peter, W., **Aflaifel, N.**, Porter, J., and Cunningham, C. 2015. The PPH Butterfly: a novel device to treat postpartum haemorrhage through uterine compression.
6. **Aflaifel, N.**, Watt, P., Porter, J., and Weeks, A. 2015. The development of simulation models for testing bimanual compression and PPH Butterfly.

National and international conference presentations

1. **Aflaifel, N.**, and Weeks, A. A hundred years of changes in the management of the third stage of labour as described by Ten Teachers. The first GLOW Conference, Liverpool, UK, October, 23, 2012. (Poster presentation)
2. **Aflaifel, N.**, Porter, J., and Weeks, A. Assessing bimanual compression pressure using a mannequin model .The first GLOW Conference, Liverpool, UK, October, 23, 2012. (Poster presentation)
3. **Aflaifel, N.**, and Zarko, A. Choice of primary outcomes in randomised trials and systematic reviews evaluating interventions for postpartum haemorrhage prevention. The second GLOW Conference, Birmingham, UK, November, 1, 2013. (Poster presentation)
4. **Aflaifel N.**, Porter, J., Watt, P., and Weeks, A. The efficacy of the PPH Butterfly to facilitate uterine compression using a mannequin model: a randomised cross-over study. The 8th World Congress of Perinatal Medicine in Developing Countries, Cancun, Mexico, September, 3-6, 2014. (Poster presentation)
5. **Aflaifel, N.**, and Zarko, A. Choice of primary outcomes in randomised trials and systematic reviews evaluating interventions for postpartum haemorrhage prevention. The 8th World Congress of Perinatal Medicine in Developing Countries, Cancun, Mexico, September, 3-6, 2014. (Poster presentation) **First place winner**
6. **Aflaifel, N.**, Porter, J., Watt, P., and Weeks, A. The efficacy of the PPH Butterfly to facilitate uterine compression using a mannequin model: a randomised cross-over study. The 9th annual North East Postgraduate Conference, Newcastle, UK, October, 31, 2014. (Oral presentation)
7. **Aflaifel N.**, Porter J., Watt, P., and Weeks, A. The efficacy of the PPH Butterfly to facilitate uterine compression using a mannequin model: a randomised cross-over study. The 20th World Congress on Controversies in Obstetrics, Gynaecology and infertility, Paris, France, December 4-7, 2014. (Oral presentation)

8. **Aflaifel, N.**, Porter, J., Watt, P., and Weeks, A. The efficacy of the PPH Butterfly to facilitate uterine compression using a mannequin model: a randomised cross-over study. The RCOG Annual Academic Meeting in Obstetrics and Gynaecology, London, UK, January 21-23, 2015. (Poster presentation)

9. **Aflaifel, N.**, Porter, J., Watt, P., and Weeks, A. The efficacy of the PPH Butterfly to facilitate uterine compression using a mannequin model: a randomised cross-over study. The third GLOW Conference, London, UK. March, 4, 2015. (Poster presentation)

List of abbreviations

ACOG	American College of Obstetricians and Gynaecologist
AMTSL	Active management of the third stage of labour
B-A	Brandt-Andrews method for delivery of placenta
BMC	Bimanual compression
BP	Blood pressure
CCT	Controlled cord traction
CENTRAL	Cochrane Central Database of Controlled Trials
CI	Confidence interval
cm	Centimeters
CONSORT	Consolidated Standards of Reporting Trial
COS	Core outcome set
DIC	Disseminated intravascular coagulation
E	Ergometrine
E/OX	Syntometrine
Embase	Biomedical and pharmacological Database
EndNote	Standard software tool for managing bibliographies, citations and references
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
g	Gram(s)
g/dl	Gram/decilitre
Hb	Haemoglobin
HIV	Human immunodeficiency virus
hrs	Hours
I4I	Invention for Innovation
ICM	International Confederation of Midwives
ICU	Intensive care unit
IIAL	Internal iliac artery ligation
IM	Intramuscular
ITP	Idiopathic thrombocytopenic purpura
IU	International unit
IV	Intravenous
Kg	Kilogram
L	Litre (s)

LUSC	Lower uterine segment compression
mcg	Microgram
mcg/L	Microgram per litre
mcg/kg	Microgram per kilogram
Medline	Medical literature analysis and retrieval system online (U.S. national library of medicine's life science database)
MeSH	Medical subject headings
MD	Mean difference
mg	Milligram
mg/dl	Milligrams per decilitre
min	Minutes
mls	Millilitres
ml/kg	Millilitres per kilogram
mm	Millimeters
mls/min	Millilitres per minute
MOHP	Ministry of health and population
NASG	The non-pneumatic anti-shock garment
NICE	The National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NRES	National research ethics service
OR	Odds ratio
ORB	Outcome reporting bias
OX	Oxytocin
P	Value of probability
PGE1	Prostaglandin E1 (misoprostol)
PGF2 α	Prostaglandin F2 α (carboprost)
PGs	Prostaglandins
PPH	Postpartum haemorrhage
PRISMA	Preferred reporting items for systematic reviews and meta-analyses.
RBC	Red blood cell
RCOG	Royal College of Obstetricians and Gynaecologists
RCT(s)	Randomised control trial
rFVIIa	Recombinant activated factor VII
ROM	Rupture of membrane
RR	Relative risk

Scopus	The world's largest abstract and citation database of peer-reviewed literature
SD	Standard deviation
SOGC	Society of Obstetricians and Gynaecologists of Canada
SPPH	Severe postpartum haemorrhage
SR	Systematic review
SSC	Sample size calculation
TBA	Traditional birth attendant
TCM	Traditional Chinese medicine
U/S	Ultrasonography
UK	United Kingdom
UN	United Nation
US	United Status
US\$	American dollar
USB	Universal serial bus
UVI	Umbilical vein injection
vs.	Versus
WHO	World Health Organisation

Initials of researchers involved in the work in this thesis:

NA=Nasreen Aflaifel

AW=Andrew Weeks

ZA=Zarko Alfirevic

Abstract

Postpartum haemorrhage (PPH) is the most common cause of maternal mortality leading to an estimated 86, 000 deaths/year. The most common cause of PPH is failure of the uterus to contract properly (uterine atony). Several measures have been introduced to prevent and treat atonic PPH, but in spite of active management of the third stage of labour (AMTSL), maternal deaths from PPH still occur. PPH can kill rapidly within two hours or less.

PPH has long been recognised as a dangerous complication for mothers. In order to optimise the prevention and treatment of PPH, different approaches have been introduced and modified over the last century. We reviewed the regimes used in the management of the third stage of labour between 1917 and 2011 as described in the successive editions of the ‘Ten Teachers’ books. Throughout the Ten Teachers series, uterotonic drugs have always been taught as being the best initial measure to manage PPH. However, the importance of bimanual uterine compression (BMC) has increased gradually, moving from third to first treatment option over the editions (Aflaifel and Weeks, 2012a) (Appendix A.1).

The components of the AMTSL package for PPH prophylaxis have recently been extensively examined in clinical trials. Its effectiveness in reducing blood loss is now known to be almost all due to the uterotonics (Aflaifel and Weeks, 2012b) (Appendix A.2). However, clinical trials evaluating the efficacy of uterotonics in treating PPH are comparatively rare. Where present they usually compare two uterotonics with an absence of control group, as it is unethical to leave a bleeding woman untreated. A recent innovation is to model the likely outcomes in the absence of uterotonic therapy through histograms. This also allows an assessment of the efficiency of treatment by measuring the number of women who stop bleeding shortly after administering treatments. This model has never previously been applied to databases in which uterotonics were used for prophylaxis. In a secondary analysis of 4 large randomised trials, small secondary histogram peaks (primarily attributed to a treatment effect) were still present even if uterotonic therapy had not been used. Furthermore, the study revealed that women were commonly treated at low levels of blood loss (< 500 mls). It was also seen that, of those diagnosed with PPH (\geq 500 mls), most stopped bleeding at blood losses of around 700 mls even if they did not

receive any uterotonic therapy. This should warn against ascribing all the effect to uterotonic therapy. As well as stopping spontaneously, other physical therapies may also have been used concurrently and may have had an effect.

The evidence from the histogram study suggested that use of additional uterotonic is not a good surrogate for PPH in the research context. Chapter 4 reports on evaluations of the outcomes that are used by researchers in PPH trials. In the 121 studies evaluated, there was a huge diversity in choosing the outcomes (PPH prevention). The most common was ‘Incidence of PPH \geq 500 mls’, which was mentioned in 21% (25/121) of trials. The study interestingly showed that use of additional uterotonic was used for sample size calculation in 6% (7/121) of studies as a surrogate for PPH.

The above findings emphasise the importance of physical measures in the early treatment of PPH. BMC is thought to help in treating PPH, although there are no clinical trials on its effectiveness. A survey was therefore conducted amongst obstetric care providers in the UK to look at the frequency of BMC use in clinical practice and the attitudes towards its use. The survey found that, although clinicians find BMC effective, it is rarely used as the procedure is considered to be too tiring and too invasive.

If, however, BMC could be performed in a less invasive manner, then it could act as an effective low-cost treatment for those PPHs arising from atony.

The thesis concludes with an investigation into a new low cost intervention that might contribute to the early physical management of PPH. The ‘PPH Butterfly’ is a new device that is designed to make uterine compression simpler, less tiring and less invasive. It was compared to the standard BMC in a mannequin model. The main objective was to compare the efficacy of the PPH Butterfly to standard BMC in producing sustained uterine compression. The study revealed that the PPH Butterfly is simple to use on a mannequin model, even among obstetric care providers with little experience. It produces an equivalent amount of pressure to BMC, but neither method produced sustained compression over the 5 minutes of use. It also demonstrates the feasibility of using a mannequin model for teaching and performing BMC.

Thesis summary

- **What is already known about postpartum haemorrhage?**

Chapter 1: A literature review

- **How was the management of the third stage of labour developed?**

Chapter 2: Obstetrics by Ten Teachers
“Historical review (1917-2011)”

Importance of bimanual uterine
compression

Uterotonics have always been taught
as being the best initial measure to
manage PPH.

Can BMC be adapted for better care?

Evaluation of uterotonic effectiveness

Chapter 5: Feasibility Studies on
the development of a new device
to aid bimanual compression

Chapter 3: Third stage blood
loss histogram: a feasibility
study

Clinicians think that BMC is effective, but
too invasive and tiring.
These problems could be overcome by the
use of a platform on a handle

“Use of additional uterotonic” is a poor
surrogate for PPH

**What outcomes have been used in
the PPH prevention studies?**

Chapter 6: Uterine compression
on mannequin model using PPH
Butterfly

Chapter 4: Clinical outcomes
of PPH prevention studies: a
systematic review

Chapter 1

Literature review

1. Introduction

The third stage of labour is referred to the period between the completed delivery of the baby and the placenta.

"This indeed is the unforgiving stage of labour, and in it there lurks more unheralded treachery than in both the other stages combined. The normal case can, within a minute, become abnormal and successful delivery can turn swiftly to disaster" (Donald, 1955).

Relatively little thought or teaching seems to be devoted to the third stage of labour compared with that given to the first and second stages. The third stage of labour is a risky time as uneventful, significant complications that threaten the mother's life can occur in this period. The most common complication is PPH. Although maternal mortality rates have declined dramatically in the developed world, PPH remains a leading cause of maternal mortality especially in developing countries. Improving maternal health is Millennium Development Goals (MDG) 5. The international targets have been set to reduce maternal mortality by 75% between 1990 and 2015. The WHO 2010 report revealed a promising result in some countries, but many other countries made no progress and are likely to miss the target unless accelerated interventions are put in place (Fathalla, 2012). Globally, the maternal mortality ratio dropped by 45% between 1990 and 2013, this still falls far short of the MDG target (United Nations, 2014). Global rates of change suggest that only 16 countries will achieve the MDG 5 target by 2015 (Kassebaum et al., 2014).

2. Primary postpartum haemorrhage

2.1. Background

PPH remains the most common cause of maternal mortality worldwide (Say et al., 2014). It is estimated that, 86, 000 women die from PPH each year, which is ten deaths every hour. It is associated with morbidity in 20 million women per year (Fawcus et al., 1995; Selo-Ojeme, 2002). PPH is responsible for around 25% of maternal mortality worldwide (WHO, 2007a), reaching as high as 60% in some countries. Although the absolute risk of death is much lower in high-income countries (1 in 100,000 births versus 1 in 1,000 births in low-income countries (WHO, 2007b). PPH can also be a cause of long-term severe morbidity, and approximately 12% of women who survive PPH will have severe anaemia (AbouZahr, 2003). Additionally, women who have severe PPH and survive “near misses” are significantly more likely to die in the year following the PPH (IMMPACT, 2007). Furthermore, haemorrhage is the leading cause of admission to the intensive care unit. Importantly, although PPH constitutes a serious health burden, it is the most preventable cause of maternal mortality.

The leading cause of PPH is thought to be uterine atony - the failure of the uterus to contract fully after delivery of the placenta. PPH resulting from uterine atony is a major preventable cause of maternal morbidity and mortality, especially in developing countries (B-Lynch et al., 2006). Morbidity and mortality due to PPH are largely preventable through skilled care during childbirth. However, delays in identifying haemorrhage, delays in transporting the woman to the appropriate point of care, and delays in receiving the recommended treatment all contribute to high rates of maternal mortality and morbidity due to PPH. In many poor countries, women may give birth without any assistance. Alternatively, a relative, a member of the community, or a traditional birth attendant (TBA), often without formal health training, may attend births occurring in the community. These women may not have access to interventions to either prevent or treat PPH (Miller et al., 2004).

There are different types of review in medical research such as systematic reviews and narrative reviews. Traditional narrative reviews differ from systematic reviews in several ways. Narrative reviews tend to be mainly descriptive, do not involve a systematic search of the literature, and therefore often focus on a subset of studies in an area which are chosen based on availability or author selection. An example of a systematic review can be seen in Chapter 4, but the current chapter is a narrative review as it is the most appropriate way to draw out the current knowledge about PPH. Different databases were searched, including PubMed, Scopus, Cochrane and the Web of Knowledge, using various key words (e.g. postpartum haemorrhage, third stage of labour, prophylaxis, treatment and prevention). The reference list of identified articles was also searched for additional relevant papers.

This section will give an overview of the literature on PPH, including its definitions, the main aetiologies and risk factors, complications, prevention and available treatment options. It will concentrate particularly on the prevention and early treatment of atonic uterus as a main cause of PPH.

2.1.1. Definitions

Bleeding after delivery can be of two types. PPH is classified into primary (within the first 24 hours) or secondary haemorrhage (between 24 hours and six weeks). Traditionally, primary PPH is defined as a “loss of blood estimated to be more than 500 mls per vaginam within the first 24 hours of delivery” (WHO, 1990; RCOG, 2009). Primary PPH after caesarean section is defined as blood loss of 1000 mls or more (Maughan et al., 2006). PPH can be minor (500-1000 mls) or major (more than 1000 mls). Major can be divided further to moderate (1000-2000 mls) or severe (more than 2000 mls) (RCOG, 2009).

However, the exact definition of PPH remains problematic as the definition is usually based on visual estimations of bleeding. The WHO definition of 500 mls is increasingly becoming irrelevant, as the effect of blood loss differs from mother to mother. Most healthy women in the developed world can withstand a blood loss of more than 500 mls without any hemodynamic compromise, whereas for severely anaemic women even a small amount of blood loss can be fatal. This is especially important for mothers living in developing countries, where significant numbers of women have severe anaemia. Additionally, McCormick and colleagues have commented on the conventional definition of PPH as not clinically helpful, because it is often not easy to precisely assess the amount of blood a woman has lost. Additionally, the blood may be mixed with amniotic fluid or urine, or may be scattered on sponges or linens, or on the floor. In many cases, especially with slow trickling blood loss, PPH remains undetected, leading to an under-estimation of blood loss following delivery. For these reasons, a more accurate definition of PPH might be any amount of bleeding that causes a change for the worse in the woman’s condition (e.g., low systolic blood pressure, rapid pulse, signs of shock) (McCormick et al., 2002), which is also the preferred definition by the International Federation of Gynecology and Obstetrics (FIGO) latest recommendations on prevention and treatment of PPH (Lalonde, 2012). There are other different diagnostic criteria for PPH definition. These include a haematocrit drop of greater than 10% from the antepartum level, which necessitates blood transfusion, and which results in signs and symptoms of hypovolaemia (Combs et al., 1991a). However, changes in haemoglobin concentrations are not a clinically useful

definition as rapid blood loss may trigger a medical emergency prior to observation of a fall.

2.1.2. Incidence of PPH and related maternal deaths

Efforts to determine the incidence of PPH are hampered by two issues: lack of a universal definition of the condition as explained above, and the inaccuracy in clinical estimates of blood loss at delivery. Additionally, the incidence of PPH is different according to the way in which the third stage is managed. Blood loss exceeding 500 mls occurs in approximately 5% of women when labour is managed actively with injectable oxytocics, early cord clamping and traction, and in 13–16% of women when managed expectantly (Khan et al., 1997; Rogers et al., 1998). Therefore, it has been found that the incidence of PPH varies widely, depending upon the criteria used to define the disorder. Examples from different population studies from several parts of the world, using different criteria for defining PPH, are demonstrated below.

It is well known that PPH is a major cause of maternal mortality in both developed and developing countries. Globally, it is estimated that severe PPH occurs in about 1.86% of women who give a live birth (Carroli et al., 2008). The incidence is thought to be much higher in developing countries where many women do not have access to a skilled attendant at delivery and where AMTSL may not be routine. WHO reports have stated that obstetric haemorrhage causes 127,000 deaths annually worldwide and that it is the world's leading cause of maternal mortality. Nearly all of these deaths are due to PPH (WHO, 2007b).

In an attempt to assess the global magnitude of PPH, depending upon the criteria used to define the disorder, Carroli and colleagues (Carroli et al., 2008) performed a systematic review of datasets from different regions around the world. They defined PPH (their inclusion criteria) as > 500 mls blood loss, and severe PPH (SPPH) as > 1000 mls of blood loss. These authors, using 224 datasets, arrived at an overall prevalence of PPH (defined as blood loss in excess of 500 mls) of 6.09% (95% CI, 6.06-6.11). However, when the blood loss was measured objectively, the rate was 10.6%. The rates were about one-half of this when the method of assessment was not specified, consistent with the concept that blood loss is typically underestimated.

These authors also found the prevalence of severe PPH (defined as blood loss >1000 mls) to be 1.86% (95% CI, 1.82-1.90). Again, the prevalence was almost doubled when the blood loss was measured objectively (3.04%; 95% CI, 2.90-3.17). Most PPH cases were found in rural rather than in urban settings. The researchers also found that the rates of PPH were highest in Africa, and they attributed this partly to a lack of adequately skilled delivery personnel.

The figure related to PPH incidence is not consistent across the world. The incidence differed according to the definition used, way of postpartum blood loss measured and the population being studied. The following is an overview on incidence of PPH on country bases, which would be more informative.

Although pregnancy-related death is rare in the US, PPH accounts for 17% of deaths (Chang et al., 2003). An analysis of population-based data from the United States National Inpatient Sample for the years 1994-2006 found that diagnosis of PPH increased 26% over this period (from 2.3 to 2.9%) (Callaghan et al., 2010). Not surprisingly, uterine atony was the most common cause of PPH and accounted for most of the increase. The proportion of women diagnosed with uterine atony increased from 1.6 to 2.4 percent over the same interval.

In the United Kingdom, although maternal deaths are extremely rare, PPH is still one of the most common causes of maternal mortality. The United Kingdom Confidential Enquiries into Maternal Deaths found that the maternal mortality rate due to PPH was 1.0 per 100, 000 maternities. During the three years from 2000 to 2002, there were 10 maternal deaths from PPH out of a total of 261 maternal deaths (CEMACH, 2004). The maternal mortality rate for 2003-2005, calculated from all maternal deaths directly or indirectly due to pregnancy identified that 14 women died from haemorrhage; a rate of 0.66 per 100,000 maternities. Out of these 14, 2 women died due to abruptio placenta, 3 cases due to placenta praevia and 9 women due to PPH (Lewis, 2007). In the triennium 2006-2008, there was a reduction in maternal deaths attributed to direct causes. This was mainly due to a reduction in deaths from thromboembolism and to a lesser extent, from haemorrhage (CEMACH, 2011). This could be mainly due to the publication and implementation of guidelines that were recommended in previous reports.

In Africa, haemorrhage is estimated to be responsible for 30% of all maternal deaths (WHO, 2009). In Sub-Saharan Africa, for every 16 women, one will die of pregnancy and childbirth-related conditions, and PPH accounts for 25% of the aetiology of maternal mortality (Miller et al., 2004). Etuk and Asuquo reported that the death rate on account of PPH is 2.2% in a teaching hospital in Nigeria (Etuk and Asuquo, 1997). In Zimbabwe, in a community-based study of maternal mortality (Fawcus et al., 1997), it has been found that obstetric haemorrhage was the main contributor to one quarter of maternal deaths, with a cause-specific maternal death rate of 40 per 100, 000 live births. More cases of maternal mortality occurred in rural areas compared to urban areas. In the same study, it was found that most women (50%) dying from PPH died at home or in transit to, or between, institutions as they did not have access to any treatment before their death. The South African Confidential Enquiries into Maternal Deaths indicated that PPH was the third most common cause of death, accounting for 313 deaths in a total of 3406 in the triennium 2002 to 2004 (Tshabalala, 2006).

In another study, blood loss at caesarean delivery was measured and defined as a loss of 1000 mls or more, a need for blood transfusion or presence of signs and symptoms of hemodynamic instability (Magann et al., 2005a). The authors found that the incidence of PPH in non-elective caesarean (6.75%) was greater than after elective caesarean (4.84%, $P=0.007$).

Combs and co-workers, in a case-control study of 9598 vaginal deliveries at Moffitt Hospital in San Francisco, found PPH (defined as a haematocrit drop of 10 points or more) in 374 cases (3.9%) (Combs et al., 1991a). In another study by the same authors, limited to women who underwent caesarean delivery, 196 of 3052 eligible deliveries were complicated by PPH, producing a rate of 6.4% (Combs et al., 1991b). In another Australian study blood loss at vaginal delivery was calculated by collecting and measuring the blood in collection devices used specifically for vaginal birth and then weighing sheets, drapes, and sponges after delivery. PPH was defined as blood loss in excess of 1000 mls and/or need for blood transfusion because of maternal anaemia and/or hemodynamic instability. Over a 4-year period, 13,868 of 19,476 women delivered vaginally, with a PPH rate of 5.15% (Magann et al., 2005b).

It is very obvious that maternal death due to PPH is much more frequent in resource-poor countries. The imbalance between resource-rich and resource-poor areas is thought to be from a combination of an increased prevalence of risk factors (e.g. grand multiparity, obstructed labour and twins), a lack of safe blood banking, no routine use of prophylaxis against haemorrhage, and a lack of measures for drug and surgical management of atony. In a secondary analysis of the multi-country survey on maternal and newborn health, Sheldon (Sheldon et al., 2014) found that the provision of uterotonics for both prevention and treatment of PPH is widespread among the health facilities that participated (95.3% of women received uterotonic prophylaxis). High coverage of essential interventions, however, did not result in reduced maternal mortality in the studied facilities. The evidence is that it is mainly services that affect mortality (Sheldon et al., 2014) and the underlying risk factors and prophylaxis have little effect. For example, in clinical trials the maternal mortality rate is very low, even in those women having a placebo. In the South Africa report (Tshabalala, 2006), patient/community-related factors, lack of emergency transport, lack of blood for transfusion, lack of appropriately skilled personnel, and substandard treatment were all included among the avoidable factors.

Overall, since haemorrhage can be difficult to detect, a universal definition is lacking, clinical estimates of blood loss are inaccurate, and there is poor recording of maternal deaths in remote regions, therefore the true incidence of PPH remains unclear. It may be even higher than the reported percentages.

2.1.3. Physiology of the third stage of labour

Over the course of a pregnancy, maternal blood volume increases by approximately 50%, from 4 to 6 L and the red blood cell (RBC) volume by 32% (Pritchard, 1965). The plasma volume increases somewhat more than the total RBC volume, leading to a fall in the haemoglobin concentration and haematocrit values (haemodilution). This decrease is smaller in women who take supplemental iron, whereas the fall may be dramatic in women who do not take supplemental iron and who have limited iron stores or are anaemic upon becoming pregnant (Chohan, 2005). The increase in blood volume serves to fulfil the perfusion demands of the low-resistance uteroplacental unit and to provide a reserve for the blood loss that occurs at delivery. The increased blood volume also protects against hypotension caused by decreased venous return and decreased vascular tone due to high progesterone levels (Baskett, 1999).

Changes also occur in the coagulation system, with a marked increase in clotting factors and a decrease in fibrinolytic activity. The platelet count may fall slightly during pregnancy because of dilution related to the increased plasma volume and as a result of low-grade consumption; however, individual platelet volume is increased and activity is maintained (Chohan, 2005). Although uterine contraction is initially responsible for controlling blood loss at the placental site, clot formation and fibrin deposition occur rapidly and are essential in maintaining haemostasis and promoting involution in the days following delivery (Sleep, 1993).

Early in pregnancy, the uterus grows dramatically, from an initial weight of roughly 30-60 g and a cavity volume of 4 mls to a term weight of 700-1000 g and a capacity of approximately 4 L. As with the haematological and coagulation changes mentioned above, high levels of oestrogen promote and allow this change in the uterus (Chohan, 2005). The initial growth of the uterus and the ultimate growth of the placenta and fetus require an equally impressive increase in blood flow to the uterus during pregnancy. At term, the estimated blood flow to the uterus is 500-700 mls/min, which represents 10-15% of cardiac output. Most of this flow traverses the low-resistance placental bed (Amin and Long, 2009).

2.1.3.1. Mechanisms of placental separation

The physiological processes occurring during the third stage are a continuation of those processes occurring during the first and second stages of labour. There is an interplay of mechanical and haemostatic factors to separate and expel the placenta, and to control bleeding from the placental site. With the delivery of the placenta, the muscle fibres surrounding the maternal vessels contract completely to prevent excessive bleeding and the mother's coagulation system is activated temporarily (Bonnar et al., 1970a).

During the third stage of labour and following the delivery of the fetus, uterine contractions continue and the placenta is sheared from the underlying endometrium. This separation primarily occurs by a reduction in the surface area of the placental site as the uterus shrinks. This process is known as retraction. This myometrial retraction, which is a unique feature of the uterine muscle, is essential to maintain its shortened length following each successive contraction. In this way, the placenta is undermined, detached, and pushed into the lower uterine segment (Amin and Long, 2009). Oxytocin, a hormone secreted by the posterior pituitary gland, stimulates uterine contractions. Oxytocin levels increase greatly in late pregnancy and even more during labour and lactation. The compression of the placenta also forces the retro-placental blood back into the sinuses in the decidua basalis. The placenta attempts to force blood through the uterine sinuses, closed off by strong myometrial contractions. The sinuses become congested and rupture. The blood escapes from the ruptured sinuses, tearing the fine septae of the spongy layer off the decidua basalis. Consequently, the placenta shears off (Khan and EL-Refaeey, 2006). Classical signs of placental separation include a small gush of blood with lengthening of the umbilical cord and a slight rise of the uterus in the pelvis, since the uterus contracts more effectively after the placenta is expelled. If the uterus does not contract normally, the blood vessels at the placental site stay open and haemorrhage results.

There are two classical methods of placental delivery which result in different bleeding patterns. These are the Schultze and Matthew Duncan methods, named after the persons who first described them (Speert, 1996). In the Schultze method, separation and descent occur in the central part of the placenta with the fetal surface protruding first, followed by the rest. As the centre of the placenta is pushed forward, it becomes inverted on itself forming a bag filled with blood. The Matthew Duncan method is characterised by detachment of the placenta edges, folding upon itself transversely in the passage, leading to the entire organ sliding down and out of the uterus sideways with the maternal side of placenta appearing first. This method is supposed to cause more bleeding than the Schultze method because of the slow separation of the placenta which allows more time for bleeding. There is however little relevance of this; distinction of the placental separation method appears to be clinically irrelevant and clinicians are incapable of predicting or changing the method of separation (Khan and EL-Refaey, 2006).

Ultrasound studies have provided fresh insights into the mechanism of the third stage of labour. An ultrasonographic imaging study was performed to investigate the mechanism of placental delivery during the third stage of labour. Continuous real-time ultrasound was performed during the third stage of labour in 101 normal deliveries (Herman et al., 2002). This study demonstrated that the process of placental separation is multiphasic and has three distinct phases. The first, or latent phase, consists of strong uterine contractions that lead to the thickening of the uterine muscle in all areas except behind the placenta (thus causing a shearing force to occur between the elastic uterine wall and the more rigid placenta). Continued contractions lead to gradual contracts of the retro-placental myometrium. Separation of the placenta commences at one of the poles and spreads slowly during the contraction or detachment phase until full separation occurs. This is followed by delivery of the placenta in the expulsion phase. The most common type of placental separation was 'down-up' separation where the process started at the lower pole. It rarely began from the upper pole (up-down separation). In cases of a fundal placenta, the separation began from either the posterior or anterior pole with the fundal part separating last (bipolar separation) (Herman et al., 2002). The up-down separation was more common in women who had a previous caesarean section, probably due to impaired lower uterine segment contractility (Mo and Rogers,

2008). The study by Herman and others (2002) also highlighted the role of retroplacental myometrial failure in causing retained placenta (Herman et al., 2002). However, the lack of contraction at the retroplacental area during early labour might have many benefits to the fetus. It could act as a protective mechanism to prevent intrapartum abruptio, and might also be protective against fetal anoxia by ensuring an uninterrupted maternal blood supply to the placental bed during contractions (Weeks, 2008).

Another study using real time B-mode ultrasound described placental separation in three types (Goto, 1984). In Type I, which occurred in 53% of the cases, placental separation from its bed occurred smoothly and it slid out immediately, usually one or two contractions after the delivery of the baby. This type was characterised by the least blood loss and the shortest duration of the third stage of labour. Placental separation in Type II started at the marginal site and gradually progressed with each recurring contraction. With this type, the bleeding tended to be greater and the time to placental separation tended to be longer. In Type III, separation of the placenta began at the central part with formation of retroplacental clots resulting in an increase in placental size. The blood loss and the duration of the third stage were generally moderate.

2.1.3.2. Haemostasis

When the placenta is separated from the uterine wall it leaves about 300 square centimetres and maybe 100 torn arteries which had been delivering around 500 mls of blood per minute to the placenta. This massive trauma requires both a physical compression of the blood vessels by the myometrial contraction, as well as vessel blockage by haemostasis (Hytten, 1995). Uterine muscles compress the maternal spiral arteries and veins of the placental bed, resulting in an obliteration of their lumina. Moreover, the strong myometrial contraction helps haemostasis by opposing the uterine walls firmly against one another and producing direct pressure on the placental site (Khan and EL-Refaey, 2006). The vessels supplying the placental bed traverse a latticework of crisscrossing muscle bundles that occlude and kink-off the vessels (Figure 1) as they contract and retract following the expulsion of the placenta. This arrangement of muscle bundles has been referred to as the "living ligatures" or "physiologic sutures" of the uterus (Sleep, 1993).

After the separation of the placenta, the placental site is rapidly covered by a fibrin net and clots form. Coagulation at the placental site has an important role in the prevention of PPH after separation of the placenta. Around the time of delivery, many changes both in coagulation factors and fibrinolysis agents take place. There is consumption of platelets and blood coagulation factors (including fibrinogen) by clot formation and haemostasis at the placental site. This causes a decrease in the peripheral plasma fibrinogen levels. In a study performed by Bonnar et al., uterine veins samples were obtained during caesarean section in 12 patients. They found that the time of placental separation was accompanied by a prominent activation of the local clotting mechanism and a sharp increase in factor VIII (Bonnar et al., 1970b). In another study of the coagulation and fibrinolytic systems in 15 healthy women during normal childbirth, there was a rapid increase in the clotting factors VIII and V and a decrease in plasma fibrinogen in the peripheral circulation. Within one hour of delivery, fibrinolytic activity returns to its non-pregnant levels, and there is an increase in the level of fibrin/fibrinogen degradation products. In early puerperium, changes promoting coagulation take place. This includes an increase in the fibrinogen level and a swift increase in platelet count. The level of factor VIII remains high (Bonnar et al., 1970a).

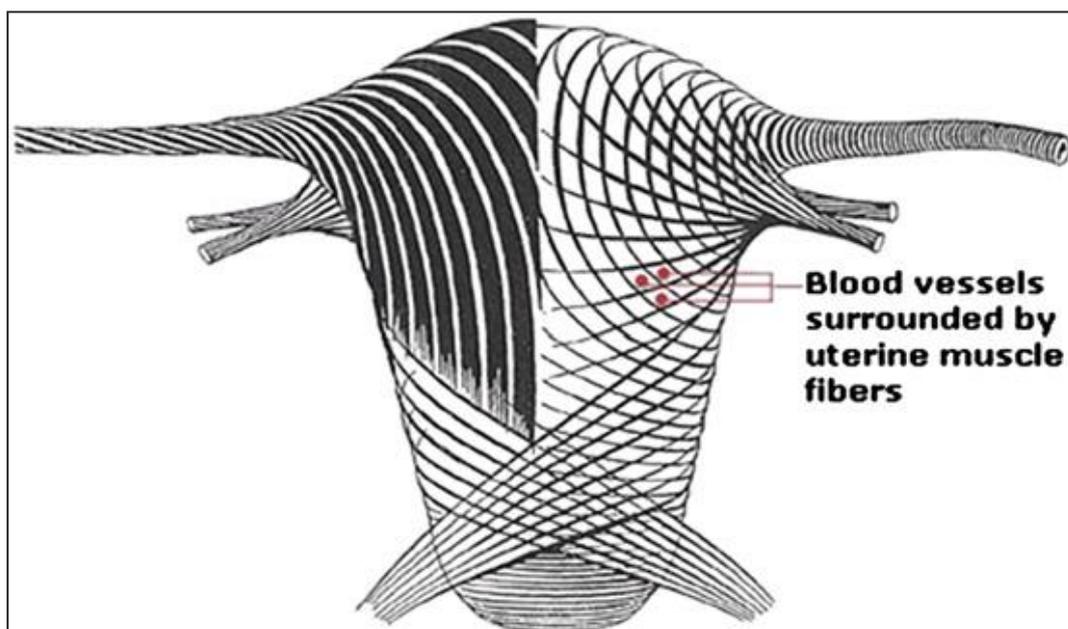


Figure 1. Muscle fibres of the uterus (Lalonde, 2012)

2.1.3.3. Length of the third stage of labour

The length of the third stage of labour determines the amount of blood loss that occurs during that period, which depends on how quickly the process of placental separation occurs. Fifty percent of placental deliveries occur within 5 minutes, and 90 percent are delivered within 15 minutes (Dombrowski et al., 1995). A third stage of labour lasting longer than 18 minutes is associated with a significant risk of PPH. When the third stage of labour lasts longer than 30 minutes, PPH occurs six times more often than it does among women whose third stage lasts less than 30 minutes (Odds ratio (OR) 6.2; 95% CI 4.6–8.2) (Magann et al., 2005c).

There is no consensus as to the length of the third stage of labour after which the placenta should be called retained. In general, it has been suggested a third stage lasting more than 30 minutes should be considered abnormal (NICE, 2007), whereas the WHO manual of childbirth suggests 60 minutes to reflect the normal time of the third stage (WHO, 2012). The length of the third stage in those who received no prophylaxis during the third stage (i.e. physiological management) can be extended to 60 minutes (NICE, 2007).

Percentage of patients with retained placenta after 30 minutes was found to be different between countries. It was 2.67% (2.00–6.26- range) in the developed countries and 1.55% (1.05–4.60- range) in the developing countries (Cheung et al, 2011). As stated by the authors the differences may be explained by differences in the aetiology and risk factors of retained placenta between countries.

The incidence of retained placenta also differs according to the method followed to manage the third stage. Incidence of retained placenta at 30 minutes has been found to be about 2% and 20% with active and expectant management of the third stage of labour respectively. When the third stage of labour lasted more than 1 hour, the incidence of undelivered placenta was found to be 0.7% for both active and physiological management (Weeks, 2008).

The association between placental location and length of the third stage of labour in normal term singleton pregnancies was evaluated in a retrospective study, including

200 consecutive singleton term live vaginal deliveries following uncomplicated pregnancies. Patients' charts were reviewed in order to determine the placental implantation site. The duration of the third stage of labour was statistically significantly longer (12.8 ± 9.526 minutes) in the 26 cases (13%) in which the placenta was located in the fundal area of the uterus (Lurie et al., 2003). However, when this was studied prospectively in 201 women in labour, the association between prolonged third stage and fundal location of placenta was not demonstrated (Altay et al., 2007). The length of the third stage of labour in that study was approximately 2 min shorter with placentas located at the fundus compared to the anterior and posterior locations. The authors explained that the mechanism responsible for the shorter duration may be the bipolar separation of fundal placentas in contrast to the usual unipolar down-up separation of anterior or posterior placentas. Another contributing factor may be the use of oxytocin infusion for the management of the third stage, as oxytocin causes contraction mainly to the upper uterine segment, facilitating separation of fundal-located placenta.

2.1.4. Causes and risk factors

Understanding the aetiology of PPH is fundamental to effectively managing the condition in an acute setting. There are several possible reasons for immediate PPH. Primary PPH is traditionally considered as a disorder of one or more of the four processes: uterine atony, retained clots or placental debris, genital lesions or trauma, and disorders of coagulation. An aide memoire is the four Ts: tone, tissue, trauma and thrombin. Tone refers to uterine atony, which is thought to occur in 75-90% of cases. Genital tract trauma is responsible for 20% of cases, and includes trauma to the broad ligament, uterine rupture, and uterine inversion as well as cervical, vaginal and perineal tears. Retained placental tissue prevents effective uterine contraction in 10% of cases. Coagulation disorders are rare (1%) (B-Lynch et al., 2006). Causes and many other risk factors associated with early PPH are summarised in Table 1.

2.1.4.1. Aetiology of PPH

2.1.4.1.1. Uterine atony

Uterine atony refers to a floppy, flaccid uterus, one in which the myometrium is unable to contract effectively and constrict the blood vessels after the expulsion of the placenta leading to haemorrhage. Uterine atony is the most common cause of primary PPH, and accounts for 75-90% of cases of PPH (Koh et al., 2009). At term, more than 500-700 mls of blood enters the uteroplacental circulation every minute (El-Refaey and Rodeck, 2003; Amin and Long, 2009). It is understandable that primary atonic PPH can be catastrophic, as over a short time of myometrial relaxation, fatal haemorrhage can occur. Uterine atony can occur after normal vaginal delivery, instrumental vaginal delivery and abdominal delivery. There are many recognised risk factors for uterine atony including an over-distended uterus caused by polyhydramnios, multiple gestations, and a large baby. Moreover, prolonged labour, oxytocin use in labour or chorioamnionitis and tocolytics/general anaesthesia can contribute to poor contractility of uterine muscle (RCOG, 2009). However, uterine atony may occur in women without any risk factors. About 26% of women who underwent hysterectomy had no identifiable risk factors (Clark et al., 1984). In the UK, uterine atony was responsible for 53% of peripartum hysterectomies between February 2005 and February 2006 (Knight, 2007).

2.1.4.1.2. Genital tract trauma

Generally, if PPH is not due to uterine atony, genital tract trauma is likely to be the cause of severe bleeding. Lacerations and hematomas resulting from birth trauma can cause significant blood loss that can be lessened by haemostasis and timely repair. Trauma may result from laceration of the cervix, the vagina sidewall, the perineum and episiotomy, or from uterine rupture. Genital tract trauma could also be iatrogenic during caesarean delivery or instrumental delivery such as forceps or vacuum.

Uterine inversion is rare, occurring in 0.05 percent of deliveries. Fundal implantation of the placenta may lead to inversion (Gabbe et al., 2002). The condition commonly occurs secondary to mismanagement of the third stage of labour, especially if traction of the cord is applied before sufficient contractions of the uterine muscle is reached, and without applying effective counter pressure to the uterine fundus (Jeganathan and Sivanesaratnam, 2011). The inverted uterus usually appears as a bluish-grey mass protruding from the vagina. Vasovagal effects producing vital sign changes disproportionate to the amount of bleeding may be an additional clue. The placenta often is still attached, and it should be left in place until after reduction (Baskett, 2002). This cause of PPH can be fatal if not recognised and treated appropriately and quickly.

Clinically significant uterine rupture occurs in 0.6 to 0.7% of vaginal births, and after caesarean delivery in women with a low transverse or unknown uterine scar (Chauhan et al., 2003; Landon et al., 2004). The risk increases significantly with previous classical incisions or uterine surgeries, and to a lesser extent with shorter intervals between pregnancies or a history of multiple caesarean deliveries, particularly in women with no previous vaginal deliveries. Compared with spontaneous labour, induction or augmentation increases the rate of uterine rupture (Landon et al., 2004). The primary signs of uterine rupture are vaginal bleeding, abdominal tenderness, maternal tachycardia, circulatory collapse, or increasing abdominal girth (ACOG, 2004).

2.1.4.1.3. Retained products of conception

Retained uterine products are the most common cause of delayed PPH (Roberts, 1995; Lalonde, 2012). In normal circumstances, uterine contractions expel the placenta within a few minutes of childbirth. The placenta is then examined, to ensure it is intact. If the placenta has not been delivered within 30 minutes of childbirth the placenta must be retrieved (Jeganathan and Sivanesaratnam, 2011). Retained placenta occurs in 0.5–3% of vaginal deliveries (Weeks and Mirembe, 2002) and may cause inadequate uterine contraction (Oyelese and Ananth, 2010). Rates of retained placenta are significantly higher in developed countries, irrespective of whether retained placenta is defined as the length of third stage or as the need for manual removal (Cheung et al., 2011). Predisposed risk for retained uterine products

includes history of previous curettage, caesarean section or endometrial infection or injury, induction of labour (Golan et al., 1983; Combs and Laros, 1991; Soltan and Khashoggi, 1997). It has been also found a statistically significant association between prolonged third stage and augmented labour (Combs and Laros, 1991).

Table 1. Causes and predisposing factors for PPH

PPH cause	Aetiology process	Clinical risk factor
Abnormalities of uterine contraction (Tone)	- over distended uterus	- polyhydramnios - multiple gestation - macrosomia
	- uterine muscle exhaustion	- rapid labour - prolonged labour - high parity
	- intra amniotic infection	- prolonged ROM
	- functional/anatomic distortion of the uterus	- fibroid uterus - placenta previa - uterine anomalies
Retained products of conception (Tissue)	- retained products - abnormal placenta - retained cotyledon or succinuriate lobe	- incomplete placenta at delivery - previous uterine surgery - abnormal placenta on U/S
	- retained blood clots	- atonic uterus
Genital tract trauma (Trauma)	- lacerations of the cervix vagina or perineum	- precipitous delivery - operative delivery
	- extensions, lacerations at caesarean section	- malposition - deep engagement
	- uterine rupture	- previous uterine surgery - induction of labour
	- uterine inversion	- excessive cord traction or fundal pressure at the 3rd stage
Abnormalities of coagulation (Thrombin)	pre-existing states - haemophilia A - Von Willebrand's Disease	- history of hereditary coagulopathies - history of liver disease
	- acquired in pregnancy - ITP - thrombocytopenia with pre-eclampsia - DIC - pre-eclampsia - dead fetus in utero - severe infection - abruption - amniotic fluid embolus	- bruising - elevated BP - fetal demise - antepartum haemorrhage
	- therapeutic anti-coagulation	- history of blood clot

2.1.4.1.4. Coagulation disorders

Coagulation disorders are a rare cause of PPH. Both inherited and acquired coagulation defects are associated with excessive blood loss postpartum. Fortunately, most coagulopathies are identified before delivery, allowing for advance planning and preventing PPH. These disorders include idiopathic thrombocytopenic purpura, Von Willebrand's disease, and haemophilia; patients can also develop HELLP syndrome (haemolysis, elevated liver enzyme levels, and low platelet levels) or disseminated intravascular coagulation. Excessive bleeding can deplete coagulation factors and lead to consumptive coagulation and disseminated intravascular coagulation, which promote further bleeding. Risk factors for disseminated intravascular coagulation include severe pre-eclampsia, amniotic fluid embolism, sepsis, placental abruption, and prolonged retention of a fetal demise (Pritchard, 1959; Alamia and Meyer, 1999).

Although PPH due to coagulation problems is categorised under thrombin, recent studies suggest that acquired fibrinogen deficiency, rather than thrombin generation, could be the main coagulation defect associated with obstetric bleeding (de Lloyd et al., 2011). In addition, fibrinogen levels could act as a prognosis factor for the severity of PPH, as it has been found that the level of fibrinogen during the first hour was the only parameter independently and significantly associated with the worsening of bleeding during PPH. Fibrinogen level < 2g/dl measured in the course of obstetric haemorrhage has been found to have a positive predictive value of 100% for progression to severe PPH (Charbit et al., 2007).

2.1.4.2. Identified risk factors for PPH

Although PPH often occurs in women with no identifiable risk factors several studies have identified risk factors for this condition (Combs et al., 1991a; Combs et al., 1991b; Magann et al., 2005a; Magann et al., 2005b; Sheiner et al., 2005). Antenatal risk factors include increasing maternal age, high body mass index, parity and other medical conditions such as type II diabetes, and connective tissue disorders (B-Lynch et al., 2006). It is appropriate that women with these predisposing risk factors should deliver in a hospital with adequate facilities to manage PPH.

In a study involving 666 PPH cases out of 154,311 deliveries, significant risk factors were: failure to progress during second stage of labour (OR 3.4; 95% CI 2.4-4.7), placenta accreta (OR 3.3; 95% CI 1.7-6.4), lacerations (OR 2.4; 95% CI 2.0-2.8), instrumental delivery (OR 2.3; 95% CI 1.6-3.4), large for gestational age (OR 1.9; 95% CI 1.6-2.4), hypertensive disorders (OR 1.6; 95% CI 1.2-2.1), induction of labour (OR 1.4; 95% CI 1.1-1.7) and augmentation of labour with oxytocin (OR 1.4; 95% CI 1.2-1.7) (Sheiner et al., 2005). There has been a long-standing debate over the association between prolonged labour and PPH. It is unclear whether this is due to a primary myometrial problem, causing the uterus to contract inefficiently both before and after delivery, myometrial acidaemia, or the association of both with increased fetal size. There is also an association with the use of oxytocin infusions in labour but randomised trials of intrapartum oxytocin show no effect on PPH rates (Saunders et al., 1989; Sosa et al., 2011).

Previous history of PPH is considered as a significant risk factor for PPH in subsequent pregnancies. A population-based study was conducted in New South Wales to investigate the occurrence and recurrence of PPH in 125,295 women over a period from 1994 to 2002. Among the participating women, 5.8% had PPH in their first pregnancy and 14.8% of these women had PPH in their second consecutive pregnancy which represents a 3-fold increased risk of PPH. The rate of PPH in women who had PPH in their first two consecutive pregnancies was 21.7% in their third consecutive pregnancy. Furthermore, the rate of PPH in the third pregnancy in women who had a first pregnancy with PPH and a second uncomplicated pregnancy was 10.2% (Ford et al., 2007).

A major risk factor for PPH is a history of antepartum haemorrhage (Breathnach and Geary, 2009) including placenta praevia (Figure 2) or placental abruption, (Figure 3). The anatomical and physiological limitations of the lower uterine segment cause ineffective uterine contraction to prevent PPH after separation of the placenta from its bed. Implantation of the placenta in the lower segment (placenta praevia) makes haemorrhage much more likely. Invasive placenta can be life threatening. Classification is based on the depth of invasion and can be easily remembered through alliteration: placenta accreta adheres to the myometrium, placenta increta invades the myometrium, and placenta percreta penetrates the

myometrium to or beyond the serosa (Gabbe et al., 2002). If the placenta invades the myometrium (placenta increta), there is no clear cleavage line and attempts to remove the placenta can cause it to tear. The remaining fragments and opened sinuses will lead to severe haemorrhage. Risk factors include advanced maternal age, previous invasive placenta or caesarean delivery, and placenta praevia (Wu et al., 2005).

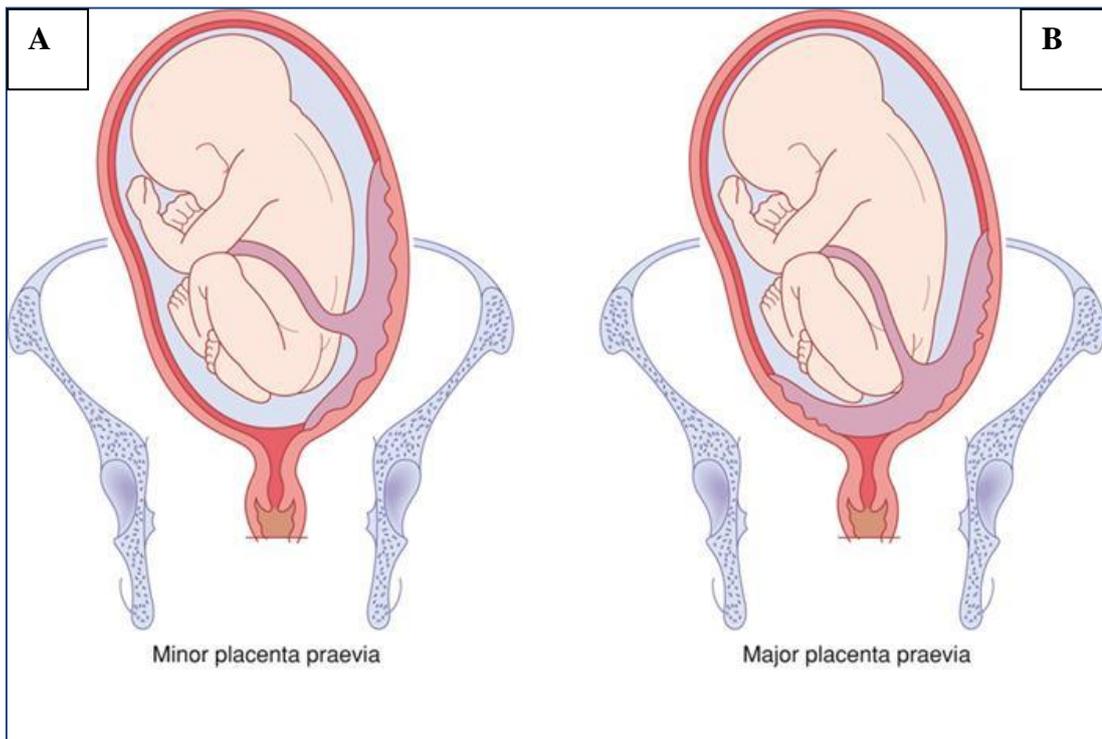
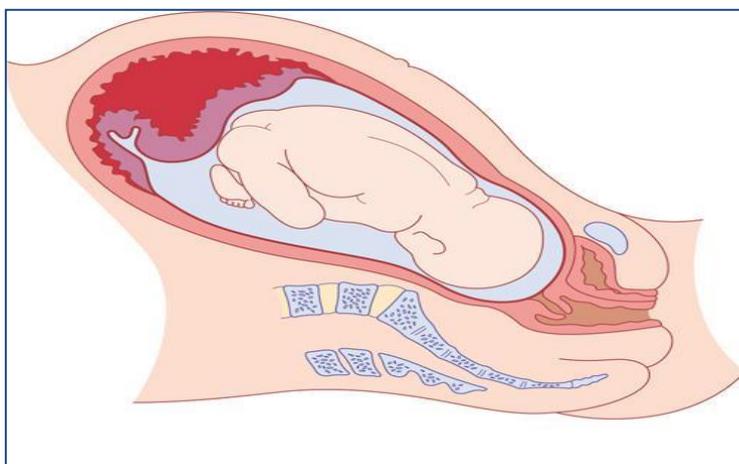
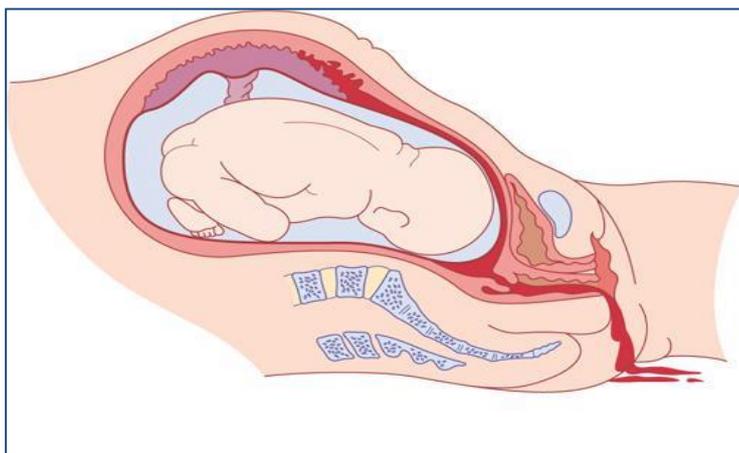


Figure 2. Placenta praevia (A) minor placenta praevia (B) major placenta praevia (Baker and Kenny, 2011)



A. Concealed haemorrhage



B. Revealed haemorrhage

Figure 3. Abruption placenta (premature separation of placenta). Two types of bleeding, revealed and concealed haemorrhage (Baker and Kenny, 2011)

In a study conducted at the King Edward Memorial Hospital, Perth, Australia, over a 4-year period, where the PPH rate was 5.15% among women who delivered vaginally, the identified risk factors were Asian race, maternal blood disorders, prior PPH, history of retained placenta, multiple pregnancy, antepartum haemorrhage, genital tract lacerations, macrosomia (> 4 kg), and induction of labour, as well as chorioamnionitis, intrapartum haemorrhage, still birth, compound fetal presentation, epidural anaesthesia, prolonged first/second stage of labour, and forceps delivery after a failed vacuum (Magann et al., 2005b).

Hypertensive disease of pregnancy has been linked to severe PPH caused by atony. This can be explained in two ways. Firstly, preeclampsia can result in thrombocytopenia, platelet dysfunction, and disseminated intravascular coagulation. In addition, magnesium sulfate, used routinely in patients with preeclampsia and eclampsia, has the side effect of compromising postpartum uterine contractility. Chorioamnionitis has repeatedly been shown to result in a poorly contractile uterus, likely in part due to inflammation. Caesarean delivery, often performed after a prolonged labour, may predispose a patient to uterine atony as a result of uterine muscle fatigue or impaired contraction at the site of the uterine incision (Bateman et al., 2010).

2.1.5. Complications and prognosis

If PPH does occur, the outcomes depend on many factors, for example, how healthy the woman is when she has PPH (particularly her haemoglobin level), how soon a diagnosis is made, and how quickly effective treatment is provided after PPH begins. Importantly, the immediate prognosis depends on the rate and the amount at which the blood is lost.

PPH can lead to a number of problems. Most PPH complications, particularly in Europe and the US, are well tolerated by women. However, in many parts of the world, especially in low-resource countries, the loss of 500 ml of blood can be a serious threat to health due to the high prevalence of severe anaemia. In low-income countries, poor nutritional status, lack of easy access to treatment, and inadequate intensive care and blood bank facilities are additional contributing factors that lead

to the high morbidity and mortality rates in these countries. Severe anaemia is a common consequence of postpartum bleeding and affects about 12% of the 14 million women with severe PPH each year (AbouZahr, 2003). Anaemia may cause weakness and fatigue; these symptoms may make maternal care of the newborn more difficult. Postpartum anaemia also increases the risk of postpartum depression (Corwin et al., 2003). Hospitalisation may be prolonged, and the establishment of breastfeeding may be affected. A blood transfusion may improve the anaemia and shorten the hospital stay, but it carries risks of transfusion reaction and infection especially of viral infections such as human immunodeficiency virus (HIV) and hepatitis B (Ekeroma et al., 1997). Access to safe blood is not universal, and PPH can sometimes strain the resources of the best blood bank. Severe PPH, retained placenta, and uterine inversion may require emergency anaesthetic services. Any exploration or instrumentation of the uterus increases the risk of sepsis.

Other significant morbidities associated with PPH include hypovolaemia shock, disseminated intravascular coagulopathy, renal failure, hepatic failure and adult respiratory distress syndrome (Bonnar, 2000), multiple organ failure, need for surgery including dilatation and curettage, and, rarely, hysterectomy. In the most severe cases, haemorrhagic shock may lead to anterior pituitary ischemia with delay or failure of lactation (postpartum pituitary necrosis or Sheehan's syndrome) (Willis and Livingstone, 1995; Sert et al., 2003). Hysterectomy and other surgical procedures to reduce blood flow to the uterus and their subsequent consequences in fertility have to be considered as consequences of PPH, although it is difficult to quantify their burden.

2.2. Prevention of primary PPH

PPH is one of the few obstetric complications with an effective preventive intervention. The aims of intervention are to prevent death, and to reduce i) the volume of blood loss, ii) the need for manual removal of placenta, iii) the need for transfusion, and iv) the need for medical or surgical treatment of PPH.

The United Nation's MDG5, to reduce maternal mortality by 75% by 2015, cannot be reached without the successful management of PPH (WHO et al., 2007; United Nations., 2008). Maternal deaths due to PPH are most common during the first seven days after the birth of the newborn. The majority of these deaths occur within 1-4 hours of delivery (Kane et al., 1992). Thus, immediate management is necessary to prevent morbidity from PPH. Different preventive measures may either increase the woman's chance of survival or prevent conditions caused by PPH. These measures can be applied during the antenatal period, in labour or during the third stage of delivery.

2.2.1. Reducing the risk of PPH antenatally and during labour

Ideally, prevention of PPH starts in the antenatal clinic by identifying mothers with risk factors for PPH. Attempts have been made to identify women at risk of atonic PPH based on historical or clinical factors, allowing steps to be taken to prevent it in this high-risk group of women. However, it has been found difficult to accurately predict PPH, because only 41% of women with an identified risk factor go on to develop PPH (Sherman et al., 1992). It is therefore widely accepted that the most effective strategy to reduce maternal mortality from PPH is to provide preventive management for all women during childbirth (RCOG, 2009). Each woman should be assessed for the likelihood of developing PPH before labour and risk reduction should be implemented. This includes the detection and treatment of anaemia, and the development of a birth plan to ensure the provision of adequate shifts and resources to manage a woman who develops PPH. Referral to a tertiary centre should be recommended for high-risk patients.

2.2.1.1. Detection and correction of anaemia

A review of associated factors, as demonstrated above, shows an association of PPH with anaemia. Anaemia increases the risk both by reducing the woman's tolerance to blood loss and through a direct effect on the myometrium (Allen, 1997). Women with moderate anaemia are less able to cope with PPH, leading to increased postpartum morbidity. It is therefore essential to diagnose and treat anaemia so that blood haemoglobin is optimised before delivery (Lewis G. and Drife J., 2001). This is especially important in the developing countries, where the prevalence of anaemia in pregnancy is high. Haemoglobin increase is best achieved with iron prophylaxis throughout pregnancy. Special consideration should be given to women with religious objections to receiving blood products. Those patients should have efforts made to maximize their haemoglobin prior to the time of delivery, including use of intravenous iron if necessary (Litton et al., 2013). They should also be advised of alternative blood products and those products that they find acceptable should be clearly defined.

2.2.1.2. Care during early labour (first and second stages)

When women present in labour it is sensible to identify women who may be at increased risk of excessive bleeding, if they have not been recognised antenatally. Such identification allows these patients to have an access to medical facilities where trained staff, blood banking, laboratories, and radiographic expertise exist to accurately manage PPH. For women with identifiable risk factors, consideration should be given to extra precautions such as IV access and cross-matching of blood. The second stage should be short and delivery assistance should commence when indicated.

Routine episiotomy is associated with a 27% increase in PPH at normal birth and so should be used cautiously for delivery (Combs et al., 1991a; Stones et al., 1993; Carroli and Mignini, 2009). Avoidance of unnecessary episiotomies may contribute to the reduction in blood loss after delivery. As in one randomised controlled trial (RCT) of routine versus selective episiotomy, in which blood loss was evaluated after childbirth, significantly less blood loss occurred in women allocated to a restrictive episiotomy policy (House et al., 1986). Moreover, a systematic review of

RCTs showed that compared with routine use, restrictive episiotomy involved less posterior perineal trauma (Risk ratio (RR) 0.67; 95% CI 0.49-0.91), less suturing (RR 0.71; 95% CI 0.61-0.81) and fewer healing complications (RR 0.69; 95% CI 0.56-0.85). The only disadvantage shown in the restrictive use of episiotomy was an increased risk of anterior perineal trauma (RR 1.84; 95% CI 1.61-2.10). There was no difference in severe vaginal or perineal trauma, dyspareunia or urinary incontinence (Carroli and Mignini, 2009). Therefore, it is advisable to perform selective episiotomy for medical and obstetric reasons only and assist the woman in the controlled delivery of the baby's head and shoulders to help to prevent tears.

2.2.2. Care during the third stage of labour

For effective PPH prevention, special attention should be given to the third stage of labour. The correct management of the third stage of labour plays an important role in the prevention of PPH. Different methods for prevention have been developed for intrapartum care to reduce maternal morbidity and mortality due to PPH. Whatever procedures are to be used to prevent PPH, all should be explained to the woman and her family, providing support and reassurance throughout.

There are two broad approaches to the clinical management of the third stage of labour: expectant and active management. In the following section the different methods of third stage management are reviewed including AMTSL and its components.

2.2.2.1. Active versus expectant management of the third stage of labour

Physiological management, also known as conservative, is where the umbilical cord is not clamped or cut until it has stopped pulsating. Placental separation from the uterine wall occurs without intervention and signs of placental separation are awaited and the placenta is delivered spontaneously or aided by gravity or nipple stimulation (Prendiville et al., 2009). Some women and practitioners prefer expectant management of the third stage of labour, since it is seen as more physiological and avoids uncomfortable procedures shortly after birth when the mother wishes to concentrate on the baby.

Evidence based research has shown that there are feasible and low cost interventions that can prevent PPH. Active management is where the physician facilitates the separation and delivery of the placenta and enhances the efficacy of uterine contractions to shorten the third stage of labour (Maughan et al., 2006). The original definition of AMTSL was intramuscular administration of 10 IU of oxytocin, controlled cord traction (CCT) and early cord clamping (Spencer, 1962). Placental delivery is facilitated by use of the Brandt-Andrews manoeuvre (Figure 4), which involves applying firm traction on the umbilical cord with one hand while the other applies suprapubic counter-pressure. Giving a uterotonic drug to prevent PPH promotes strong uterine contractions and leads to faster retraction and placental separation and delivery.

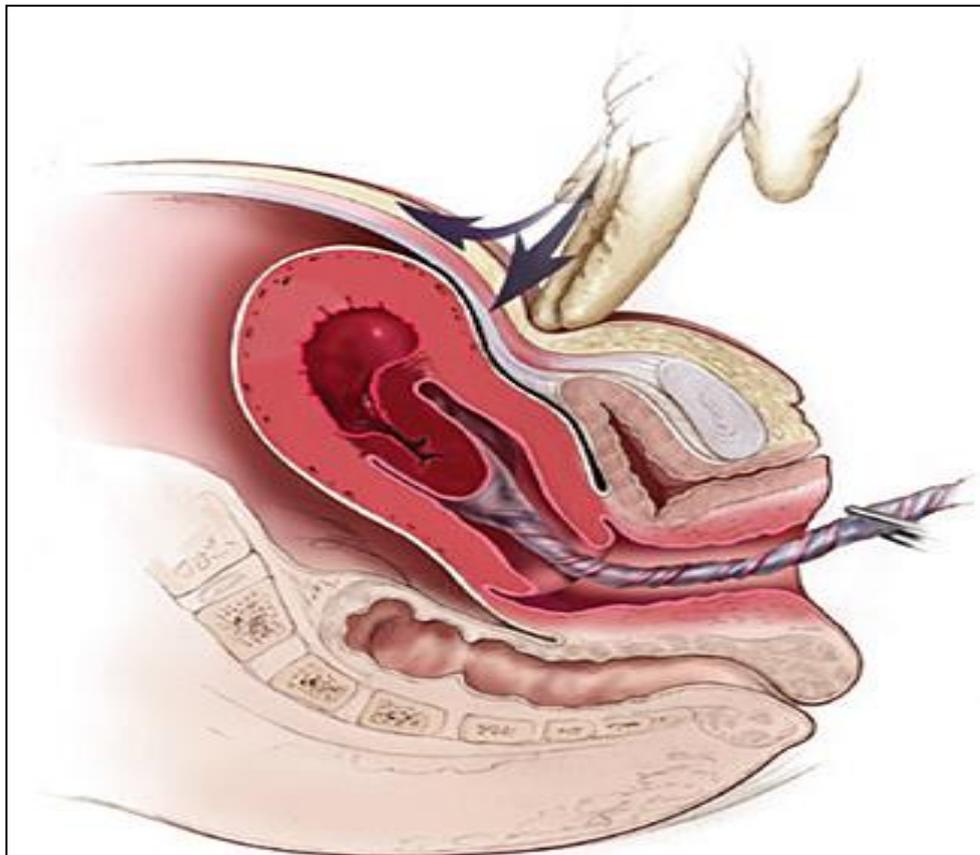


Figure 4. Brandt-Andrews manoeuvre for cord traction (Anderson and Etches, 2007)

The effects of active and expectant management of the third stage of labour were compared in four high quality randomised trials (two were conducted in the United Kingdom and one each in the United Arab Emirates and Ireland) (Prendiville et al., 1988; Begley, 1990; Khan et al., 1997; Rogers et al., 1998). It is not easy to compare these studies as different uterotonic drugs (oxytocin, ergometrine, either drug, or both drugs) with different dosages and routes of administration were used. Despite this, their results are informative. The results of all the four studies demonstrated that AMTSL was associated with a reduction in PPH (up to 70%), and with a reduction in the length of the third stage of labour, suggesting a clear benefit of AMTSL over expectant management in reducing PPH. According to Prendiville and colleagues, AMTSL involves giving a prophylactic uterotonic, early cord clamping and CCT to deliver the placenta (Prendiville et al., 1988). The most recent Cochrane systematic review compared active versus expectant management of labour in seven studies (involving 8,247 women), and found that AMTSL in hospitals with mixed levels of PPH risk reduces the risk of PPH > 1000 mls (RR 0.34; 95% CI 0.14-0.87, three studies, and 4,636 women), but the evidence was of very low quality. In the subgroup of women at low risk of excessive bleeding, there were similar findings (RR 0.31; 95% CI 0.05-2.17, two studies, 2941 women), except there was no significant difference identified between groups for severe haemorrhage or maternal Hb less than 9 g/dl (at 24 to 72 hours). Overall the authors stated that active management showed a significant decrease in primary blood loss greater than 500 mls, and mean maternal blood loss at birth, maternal blood transfusion and therapeutic uterotonics during the third stage or within the first 24 hours, or both. The review concluded that active management also increases the risk of side effects such as postnatal hypertension, after pains and return to hospital due to bleeding. The trials included in this review used syntometrine[®] or ergometrine in their intervention arm which could explain the occurrence of these adverse outcomes. AMTSL is also associated with a reduction in the birth weight which may reflect a reduction in the neonate blood volume due to early cord clamping (Begley et al., 2015).

The implementation of AMTSL remains controversial, despite the evidence of its efficacy in randomised trials (Vivio and Williams, 2004). This might be because there are variations in the components of active management. For example several types of AMTSL are described: uterotonic, with CCT and fundal massage (FIGO/ICM, 2004) or uterotonic, with early cord clamping and CCT (Prendiville et al., 1988). There are also differences in the timing of cord clamping: this can be immediately after the delivery of the baby or within a set time after the childbirth. Timing the initiation of CCT is also an issue, with some waiting for signs of placental separation and others not (Begley et al., 2015). Examples of the variation in practice of AMTSL in different organisation/countries are shown in Table 2.

These recommendations; however, are not exactly followed in practice when the policy of AMTSL is assessed. For example, three settings included in the table below namely Egypt, Kenya and Uganda were assessed for their existing policy of AMTSL as a primary step of a multicentre trial on the effect of AMTSL with and without CCT conducted in 8 countries (Gulmezoglu et al., 2012). All the three sites practised CCT, intramuscular or intravenous oxytocin 10 IU, but the timing of administration was different. In Kenya, cord clamping was described as delayed, whereas other sites were practising immediate cord clamping, which was not recommended in Egypt. Uterine massage after placental delivery was part of routine management in about 50% of cases in Egypt. In Kenya and Uganda, uterine massage is part of the AMTSL recommendation (Table 2) but it was not practiced.

Table 2. Recommendations for AMTSL according to the organisation/country, (FIGO= International Federation of Gynaecology and Obstetrics, ICM= International Confederation of Midwives, WHO = The World Health Organisation, RCOG= Royal College of Obstetrics and Gynaecology, ACOG= The American College of Obstetricians and Gynaecologists, NICE= The National Institute for Health and Clinical Excellence, MOHP= Ministry of Health and Population).

Organisation/ country	Oxytocin	Cord clamping	Time of oxytocin	CCT	Uterine massage	Cord drainage
FIGO/ICM (FIGO/ICM, 2003)	Yes	—	Within one minute after delivery of baby	Yes	Yes	—
RCOG (RCOG, 2009)	Yes 5 or 10 IU IM	Early- only when indicated			—	—
NICE (NICE, 2007)	Yes 10IU IM	Early	—	Yes	—	—
WHO (WHO, 2006)	Yes 10 IU	Delayed (at around 3 minutes)	Within one minute after delivery of baby	Yes	Yes	—
WHO (WHO, 2007a)	Yes 10 IU	Delayed (at around 3 minutes)	Within one minute after delivery of baby	Yes	Yes	—
WHO (WHO, 2012)	Yes 10 IU (IV/IM)	Delayed (1-3 minutes)	—	Optional	No	—
Egypt (MOHP, 2001)	Yes (5 IU) IM	Delayed	At the time of the delivery of the anterior shoulder	Yes	—	—
SOGC (Leduc et al., 2010)	Yes 10IU IM	Delayed	After delivery of the anterior shoulder	—	—	No
Kenya (Kimathi et al., 2002)	Yes 5 IU	—	After delivery of baby	Yes	Yes	—
Uganda (Armbruster, 2007)	Yes	—	Within one minute after delivery of baby	Yes	Yes	—

Furthermore, evidence of the variation was also seen in a survey, involving 14 European countries designed to ascertain and compare policies for management of the third stage of labour following vaginal delivery (Winter et al., 2007). The result showed considerable differences in policies for managing the third stage of labour both between and within countries. Policies for using uterotonics for the management of the third stage were widespread, but the oxytocic agents, timing, clamping of and cutting the umbilical cord and the use of CCT differed widely. Overall, 90% (1052/1175) of units surveyed recommend uterotonic prophylaxis, 66% (770/1175) recommend early cord clamping and 41% (481/1175) recommend CCT (Winter et al., 2007).

There is no consensus on the optimal time for cord clamping. Delayed umbilical cord clamping is recommended for improved maternal and infant health and nutrition outcomes. Delayed umbilical cord clamping (not earlier than 1 min after birth) should be understood as the lower limit period supported by published evidence. WHO recommends that the umbilical cord should not be clamped earlier than is necessary for applying cord traction to reduce PPH and speed delivery of the placenta (WHO, 2012), which the guideline development group clarified would normally take around 3 min.

Huge numbers of studies have been conducted examining different aspects of routine management of the third stage of labour. However, in spite of all the previous work on AMTSL, there remains confusion amongst clinicians over the optimal AMTSL packages to balance the benefits and harms. There is also frequent disagreement over in which order the components of AMTSL should be given. For example, in case of uterotonic the type, doses, time, as well as the route of administration, remain controversial. It is suggested that the prophylactic administration of uterotonic will reduce bleeding and the risk of severe haemorrhage. However, active management is associated with a number of unpleasant side effects (e.g. nausea, vomiting, and hypertension). Additionally, in specific developing countries the feasibility of widespread of active management requires consideration of the costs, the storage and distribution needs of drugs, the availability of skilled birth attendants, and the quality of the health services.

The FIGO and the ICM recommend that skilled birth attendants provide AMTSL for all vaginal births (FIGO/ICM, 2003). The WHO, however, recently recommended that all women should be offered uterotonics, but not the whole package of the active management

(WHO, 2012). The recommendations were against uterine massage and early cord clamping as being one of practices of AMTSL, rather CCT was left to the preference of the woman and healthcare provider. In the absence of a skilled birth attendant who can provide all of the components of AMTSL, the WHO, FIGO, and ICM recommend that oxytocin (10 IU) or misoprostol (600 mcg orally) should be given by a health worker trained in its use to prevent PPH. Oxytocin is preferred to other uterotonic drugs where its use is feasible (Mathai et al., 2007; WHO, 2012).

The different components of the AMTSL have been investigated to find out the effect of different practices on the reduction of postpartum blood loss and the possible adverse effects. These included the type and timing of administration of the uterotonics and the timing of cord clamping, uterine massage and whether to apply cord traction for placental delivery or not. The following section will discuss these components and other different measures used to prevent PPH.

2.2.2.2. Type of drug used for the prevention of PPH

The routine prophylactic administration of an uterotonic agent is an integral part of the AMTSL. There is a variation in the clinical opinion about which is the most effective uterotonic and its appropriate route of administration (parenteral IV/IM, sublingual, oral, or rectal). An ideal uterotonic agent should produce quick, strong and sustained uterine contractions without any significant adverse effects. Uterotonic agents are divided into three categories: oxytocin, ergot alkaloids and prostaglandins. There are several published Cochrane systematic reviews about the use of various uterotonic drugs in the third stage of labour for PPH prevention (McDonald et al., 2004; Liabsuetrakul et al., 2007; Su et al., 2012; Tuncalp et al., 2012; Westhoff et al., 2013).

A. Uterotonic drugs

I. Prophylactic oxytocin (Syntocinon[®], Pitocin[®])

Oxytocin is a hormone which causes contraction of the myometrium and the myoepithelial cell of the breast. It has been showed that the hormone is synthesised in the hypothalamus, then transported to the posterior pituitary for storage, and stimulates uterine activity (Dale, 1909). Blair Bell first reported its efficacy in the treatment of PPH (Blair Bell, 1909). In 1953 Vincent DuVigneaud was able to identify the structure of oxytocin and synthesise the

hormone a year later (Francis and Francis, 1956). He gained a Nobel Prize for this work. The mode of action of oxytocin involves stimulation of the upper uterine segment to contract in a rhythmical fashion which constricts spiral arteries and decreases blood flow through the uterus. Its effect is seen with within 2-3 minutes lasting for up to 60 minutes when given by intramuscular route. It acts within less than a minute after intravenous administration, with the uterine response subsiding within 1 hour of cessation of IV administration. Metabolism of oxytocin is via the liver and its excretion is through the renal and hepatic routes. Because of the structural similarity between oxytocin and vasopressin, oxytocin has an anti-diuretic effect; therefore, prolonged infusion can cause water intoxication, particularly if given in a large volume of electrolyte-free solution, so that hyponatraemia, confusion, convulsions, coma and cardiac failure may occur (Breathnach and Geary, 2009).

Several studies have provided evidence on the effectiveness of routine prophylactic administration of an oxytocic in AMTSL for reducing PPH. The most recent Cochrane review included 10,806 women in 20 trials with considerable variation in the doses and the route of administration. It found a clear benefit of the use of oxytocin in the third stage of labour compared to no uterotonic (Westhoff et al., 2013). Oxytocin use was associated with a lower incidence of PPH > 500 mls (RR 0.53; 95% CI 0.38-0.74; six trials, 4203 women) and less need for therapeutic uterotonics (RR 0.56; 95% CI 0.36-0.87, four trials, 3174 women). When compared to ergot alkaloids, prophylactic oxytocin was superior to ergot alkaloids in preventing PPH greater than 500 mls (RR 0.76; 95% CI 0.61-0.94; five trials, 2226 women). Use of prophylactic oxytocin was associated with fewer side effects compared with use of ergot alkaloids. However, the authors stated that there is limited high-quality evidence supporting a benefit of prophylactic oxytocin over ergot alkaloids. However, the use of prophylactic oxytocin was associated with fewer side effects, specifically nausea and vomiting, making oxytocin the more desirable option for routine use to prevent PPH. The finding that oxytocin decreases the risk of PPH by about 60% (RCOG, 2009), and the need for therapeutic oxytocics, compared with no uterotonic (Westhoff et al., 2013), means that oxytocin is now the drug of choice to be given routinely as a part of the AMTSL to all mothers (RCOG, 2009).

Some of the known disadvantages are that oxytocin has a short half-life (mean 3 minutes); it is not very heat stable (stable at temperatures up to 25°C) so requires refrigeration, it needs parenteral administration with sterile equipment and to be given by skilled personnel. These obstacles restrict the use of oxytocin in many low-resource settings and home births where delivery is usually conducted by an unskilled birth attendant.

The solution for some of the oxytocin known problems can be achieved by using oxytocin-Uniject. The oxytocin-Uniject device is a plastic, nonreusable, disposable syringe prefilled with a single dose of 10 IU of oxytocin. The oxytocin is enclosed in a sealed blister, and a permanent needle is attached (Strand et al., 2005). Introduction of the Uniject may facilitate the application of the AMTSL, particularly in the developing countries, thus reducing maternal mortality due to PPH. A study conducted in Angola found that Uniject showed a marked reduction in the rate of blood loss ≥ 500 mls (316/782 (40.4%) vs. 67/814 (8.2%), $p < 0.001$) (Strand et al., 2005). Tsu and co-workers conducted two separate studies in Indonesia and Vietnam on the use of oxytocin in prefilled Uniject injection devices for managing third-stage labour (Tsu et al., 2003; Tsu et al., 2009). These studies reveal that the use of the device is easier and more practical than the traditional way using a needle, syringe and ampoule. Midwives, with the use of a prefilled injection device, overcame many of the barriers cited by midwives with regard to the use of oxytocin in ampoules, such as trying to break ampoules and fill syringes in a hurry. This device enabled midwives to deliver the correct dose of oxytocin in the third stage of labour in a safe and timely way. Use of such an injection device for oxytocin may increase the acceptability and practice of AMTSL in primary level facilities.

The timing of oxytocin administration also differs greatly between clinicians, as various professionals use oxytocin immediately after the delivery of the baby. In the AMTSL, it has been recommended to administer relevant drugs at the delivery of the anterior shoulder. The administration of uterotonic prior to placental delivery raised the concerns that this could inhibit the delivery of the placenta. However, available data propose that immediate administration of oxytocin does not lead to greater need for manual removal of the placenta (Rajan and Wing, 2010; Begley et al., 2015). The impact of early administration on blood loss remains uncertain. There was no difference in the incidence of PPH between women who had oxytocin immediately after the delivery and those who had oxytocin after the delivery of the placenta (56/745 [7.5%] vs. 72/741 [9.7%], $P=0.15$)

(Jackson et al., 2001). The most recent Cochrane review of the timing of prophylactic uterotonics found that timing of the administration of oxytocin either before or after the expulsion of the placenta did not have any significant effect on the rate of PPH, the length of the third stage of labour or the rate of placental retention (Soltani et al., 2010). This review included a small number of trials and investigated only intravenous infusion of the oxytocin. Therefore, the authors recommended further studies to examine different routes of administration and different maternal and neonatal outcomes.

The dose of oxytocin has not been directly subjected to study, but it has been noted that administration of 5 IU intravenous bolus of oxytocin can result in profound hypotension due to a decrease in the resistance of vascular smooth muscles, (Figure 5) (Weeks, 2010). Therefore, oxytocin should be given preferably as a small volume infusion. It is recommended to use 5 IU oxytocin as a slow intravenous injection and replace it with a continuous infusion of 20 IU oxytocin in 500 mls crystalloid solution to maintain uterine contraction. It has been stated that administration of 10 units of oxytocin intramuscularly or 20 units diluted in 500 mls of normal saline to be given as an intravenous bolus appear to be the most effective drug doses (Maughan et al., 2006). Owing to its short plasma half-life for a sustained effect, IV infusion is preferred because it provides a steady flow of the drug (FIGO/ICM, 2003; Lalonde, 2012).

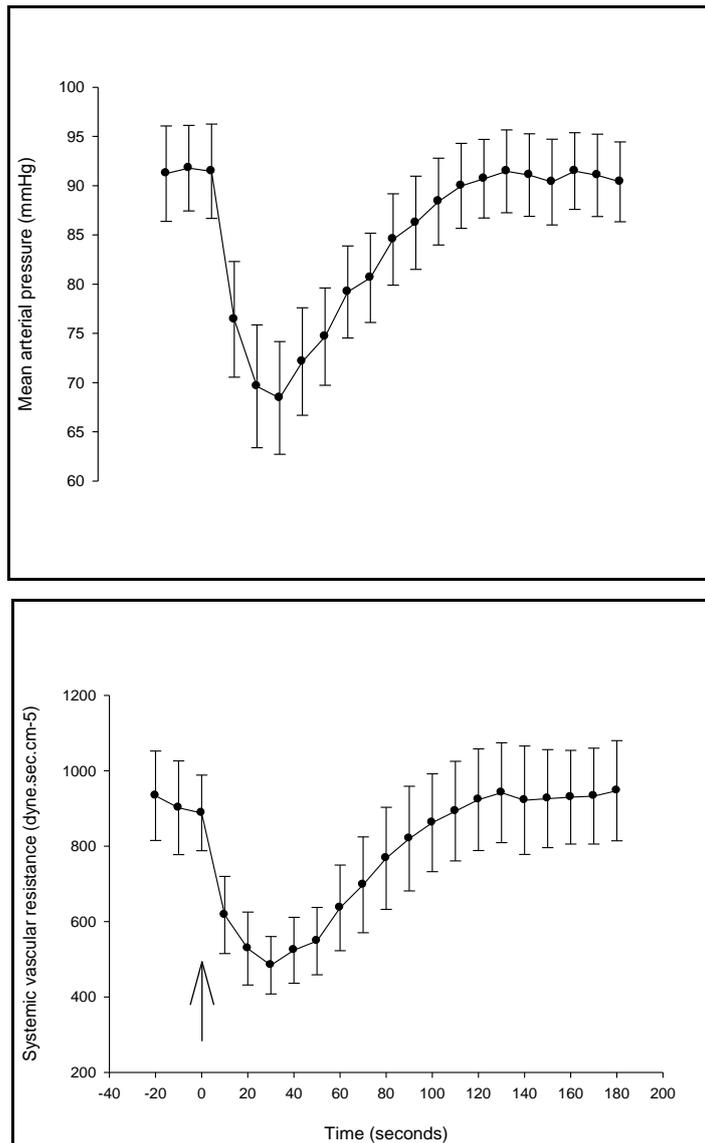


Figure 5. Systemic vascular resistance, mean arterial pressure and cardiac output represented as means vs. time (seconds). Arrow indicates timing of 5 unit oxytocin bolus (Weeks, 2010)

II. Oxytocin agonist (Carbetocin)

Carbetocin is a synthetic oxytocin analogue structurally modified to possess long-acting agonist properties. It was first described in 1987 (Atke and Vilhardt, 1987). The clinical and pharmacological characteristics of carbetocin are similar to those of naturally occurring oxytocin. The drug binds to oxytocin receptors present on the uterine smooth muscle, causing rhythmic contractions of the uterus, increased frequency of existing contractions, and increased uterine tone by releasing calcium ions. Carbetocin can be administered by intravenous or intramuscular route. It has been found that an intramuscular dose of carbetocin acts for a longer time than intravenous carbetocin. The uterine activity for an IM injection persisted for approximately 120 minutes and for intravenous injection for about 60 minutes (Hunter et al., 1992). This can be explained by the time required for the absorption of carbetocin into the circulation from the intramuscular site. Oxytocin requires repeated injections or an infusion of several hours, with a variability of the administered doses; carbetocin has 4-10 times longer half-life (about 40 minutes) than oxytocin given in a single injection (Hunter et al., 1992). The optimal dosage of carbetocin used in the third stage of labour is 100 mcg (Boucher et al., 1998).

The efficacy of carbetocin in the AMTSL has been investigated following vaginal and caesarean deliveries. Some evidence demonstrates similarity in PPH prevention between carbetocin and oxytocin (5 IU) following caesarean section. The evidence also suggests that 100 mcg intravenous carbetocin could significantly reduce the use of additional uterotonic agents (Attilakos et al., 2010). A RCT compared the efficacy of 100 mcg intramuscular carbetocin against a 2-hour 10 IU oxytocin IV infusion, for reducing the incidence and severity of PPH in women at risk of PPH who underwent vaginal delivery. Although the result showed reduced need for additional uterotonic, uterotonic intervention was clinically indicated in 37 of the women (44.6%) who received carbetocin compared to 49 of the women (63.6%) given an IV oxytocin infusion ($P < 0.02$). The study found insufficient evidence in terms of the benefit of carbetocin over oxytocin for preventing PPH (Boucher et al., 2004).

In a Cochrane review includes 11 studies (2,635 women) (Su et al., 2012). The review compared carbetocin with oxytocin (IV), syntometrine[®] (IM) or placebo. Carbetocin was administered as 100 mcg IV in all the trials. Six trials compared carbetocin with oxytocin; four of these were conducted with women undergoing caesarean deliveries, one was for women following vaginal deliveries and one did not state the mode of delivery clearly. Use of carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics (RR 0.62; 95% CI 0.44-0.88; four trials, 1173 women) compared to oxytocin for those who underwent caesarean section, but not for vaginal delivery. Compared to oxytocin, carbetocin was associated with a reduced need for uterine massage following both caesarean delivery (RR 0.54; 95% CI 0.37-0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95% CI 0.51-0.94; one trial, 160 women). Carbetocin also resulted in a lower risk of PPH (\leq 500 mls) compared to oxytocin in women who underwent caesarean delivery (RR 0.55; 95% CI 0.31-0.95; three trials, 820 women). Comparison between carbetocin and syntometrine[®] showed a lower mean blood loss in women who received carbetocin compared to syntometrine[®] (Mean difference (MD) -48.8 mls; 95% CI -94.8 to -2.9; four trials, 1030 women). There was no statistically significant difference in terms of the need for therapeutic uterotonic agents, but the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group: nausea (RR 0.24; 95% CI 0.15-0.40; four trials, 1030 women); vomiting (RR 0.21; 95% CI 0.11-0.39; four trials, 1030 women). The incidence of postpartum hypertension was also significantly lower in women who received carbetocin compared to those who received syntometrine[®]. Overall, the authors concluded that there is evidence to suggest that 100 mcg of intravenous carbetocin is more effective than oxytocin for preventing PPH in women undergoing caesarean deliveries, but more studies are needed to validate this finding (Su et al., 2012).

Adverse events reported by at least 10% of women who received prophylactic intravenous carbetocin following caesarean delivery include headache, tremor, hypotension, flushing, nausea, abdominal pain, itching and a feeling of warmth. Uncommon or sporadic adverse events are tachycardia, sweating, dizziness, chest pain, vomiting and a metallic taste in the mouth (Rath, 2009).

III. Ergot alkaloids

John Stearns was the first to highlight the use of ergots for PPH in 1882. Oral administration of aqueous ergot extract is associated with dramatic and very strong contractions of the uterine musculature. This was demonstrated by Moir in 1932 who described it as the 'John Stearns effect' (Dunn, 2002). In 1935, Dudley and Moir isolated the pure crystallised substance from the water soluble extract of ergot that was responsible for the 'John Stearns effect' and they called it 'ergometrine' (Dudley and Moir, 1935). The drug is known under different names in different countries. The Americans call their preparation ergonovine, in the UK it is named ergometrine and the Swiss use the name ergobasine. Ergot alkaloids (ergometrine and methyl ergometrine) are usually given intramuscularly or intravenously, although the oral route is also possible. The most common type of ergot alkaloid is methyl ergometrine; this ergometrine was the first uterotonic drug used in the early 1950s. It is known to increase the tone of the uterine muscles via stimulation of myometrial alpha adrenergic receptors. It prevents haemorrhage by compressing the myometrial blood vessels through fast (less than a minute) rhythmic contraction of the myometrium and long-lasting tetanic contractions. The onset of action is 2-5 minutes after intramuscular injection of the standard dose (0.25 mg of ergometrine). Its mean plasma half-life is 30 minutes and the clinical effect continues for 3 hours. The metabolism is by the hepatic route. The drug is both heat- and light-sensitive therefore it should be stored at temperatures below 8°C, away from light but should also be protected from freezing (Lalonde, 2012).

For the AMTSL, ergot alkaloids were compared to no uterotonic agent in a Cochrane systematic review. Parenteral administration of ergot alkaloids significantly decreased the mean blood loss and the risk of PPH > 500 mls (RR 0.38; 95% CI 0.21-0.69). On the other hand, more treated women had elevated blood pressure (RR 2.60; 95% CI 1.03-6.57), vomiting (RR 11.81; 95% CI 1.78- 78.28) and after pain requiring analgesia (RR 2.53; 95% CI 1.34-4.78) (Liabsuetrakul et al., 2007). Other side effects include nausea, vomiting, headache, dizziness and increased blood pressure (Breathnach and Geary, 2009). Additionally, ergometrine was found to be associated with increased risk of coronary artery spasm (Carey, 1993). As ergot alkaloids mediate their action via stimulation of the α -adrenergic receptors which can result in vasoconstriction, the drug is contraindicated in women with hypertension, pre-eclampsia, heart disease, and peripheral vascular disease

(Breathnach and Geary, 2009). Most studies used intramuscular ergometrine. However, the one study that used the intravenous route reported that 0.5 mg intravenous ergometrine was associated with a significant increase in the incidence of manual removal of the placenta (3%) compared to the physiological management of the third stage of labour (0.1%) (Begley, 1990). The one trial that examined the oral route showed no significant benefit of ergot alkaloid over a placebo, and concluded therefore that oral ergometrine is not an alternative to oxytocin in the management of the third stage of labour (deGroot, 1996). Overall the evidence suggests that although ergometrine is effective at PPH prophylaxis, oxytocin is much better tolerated.

In 1961, the intramuscular combination of oxytocin and ergometrine was studied tocographically. The author found that the combination of both drugs resulted in the strength and duration of action of ergometrine, and the speed of oxytocin (effective within 2.5 minutes) (Embrey, 1961). Syntometrine[®], consisting of 5 units of oxytocin and 0.5 mg of ergometrine, has been, therefore, designed to take advantage of the rapid onset of action of oxytocin with the longer action of ergometrine. The Cochrane review of the prophylactic use of syntometrine[®] versus oxytocin found that syntometrine[®] reduced the occurrence of PPH > 500 mls (OR 0.82; 95% CI 0.71-0.95) but not of PPH > 1000 mls (OR 0.78; 95% CI 0.59-1.04). Syntometrine[®] was associated with significantly more risk of side effects such as hypertension (OR 2.81; 95% CI 1.17-6.73) and vomiting (OR 4.92; 95% CI 4.03- 6.00) (McDonald et al., 2004). Therefore, although oxytocin would appear to be marginally less effective than syntometrine[®], it is generally recommended as a first-line treatment due to its low rate of side effects and greater stability in light and heat.

IV. Prostaglandins

4.1 Intramuscular prostaglandins

Prostaglandins are found in most tissue and organs including decidua, fetal membranes and placenta. Synthetic prostaglandins have strong uterotonic properties and are used widely in obstetric and gynaecological practice for cervical ripening, induction of labour and termination of pregnancy. They are available in different forms of preparations according to their use: injectable, tablet or gel. They include prostaglandin 15-methyl-PGF₂ α , (Dinoprost[®]) and its analogue (Carboprost, Hemabate[®]), prostaglandin E₂ analogue (Dinoprostone, Sulprostone [Nalador[®]]) and prostaglandin E₁ analogues (Misoprostol and Gemeprost).

Prostaglandin F₂ α and prostaglandin E₂ are mainly used for the treatment of PPH and the data on their application for PPH prophylaxis is very limited. In the Cochrane review for prostaglandins for preventing PPH, when compared with no uterotonic, injectable prostaglandins resulted in less mean blood loss (MD -224ml; 95% CI -420.35 to -27.60 ml), and shorter duration of the third stage of labour, compared to conventional uterotonics (MD -1.25 minutes; 95% CI -1.42 to -1.08 minutes) (Tuncalp et al., 2012). However, concerns about its safety, costs and availability restrict its appropriateness over other conventional injectable uterotonics for routine prophylactic management of the third stage of labour and especially in low-resource settings. Owing to its vasoconstrictive and bronchoconstrictive effects, intramuscular prostaglandins were also found to commonly cause vomiting, nausea, abdominal pain and diarrhoea and bronchospasm (Tuncalp et al., 2012). Contraindications include cardiac and pulmonary disease. The nature of other side-effects (nausea, vomiting and diarrhoea) could affect the immediate relationship between the mother and her newborn baby in the early hours after delivery. Furthermore, the drug is both light- and heat-sensitive and must be kept refrigerated at 4°C. Overall, although injectable prostaglandins appear to be superior to placebo, they were not preferable to conventional uterotonics in the management of the third stage of labour. Injectable prostaglandins are therefore restricted to use for treatment of PPH rather than for prophylaxis (Bohlmann and Rath, 2013).

V. Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl, PGE1) is a synthetic form of prostaglandin E1 analogue. The drug was initially developed for the prevention of peptic ulcers induced by non-steroidal anti-inflammatory drugs as it has mucosal protective properties (Silverstein, 1998). Misoprostol selectively binds to the myometrial EP-2/EP-3 prostanoid receptors, thereby promoting uterine contractility. It is metabolised via the hepatic route. Misoprostol can be given orally, sublingual buccally, vaginally, intraumbilically and rectal. After oral administration, misoprostol is rapidly absorbed and converted to its pharmacologically active metabolite, misoprostol acid. It appears in the serum within 2 min and reaches peak levels after 20 min (Abdel-Aleem et al., 2003). Oral or sublingual misoprostol shows promising results when compared with placebo in reducing blood loss after delivery (Tuncalp et al., 2012). A study conducted in rural India has revealed the efficacy of misoprostol tablets for prevention of PPH. Over 1600 low-risk women were randomly selected to receive oral misoprostol (600 mcg) or placebo at the time of delivery (Derman et al., 2006). Blood was collected for the first hour postpartum. In the misoprostol group, the risk of PPH (> 500 mls) was halved, and the risk of severe PPH was reduced by 80%. The authors conclude that "oral misoprostol is safe, effective, and inexpensive (\$1.00 per 600 mcg dose) for women giving birth in low-resource settings". Finding that misoprostol is inexpensive, easy to administer and stable at room temperatures, in the management of the third stage of labour, misoprostol is potentially the most crucial uterotonic to be used in low-recourse settings (Parsons et al., 2007; Mousa et al., 2014). Additionally, although other prostaglandins (prostaglandin E2 and prostaglandin F2 α) can cause myocardial infarction and bronchospasm, misoprostol does not (Ulmann and Silvestre, 1994). However, its use in obstetrics and gynaecology is still off-label in many countries over the world and until recently, it was not approved by the Food and Drug Administration (FDA) for use in pregnant women. In spring 2002, FDA made new changes to the misoprostol label; the statement that misoprostol is contraindicated in pregnancy has been removed and a labour and delivery section has been added.

The drug poses some unpleasant adverse effects. The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia which are known to be dose- and route -related (Hofmeyr et al., 1998; Hofmeyr et al., 2009; Elati and Weeks, 2012). Higher rates of shivering and fever are associated with oral and sublingual routes of administration, as compared with rectal administration (Chong et al., 2004). In terms of misoprostol dose-related side effects, meta-analysis results indicated that during the third stage of labour, the risk of pyrexia increased 3 fold with 400 mcg misoprostol and six fold with 600 mcg misoprostol when compared with placebo (Hofmeyr and Guemezoglu, 2008). However, misoprostol side effects are transient (resolving within 12 hours or less) (Durocher et al., 2010).

The WHO currently recommends the use of oxytocin rather than misoprostol for the prevention of PPH as an integral part of the AMTSL. Nevertheless, in settings where active management is not being practiced or the birth attendants are of limited skills, they recommend the use of misoprostol (WHO, 2012). In their review, the Bellagio expert group found that misoprostol prophylaxis using an oral or sublingual dose of 600 mcg is more effective than placebo at preventing PPH in community births (RR 0.59; 95% CI 0.41-0.84), but not in hospital settings (RR 1.23; 95% CI 0.86-1.74) (Alfirevic et al., 2007). Therefore, they recommended a single dose of 600 mcg of oral or sublingual misoprostol and that it should not be repeated for 2 hours. According to the latest Cochrane review on the use of misoprostol in the prevention of PPH in a community setting it has been concluded that misoprostol has been effective and safe (Tuncalp et al., 2012). This consistent with the most recent WHO Essential Medicine List which approved “misoprostol for prevention of PPH in setting where oxytocin is not available or cannot be safely used” (WHO, 2011).

There is now a tendency towards community distribution of misoprostol by healthcare workers. Some suggested that oral misoprostol can be given by birth attendants at home birth without additional equipment (Rajbhandari et al., 2010). Oral misoprostol could be the only option in home births in low-resource settings. There is currently an effort toward self-administration of misoprostol as it might contribute to reducing PPH at a home delivery. This has been implemented and subjected to a study in a placebo-controlled trial (MamaMiso) carried out in Uganda. The main aim of the study was to assess the effectiveness and safety of antenatal administration of misoprostol tablets (600 mcg) for

self-administration immediately following home delivery for the prevention of PPH (Weeks, 2012).

B. Other pharmacological measures

I. Tranexamic acid

Tranexamic acid is a synthetic preparation that is derived from the amino acid lysine. It acts as an antifibrinolytic agent that produces its antifibrinolytic effect via the reversible blockage of lysine-binding sites on plasminogen molecules and prevents binding of plasminogen and plasmin to fibrin (Dunn and Goa, 1999). The drug is valuable in a wide range of haemorrhagic conditions as it found to decrease blood loss as well as postoperative blood loss and the need for blood transfusion in a number of different surgeries (Katsaros et al., 1996; Dunn and Goa, 1999). A systematic review of RCTs of antifibrinolytic agents in different types of elective surgery (e.g. cardiac, vascular, liver transplantation and orthopaedic) has found that tranexamic acid reduced the risk of blood transfusion by approximately 39%, and reduced the transfused blood volume by 1.1 units in the patients who required blood transfusion (Henry et al., 2007).

In the field of obstetrics and gynaecology, it has been concluded that tranexamic acid reduces menstrual blood loss with no evidence of adverse side-effects (Lethaby et al., 2000). It is therefore widely used for women's menorrhagia. During the delivery of the placenta, the fibrinolytic system is activated leading to an increase in the plasminogen activators and fibrin degradation products with an increased rate of degradation of fibrinogen and fibrin. This activation can last from 6 to ten hours postpartum, which may contribute to increased haemorrhage (Astedt, 1987). In the context of preventing PPH during the third stage of labour, beside the currently used prophylactic uterotonic, intravenous tranexamic acid could be used to reduce the blood loss. A Cochrane review of using tranexamic acid for preventing PPH found that the drug decreases postpartum blood loss after vaginal birth and after caesarean section in the dosage of 1 g or 0.5 g IV (RR 0.51; 95% CI 0.36-0.72; two studies, 453 women) (Novikova and Hofmeyr, 2010). However, the authors recommended further investigations to confirm the efficacy and safety of this regimen for preventing PPH.

An additional advantage of using tranexamic acid is its cost-effectiveness. In one study on total hip arthroplasty, prophylactic tranexamic acid preoperatively was found to save blood transfusions and money (47 Euros per patient) (Johansson et al., 2005). However, the drug is not free from side effects. Tranexamic acid was associated with gastrointestinal symptoms with diarrhoea, nausea and vomiting occurring in about 10% of patients. Hypotension, blurred vision, thrombosis, renal cortical necrosis and retinal artery obstruction are rare complications of tranexamic acid (Astedt, 1987).

II. Traditional Chinese medicine

Traditional Chinese Medicine (TCM) is an ancient medical system in China that has been used for many centuries. TCM combines the use of medicinal herbs, acupuncture, food therapy, massage and therapeutic exercise. TCM has specific theories for concepts of disease prevention, aetiology, systems of diagnosis and treatment which are vital to its practice (Fulder, 1996). TCM treatment consists typically of complex prescriptions of a combination of different components. The combination is based on the Chinese diagnostic patterns (that is inspection, listening, smelling, inquiry, and palpation) and follows a completely different rationale than many Western drug treatments (Liu et al., 2001). Typical treatment in TCM is based on one or several herbs, which are taken from plants, as the basic drug for a disease.

In the context of preventing PPH, TCM has its own approach and has been used for thousands of years. The traditional way to use TCM in preventing PPH is to orally take a “decoction”, a water extraction of mixed herbs, immediately after delivery. However, some TCM is also given in the form of an injection. In a special TCM formulation for PPH, each herb has some special function; some herbs act to improve the blood flow, some to stop bleeding, and some for uterine relaxation. For example, modern pharmacological research has demonstrated that Yimucao or Leonorus (known in England as Chinese motherwort), has an ergonovine-like action, acting directly on the uterus (Jin, 2003), leading to contraction of uterine musculature (Yang et al., 2001), and causing ischemia in the uterine muscular tissue (Zhang and Wang, 2002).

In clinical practice, TCM may be used alone, or combined with conventional medicine, for example, injecting Yimucao alone or injecting Yimucao with oxytocin. Lin and others conducted a multi-centre study on the effect of motherwort injection in preventing PPH after caesarean section, compared with oxytocin alone or in combination. The study was designed as a randomised and single blind multi-centre research. Three groups of participants were divided as follows: 147 cases were given motherwort; 144 cases were given motherwort and oxytocin, 149 cases were given oxytocin alone. The incidence of PPH was 32.0% (47/147) in the motherwort group, 11.1% (16/144) in the motherwort and oxytocin group, and 18.8% in (28/149) in the oxytocin alone group. When comparing the lowest rate of postpartum blood loss in the group of motherwort plus oxytocin, and the highest rate in the motherwort group, this displayed a statistical difference ($P < 0.01$). The authors concluded that combining motherwort and oxytocin is safe and effective in preventing PPH at caesarean section (Lin et al., 2009).

2.2.2.3. Management of umbilical cord

A. Early versus late umbilical cord clamping

Clamping and cutting of the umbilical cord at delivery is by far the oldest and most frequently used 3rd stage intervention in humans. The cord is usually clamped in two places and cut between the two clamps, making it easy for the birth attendant to apply CCT, and promoting quick delivery of the placenta. In that strategy, the umbilical cord is usually clamped shortly after childbirth, this is in general carried out in the first 30 seconds after birth, regardless of whether the cord pulsation has stopped or not (McDonald and Middleton, 2008). After delivery of the baby, the placenta continues to function and the cord blood continues to flow carrying oxygen to the newborn. So as long as the cord remains unclamped, the average transfusion to the newborn is 19 ml/kg birth weight, corresponding to 21% of the neonate's final blood volume (Hutton and Hassan, 2007). Around 75% of the transfusion occurs in the first minute of infant life. The transfusion rate in the first minute can be increased by the use of intravenous uterotonics (to 89%), or by holding the newborn 40 cm below the level of the placenta (Yao et al., 1968).

The optimal timing of cord clamping has been subject to debate for many years. There are differences in the rate and timing of clamping of the cord in the current packages of AMTSL, as clamping of the umbilical cord can be done immediately after delivery of the baby, or within a set time after the childbirth. In a survey of 14 European countries that compared policies of management of the third stage of labour, the rate of early cord clamping varied from 17% (4/23) of units in Denmark to 90% (98/109) in France (Winter et al., 2007).

Several reviews have concentrated on the potential advantages and risks of late versus early clamping of the umbilical cord. Hutton and Hassan, (2007) have noticed that early cord clamping has been proposed as a main cause of anaemia in infancy (Hutton and Hassan, 2007). In contrast, late clamping has been shown to possess some potential benefits in preterm babies in terms of a decreased need for blood transfusion and a lower risk of intraventricular haemorrhage (Rabe et al., 2004). Late cord clamping can be advantageous for the infant by improving their iron level, which may be of clinical value, particularly in infants with poor nutritional condition in low-income settings (van Rheezen and Brabin, 2006).

The effects of delayed cord clamping on infant health beyond the neonatal period were subjected to study in low- and middle-income countries. Results from meta-analyses showed that delayed cord clamping results in higher levels of serum ferritin at 3–6 months of age (Hutton and Hassan, 2007). A similar result was found in a high-income country (Sweden) where higher mean ferritin concentration (117 mcg/L vs 81 mcg/L, $P < 0.001$) and a lower prevalence of iron deficiency (1 (0.6%) vs 10 (5.7%), $P = 0.01$) were found at 4 months of age among infants who had delayed cord clamping, compared to early cord cutting (Andersson et al., 2011). Some may argue that the high blood volume in the circulation of the infant that results from delayed cord clamping can harm the baby as it might result in overloading the neonatal blood volume and consequently increase the likelihood of respiratory distress, polycythemia (Hutton and Hassan, 2007) and increase the risk of jaundice requiring phototherapy (Neilson, 2008). However, no significant differences were found between the effects of delayed versus early umbilical cord clamping on postnatal respiratory symptoms, polycythaemia, or hyperbilirubinaemia requiring phototherapy (Andersson et al., 2011).

Despite all of this evidence, the policy of early cord clamping has still been the dominant one. A survey involving 14 European countries, designed to ascertain and compare policies for management of the third stage of labour following vaginal delivery, revealed that 66% (770/1175) of surveyed maternity units recommend early cord clamping (Winter et al., 2007). Most importantly, the result from meta-analysis (McDonald et al., 2013) comparing early and deferred cord clamping showed that delaying cord clamping does not seem to increase the risk of PPH [severe PPH (RR 1.04; 95% CI 0.65-1.65) or for PPH of 500 mls or more (RR 1.17; 95% CI 0.94-1.44)] and has no effect on the length of the third stage of labour.

B. Controlled cord traction

Cord traction was first described by Brandt (1933) and Andrews (1940) and introduced into routine obstetric practice as the Brandt-Andrews manoeuvre (Spencer, 1962). In 1962, the term CCT was introduced by Spencer as a modification which aims to facilitate the separation of the placenta once the uterus contracts, and thus shorten the third stage of labour. The procedure of CCT is applied while the uterus is contracting, after delivery of the baby, by elevating the uterus suprapubically while maintaining steady traction on the cord (Spencer, 1962). CCT for delivery of the placenta was thought to be an effective technique in decreasing the incidence of PPH, and retained placenta, as well as further need of uterotonic (Khan et al., 1997). However, a recent large multi-centre controlled trial examined the effect of AMTSL with and without CCT on severe PPH (blood loss equal or > 1000 mls) which included 12,163 subjects in the CCT group. Gulmezoglu and colleagues followed a simplified package in the experimental group for the management of the third stage of labour, where all women received an oxytocin injection, the cord was clamped around 1–3 min after delivery of the baby and placental delivery was allowed to occur with the aid of gravity and maternal effort by encouraging women to cough or push after noting the signs of placental separation. Measurement of the blood loss was through the use of the gravimetric method. The primary (non-inferiority) outcome was blood loss of 1000 mls or more (severe haemorrhage). The study findings suggest that omission of cord traction results in very little, if any, increased risk of severe haemorrhage, the blood loss of 1000 mls or more had a RR of 1.09 (95% CI 0.91-1.31) and the upper 95% CI limit crossed the pre-stated non-inferiority margin. Additionally, uterine inversion occurred in one case of the full package group. Uterine inversion is a rare but a life-threatening

condition. It occurs secondary to strong cord traction during the delivery of the placenta, especially if traction is applied before sufficient contractions of the uterine muscle are reached, and without applying effective counter-pressure to the uterine fundus. As CCT requires high levels of manual skills, it is used in limited settings with trained birth attendants in order to apply it safely (Gulmezoglu et al., 2012). The study provides the largest evidence so far on the effect of CCT as part of AMTSL. CCT adds only marginally to the beneficial effect of the full package. The rate of manual placental removal was a significantly higher in the simplified package group (153 cases in the simplified package and 105 women in the full package (RR 1.45; 95% CI 1.14-1.86). In the Cochrane review the results revealed that there was no significant reduction in severe PPH (blood loss > 1000 ml), but a small reduction was observed in PPH (blood loss > 500 ml) and mean blood loss with CCT (Hofmeyr et al., 2015). The reviewers stated that the routine use of CCT can be omitted from the 'active management' package without increased risk of severe PPH, they therefore, did not encourage any changes in the current practice in terms of training in CCT skills for birth attendants who do not have formal training. The review authors stated that “the results of their review are dominated by the large WHO trial, but are consistent with the results of the other included smaller trials”.

C. Placental cord drainage

Placental cord drainage involves immediate unclamping of the previously clamped and cut umbilical cord after delivery of the baby from the maternal side. This will allow drainage of blood freely from the placenta into a container. Sharma et al., was the first one to carry out placental cord drainage in a caesarean section and the technique could be named Sharma's method (Sharma et al., 1995; Sharma et al., 2005). It has been proposed by Wood and Roger (1997) that drainage of placental blood can result in reduction of placenta bulk, allowing adequate contraction and retraction to the uterine muscle, hence facilitating quick delivery of the placenta (Wood and Rogers, 1997). Some clinicians believe that placental cord drainage enhances the delivery of the placenta and lessens complications of the third stage of labour. According to the Cochrane review (Soltani et al., 2011) cord drainage reduced the length of the third stage of labour (MD -2.85 minutes, 95% CI -4.04 to -1.66) and reduced the average amount of blood loss (MD -77.00 ml, 95% CI -113.73 to -40.27). Sharma argues that fetomaternal haemorrhage and discomfort or pain during the

third stage can also be affected by the amount of residual blood in the placenta (Sharma et al., 2005).

It could be argued that deferred cord clamping would have similar effects to that of placental cord drainage, as both methods include draining blood from the placenta. The result from meta-analysis (McDonald et al., 2013) comparing early and deferred cord clamping showed that delaying cord clamping does not seem to increase the risk of PPH.

D. Umbilical vein injection

In 1826, Mojon and Asdrubali first described umbilical vein injection (UVI) for the treatment of retained placenta (Mori et al., 2012). Several studies and systematic reviews have examined the use of intraumbilical oxytocics for the treatment of retained placenta to prevent PPH (Gazvani et al., 1998; Weeks et al., 2010). The Cochrane review of UVI of saline solution plus oxytocin demonstrated no clear evidence of its effectiveness in the management of retained placenta (Nardin et al., 2012). The result however is borderline and the NICE guidelines in the UK have recommended the use of umbilical oxytocin for the treatment of retained placenta (NICE, 2007). The WHO in its latest recommendations says that there is insufficient evidence to recommend an intraumbilical vein injection of oxytocin to treat retained placenta (WHO, 2012).

Routine UVI has been suggested as an alternative way of managing the third stage of labour, as it directs the treatment to the placental bed and uterine wall, resulting in an earlier uterine contraction and placental separation (Neri et al., 1966). It also allows higher doses to be used with a reduction in systemic side-effects. Different studies have been published on the use of an UVI of oxytocin as a prophylactic method in reducing blood loss during the third stage of labour (Ghulmiyyah et al., 2007; Tehseen et al., 2008; Gungorduk et al., 2010). The use of UVI with AMTSL significantly reduced postpartum blood loss, as women in study group who received UVI oxytocin lost 234 mls of blood, while the control group lost 276 mls ($P=0.001$). It also shortened the mean duration of the third stage; 2.59 minutes in the study group and 7.67 minutes in the control group ($p<0.001$) (Tehseen et al., 2008). Balanced against this is a need for training in the technique and a possible higher cost of materials. Use of UVI of saline alone or in combination with oxytocin, has been proposed for third stage management (Ghulmiyyah et al., 2005). However, according to the latest Cochrane review it is not recommended during

the third stage of labour to routinely use oxytocin or any other uterotonics with normal saline via UVI until new evidence is available (Mori et al., 2012). The authors encourage further research to show the effectiveness of oxytocin with normal saline via UVI.

2.2.2.4. Uterine manipulation

A. Fundal squeezing

Crede's manoeuvre is a method that has been advocated to separate the placenta after delivery. However, there is complete disagreement to its benefits because it has been found to cause shock (Claassens, 1957). The procedure of fundal pressure is performed by placing one hand on the uterine fundus and squeezing the uterus between the thumb and fingers to facilitate placental separation and expel the placenta through the birth canal. Although effective, this manoeuvre produces great pain and if performed incorrectly, can lead to haemorrhage and uterine inversion. It is generally no longer recommended in national guidelines.

B. Uterine massage

Following delivery, uterine massage can be used for a variety of purposes. For example, it can be used to ensure that there is no undiagnosed twin after delivery of a baby or assessing or simulating uterine contractility. The joint statement of the FIGO and ICM (FIGO/ICM, 2003) recommend routine massage of the uterus after delivery of the placenta as one component of AMTSL (Table 2). In contrast, in their published comprehensive guidelines on intrapartum management in 2007, NICE did not include uterine massage in its guidelines (NICE, 2007). Uterine massage involves placing a hand on the woman's lower abdomen and stimulating the uterus by rhythmic massage or squeezing movements. Massage is thought to reduce postpartum bleeding through stimulation of myometrial contraction, probably by stimulating the release of local prostaglandin (Abdel-Aleem et al., 2011).

Uterine massage is economical and requires no access to medication or other specialised services, and can be used in any birth location even at home birth. It is noticed that there are very few studies that assess the effectiveness of this method. Abdel-Aleem and others conducted the first RCT aimed to evaluate the effect of persistent uterine massage on blood loss after delivery. The 200 subjects were randomly selected to receive routine

AMTSL (oxytocin 10 IU IV. or IM, immediate cord clamping and CCT) with uterine massage every 10 minutes for the first 60 minutes, or active management without uterine massage. The trial demonstrated a significant reduction in blood loss by 78 mls and a 80% reduction in the need for additional uterotonics in the massage group, compared to the non-massage group. There was no significant reduction in the rate of PPH (4/98 (5%) vs., 8/102 (7%)) (Abdel-Aleem et al., 2006). Another trial which recruited 1,964 women was conducted in Egypt and South Africa. Women in the second study were randomly allocated to 1 of 3 treatment groups: intramuscular oxytocin, sustained uterine massage, or both treatments before delivery of the placenta. Blood loss within 30 minutes of delivery was recorded. The trial showed that uterine massage alone was associated with more blood loss within 30 minutes after delivery compared with treatment with oxytocin with or without massage. In the latest Cochrane review Hofmeyr et al., (2013) stated that “the results of the review are inconclusive, and should not be interpreted as a reason to change current practices” (Hofmeyr et al., 2013). They suggested the need for a larger study to show the effect of uterine massage.

Recently, a multi-centre study in China evaluated the effect of uterine massage after delivery of the placenta (Chen et al., 2013). The study included 2,340 women and the participants received oxytocin plus uterine massage or oxytocin only. The placenta was delivered by CCT in both groups. The incidence of blood loss of 400 mls or more at 2 hours after delivery was not significantly different between the two groups (143/1,170 [12.2%] compared with 144/1,170 [12.3%]; RR 0.99, 95% CI 0.88-1.13).

In summary, uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin, as it may cause maternal discomfort, requires a dedicated health professional, and may not lead to a reduction of blood loss. However, surveillance of uterine tonus through abdominal palpation is recommended in all women for early identification of postpartum uterine atony (WHO, 2012).

C. Uterine compression

Chantrapitak and colleagues recently addressed 'lower uterine segment compression' (LUSC) as a new manoeuvre for prevention of PPH (≥ 500 mls) after vaginal delivery. The subjects (686 women) were divided into two groups and both groups received standard therapy for PPH prevention with IV oxytocin 10 IU, delayed cord clamping (within 3 minutes) and CCT. After delivery of the placenta, uterine massage was done for all subjects. In the experimental group, the authors added the manoeuvre of lower uterine segment compression for 10 minutes. LUSC were done by two ways depending on the women's condition. If the woman had thick abdominal wall (obese, primigravida), the first technique was used by placing one hand (or both) on the abdomen to compress the lower uterine segment as hard as the mother could tolerate it. The second way was used in mothers with a thin abdominal wall (slimmer women, multipara) where one hand compressed the fundus and the other hand compressed the lower uterine segment. The result showed that LUSC significantly reduced the rate of PPH (2.9% vs. 6.8%; RR 0.43, 95% CI 0.21-0.90, $p = 0.02$). The amount of blood loss was also reduced by 29.26 mls, $p = 0.012$ (Chantrapitak et al., 2011).

2.2.2.5. Nipple stimulation

Early suckling or nipple stimulation is thought to increase uterine contractility. A cluster RCT was carried out to examine the effect of suckling immediately after birth on the frequency of PPH and mean blood loss after delivery (Bullough et al., 1989), involving 2104 mothers in the early suckling group and 2123 subjects in the control group. In that study early suckling was not found to reduce the rate of PPH of 500 mls or more (OR, 0.93; 95% CI 0.75-1.17). The frequency of PPH was 7.9% in the suckling group and 8.4% in the control group, with mean blood losses of 258 mls and 256 mls respectively. Early suckling should still be encouraged because it promotes bonding and breastfeeding and may help to maintain uterine tone.

2.2.3. Care after delivery of the placenta

It is advisable after delivery of the placenta to routinely inspect the vulva, vagina, perineum, and anus to identify genital lacerations, to routinely inspect the placenta and membranes for completeness, and to monitor the woman for vaginal bleeding and uterine hardness every 15 minutes for at least the first two hours. The palpation of uterus is to check that the uterus is well contracted, with massage being performed as needed, to keep the uterus well-contracted and firm (FIGO/ICM, 2004; Hofmeyr et al., 2008).

2.3. Third stage blood loss estimation and diagnosis of PPH

Mortality reports have found that the majority of PPH deaths involve delayed and substandard care in the diagnosis and management of PPH (Berg et al., 2005; Lewis, 2007). A timely and precise diagnosis of PPH is therefore essential, allowing prompt initiation of appropriate interventions, drugs, surgery, and referral when necessary (Prata and Gerdt, 2010). Several studies assessed the amount of blood loss during childbirth using different methods: the mean blood loss reported was approximately 400 to 600 mls and 1000 mls after vaginal and caesarean deliveries, respectively. Clinicians were seen to more commonly underestimate than overestimate the volume of blood lost (Stafford et al., 2008). Estimation of blood loss during the third stage of labour still presents a great challenge to most practitioners. Since haemorrhage is a major cause of maternal mortality, methods to precisely measure blood loss and PPH are required. Over several years, different techniques have been used for the estimation of postpartum blood loss, including visual estimation, direct measurement, gravimetric, photometry and others.

In practice, blood loss after delivery is seldom measured and it is not clear whether measuring blood loss improves the care and outcome for the women. One study (Zhang et al., 2010) found that even if the blood loss was measured it does not affect the incidence of PPH.

I. Visual estimation

Visual estimation is the most frequently used method for estimation of blood loss after child birth (Tourne et al., 2004). Although repeated studies have shown the inaccuracy of the visual estimation method, it is still used. It has been long recognised that actual blood loss was higher than visually estimated blood loss during vaginal births (Brant, 1967), with studies finding that visual estimates are about 30-50% of actual blood losses (Razvi et al., 1996; Chua et al., 1998). Importantly, this inaccurate estimation rises with increasing blood loss (Brant, 1967; Duthie et al., 1991). In clinical practice, underestimation may result in delaying or deterring the recognition and diagnosis of PPH. The accuracy of estimated blood loss was found to be independent of the age or clinical experience of the healthcare provider (Meiser et al., 2001; Dildy et al., 2004). Interestingly, several studies demonstrate that the inaccuracy of visual estimation method of blood loss can be improved with staff teaching and by quantification of blood loss using calibrated under-buttocks drapes for blood collection (Dildy et al., 2004; Bose et al., 2006).

II. Direct measurement

Direct measurement is one of the oldest methods used to precisely determine the amount of blood loss during child birth. Several types of drapes were used in various studies to assist with direct blood collection. This method has many advantages as it requires only containers for collection and a graduated container for measuring. Women can give birth in any position or location. It still needs some estimation of blood that may be on gloves, linens, gowns or other materials. One limitation is that it is not possible to avoid all other forms of fluid, such as amniotic fluid or urine. If those fluids are unintentionally collected, the results may be erroneous. In a study in rural India it was found that the calibrated-drape estimation of blood loss is more accurate than visual estimation for PPH; a specially designed blood collection drape was used to estimate postpartum blood loss. The assessed blood loss by visual estimation was 33% less than the drape measurement and the correlation between the drape determination and photospectrometry was 0.92, proving its accuracy (Patel et al., 2006).

III. Gravimetric (measurement by weight)

The gravimetric method of blood loss estimation is an alternative objective techniques used in calculating postpartum blood loss. It involves the weighing of collected blood lost during childbirth along with materials such as all contaminated linens, pads, towels, or swabs on a sensitive scale and then deducting the known dry weights of these materials to find out the actual amount of blood loss (Lee et al., 2006). However, other types of fluid, such as amniotic fluid or urine that are present at the time of delivery cannot be avoided or discriminated from the blood during the process of weighing; this would affect the final results of the actual amount of blood loss. In addition, the weighing must be done quickly to minimise evaporation loss. This method can be easily taught, but is both time-consuming and labour-intensive (Schorn, 2010). In a prospective cohort study comparing visual estimation versus gravimetric measurement of postpartum blood loss, there was a significant difference between the calculated amounts of blood loss using a sensitive gravimetric machine. Both healthcare providers' (physicians and obstetric nurses) visual assessment had a tendency to underestimate the loss on average by 30% (Al Kadri et al., 2011). Again this study shows that the background knowledge and experience of the assessing healthcare provider did not affect the accuracy of the estimation. Schorn has stated that a combination of direct measurement and gravimetric methods are the best method to be used in the estimation of blood loss (Schorn, 2010).

IV. Photometry

A photometric technique (also known as the alkaline haematin method) involves the conversion of blood pigment to alkaline haematin. This technique is considered as the gold standard for measuring blood; other methods are compared against it to determine accuracy (Schorn, 2010). Chua et al., (1998) have taken blood collected from a gynaecologic surgery and simulated postpartum conditions by pouring this blood onto sanitary pads and towels (Chua et al., 1998). These pads and towels were collected and given to a laboratory technologist who did not know the original measured amount of blood. The blood loss measured in the laboratory showed an error of between 0% and 9.4%. Although photometric methods are considered the most accurate technique for estimation of blood loss, the procedure poses several limitations. For example, the method is not cheap, it needs specialised equipment, and a formula is required after the meter reading is obtained. Furthermore, errors can occur at any stage of blood collection:

extraction of blood from the pads, conversion of haemoglobin to alkaline haematin, or during the time of comparison in the spectrophotometer. The availability of highly skilled personnel with laboratory equipment is also necessary (Schorn, 2010).

V. Miscellaneous methods

There are other different techniques used in estimation of blood loss, but none have been found to be practical or reliable methods (Schorn, 2010). The measurement of the diameter of the inferior vena cava by ultrasound was one of these methods. Performing this technique in traumatised patients in the emergency room has shown that there was a significant association between the diameter of the inferior vena cava and the amount of blood loss. The diameter of the inferior vena cava was smaller with large blood loss and was present before the development of other signs of shock, the decreased size in the inferior vena cava was observed when the blood loss was > 450 mls (Lyon et al., 2005). Another method is comparing haemoglobin drawn at the last prenatal visit before birth with post-delivery haemoglobin (day 3 and 10 weeks postpartum). However the result was not significant as there was no correlation, especially between haemoglobin levels at 10 weeks postpartum and estimated blood loss (Palm and Rydhstroem, 1997).

Overall, underestimation of blood loss at delivery can lead to a delay in the diagnosis, and consequently the treatment, of PPH. Overestimation of blood loss can also have significant implications such as unnecessary cross-matching of blood, wasting valuable time and resources. One confounding factor could be the flow rate over time. Therefore, it is well acknowledged that the best definition and diagnosis of PPH should be made on a clinical basis. The diagnosis of PPH can be based on the status of the physiological response to the circulating blood volume loss (Bose et al., 2006). Moreover, since there is insufficient evidence to recommend quantification of blood loss over clinical estimation the WHO currently strongly recommend diagnosis of PPH to be based on clinical parameters (WHO, 2009). So the birth attendant should be aware of excessive bleeding that leads to development of symptoms such as pallor, headache, weakness, palpitations, excessive sweating, restlessness, confusion and coma and/or results in signs of shock due to hypovolemia, for example, hypotension, tachycardia, oliguria, and low oxygen saturation (less than 95%).

There is no single gold standard method that could be used for measuring postpartum blood loss. Researchers usually are left to use methods that are cheap, feasible and easy to teach. For research purpose, it can be recommended that combining two methods would be ideal to reduce errors and increase accuracy when measuring postpartum blood loss. Combining the gravimetric method along with direct blood measurement can be proposed as appropriate blood loss estimation technique. This would be a cheap method and increase the accuracy of blood loss estimation.

2.4. Treatment of established PPH

As mentioned above, PPH is an unpredictable emergency condition that if uncontrolled can very quickly lead to maternal death. In one series, almost one third (32%) of deaths occurred within 24 hours after delivery, with one fifth of all deaths occurring within 1-4 hours of delivery (Kane et al., 1992). Thus, in the absence of timely and appropriate action, a woman could die within a few hours.

Once the diagnosis of the primary PPH is established, the condition requires early recognition of its cause, immediate control of the bleeding source by multiple interventions (medical, mechanical, invasive-non-surgical and surgical procedures), and rapid stabilisation of the mother's condition. Most importantly, a multidisciplinary approach must be employed. The practical management of PPH may be considered as having at least four components: communication with all relevant professionals; resuscitation; monitoring and investigation; and measures to arrest the bleeding. All of these components must be initiated and progressed simultaneously for optimal patient care.

2.4.1. General measures

Women should be assessed carefully to find out the cause of bleeding and they should be resuscitated if they develop signs and symptoms of haemorrhagic shock. The first action should be to call for help and to alert an experienced obstetrician, followed by resuscitation of the patient and, assessment of the uterine tone to rule out the possibility of retained products of conception, genital tract trauma and coagulopathy. Bladder evacuation and keeping a catheter in place is very important as a distended bladder could be the only cause of uterine atony and PPH. While investigating the aetiology of PPH and treating the cause, resuscitation and volume replacement should immediately take place. The haematologist

and blood transfusion laboratory should be notified. Anaesthesia should be also notified to be ready for surgical interventions once needed. A baseline investigation should be ordered, such as a complete blood count, as well as prothrombin time and partial thromboplastin time (RCOG, 2009).

Communication "Call for help"

Because emergency situations create opportunities for errors in care, it is essential that obstetricians and other maternity care providers work together to develop systems within their units to address the coordinated management of woman experiencing PPH. Early involvement and communication of all appropriate obstetric staff, including experienced midwives, a member of the team to record events, fluids, drugs and vital signs, as well as porters for delivery of specimens/blood, senior staff (including anaesthesia team), and laboratory specialists including a consultant clinical haematologist, are fundamental to the management of PPH.

Resuscitation

A, B and C – assess airway, breathing and evaluate circulation

Immediate resuscitation of hypovolemia should be achieved with large bore IV cannula and IV fluids. A high concentration of oxygen (10-15 litres/minute) via a facemask should be administered, regardless of maternal oxygen concentration. If the airway is compromised owing to an impaired conscious level, anaesthetic assistance should be sought. Blood samples should be taken and sent for diagnostic tests, including ABO/RH grouping and cross matching, full blood count, coagulation screen, urea and electrolytes.

Fluid replacement

A total volume of 3.5 litres of warmed solution should be infused as rapidly as possible. In the 2012 WHO recommendations, the treatment of PPH using isotonic crystalloid is recommended in preference to the use of colloid for the initial IV fluid (WHO, 2012). However the RCOG guidelines state that the nature of fluid infused is of less importance than rapid administration and warming of the infusion. The woman needs to be kept warm using appropriate measures.

Blood transfusion

Women diagnosed with massive PPH may need rapid RBCs which improve the blood's oxygen-carrying capacity. Therefore, it is recommended that women with known risk factors for PPH should not be delivered in a hospital without a blood bank on site (CEMACH, 2004). If fully cross-matched blood is unavailable by the time that 3.5 litres of clear fluid have been infused, the best available alternative should be given. It is recommended that if transfusion is needed before type-specific or cross-matched blood can be obtained, if possible type-O, Rh-negative blood should be utilised because of the future risk of Rh sensitisation; however if not readily available Rh-positive blood should not be withheld if clinically required (Fuller and Bucklin, 2007).

Platelets are also needed to help coagulation. Massive haemorrhage will lead to a rapid decrease in the fibrinogen levels and hypofibrinogenaemia will increase the severity of uterine bleeding. Fresh frozen plasma can increase fibrinogen and replace clotting factors. Cryoprecipitates provide a more concentrated form of fibrinogen as each 40 mls raises the fibrinogen level by 10 mg/dl (Rajan and Wing, 2010).

A new thrombelastometry system (ROTEM[®]) is available for early diagnosis of coagulation disorders. It can be used in the laboratory or at the patient's bedside. The FIBTEM[®] test of the ROTEM[®] can be used to assess the fibrinogen level. It might be helpful in identifying fibrinogen deficiency early in the PPH leading to its rapid correction (Huissoud et al., 2009).

Monitoring and investigation

Close monitoring of vital signs is critical (temperature, pulse and automated blood pressure recording [every 15 minutes]). Fluid replacement and the use of blood and blood products should be strictly monitored. Bladder catheterisation is very important as a distended bladder could be the only cause of uterine atony. It further assists to monitor the urine output. The full blood count will include an estimation of haematocrit and platelet count. The clotting screen should include prothrombin time, thrombin time, partial thromboplastin time and fibrinogen assay.

2.4.2. Life-saving procedures

In achieving a definitive treatment for PPH, there may be delays due to the need for transfer to a higher-level facility or, if already in such a facility, obtaining blood and surgery. A variety of mechanical measures have been developed to deal with this situation such as BMC, aortic compression and the pneumatic anti-shock garment.

1. Bimanual compression (BMC)

Bimanual compression of the uterus is an emergency procedure used to stop PPH caused by uterine atony. It is of two types internal and external.

It is thought that internal bimanual compression might be more effective than external bimanual compression in controlling blood loss, but it can only be performed if the mother has had adequate anaesthesia (Billington and Stevenson, 2007).

a. External bimanual compression

This method, illustrated in Figure 6, is performed by applying the left hand on the fundal area of the uterus while the right hand is applied on the abdominal wall just below the umbilicus. The objective of this technique is to produce pressure on the blood vessels of uterus through the abdominal wall so as to diminish the bleeding and achieve haemostasis.

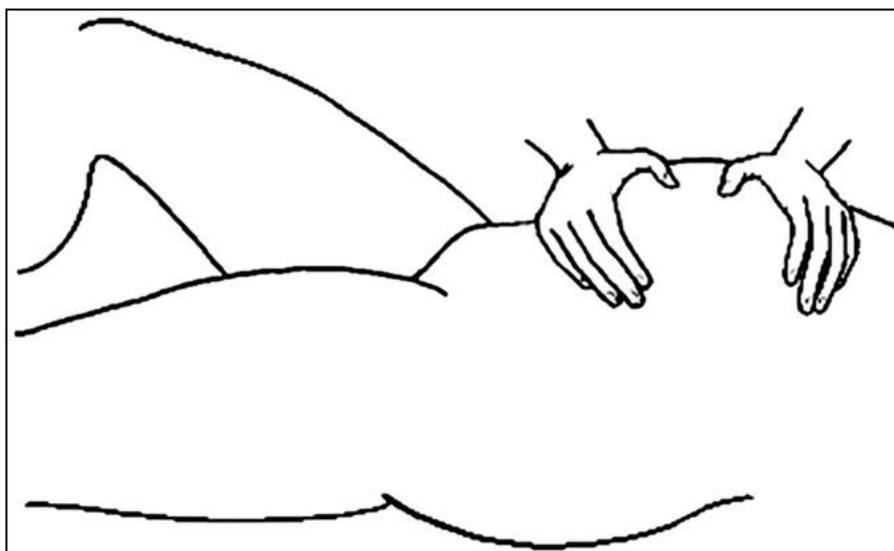


Figure 6. External bimanual compression (Lalonde, 2012)

b. Internal bimanual compression

Internal bimanual compression is usually applied when the uterus continues to bleed after the placenta has spontaneously or manually delivered. For this method, adequate anaesthesia is required. Under aseptic conditions, the right hand is inserted into the vagina, making a fist that faces upward in the anterior fornix. The left hand is applied on the abdominal wall just behind the uterus to push it firmly in the direction of the symphysis pubis (Figure 7). Similar to the external method, the aim of this technique is to compress the blood vessels of the uterus through the abdominal wall in order to diminish the bleeding and achieve haemostasis as well as well uterine contractility.

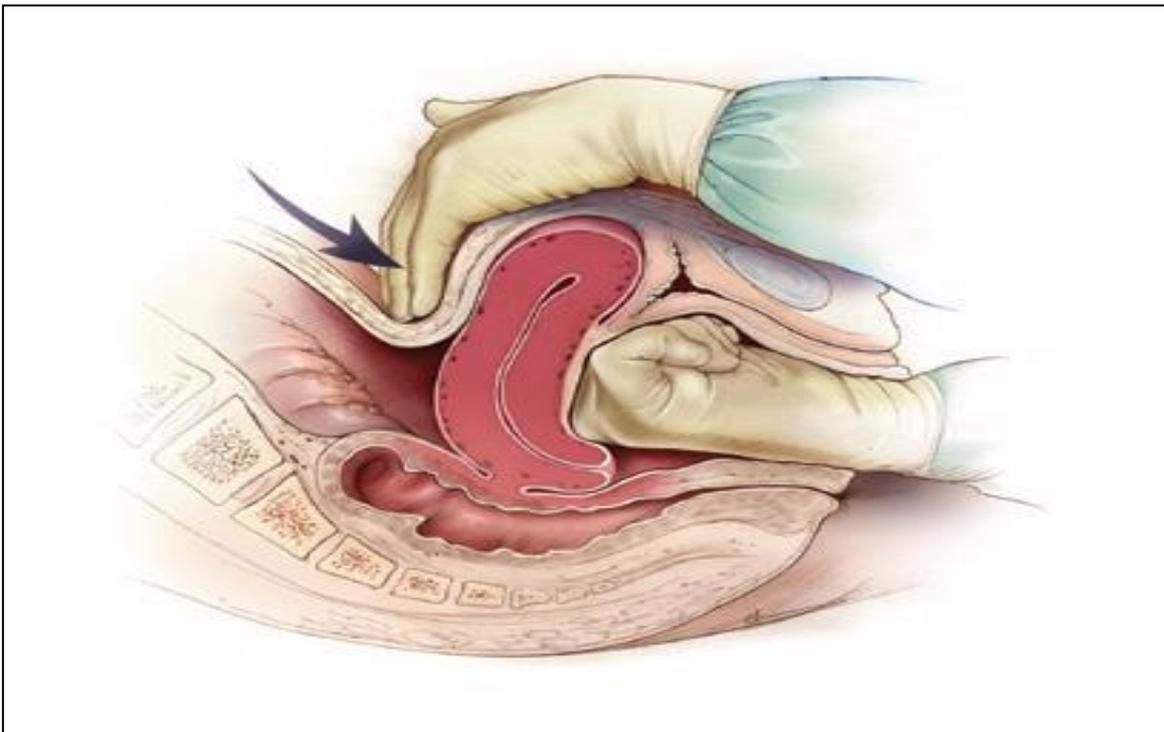


Figure 7. The technique of internal bimanual uterine compression for uterine atony (Anderson and Etches, 2007)

BMC of the uterus is used by many healthcare professionals in emergencies, and in environments where there is no medical support such as home birth or in the case of severe bleeding in any setting. It is generally used as a stop-gap measure to maintain homeostasis until the arrival of medical help and further implementation of pharmacological or surgical measures.

2. Compression anti-shock garments

The non-pneumatic anti-shock garment (NASG), shown in Figure 8, is a first-aid compression garment device made of neoprene and a hook-and-loop fastener comprising lower-extremity segments, a pelvic segment, and an abdominal segment, which includes a foam compression ball that goes over the uterus (Miller et al., 2007). The NASG reverses shock by compressing the lower-body vessels and, decreasing the container size of the body, so circulating blood is directed mainly to the core organs: the heart, lungs, and brain. It also compresses the diameter of pelvic blood vessels, thus decreasing blood flow (Lester et al., 2011). In preliminary pre-intervention/intervention trials in tertiary facilities in Egypt and Nigeria, the NASG was shown to significantly improve shock (Miller et al., 2010), decrease blood loss, reduce emergency hysterectomy for atony, and decrease maternal mortality and severe maternal morbidities associated with obstetric haemorrhage (Turan et al., 2011). The NASG offers considerable potential for use in low-resource settings as it is simple to apply, reusable and relatively inexpensive (US\$160 per garment) (Weeks, 2010).



Figure 8. Picture of compression anti-shock garments fully applied on the patient (Miller et al., 2008)

3. Aortic compression

Another life-saving intervention is aortic compression, illustrated in Figure 9. It is carried out when there is heavy postpartum bleeding, whatever the cause. It may be considered at several different points during management of PPH. Aortic compression does not prevent or delay any of the other steps to be taken to clarify the cause of PPH and treat it. Circulating blood volume is restricted to the upper part of the body and, thereby, to the vital organs. Blood pressure is kept higher, blood is prevented from reaching the bleeding area in the pelvis, and volume is thus conserved. The manoeuvre is carried out by placing the left hand just above and to the left of the woman's umbilicus. Before exerting aortic compression, the femoral artery should be felt for a pulse using the index and third fingers of the right hand. Once the aorta and femoral pulse have been identified, the clinician should slowly lean over the woman and increase the pressure over the aorta to seal it off. Absence of femoral pulsation is an indication that the compression is effective (Lalonde, 2012).

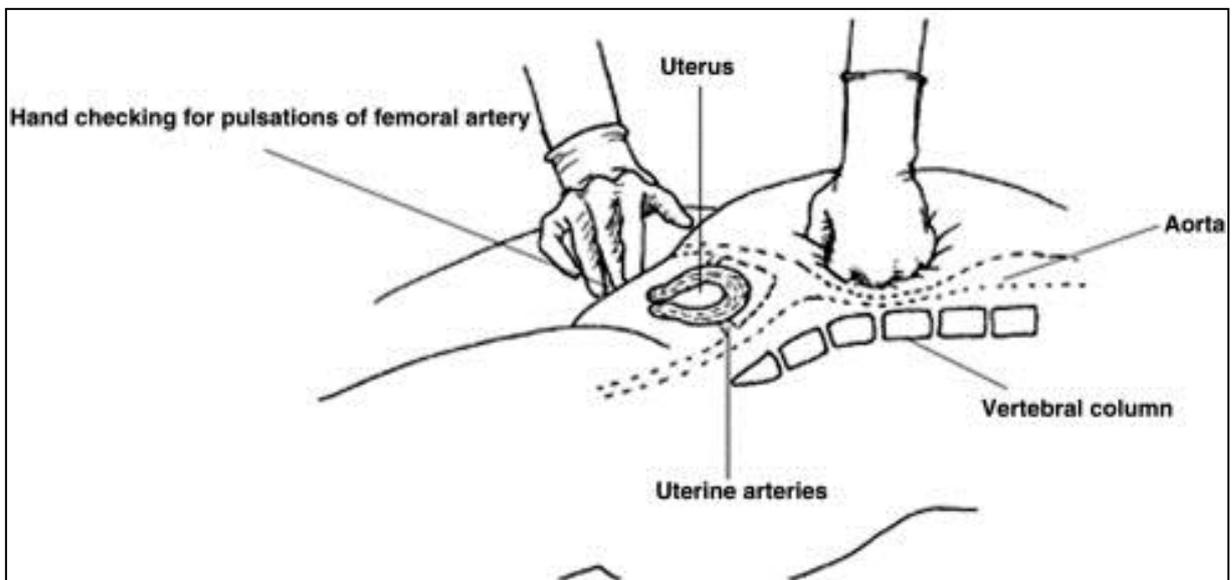


Figure 9. Compression of abdominal aorta and palpation of femoral pulse (Lalonde, 2012)

2.4.3. Stopping the bleeding

As stated above, the causes for PPH relate to one or more of ‘the four Ts’: tone, tissue, trauma and thrombin. Establishing the cause of haemorrhage is an essential step towards correcting the problem. For a patient who delivers vaginally, once the placenta is delivered, excessive bleeding should prompt careful exploration of the placenta and genital tract. This will usually allow an assessment of the first 3 aetiologies, but a clinical examination may not be able to diagnose a coagulation abnormality. In the following section, PPH management will be reviewed according to its cause.

A. Tone

Uterine tone and size are assessed by resting one hand on the fundus and palpating the anterior aspect of the uterus. A bimanual examination may facilitate this assessment. If the uterus is large and boggy to palpation, then the bleeding is likely to be caused by uterine atony. Because uterine haemostasis depends on myometrial contraction, atony is treated initially by BMC and massage, followed by drugs that promote uterine contraction.

B. Tissue

If the placenta has not been delivered within 15-30 minutes of childbirth or in cases where retained placental fragments are suspected, the uterus must be emptied (Tamizian and Arulkumaran, 2002).

WHO recommend use of oxytocin and CCT before commencing UVI (WHO, 2009). If the UVI is bypassed, or not successful, adequate regional anaesthesia or general anaesthesia should be ensured; current haemostatic parameters should be reassessed with cross-matched blood available, broad spectrum antibiotics administered and an oxytocin drip (40 IU oxytocin in 500 mls of 0.9% saline) should be started before attempting manual removal of the placenta (Rajan and Wing, 2010). The best way to remove retained products is to approach transvaginally, finding the line of cleavage then gently separating the placental parts from the uterus, sweeping the fingers in a side-to-side motion. After this has been completed, the uterine cavity should again be checked to ensure it is empty

(Tamizian and Arulkumaran, 2002). If the line of cleavage cannot be found, then invasive placenta should be considered. The most common treatment for invasive placenta is hysterectomy (Wu et al., 2005).

C. Trauma

In order to gain effective control of the bleeding, the injured area should be sutured, starting at the apex of the tear. If the apex cannot be reached, the suture should be started as close to the apex as possible, then, once the remainder of the tear has been approximated, place traction to reach the previously hidden apex. If there is extensive trauma to the vaginal wall, with multiple lacerations, bruising and oozing repairs, a vaginal pack can be used to provide haemostasis and maintained for 12-24 hours (Tamizian and Arulkumaran, 2002).

In case of uterine inversion every attempt should be made to replace the uterus quickly (Watson et al., 1980). The Johnson method of reduction begins with grasping the protruding fundus (Figure 10A) with the palm of the hand with fingers directed towards the posterior fornix (Figure 10B). The uterus is returned to its position by lifting it up through the pelvis and into the abdomen (Figure 10C). Once the uterus is reverted, uterotonic agents should be given to promote uterine tone and to prevent recurrence. If the initial attempts to replace the uterus fail or a cervical contraction ring develops, administration of tocolytic therapy or general anaesthesia may allow sufficient uterine relaxation for manipulation. If these methods fail, the uterus will need be replaced surgically (Beringer and Patteril, 2004).

Uterine rupture is a rare, life threatening emergency that requires laparotomy for surgical repair of the defect or hysterectomy. Surgical repair is used for simple scar dehiscence or a small tear. Major tears, however, with uncontrolled haemorrhage will require a hysterectomy (Jeganathan and Sivanesaratnam, 2011).

D. Thrombin

In patients who have not responded to the usual measures to treat PPH, and in those who are not forming blood clots or are oozing from puncture sites, coagulation defects should be suspected. Evaluation should include a platelet count and measurement of prothrombin time, partial thromboplastin time and fibrinogen level. The ROTEM[®] diagnostic system can also assist in the bedside rapid diagnosis. Management consists of treating the underlying disease process, supporting intravascular volume, serially evaluating coagulation status, and replacing appropriate blood components (Price et al., 2004).

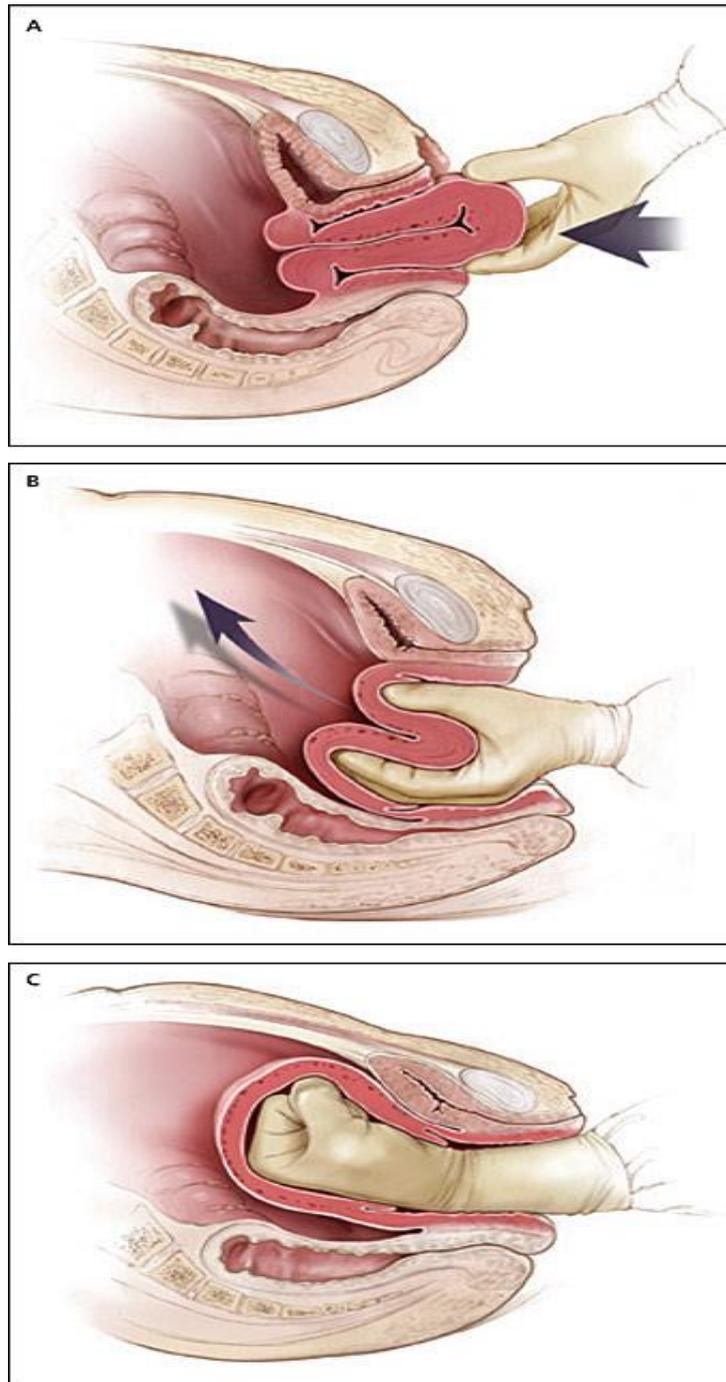


Figure 10. Reduction of uterine inversion (Johnson method) (A) the protruding fundus is grasped with fingers directed toward the posterior fornix. (B, C) the uterus is returned to position by pushing it through the pelvis and into the abdomen with steady pressure towards the umbilicus (Anderson and Etches, 2007)

2.4.4. Medical treatment of atony

If initial interventions fail to control PPH, a stepwise progression of medical therapy is carried out, using available uterotonics to facilitate the contraction of the uterus. Different uterotonic agents can be used in treatment of atonic PPH. The early medical treatment of uterine atony involves the administration of oxytocin or ergometrine. Despite extensive and extended use of injectable uterotonics over the last few decades, there have been no clinical trials comparing oxytocin and ergometrine for treatment of uterine atony.

The WHO recommends 20-40 IU in 1 litre of intravenous fluid at 60 drops per minute, and 10 IU intramuscularly as first-line treatment. Ergometrine (with or without oxytocin) and intramuscular prostaglandin F₂ α (carboprost) are considered a valid alternative (WHO, 2009; Tuncalp et al., 2013). If there is not adequate uterine tone with oxytocin, the second line agent used will depend on the medication's side effects and contraindications. Methylergonovine may be used, with a typical dose of 0.2 mg administered intramuscular and repeated 2-4 hrs later for a maximum of 5 doses (1 mg) in a 24-hour period, as long as the patient does not have hypertension or preeclampsia (Lalonde, 2012; Tuncalp et al., 2013).

Prostaglandin F₂ α is considered as the third line for the management of PPH in a uterus unresponsive to oxytocin or ergometrine (WHO, 2009). However, there were no trials comparing it with other uterotonics. Carboprost can be administered intramyometrially or intramuscularly in a dose of 0.25 mg; this dose can be repeated 3 times every 15 minutes for a total dose of 2 mg (Lalonde, 2012). The use of intramuscularly administered PGF₂ α in uncontrollable atonic PPH has been shown to be a valuable life-saving medical tool in critical cases (Topozada et al., 1981). The direct intramyometrial route has a rapid onset of action and can be achieved under direct vision during caesarean section or transabdominally or transvaginally after vaginal delivery (Jacobs and Arias, 1980). The peak plasma concentration of the intramuscular route is achieved at 15 minutes and at less than 5 minutes for the intramyometrial injection. Carboprost has been proven to control haemorrhage in up to 88% of patients (in 208 of 237 cases) if used alone or in combination with other uterotonic agents (95%). In cases where it is not effective, chorioamnionitis or other risk factors for haemorrhage are often present (Oleen and Mariano, 1990). The use of prostaglandin E₂ analogue (sulprostone) in the treatment of PPH was associated with

cardiac arrest in three participants and therefore, it was voluntarily withdrawn by the manufacturers (Sharma and El-Refaey, 2003).

Misoprostol could be an appropriate alternative when parenteral prostaglandin is not available or when it is contraindicated. Misoprostol is effective in the treatment of PPH, but side effects may limit its use (Hofmeyr et al., 2005). It can be administered sublingually, orally, vaginally, and rectally with doses ranging from 200 to 1,000 mcg (Hofmeyr et al., 2005). Oral misoprostol produces the fastest and strongest uterotonic effect, but with the most side effects including shivering, pyrexia, and diarrhoea (Chong et al., 2004). The authors of the latest Cochrane review for treatment of PPH concluded that the available evidence was not enough to support the use of misoprostol instead of oxytocin and ergometrine as a first line treatment of PPH (Mousa et al., 2014). Further recent research has shown that a single dose of misoprostol 800 mcg administered sublingually is a safe and effective treatment for PPH, due to uterine atony in women who have received oxytocin prophylaxis, as well as those who have received no oxytocin prophylaxis during the third stage of labour (Blum et al., 2010; Winikoff et al., 2010). In home births without a skilled attendant, misoprostol may be the only technology available to control PPH. Studies on treatment of PPH found that misoprostol significantly reduces the need for additional interventions (Prata et al., 2005). There is evidence that misoprostol provides no added benefit when given simultaneously with other injectable uterotonic drugs for the treatment of PPH, and therefore misoprostol as an adjunct treatment with oxytocin for PPH is not recommended (Widmer et al., 2010).

The questions relating to the management of women with major primary PPH unresponsive to uterotonic therapy remain largely unanswered. In the absence of RCTs, clinicians are left to make their own judgement on the best combination of surgical, radiological and/or pharmaceutical interventions that should be used to control the bleeding (Mousa and Alfirevic, 2007).

2.4.5. Other pharmacological interventions

Haemostatic drugs, including tranexamic acid and recombinant activated factor VII (rFVIIa) have been used for the treatment of intractable haemorrhage.

Tranexamic acid may have a role in the control of PPH, particularly where coagulation is compromised. The drug is potentially attractive for PPH management as it would provide an alternative way of achieving haemostasis and reducing bleeding irrespective of whether it came from uterine atony or lacerations (Weeks, 2010). However, Searle et al., (2008) raised theoretical concerns regarding its use in women with severe PPH as they can develop disseminated intravascular coagulation, and tranexamic acid would theoretically increase the damaging microvascular thrombosis that occurs in this process (Searle et al., 2008). In addition, rapid intravenous administration of tranexamic acid can also cause hypotension, thus exacerbating the hypotensive effects of PPH.

There is currently an ongoing randomised, double-blind, placebo-controlled trial among women with a clinical diagnosis of PPH (WOMAN trial), coordinated by the London School of Hygiene and Tropical Medicine (University of London), which aim to reliably determine the effect of the early administration of tranexamic acid on death, hysterectomy and other morbidities (surgical interventions, blood transfusion and risk of non-fatal vascular events), in woman with PPH (Shakur et al., 2010).

The use of rFVIIa as a haemostatic agent for refractory PPH has been described in a number of case reports (Bouwmeester et al., 2003; Segal et al., 2003). The mode of action of this agent involves enhancement of the rate of thrombin generation, leading to formation of a fully stabilised fibrin plug that is resistant to premature lysis. Reported cases involve haemorrhage unresponsive to numerous conventional treatments including hysterectomy and pelvic vessel ligation, where use of this agent was remarkably successful at arresting seemingly intractable bleeding within a matter of minutes. Doses of 60–120 mcg/kg intravenously were used.

2.4.6. Surgical methods

The surgical procedures that can be applied in case of PPH are of two types, non-invasive or invasive measures:

2.4.6.1. Surgical non-invasive measures

Uterine tamponade

Active attempts have been made to introduce conservative procedures to control bleeding, and importantly to avoid hysterectomy including the use of uterine packing and uterine tamponade. Uterine packing applies these principles, making it a popular technique for over a century, whereas the balloon tamponade is a more recent development.

Uterine packing, using “several yards of wide gauze” placed inside the uterine cavity, fell out of favour in the 1950s as it was thought to conceal haemorrhage and cause infection (Eastman, 1950). However, this technique re-emerged in the 1980s and 1990s after these concerns were not confirmed. Surgeons found that, whether uterine packing was used early or late in patient management for the control of PPH, it was a safe, quick, and effective way to create haemostasis (Maier, 1993). It is particularly useful in the developing countries. It is important to note the fundal level at the time of packing. If, on subsequent examinations, the fundus seems to have moved higher then there may be ongoing haemorrhage. Broad-spectrum antibiotics should always be used prophylactically to prevent septic complications (Rajan and Wing, 2010). To remove the pack, some practitioners administer an anxiolytic. Oxytocin, administered for 12-24 hours after the pack is removed, provides adequate muscle contraction, thus preventing the re-initiation of bleeding (Drucker and Wallach, 1979).

Internal tamponade can also be achieved using an intrauterine balloon. Examples of balloon catheters are the Foley catheter, Rush catheter, SOS (Surgical Obstetric Silicone) Bakri catheter, and the Sengstaken-Blakemore balloon. Balloon catheters can also be made using a sterile rubber glove or condom attached to a rubber urinary catheter (Figure 11) (Georgiou, 2009). The general idea is to insert a sterile balloon into the uterine cavity, then fill the balloon with warm water to see if additional pressure can control the patient's

haemorrhage. The Sengstaken-Blakemore tube, Foley catheter and Bakri balloon have the advantage of providing an outflow tract for the continuous bleeding (Majumdar et al., 2010).

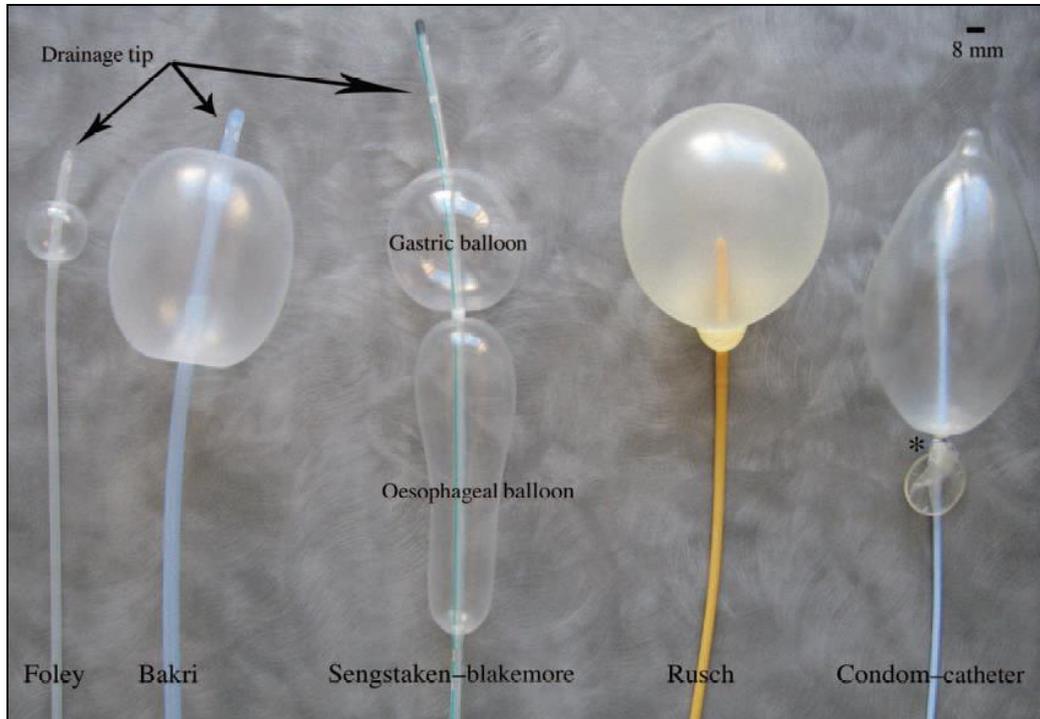


Figure 11. Distal component of tamponade balloons (Georgiou, 2009)

Bakri first published the concept of intrauterine balloon technology in the management of PPH secondary to placenta praevia accreta during caesarean section (Bakri, 1992; Bakri, 1999). The Bakri ‘SOS’ balloon was described as having a capacity of up to 500 mls of saline achieving a pressure and tamponade effect to control the bleeding. In 2001 Bakri and his colleagues (Bakri et al., 2001), demonstrated that the tamponade balloon was effective in controlling PPH originating from the placental site of the lower uterine segment (five women with PPH caused by low-lying placenta/placenta previa) and bleeding from the implantation site of cervical ectopic pregnancy (one woman with cervical pregnancy).

In addition to the Bakri balloon, there are other designed uterine balloons such as the EbbTM balloon and BT-Cath[®] (Figure 12) (Georgiou, 2012). The BT-Cath[®] is a soft silicone balloon tamponade catheter that provides direct uterine pressure to control PPH. The BT-Cath[®] also has a lumen allowing intrauterine blood drainage. This allows timely confirmation of the tamponade effectiveness. The intrauterine drainage port is flush with the top of the inflated balloon (no tubing protruding from the balloon) allowing placement near the uterine fundus (<http://www.utahmed.com/btcath.htm>, 2012).

In 1994, Katesmark and colleagues described the use of a Sengstaken-Blakemore tube (generally used for tamponade of acute upper gastrointestinal bleeding due to oesophageal varices) to control PPH (Katesmark et al., 1994). Warm saline was used to fill the balloon until it was visible at the cervical canal-using approximately 300 mls of fluid. Johanson and co-workers (Johanson et al., 2001), described the same process using a Rusch balloon catheter, a type of urologic hydrostatic balloon catheter. In two cases of failed medical therapy for PPH, where the catheter had been tried, further surgical interventions were avoided. The balloon was inserted into the uterine cavity and inflated through the drainage port, using approximately 400-500 mls of warm saline.

Although there is no evidence to direct how long the balloon should be left inside, it is recommended to be maintained for 12-24 hours. The previously started oxytocin infusion should be continued and broad spectrum antibiotics should be given to decrease the patient's risk of sepsis.

A successful tamponade demonstrates decreased or minimal bleeding after balloon inflation, thus terminating the need for surgical treatment (Doumouchsis et al., 2008). Uterine balloons have proved very popular with success rates of 81% for the Sengstaken-Blackemore tube and 59% success for Rusch balloon (Majumdar et al., 2010). Therefore, a uterine balloon tamponade is considered an important tool for the treatment of PPH. But it is important to note that the effectiveness of different tamponade methods have only been described in case series. RCTs are unlikely to be conducted as the cases which need uterine tamponade are relatively rare.

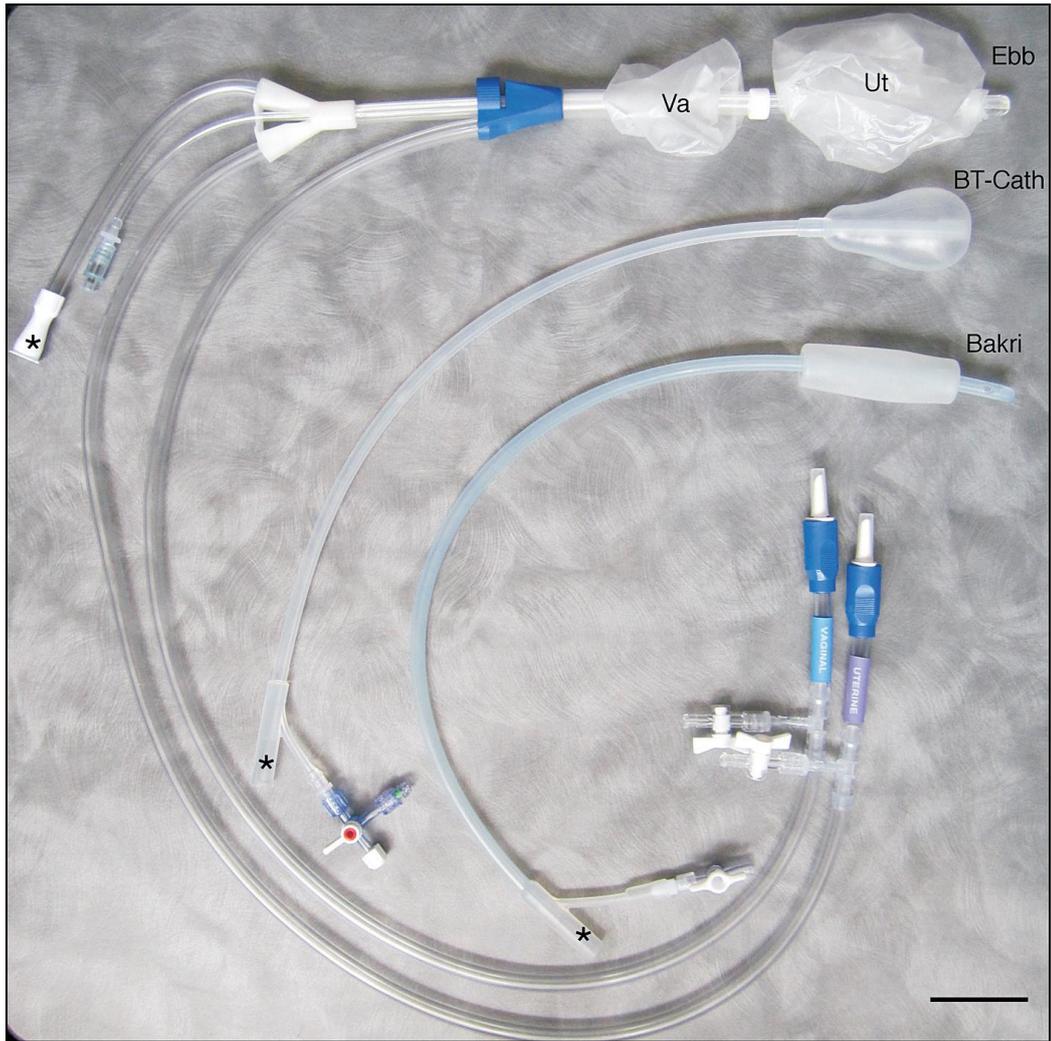


Figure 12. Uterine specific balloons. The Bakri balloon and the BT-Cath[®] are single balloon devices. The Ebb balloon is designed for one balloon in the uterine cavity (Ut) and the other within the vagina (Va). *Drainage channel for each balloon system. Bar = 5 cm (Georgiou, 2012)

2.4.6.2. Invasive surgical interventions

If conservative non-surgical treatment has failed, other surgical options are available. These include selective arterial embolisation, a variety of compression suture techniques, selective arterial ligation and, as a final option, hysterectomy. The choice of the type of surgical intervention depends on several factors, the most important being the experience of the surgeon. Other factors include parity and desire for future children, the extent of the haemorrhage, the general condition of the woman, and the availability of equipment, especially in case of radiological embolisation.

1. Selective arterial embolisation (radiological embolisation)

Selective radiological embolisation of the bleeding vessel may be an option in centres where interventional radiologists are available and the bleeding is not life threatening. It is a less invasive intervention and involves insertion of a catheter through the femoral artery into the aorta and then to the uterine arteries. Gel foam (gelatin) pledgets are the most commonly used material in cases of emergency embolisation with a potential for recanalisation three weeks later (Pelage et al., 1999). The uterine artery is the most commonly embolised vessel, followed by the pudendal, hypogastric, obturator, vaginal and cervical arteries (Vegas et al., 2006). Pelage and colleagues evaluated the role of selective arterial embolisation in 35 patients with unanticipated PPH (Pelage et al., 1999). Bleeding was controlled in all except one who required hysterectomy for re-bleeding five days later. All women who had successful embolisation resumed normal menstruation. Fever, contrast media renal toxicity, and leg ischaemia are rare but reported complications of this procedure (ACOG., 1998). Unfortunately, the efficacy of selective arterial embolisation is often limited to a small number of hospitals where a trained, available interventional radiologist is present (Tamizian and Arulkumaran, 2002). It is less effective in the presence of disseminated intravascular coagulation and placenta accreta (Rouse, 2013). When embolisation is successful, the patient can rapidly recover without undergoing additional surgery. The procedure has many advantages, including minimal morbidity and low complication rates, shorter hospital stay, preservation of fertility and the fact that it can be carried out under local anaesthesia (Ledee et al., 2001).

2. Compression sutures

Haemostatic uterine suturing or uterine compression sutures have been used to control PPH. The technique was introduced in 1997 as a type of vertical brace suture (Figure 13). It works by opposing the anterior and posterior walls of the uterus. The original technique was the B-Lynch suture, created by Dr. B-Lynch, a British Obstetrician and Gynaecologist. Single or multiple stitches may be inserted at the same time and, according to the shape, they may be called the brace suture (B-Lynch et al., 1997), square sutures (Cho et al., 2000) or simple brace (Hayman et al., 2002).

In his 2007 article, Baskett offers results of a 7-year study of compression sutures, all done at the time of caesarean delivery, showing that compression sutures were able to control bleeding in 23 of 28 (82%) of women, thereby preventing hysterectomy. Of these women, 7 were able to have subsequent uncomplicated term pregnancies (Baskett, 2007). The usefulness of the B-Lynch suture is attributed to its simplicity, safety, ability to preserve life, the uterus and fertility (Somunkiran et al., 2007). Despite the effectiveness of uterine compression sutures, unexpected occlusion of the uterine cavity with subsequent development of infection (pyometra) has been reported (Ochoa et al., 2002), and uterine necrosis was also documented (El-Hamamy and B-Lynch, 2005).

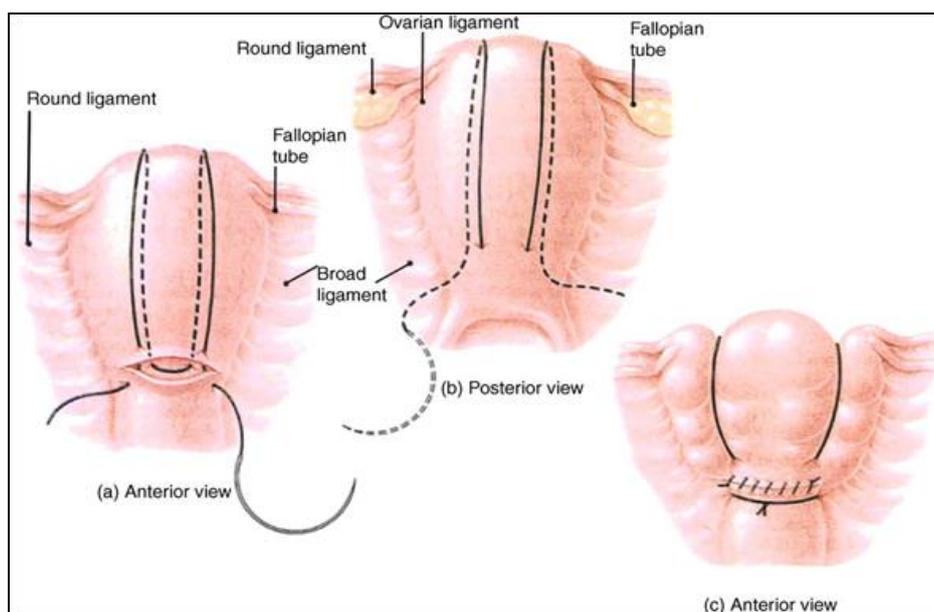


Figure 13. Uterine compression using B-Lynch suture for treatment of atonic uterus (B-Lynch et al., 2006)

3. Ligation of arterial blood supply

Of the uterus-sparing options, arterial ligation is one of the most frequently used worldwide. Ligation of the uterine artery or its main supply internal iliac artery may be considered in selected cases. Bilateral uterine artery ligation, as first described by O'Leary and O'Leary (O'Leary and O'Leary, 1966; O'Leary and O'Leary, 1974), consists of a mass ligation of the uterine vessels (including arteries and veins) and the myometrium at the level of the lower uterine segment. The procedure is considered one of the most effective surgical measures to control PPH as its occlusion reduces 90% of the uterine blood flow. Despite this percentage, an adequate blood supply is still available (Gilstrap and Ramin, 1994). The technique is easy to perform, associated with minor morbidity and has shown to be successful (not requiring hysterectomy) in 80-96 % of cases (O'Leary, 1995; Morel et al., 2011). Incomplete ligation is the most common cause of persistent bleeding and failure of the method (Fargeaudou et al., 2010; Zwart et al., 2010). Fears regarding uterine compromise with subsequent pregnancies have been proven unfounded as a number of women have become pregnant after undergoing uterine ligation (Shah and Wright, 2009).

Systematic pelvic devascularisation, including additional ligation of the internal iliac arteries, has been advocated as an effective measure for controlling intractable PPH and preventing maternal death (Joshi et al., 2007; Mukherjee and Arulkuman, 2009). Unfortunately, this procedure has a low success rate (estimated at 40%), mostly attributed to the late stage at which the ligation is attempted and that it is frequently complicated by hematoma formation and tissue oedema that obscure the anatomy (Tamizian and Arulkumaran, 2002). In a case-series including 88 patients with a therapeutic internal iliac artery ligation (IIAL) mainly due to uterine atony, genital tract injury and placenta praevia, IIAL failed to arrest haemorrhage in nearly 40% of cases requiring subsequent hysterectomy (Joshi et al., 2007). IIAL is more difficult to perform and not more effective compared to other conservative operative procedures for controlling PPH, requires advanced surgical skill, and carries an increased risk of venous, ureteral and nervous damage. Complications of this procedure can be severe, including ischemic damage to the pelvis, and decreased blood flow to the gluteal muscles (Tamizian and Arulkumaran, 2002). As shown by numerous case reports and small case series, IIAL has no adverse effect on subsequent fertility or pregnancy outcome (Sziller et al., 2007).

4. Hysterectomy

Porro in 1876 was the first to describe caesarean hysterectomy to prevent death from uterine haemorrhage (Mousa and Alfirevic, 2007). Hysterectomy is the last line of treatment available for treating PPH. It is only used for haemorrhage unresponsive to other management attempts mentioned above, as it removes the patient's option to bear additional children (Yucel et al., 2006). Some clinicians go immediately for hysterectomy as a life-saving procedure. The subtotal hysterectomy (also called supra-cervical) has become a preferable procedure, as it is quicker, associated with less blood loss, and carries a reduced need for further blood transfusion (Chanrachakul et al., 1996). However, if the bleeding source is in the lower segment of the uterus, a total hysterectomy is needed (Tamizian and Arulkumaran, 2002). Unfortunately, both subtotal and total hysterectomies completed for PPH are associated with high rates of maternal mortality (Yucel et al., 2006).

Conclusion

PPH is a major contributing factor for maternal morbidity and mortality. PPH has numerous causative factors, which makes its occurrence and severity difficult to predict. The exact definition of PPH and consequently its incidence are continuing to be a matter of debate, and there is currently no single, satisfactory definition for PPH. It is agreed that the failure of the uterus to contract properly is the most common cause of primary PPH. AMTSL is able to decrease the rate of PPH and the duration of the third stage of labour. The role of AMTSL in preventing PPH is thought to be attributed to oxytocin. However, preventing deaths from PPH require more than this. It requires skilled attendants, the availability of uterotonic drugs (including purchase, cold chains and long-term storage) and most importantly good quality health facilities. There still exists a significant amount of uncertainty regarding the optimal mode of prevention and management of PPH. Hence, a more robust approach to the prevention of PPH and a new method of treatment may be needed.

Chapter 2

Historical review

*A hundred years of the third stage:
development in the management of the third stage of labour as described
by Ten Teachers*

1. Background

As mentioned before, the third stage of labour is recognised as being the most dangerous time of childbirth for the mother. Many of today's obstetricians were brought up believing that 'active management' of the third stage (oxytocics, early cord clamping and CCT) was the only safe way to deliver the placenta. However, recent studies have shown that although prophylactic oxytocics are beneficial, early cord clamping is of no benefit (and could be harmful), and CCT has little benefit (Aflaifel and Weeks, 2012b). We therefore sought to place these changes in context through a historical study of obstetric practice over the last century.

The undergraduate textbook 'Obstetrics by Ten Teachers' has been a favourite with students, lecturers and practitioners for many generations. First published in 1917 as 'Midwifery by Ten Teachers' (Berkeley et al., 1917), the book was renamed 'Obstetrics by Ten Teachers' in 1966 (Clayton et al., 1966). New editions have been published every 3 to 8 years, giving 19 editions over the last century. Throughout these years, each book has been written by 10 leading obstetricians from the British Isles with the authors chosen by the senior editor. Famous previous editors include Stanley Clayton, George Pinker, Geoffrey Chamberlain, and Stuart Campbell. With a complete absence of references in the text, the series provide an excellent example of 'eminence-based' medicine and gives a fascinating insight into changes in labour ward culture over the last century.

2. Methods

In this study, we reviewed the regimes that were recommended for the management of the third stage of labour between 1917 and 2011 as described in the successive editions of the 'Ten Teachers' books. Copies were obtained from the Harold Cohen library of the University of Liverpool and from interlibrary loans as necessary. Teaching on the routine management of the third stage of labour and the treatment of atonic PPH were tabulated and graphically displayed (Appendixes B.1 and B. 2).

3. Results

Routine third stage management (Figure 1)

Routine third stage management is focussed on reducing blood loss and achieving rapid and complete delivery of the placenta. Changes over the last century are shown in Figure 1.

From 1917 until 1972, the ten teachers taught students to give uterotonic drugs and deliver the placenta through maternal effort. The cord was clamped only after the baby had cried vigorously, cord pulsations had stopped and the umbilical vein had collapsed (the authors describe their concern about depriving the neonate of 60-90 mls of blood if the cord was clamped immediately). The first uterotonic available was liquid extract of ergot, which was given after the delivery of the placenta either orally as “one teaspoonful in a wine-glass of water” or by hypodermic injection. In the late 30s the intramuscular injection of ergometrine was also recommended as an alternative. In 1948, oxytocin injection was first described, at first on its own and then from 1966 in combination with 500 mcg ergometrine as syntometrine[®]. In the mid-50s, the timing of the administration was changed from after placental delivery to immediately after delivery of the baby.

Although the use of uterotonic drugs in various forms have been used ever since the first edition as mentioned above, the practice of early cord clamping and CCT only became routine after the AMTSL package was popularised in the mid-sixties.

The 1966 edition was the first to separate management options into conservative and active methods. In the active method, ergometrine or syntometrine[®] is given “after delivery of the anterior shoulder”. The placenta is then actively delivered by the Brandt-Andrew method or, more recently, using CCT. In the Brandt-Andrew method, the cord is held taut whilst the placenta is extracted by upward pressure on the uterus with the palmar surface of the fingers. In CCT however, the birth attendant pushes the uterine fundus upwards with one hand while the other hand applies continuous traction on the umbilical cord to extract the placenta.

The textbook also taught that, as part of the active management package, the cord should be cut early. However, this advice only lasted 14 years until the 1980 edition when the early cord clamping was dropped from the teaching, and the teaching became that cord clamping should be delayed for few minutes (unless neonatal resuscitation was needed). This was the recommended practice until 2011 when the authors reverted to their recommendation of early cord clamping. The position of the newborn baby whilst the cord is being clamping was also the subject of interest for the teachers from 1966. Initially they recommended placing the baby below the level of placenta to facilitate blood flow to the baby. But from 1980 onwards, the authors preferred to keep the baby at the same level as the placenta and advised against ‘milking the cord’ to force the blood from the placenta to the baby.

The treatment of atonic PPH (Figure 2)

Throughout the ‘Ten Teachers’ series, uterotonic drugs have always been taught as being the best initial treatment for atonic PPH, with ergot derivatives as the drug of choice. From the earliest edition until 1942, a combined dose of ergotin and pituitary extract was recommended, although it changed in 1942 to intravenous or intramuscular ergometrine. The drug was always given after delivery of the placenta. However, with the increasing availability in hospitals of anaesthesia, surgical procedures and blood transfusion transfer to a facility became important. From 1955, ergometrine was advised to be given before delivery of the placenta if the patient was located outside of a well-equipped hospital. It was argued that this would either cause expulsion of placenta, or stop the bleeding by contracting the uterus around the placenta so that she can be transferred to hospital for a manual removal of placenta. Since 1948, the teachers have recommended a repeat dose of uterotonic if the first was unsuccessful. The standard drug was ergot, but others have included transabdominal intramyometrial ergometrine (1961-1972) and oxytocin (1948). From 1995 onwards the choice of uterotonics increased to include IV syntometrine[®], oxytocin infusion, prostaglandin F_{2α} (IM or directly into the uterine muscle), and misoprostol.

Aside from drug therapy, uterine massage (sometimes in combination with squeezing the uterus through the abdominal wall) has always been taught as the first line non-drug intervention. Early alternatives include a 180°F intrauterine douche (with dettol in 1938-1942), and external or intra-abdominal aortic compression. The importance of BMC has increased gradually, moving from third to first option over the editions. Throughout the century, the importance of its early use was stressed in the event of severe bleeding.

Hysterectomy is usually kept as the last line of treatment, but a number of physical methods have been taught to try to avoid this. In early editions, packing the uterus was suggested (1917-1935). This technique returned in the 2000 edition along with balloon tamponade and arterial embolisation as alternatives to arterial ligation. In 2011 uterine compression sutures were also recommended as a further alternative to hysterectomy.

4. Discussion

The ‘Ten Teachers’ collection provides an intriguing insight into the history of medical care in pregnancy through the last 100 years. Although only a snapshot of the teaching from a single textbook, it has provided us with the opinions of some of the most respected obstetricians of their day. It is therefore likely to be representative of medical student teaching generally at that time, especially in the first half of the century when ‘Ten Teachers’ was one of very few textbooks available.

An examination of a century of practice provides us with three lessons. First, with scientific evidence absent for much of the century, the management practices have tended to ebb and flow according to the experts’ opinion and cultural acceptability. This is most clearly seen with the use of CCT for routine delivery of the placenta. However, the recommendations regarding the timing of cord clamping are also of interest. Throughout the century, right up until the latest edition, teachers have taught that the cord should be clamped only after the baby stopped crying and the cord stopped pulsating (although the option of early cord clamping was introduced in the 1960s as part of the active management). This teaching persisted up to the most recent edition when the teaching changed and students were taught to clamp the cord early. Oddly, the authors reverted to their recommendation of early cord clamping in the 2011 edition, it comes just at a time when there is a widespread change back to delayed cord clamping again, led by national

and international evidence-based guidelines (WHO, FIGO and the RCOG), demonstrating the well-recognised disconnect between ‘evidence-based’ and ‘eminence-based’ medicine.

Second, the change in teaching shows clearly a lowering of the threshold for invasive therapies. As safe anaesthetics and antibiotics became available, so invasive therapies could be introduced at a much earlier stage for life saving. Hysterectomy for controlling severe haemorrhage was not mentioned in the first half of the century, presumably because the mortality from the surgery was so high that it was not worth attempting in a woman who is already severely shocked from haemorrhage. In the 1966 edition, however, it was introduced as a possible life-saving operation. This was only made possible with the introduction of blood transfusions, a technique that allowed women to be resuscitated before this high-risk surgery. Finally, several recent ‘innovations’ are found to simply be rediscoveries of old technologies that have been used successfully in the past but went out of fashion. This is seen with ‘delayed’ cord clamping as outlined above and uterine packing (although the tamponade is usually done now by an intrauterine balloon).

This review highlighted two important points. The first is that, throughout the century uterotonics were always used to start with in prophylaxis or in treatment. The other important point is the increasing importance of BMC, seen by it moving from third to first option in the management pathway. The following chapter will evaluate the effectiveness of uterotonics in treatment of PPH by examining histograms from large clinical trials.

	1917	1920	1925	1931	1935	1938	1942	1948	1955	1961	1966	1972	1980	1985	1990	1995	2000	2006	2011		
<u>Drugs</u>	Ergot (oral, in a win-glass)																				
	Ergot (hypodermic injection)					Ergometrine (im)															
								Oxytocin (im)		Ergometrine (iv)											
											Syntometrine (im)										
															Oxytocin (im)						
<u>Placental delivery</u>	Maternal effort																				
										Cord traction											
											Brandt-Andrew method										
																Controlled cord traction					
<u>Cord clamping</u>	After baby cries vigorously and pulsation stops																				
														Early in active method or if resuscitation needed			Delayed		Early		
<u>Position of baby</u>											Below the placenta		Same level as the placenta				Between mother's legs				

Figure 1. Routine third stage management (im= intramuscular; imm= intramyometrial; iv= intravenous)

	1917	1920	1925	1931	1935	1938	1942	1948	1955	1961	1966	1972	1980	1985	1990	1995	2000	2006	2011				
Drugs	Ergotin and pituitary extract (im)							E(im)	Ergometrine (iv)								E/O X	E (im)					
							E(iv,im)	Ox(im)										Ox(iv)					
																			E/OX				
																		PGF2α (im,imm)					
																		PGE1					
Techniques																							
First line	Uterine massage (or squeezing)																						
																			Bimanual compression				
Second line	Intrauterine douche						Bimanual compression																
Third line	Bimanual compression						Intrauterine douche		Drug (repeat dose of ergot)														
Last resort	Uterine packing																	Uterine packing					
																		Balloon tamponade					
																		Radiological embolisation					
																	Arterial ligation						
																			Compression sutures				
											Hysterectomy												

Figure 2. The treatment of atonic PPH (E= Ergometrine; Ox= Oxytocin; E/OX= Syntometrine; PG= prostaglandin; im = intramuscular; iv= intravenous; imm= intramyometrial)

Chapter 3

Blood loss histogram

The use of histograms to assess the efficacy of uterotonic treatment for postpartum haemorrhage: a feasibility study.

1. Background

PPH is a major killer of women worldwide, but its treatment has largely been developed empirically. There are, understandably, few randomised trials to assess the efficacy of treatments. Experts have often, therefore, had to rely on expert opinion and cohort studies to assess the efficacy of various therapies.

Given that an atonic uterus is thought to be the most common cause of PPH, the standard management of PPH starts with the administration of a dose of uterotonic, even if the mother has received a prophylactic dose of the same or other uterotonic. There is little evidence behind this treatment strategy. However, the finding that a single dose of a uterotonic markedly reduces both the mean blood loss and rates of PPH (Liabsuetrakul et al., 2007; Tuncalp et al., 2012; Westhoff et al., 2013) justifies the use of uterotonics as the first-line treatment option. Furthermore, it is reasonable to use oxytocin as first-line treatment for PPH as it has fewer side effects than other uterotonics (McDonald et al., 2004). Recent research has shown that a single dose of misoprostol 800 mcg administered sublingually can be used for atonic PPH in women who have received oxytocin prophylaxis, as well as those who have received no oxytocin prophylaxis (Blum et al., 2010; Winikoff et al., 2010). It is not known, however, whether oxytocin treatment has benefits over placebo alone due to the ethical imperative to provide treatment for all women. Furthermore, recent evidence from double-blind RCTs suggests that concurrent treatment with two drugs (i.e. misoprostol in addition to oxytocin, or an oxytocin infusion in addition to an oxytocin bolus) has little or no benefit (Widmer et al., 2010; Sheehan et al., 2011). A question remains therefore over the absolute efficacy of uterotonic therapies.

The technique of evaluating the effect of an intervention by measuring a size of a post-intervention response in continuously collected data is widely used in laboratory experiments, but rarely in epidemiology. With accurate measurement of blood loss however, the same principles can be applied to large blood loss datasets. In this situation, the response to uterotonic treatment is seen on blood loss histograms as a 'post-treatment peak', which represents the number of mothers who responded to the treatment. This was seen in a recent secondary analysis of 2 large RCTs, (Blum et al., 2010; Winikoff et al., 2010) where Weeks and others measured the size of the post-treatment peaks to compare the effect of misoprostol and placebo on women who had received oxytocin prophylaxis or none (Weeks et al., 2014). This showed that although both misoprostol and oxytocin were effective therapies, a second dose of uterotonics seems to be less effective in stopping the bleeding if the women had already received oxytocin prophylaxis. It is not known however whether this data can be replicated in other data sets, or whether the same attenuation of efficacy is seen following misoprostol or ergometrine prophylaxis.

We therefore explored the data sets from large randomised studies in which participants have been managed according to an explicit protocol for the prophylaxis and treatment of PPH, and who have had their postpartum blood loss measured.

The objectives of this research were therefore: (1) to explore whether post treatment peaks are routinely seen in postpartum blood loss histograms and whether the peaks are only seen in treated women. (2) To evaluate the efficacy of different uterotonic drugs in the treatment of PPH by measuring the size of the post-treatment peak on the blood loss histogram.

2. Methods

This study sought to examine the databases of all clinical trials of postpartum haemorrhage prophylaxis of over 1000 women which included individual patient data on measured blood loss, type of prophylaxis used and type of treatment used.

In order to identify suitable studies, we searched the Cochrane library database including Cochrane Central of Controlled Trials (CENTRAL), the Embase, the Ovid version of Medline, the Web of Knowledge and Scopus for relevant RCTs, using different keywords and medical subject headings (MeSH) without language restrictions. Examples of used MeSH and keywords are ‘postpartum haemorrhage’, any intervention used for PPH prevention such as ‘oxytocin’, ‘ergometrine’, ‘misoprostol’, ‘carbetocin’, ‘oxytocin analogues’, ‘prostaglandin’. Wildcards were used to improve the sensitivity of the search.

Titles and abstracts of 4170 papers were identified initially; removal of duplicates resulted in 1975 articles. Several types of studies were assessed as not eligible for inclusion into the study, such as research on cost effectiveness or hemodynamic effect of drugs or the assessment of drug side effects within population. Conference abstracts, non-randomised, observational and retrospective studies were also not included. These further exclusions left 125 papers for review and nineteen fulfilled the study inclusion criteria described above. These studies’ principal investigators were contacted by email to request their original data for secondary reanalysis. The protocol of the study was emailed to those who initially agreed to participate, and the datasets from 4 studies were obtained for analysis (Figure 1). The characteristics of these studies are summarised in Tables 1 and 2. The dataset for each randomised trial was divided into groups according to the type of prophylaxis used. The reported final blood loss for each woman was categorised into 100 mls increments from 0-2000 mls, according to the definition of PPH in the included studies. The percentage of women in every increment was obtained by dividing the number of women in each increment by the total number of women within the study arm from which women extracted. This process was repeated for each group (graphically displayed in a histogram).

In order to assess whether the peaks seen in the histogram had occurred as a result of the treatment administered, a second graph was produced containing only the data for those women who received treatment with a uterotonic. This allowed an assessment of whether any fluctuation in the histogram was due to uterotonic treatment. Women with missing data on total blood volume were excluded.

All studies received ethical approval prior to recruitment to the individual randomised trials and the data upon which this analysis was based had already been published. No further ethical approval was therefore sought for this secondary analysis of data.

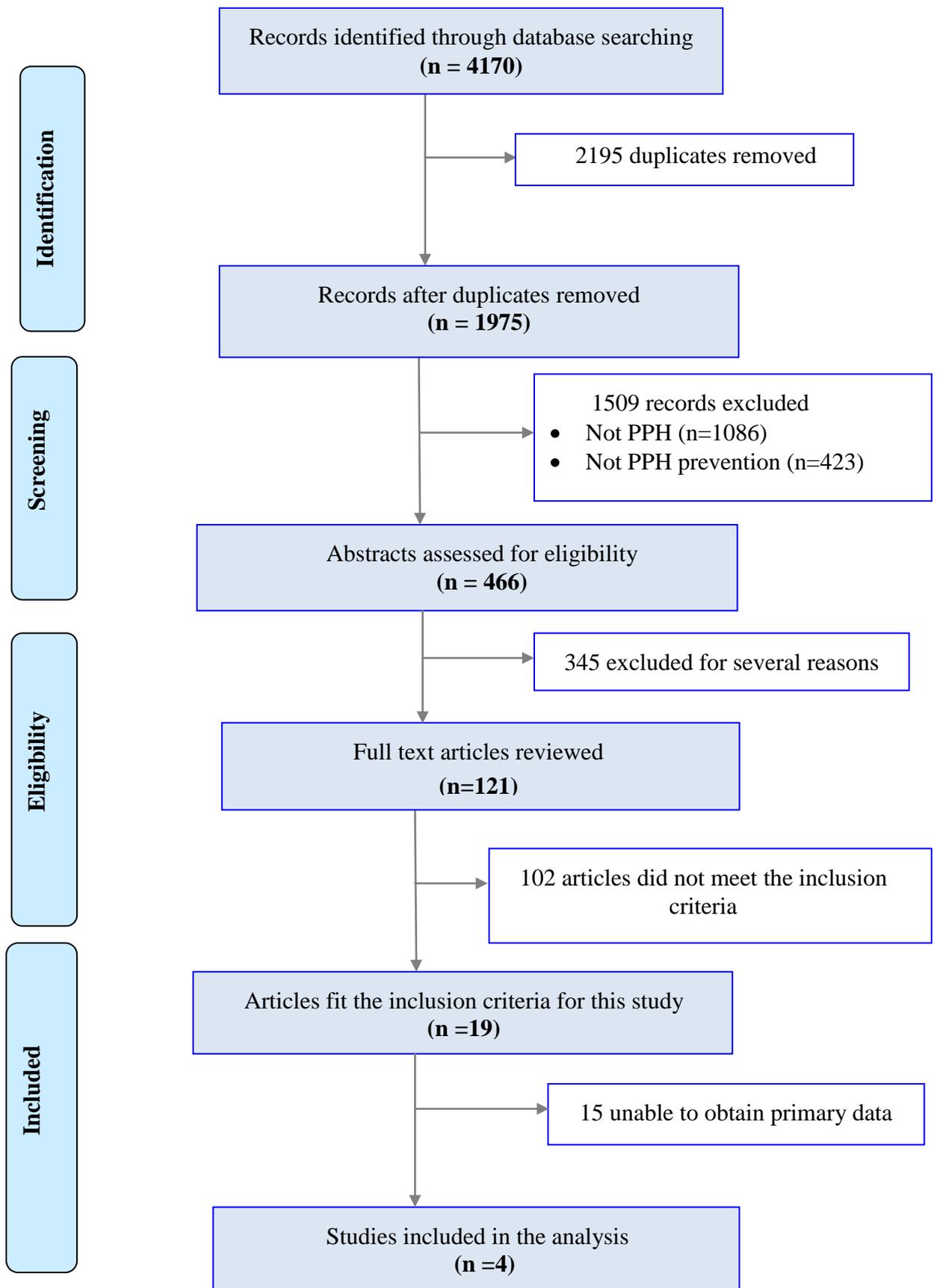


Figure 1. Flow diagram of included studies

3. Results

All of the included studies compared prophylactic misoprostol (either alone or in addition to other uterotonic) with another uterotonic or placebo in women having a vaginal birth. Two of the included studies were conducted in primary healthcare centres in India and compared 600 mcg of oral misoprostol either with ergometrine (Chandhiok et al., 2006) or with placebo (Derman et al., 2006), in low risk women. The two other trials were placebo-controlled, double-blind trials which examined the effect of the additional administration of 400 mcg of sublingual misoprostol to a routine prophylactic uterotonic. One was conducted in Nigeria (Fawole et al., 2011) and the other was multi-country (Hofmeyr et al., 2011).

1. Chandhiok, 2006

Chandhiok and colleagues (2006) investigated whether oral misoprostol administered by paramedical workers from rural primary health centres in India was effective at preventing PPH. The researchers used prophylaxis with 600 mcg misoprostol or ergometrine in low risk women undergoing vaginal delivery. The blood loss was collected and measured for 1 hour after delivery (or 2 hours for those bleeding was persisting). In this study, there was a low incidence of PPH (<1%) in both groups, but a significant reduction was noticed in median blood loss after delivery (100 mls vs. 200 mls; $p < 0.001$) in the misoprostol arm (Figure 2). In the misoprostol arm 2 small peaks were seen consisting of 4 women who were treated with uterotonic. The first peak was at a total blood loss 600-900 mls and the other was at 1200-1300 mls (Figure 3).

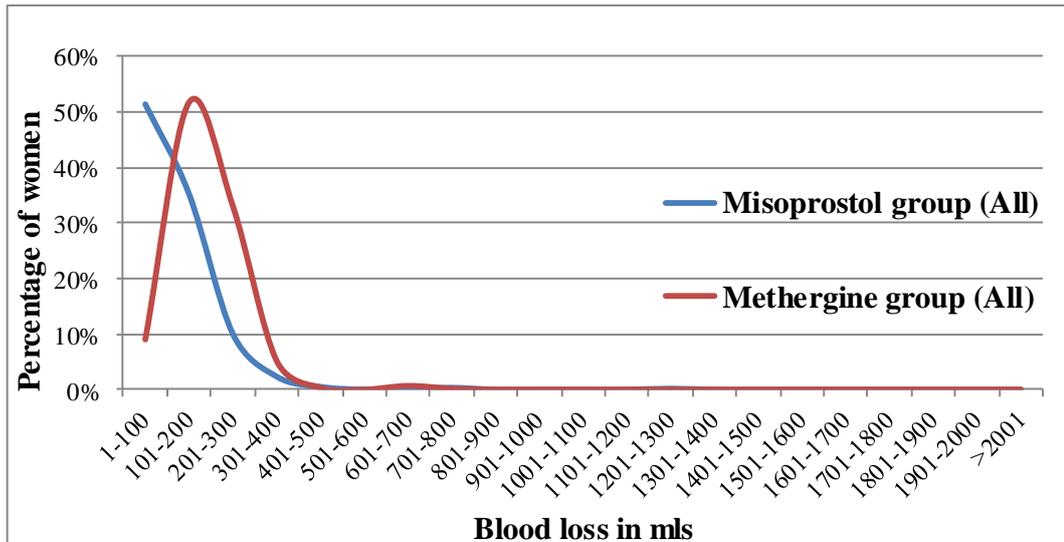


Figure 2. Histogram showing the main study results in the Chandhiok trial (2006). The red line represents the blood loss in all participants in the methergine group. Whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm. The study definition of PPH was > 500 mls; increments were therefore defined so that “500 mls” was included with the 400-500 range

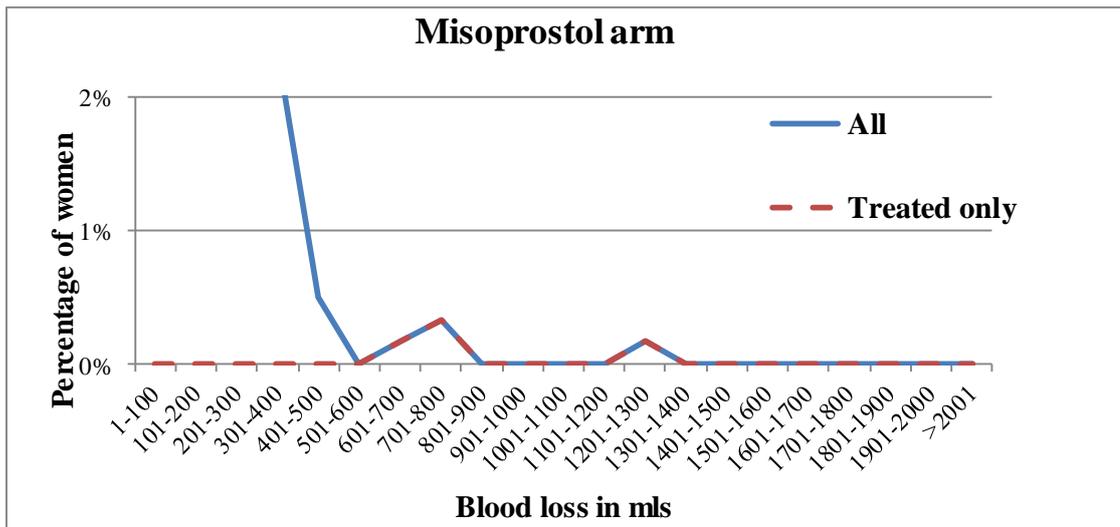


Figure 3. Histogram showing blood loss distributions of women in the Chandhiok trial (2006) who were randomised to receive misoprostol. The blue line shows the distribution for all women who received misoprostol prophylaxis, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

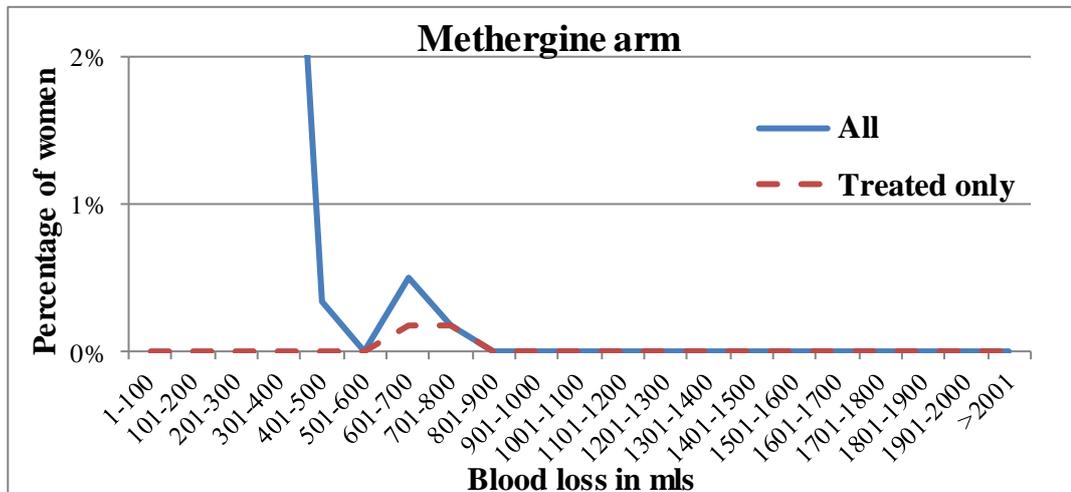


Figure 4. Histogram showing blood loss distributions of women in the Chandhiok trial (2006) who were randomised to receive methergine. The blue line shows the distribution for all women in the methergine arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

In the methergine group, 4 women were diagnosed with PPH and of these, only 2 women received treatment. Two others, with a total blood loss between 600 and 800 mls, did not receive a uterotonic but stopped bleeding spontaneously (Figure 4). The treatment peaks of similar size were noted in misoprostol and methergine groups.

In this study, very few women had a PPH, and all settled quickly with maximum blood loss of 1200-1300 mls. No women with a blood loss of < 500 mls received treatment and almost all those diagnosed with PPH had treatment.

2. Derman, 2006

The second study was a RCT conducted by Derman and co-workers (2006). This was a placebo-controlled trial of 600 mcg oral misoprostol for the prevention of PPH conducted in rural India. Oral misoprostol was associated with a significant reduction in the rate of PPH \geq 500 mls (12.0% to 6.4%, $p < 0.0001$) and severe PPH \geq 1000 mls (1.2% to 0.2%, $p < 0.0001$). Misoprostol was also associated with a decrease in mean postpartum blood loss (262.3 mls to 214.3 mls, $p < 0.0001$). This is shown graphically in the histogram in Figure 5.

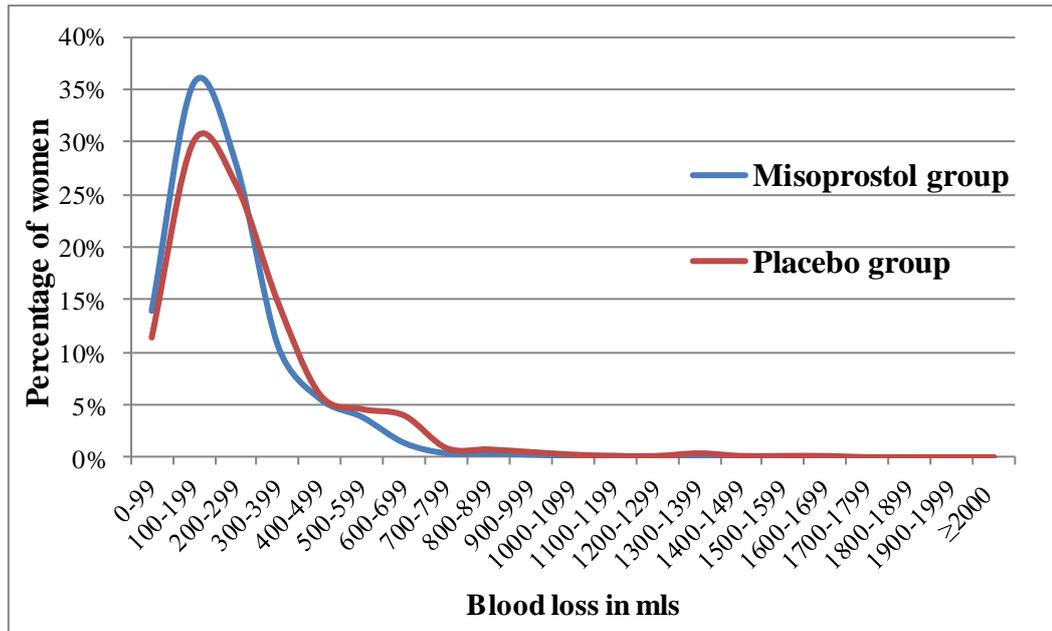


Figure 5. Histogram showing the main study results in the Derman trial (2006). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm. The study definition of PPH was 500 mls or more; increments were therefore defined so that ‘500 mls’ was included with the 500-599 mls range

Despite the frequency of PPH in both study groups (6.4% in the misoprostol group and 12.0% in the placebo group), very few women with PPH received treatment (2 in misoprostol group and 6 in the placebo arm). In addition, some women with blood loss < 500 mls received treatment (Figures 6 and 7). In the misoprostol arm, both treated women had final blood losses of under 500 mls, whilst all of those with a PPH of over 500 mls stopped bleeding spontaneously without receiving further uterotonic therapy. In the placebo arm, one woman received treatment despite a final blood loss of only 200 mls. The remaining 5 treated women all had blood losses of over 500 mls. However, of 97 women with PPH in the placebo arm, only 5 women (5%) received treatment - the remainder stopped spontaneously without the need for oxytocic therapy.

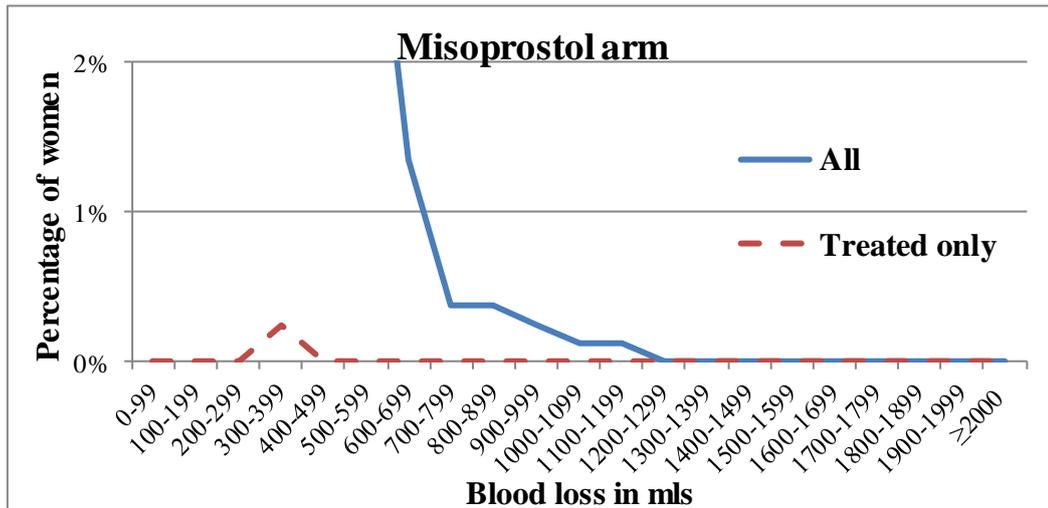


Figure 6. Histogram showing blood loss distributions of women in the Derman trial (2006) who were randomised to receive misoprostol. The blue line shows the distribution for all women who received misoprostol prophylaxis, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

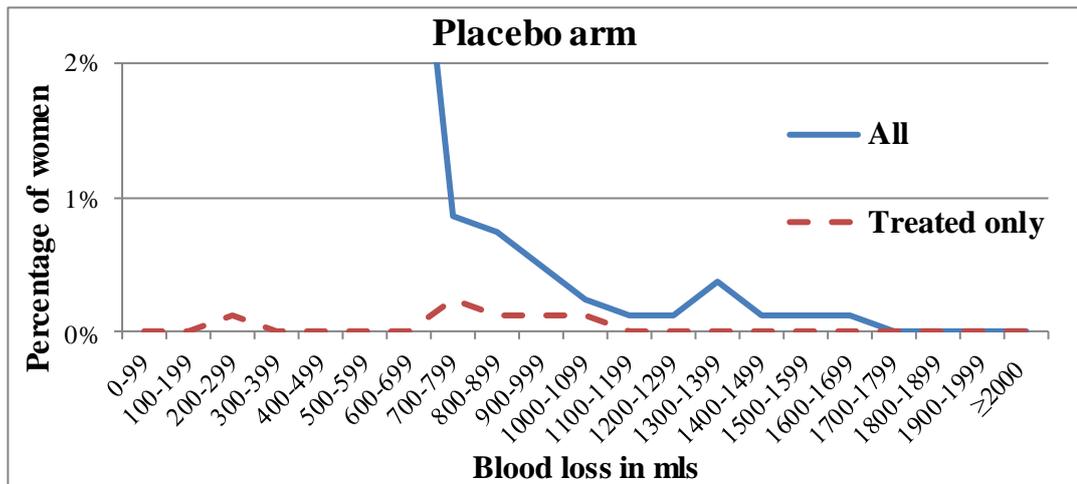


Figure 7. Histogram showing blood loss distributions of women in the Derman trial (2006) who were randomised to receive placebo. The blue line shows the distribution for all women in the placebo arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

3. Hofmeyr and Fawole

The two final studies compared the use of misoprostol and placebo in addition to routine uterotonic prophylaxis (Fawole et al., 2011; Hofmeyr et al., 2011). These two studies were double-blind, placebo-controlled multicentre randomised trials undertaken in hospitals to investigate the administration of 400 mcg sublingual misoprostol to augment routine AMTSL to prevent PPH. In both studies the measurement of blood loss was for one hour after delivery. Neither trial found any significant difference in the primary outcome of blood loss of 500 mls or more within 1 hour of randomisation: misoprostol 40 (6.1%) versus placebo 42 (6.4%) (Fawole et al., 2011) and misoprostol 22 (4.0%) versus placebo 35 (6.3%) (Hofmeyr et al., 2011). This can be also seen graphically in the histograms in Figures 8 and 11.

In both studies, the majority of women who received treatment had blood losses of under 500 mls (Figures 9, 10, 12 and 13). As with the previous studies, small secondary peaks were seen in all study arms, despite many women within the secondary peaks not having received uterotonic therapy.

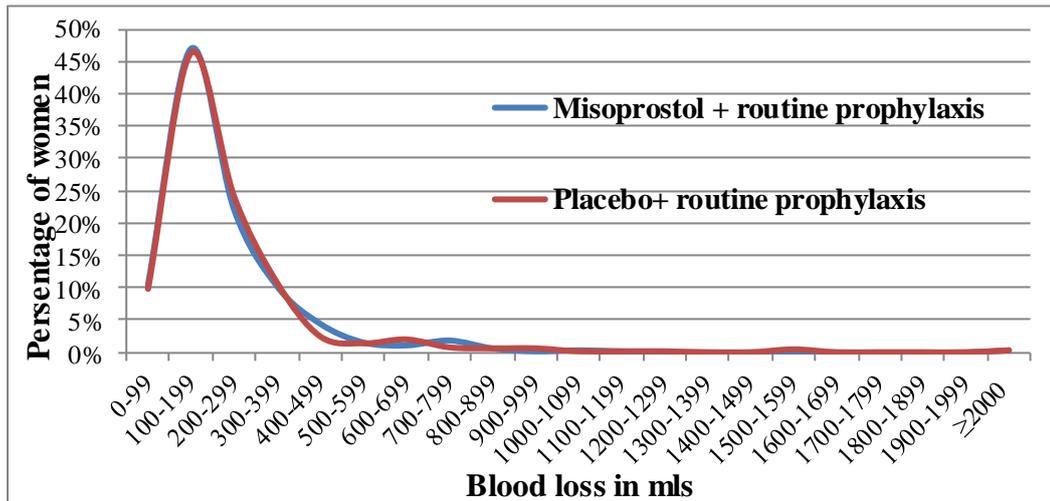


Figure 8. Histogram showing the main study results in the Fawole trial (2011). The red line represents the blood loss in all participants in the placebo arm, whilst the blue line shows the blood loss distribution for all women in the misoprostol arm. The study definition of PPH was 500 mls or more; increments were therefore defined so that ‘500 mls’ was included with the 500-599 mls range

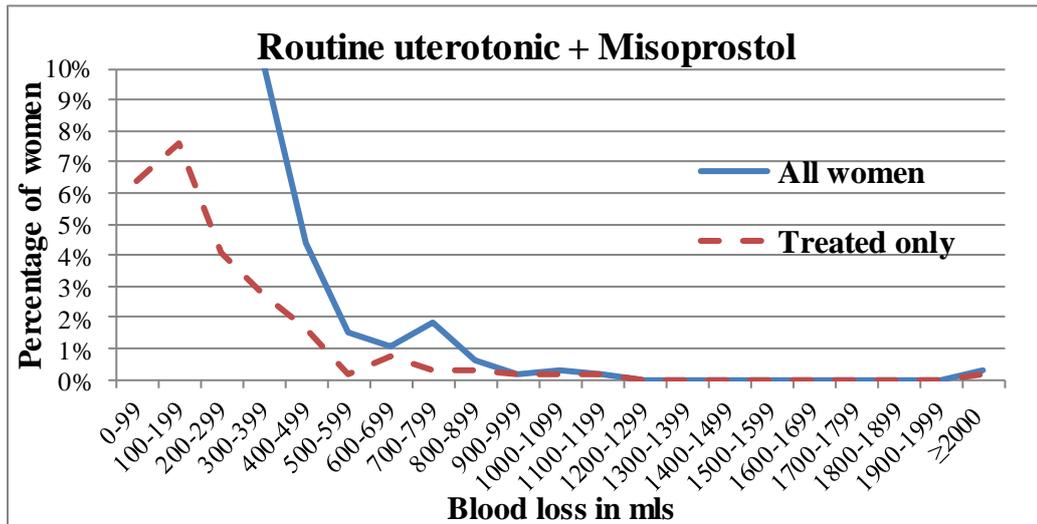


Figure 9. Histogram showing blood loss distributions in women in the Fawole trial (2011) who were randomised to receive misoprostol. The blue line shows the distribution for all women in the misoprostol arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

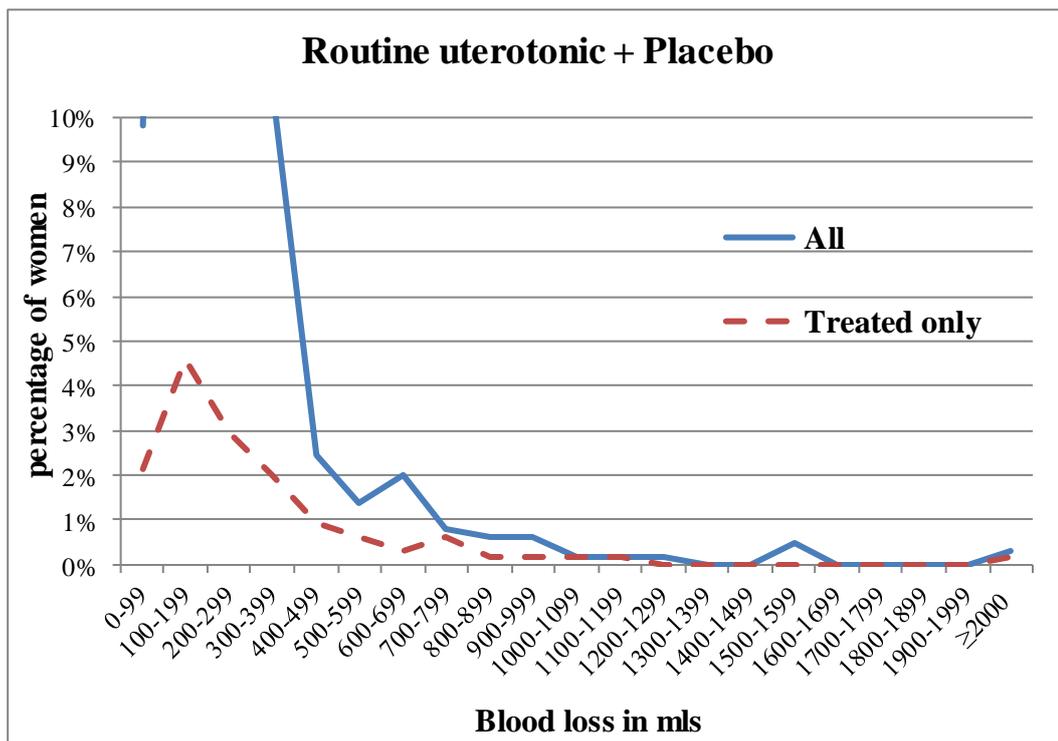


Figure 10. Histogram showing blood loss distributions of women in the Fawole trial (2011) who were randomised to receive placebo. The blue line shows the distribution for all women in the placebo arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

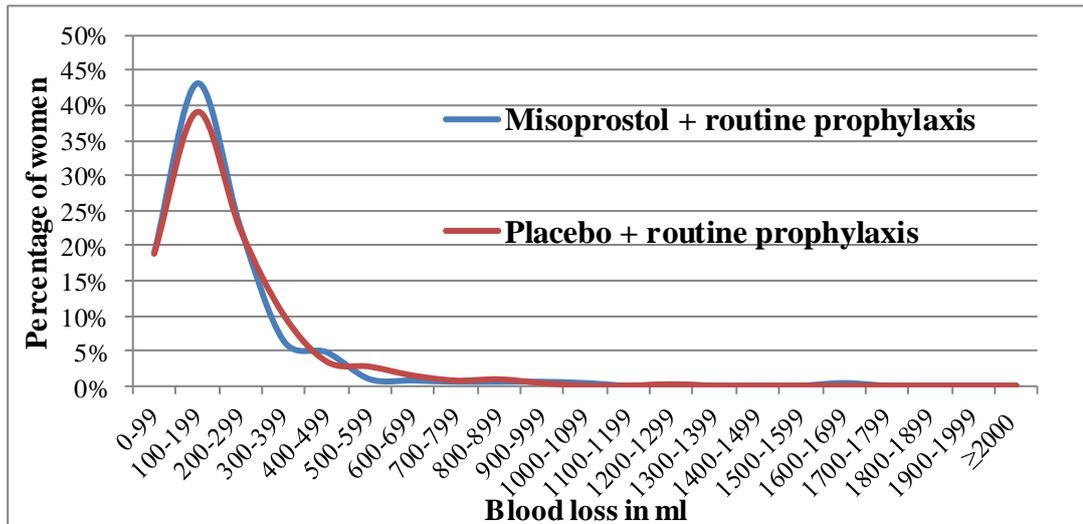


Figure 11. Histogram showing the main study results of the Hofmeyr trial (2011). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm. The study definition of PPH was 500 mls or more; increments were therefore defined so that ‘500 mls’ was included with the 500-599 mls range

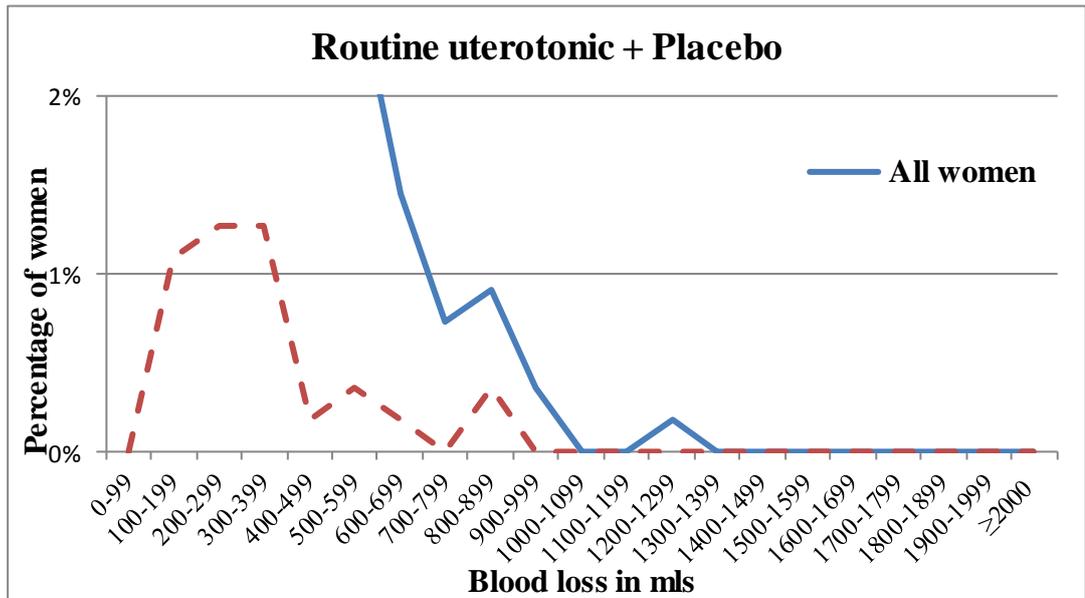


Figure 12. Histogram showing blood loss distributions in women in the Hofmeyr trial (2011) for those randomised to receive placebo. The blue line shows the distribution for all women in the placebo arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

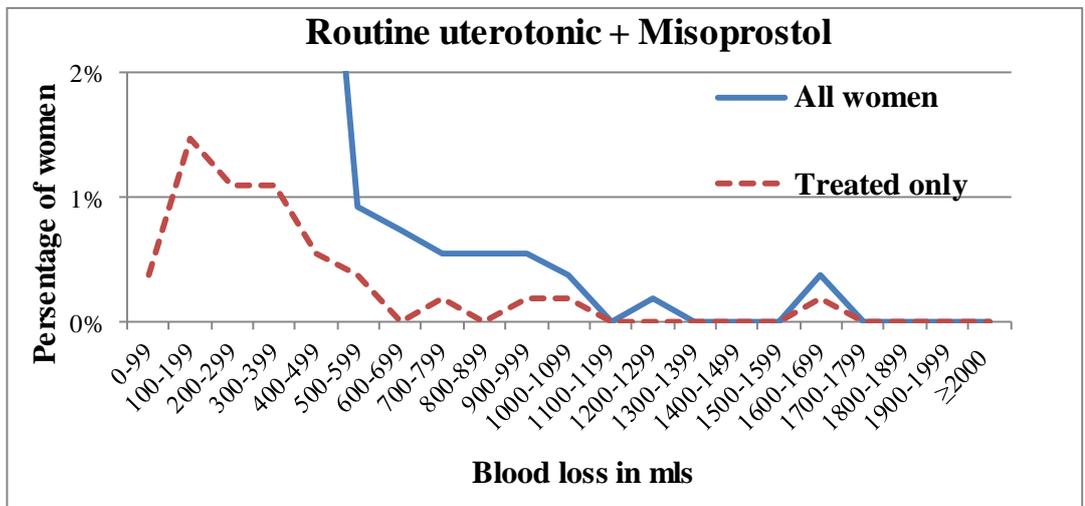


Figure 13. Histogram showing blood loss distributions in women in the Hofmeyr trial (2011) for those women randomised to receive misoprostol. The blue line shows the distribution for all women in the misoprostol arm, whilst the dotted line represents the blood loss in the subgroup of women who received treatment

4. Discussion

This exploratory study examined the distribution of blood loss for women during the third stage of labour using histograms. All of the included studies compared the prophylactic effect of oral or sublingual misoprostol (either alone or in addition to routine uterotonic) with placebo or another uterotonic in preventing PPH during vaginal birth.

The only previous description of this methodology is a study examining the data from 2 large randomised trials conducted by Gynuity Health Projects in which 40,403 women were recruited and had intrapartum blood loss measured. Those with blood loss over 700 mls were randomised to receive 800 mcg sublingual misoprostol or 40 IU intravenous oxytocin. In a secondary analysis similar to this one, no peak was seen for non-treated cases, but clear peaks were measurable for those who received either oxytocin or misoprostol (Weeks et al., 2014). The size of the treatment peak was attenuated by the use of oxytocin prophylaxis. The data analysed here is from smaller studies which were examining the effect of prophylaxis on blood loss. The time at which treatment was initiated was left to the clinical team and the histograms thus represent 'real life' care. Whilst it cannot be stated that the uterotonic treatment was given immediately before bleeding stopped, the final blood loss represents the maximum blood loss at which it could have been given. The treatment graphs are therefore conservative examples, representing the highest blood loss at which uterotonic treatment could have been used. This is in contrast to the Gynuity PPH management studies. In those, there were rigorous diagnostic and treatment protocols which were necessary because they were specifically examining PPH treatment, and so the accuracy of the diagnosis, randomisation and initiation of treatment were critical.

The peak that appeared in the graphs represents the total blood loss a woman had lost. An important finding from this study is that presence of a peak was not specific for treated cases. A secondary peak was noted in many of the histograms and contains many women who did not receive uterotonic treatment. In the Chandhiok study for example the group who received ergometrine for prophylaxis but did not receive any treatment still had a small secondary peak at a blood loss of around 600-

800 mls (Figure 4). This could reflect the effect of other therapies rather than uterotonics in treating PPH such as BMC or/and uterine massage. The presence of this peak should caution against the over-interpretation of histogram data and ascribing the presence of treatment peaks to uterotonics alone.

Although postpartum blood loss was objectively measured in all of the included studies, the use of oxytocic therapy was not consistent in the use of therapy only at the traditional blood loss cut off of 500 mls. In the studies of Fawole (2011) and Hofmeyr (2011) the vast majority of uterotonic therapy was given to women with a final blood loss of under 500 mls. This reflects reality, where the decision to initiate therapy is based not only on the volume of blood lost, but also on the speed of the blood flow, the underlining cause of the bleeding and the woman's clinical condition. Thus a severely anaemic woman with a prolonged labour who has a gush of blood postnatally would rightly be given treatment immediately, even though the final blood loss might amount to only 200 mls in total. Although this reflects usual practice, it limits the use of the histogram analysis to studies with a very clear and rigorously enforced protocol for the uterotonics use.

Of more concern is the number of women who bled over 500 mls but did not receive uterotonic therapy. This again reflects clinical practice where underestimation of blood loss is common, especially if the woman is otherwise healthy, and there is a slow trickle of blood thought to be coming from vaginal lacerations. This surprise finding provides a fascinating insight into clinical practice in PPH treatment.

The implications of these findings are that: a) in prophylaxis trials, the rate of uterotonic use appears to be a poor surrogate for PPH; b) the recommendations to treat PPH at 500 mls may not be commonly used in clinical practice, and needs to be reviewed; and c) the size of the histogram 'treatment peaks' are not a good indicator of the efficiency of uterotonics, unless the clinicians follow a very strict treatment protocol (which may not reflect clinical practice).

Furthermore, it appears that vaginal blood loss in women having a PPH commonly stops spontaneously even without uterotonic therapy. This presents a dilemma for clinicians. Whilst reassuring, it is impossible to predict who will spontaneously stop bleeding and who will continue bleeding to life-threatening levels. In addition, PPH

causes significant problems through postpartum anaemia and the use of uterotonics is likely to hasten the cessation of bleeding. Understandably therefore, clinicians tend to use uterotonics frequently and at very early stages to prevent progression.

In summary, the findings from this study do not support the routine use of histogram analysis to assess the efficiency of uterotonic therapy. The analysis of histograms should be limited to PPH treatment studies in which strict protocols are used for the timing and nature of PPH treatment. Even then, the finding of a secondary peak in untreated women in these studies should warn against ascribing all the effect to uterotonic therapy; other physical therapies may also be used concurrently and may also have an effect.

In addition, the analysis of these histograms provide further insights into clinical practice, with clinicians frequently using uterotonic therapies even when the volume of the blood loss is low. This demonstrates how uterotonic use in practice is often not linked with the standard 500 mls definition of PPH - this is important both for researchers and for those producing clinical guidelines.

Table1. Methodological details of included studies

Study	Participants risk of PPH	Study type	Setting	Prophylaxis received	PPH definition and measurement
Chandhiok, 2006	1200 – low risk	Cluster randomised	30 peripheral health centres from 5 states in India	Intervention: 600 mcg of oral misoprostol (600) Control: (600) an intramuscular injection of 0.2 mg of methergine (88.5%) or oral tablet of 0.125 mg methergine (9.7%)	PPH was defined as > 500 mls bleeding. A calibrated blood collection drape (BRASS-V) was used to measure blood loss for 1 hour after delivery (and for 2 hours if bleeding persisted)
Derman, 2006	1620- low risk	RCT	Four primary health centres areas in rural India	Intervention: A single oral dose of 600 mcg of misoprostol (812) Control: Placebo (808)	PPH was defined as \geq 500 mls bleeding and was assessed using a polyurethane blood collection drape for 1hour after delivery (and for 2 hours if bleeding persisted)
Fawole, 2011	1345- not specified	RCT	6 hospitals in Nigeria	Intervention: A sublingual dose of 400 mcg of misoprostol (672) Control: A placebo (673). Both arms also received standard active management of the third stage of labour (oxytocin or ergometrine)	PPH was defined as \geq 500 mls bleeding and was assessed using a low-profile plastic bedpan for a period of 1 hour
Hofmeyr, 2011	1103- not specified	RCT	4 hospitals in South Africa, Uganda, and Nigeria	Intervention: A sublingual dose of 400 mcg of misoprostol (547) Control: A placebo (556). Both arms also received standard active management of the third stage of labour (oxytocin or ergometrine)	PPH was defined as \geq 500 mls bleeding and was assessed using a low-profile plastic bedpan for a period of 1 hour or until bleeding stopped

Table 2. Study outcomes from included studies

Study	Number of women with PPH	Uterotonic given	Additional interventions used
Chandhiok, 2006	Total: 9 Intervention: 4 (0.7%) Control: 5 (0.8%)	Total: 6 Intervention: 4 Control: 2 Type: Methergine and oxytocin injection	<ul style="list-style-type: none"> • Manual removal of placenta (30 women in the methergine group) • One woman in the intervention group lost > 1000 mls of blood. Uterine exploration was carried out and a blood transfusion administered
Derman, 2006	Total: 149 Intervention: 52 (6.4%) Control: 97 (12.0%)	Total: 10* Intervention: 3 Control: 6 Type: Methergine, oxytocin and carboprost injection	<ul style="list-style-type: none"> • One in the intervention group and 8 in the placebo arm had surgical interventions (repair of perineal, cervical, and high vaginal lacerations, manual removal of placenta) • One woman in the placebo group received bimanual uterine compression alongside medical treatment
Fawole, 2011	Total: 82 Intervention: 40 (6.08%) Control: 42 (6.36%)	Total: 259 Intervention: 162 Control: 97 Type: Methergine and oxytocin injection	<ul style="list-style-type: none"> • Manual removal of placenta (23 in misoprostol group, 27 in placebo group)
Hofmeyr, 2011	Total: 57 Intervention: 22 Control: 35	Total: 58 Intervention: 31 Control: 27 Type: : Methergine oxytocin and syntometrine injection	<ul style="list-style-type: none"> • Manual removal of placenta (32 in misoprostol group, 33 in placebo group)

*Data on total blood loss were not available for one woman.

Chapter 4

Clinical outcomes in studies evaluating intervention to prevent PPH

Choice of outcomes in randomised trials and systematic reviews evaluating interventions for postpartum haemorrhage prevention: a systematic review

1. Background

PPH remains a concern as it is considered to be a major cause of maternal mortality in both low- and high-income countries. Prevention of PPH is therefore of great importance in order to improve women's healthcare and to save lives. It is well-recognised that some research designs are more powerful than others in their ability to answer research questions about the effectiveness of interventions. This concept has given rise to the notion of hierarchy of evidence (Akobeng, 2005). The ranking has an evolutionary order, moving from simple observational methods at the bottom, through to increasingly rigorous methodologies at the top. Systematic reviews of RCTs, with or without meta-analysis, usually appear at the top of the hierarchy as they can provide the most powerful forms of evidence. RCTs are the most valid scientific method for evaluating interventions. This is because the processes used during the conduct of a RCT minimise the risk of confounding factors influencing the results. The results of RCTs are used to inform decisions (Guyatt and Rennie, 2002; Akobeng, 2005). In order for the results of RCTs to be useful, they should measure outcomes that are relevant to both patients and the healthcare professionals involved in making clinical decisions about an individual patient, group, or population. To support the implementation of effective methods of intervention in clinical practice, it is important to carry out a clinical appraisal of systematic reviews including their most important outcomes, whether or not these endpoints were measured in a consistent way, and whether the studies were adequately powered to detect the clinical benefits of the interventions being studied. Evidence-based comparisons of interventions can therefore be challenging because of the diversity of outcomes in RCTs.

Outcomes in clinical trials

Interventions used in healthcare may have various beneficial and harmful effects. These are known, in clinical practice and research, as outcomes. It is therefore critically important that the right outcomes are evaluated in clinical research in general, and in RCTs and systematic reviews in particular.

The primary outcome is an integral component of the research question. It should be explicitly stated and described, because it reflects the objective of the trial, and determines the sample size required (Moher et al., 2001). There is usually only one primary outcome, which should relate to the research question. In some situations, more than one primary outcome can be measured, in order to assess treatments more comprehensively. This can be useful if it is unclear which single primary outcome would best answer the research question.

Most trials also measure secondary outcomes, in order to evaluate other beneficial or harmful effects of treatments. These must be clearly stated and described in the study protocol and report (International Conference on Harmonisation, 1999). They should be selected judiciously, because as the number of secondary outcomes increase, the more likely it becomes that one will show a statistically significant result due to chance alone (Pocock, 1997).

There are tens of thousands of research studies which might provide the evidence needed to make well-informed decisions about healthcare. The task of working through all this material is overwhelming. Studies that describe their findings in different ways, make it difficult, if not impossible, to draw out the relevant information. Systematic reviews aim to identify, evaluate and summarise the findings of all relevant individual studies, thereby making the available evidence more accessible to decision makers. When appropriate, combining the results of similar studies gives a more reliable and precise estimate of an intervention's effectiveness than one study alone (Sacks et al., 1987). Systematic reviews adhere to a strict scientific design based on explicit, pre-specified and reproducible methods. Because of this, when performed well, they provide reliable estimates about the effects of interventions so that their conclusions are defensible. They clearly depict what is known about a particular intervention, but also demonstrate where knowledge is lacking (Petticrew, 2003). This can then be used to guide future research (Brown et al., 2006).

Recently, there has been much concern regarding the selection of outcome measures in clinical trials as evidence generated from clinical trials guides the changes in clinical practice (COMET, 2012). The Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011), states that a review question should specify not only the interventions and participants of interest but also the types of outcomes of interest. The Handbook also discusses some of the issues associated with drawing conclusions about outcomes found in a systematic review. The Handbook states that in addition to considering the strength of

evidence underlying any conclusions that are drawn, “reviewers should consider all of the potentially important outcomes of an intervention when drawing conclusions, including ones for which there may be no reliable data from the included trials. They should also be cautious about any assumptions they make about the relative value of the benefits, harms and costs of an intervention. Including all important outcomes in a review will highlight gaps in the primary research and encourage researchers to address these gaps in further studies”.

It can be difficult to know which outcomes should be measured in RCTs. Some groups advocate the development of core outcome sets, a minimum set of outcomes that should be measured, and reported, in all clinical trials involving a given condition (COMET, 2012). There were however no robust recommendations about which outcomes to measure in RCTs of PPH, which is a condition of considerable global importance.

Our aims were to assess whether the absence of a core set outcomes for RCTs of PPH prevention meant that certain outcome measures were measured less frequently than others, and whether there was non-uniformity between studies in terms of outcomes selected.

We have also examined the consistency of primary outcome reporting within systematic reviews of PPH prevention. The reason for choosing only primary outcomes from systematic reviews is that they reflect the key research question (objective) of the review, whilst the secondary outcomes are, as a rule, hypothesis generating.

2. Objectives

A. To assess which outcomes had been measured in clinical trials of PPH prevention and:

1. Systematically collect and organise these outcomes (primary and secondary).
2. Examine the clarity of stating primary and secondary outcomes within the trials.
3. Rank the outcomes in order of those most commonly used in RCTs (primary and secondary).
4. Determine whether there was consistent selection of primary outcomes.
5. Assess frequency of reporting of sample size calculations (SSC) and find out the percentage of primary outcomes that underpin SSC.

B. To assess which outcomes had been measured in systematic reviews of PPH prevention and:

1. To systematically identify and analyse the primary outcomes reported in systematic reviews of PPH prevention.
2. To rank these outcomes in order based on the frequency of reporting.

C. Compare the choice of primary outcomes between systematic reviews and RCTs evaluating intervention for PPH prevention.

Study design: a systematic review of RCTs and systematic reviews on the outcomes used in routine third stage management for prevention of PPH.

3. Methods

Criteria for considering reviews for inclusion

1. **Study type and participants:** in this study, we included all published RCTs and systematic reviews (all Cochrane and non-Cochrane systematic reviews) of interventions used in the routine management of the third stage of labour with the primary aim to prevent PPH, from January 1997 to December 2012.

In the mid-nineties, concerns about the quality of reporting RCTs resulted in the development of Consolidated Standards of Reporting Trial (CONSORT) (Begg et al., 1996). The statement was found to be associated with an improvement in the reporting of RCTs (Plint et al., 2006), therefore, only studies published after the first CONSORT statement were included.

2. **Interventions:** any interventions given with the aim of preventing PPH.

3. **Outcomes:** the percentage of different outcomes that have been used in the selected articles of the routine management of the third stage of labour with the aim to prevent PPH.

Search strategy

In order to optimise the probability of identifying all relevant studies, a variety of medical literature databases were searched. The Cochrane library database was searched (including Cochrane Central of Controlled Trials [CENTRAL]), as were Embase, the Ovid version of Medline, the Web of Knowledge, and Scopus, for relevant RCTs and systematic reviews using different keywords and MeSH. In order to achieve the broadest range of results synonyms and alternatives were also used in the search terms. Examples of the MeSH and keywords used are postpartum haemorrhage, any intervention used for PPH prevention such as oxytocin, ergometrine, misoprostol, carbetocin, oxytocin analogues, prostaglandin, uterine massage, cord clamping, fundal pressure, controlled cord traction, cord drainage, intraumbilical cord injection and others. Wildcards were used to improve the sensitivity of the search. Wildcard characters, denoted by a question mark, account for spelling variations. For example 'postpartum h?emorrhage' would identify the terms 'haemorrhage' and 'hemorrhage'. Boolean operators were used in the first step, using the 'OR' operator to

broaden the search, and then combining them using the ‘AND’ operator in the final step to narrow and focus the search. The search strategy is included in Appendix C.1.

Language restrictions

We did not apply any language restrictions.

Ethical approval

This study did not require ethical approval as the data used in this systematic review have been published previously and are in the public domain.

The search result

Search results from each of the databases were combined into the reference manager software program EndNote X5. Once all of the references from each of the databases had been uploaded into the reference manager, a search for duplicates was conducted. A duplicate search is necessary as many of the different databases reference the same articles when searched using similar criteria. Once a database that consisted of unique references was constructed, examination of the abstracts began for identification of eligible references for the review. Abstracts were identified as eligible according to the parameters described above. Those abstracts that appeared eligible for the review were marked for collection of a hard copy, and the reference hard copies underwent a final more thorough eligibility analysis and, if eligible, underwent data extraction.

Not all references marked as relevant at the abstract stage were accessible directly as a hard copy via the University library. If not, we obtained interlibrary loans via the University of Liverpool library. As we did not apply a language restriction, the search yielded 19 articles which were in languages other than English. All non-English articles were sent for translation and translated using a translation sheet (Appendix C.2).

Studies excluded from the review

Several types of studies were assessed as not eligible for inclusion into the review. There are many areas of PPH research that do not explicitly evaluate prevention of PPH. These alternative areas of research include cost effectiveness, or the hemodynamic effect of drugs, or the assessment of drug side effects within a population. Conference abstracts do not always reach full publication, and those that are published have been shown to be 'systematically different' from those that are never published in full (Lethaby et al., 2000). Therefore, conference reports and abstracts were excluded because of difficulties in evaluating incomplete information. Nonrandomised, observational and retrospective studies were also not included, and neither were feasibility studies.

We excluded non-systematic reviews, protocols of systematic reviews and systematic reviews that had been withdrawn. When more than one version of a Cochrane review was found, only the most recent one was included.

Selection of studies for inclusion

Having excluded a number of studies for the reasons outlined above, we then assessed the potential studies left for inclusion. The study was included if it was: 1) a full report; 2) a RCT or systematic review; 3) published after the first CONSORT statement; and 4) evaluating the efficacy of any intervention for the prevention of PPH. We also included studies that aimed to prevent uterine atony as a main cause of PPH. Uncertainty regarding any decision of inclusion was resolved with discussion with the supervisor (ZA). The full-text articles of all the reports meeting the inclusion criteria were analysed.

Data extraction and management

Once a reference had undergone the eligibility checks and was considered eligible data were extracted using a predefined data extraction form (Appendixes C.3 and C.4). From each RCT, the following data were extracted:

1. Reference identity data, including the type of report, name of the author and the year of publication.
2. Other study features: information regarding the interventions used; participants and number of women included; study location and setting; study objectives; methods of defining and measuring PPH and blood loss, and others.
3. All outcomes reported: outcome measure data consisted of the name of each outcome measure, whether the primary outcome measure was specified in the abstract or main text, and a list of all the stated primary and secondary outcomes.

We designed a special data extraction form to collect the data from the systematic reviews (Appendix C.4). For each systematic review, data were extracted on reference identity data and a list of primary outcomes reported in each of the included reviews was organised and tabulated. Further categorisation of these outcomes was carried out, according to the definition used for PPH, maternal outcomes, neonatal outcomes, changes in blood indices and others. We considered the primary outcomes as the ones that were explicitly stated within the review.

Any disagreements were resolved after discussion with the supervisor.

Statistical methods

All data were entered into a Microsoft access database, double-checked for accuracy, and analysed using Microsoft Excel 2010. For each particular outcome we calculated the percentage of reporting and ranked them accordingly.

Data analysis and presentation

For each RCT the outcome was grouped into one of the two main outcome categories:

A. primary outcomes

The primary outcomes were further divided into subgroups as follows:

1. Outcomes used for SSC and explicitly stated as primary
2. Outcomes used for SSC but not explicitly stated as primary
3. Primary outcomes explicitly stated but no SSC or not used for SSC (in the trials that stated SSC with more than one primary outcome)
4. Outcomes neither used for SSC nor stated as primary but the authors stated them as their main outcomes
5. Outcome not stated as primary or secondary, or used for SSC, but was the only one in the study and stated in the study objective.

B. Secondary outcomes

Any outcomes reported in the trials that did not fit the criteria for the primary outcomes were considered as secondary. For the trials that did not differentiate between the primary and secondary outcomes and no SSC was done, all the trial outcomes were considered as secondary outcomes.

Population stratification

We considered the participants' risk as low if this was stated explicitly in the title or text, or if PPH risk factors were listed in the exclusion criteria. The high risk category was assigned if the authors stated that they included only women with a high risk of PPH. We also considered the participants to be high risk if high risk factors were not considered as exclusion criteria.

We also divided the duration of the pregnancy of the included women into different categories. Term studies were labelled as such when the gestational age of the participants included in the study was ≥ 37 weeks. Gestations below 37 weeks but ≥ 24 weeks were considered as preterm.

We looked at the settings where the studies were conducted (e.g. hospital, home). Studies carried out at tertiary or university hospitals were categorised under one group, while studies conducted in primary care centres or rural clinics were put under a separate category. Home deliveries were put also under a separate group.

4. Results

Generation of included studies

Titles and abstracts of 4170 papers were identified initially. After removal of duplicates, and exclusion of non-eligible studies, 466 full papers were evaluated. Further analysis reduced this to 138 full-text papers whose primary aim was to prevent primary PPH. We were unable to obtain 4 RCTs leaving 134 full-text articles for the analysis. These included 121 RCTs, nineteen of which were not in English so had to be translated, and 13 systematic reviews. Full details are shown in Figure 1. Further information on the included systematic reviews will be found in section B of the results.

Properties of the included RCTs

The types of interventions assessed are listed in Table 1. The majority (88%) assessed pharmacological measures to prevent primary PPH, in which uterotonics accounted for 92% (98 out of 106). Cord management methods, including cord clamping, placental cord drainage, CCT and UVI, were evaluated in 7% of the trials. Only 2% assessed active versus expectant management, and the remaining 2% looked at a range of other interventions including uterine massage.

Over half of the trials were conducted in the Middle East and Asia (55%; Table 2). Almost one fifth of the studies (17%) were carried out in Africa, and only 2% of the included trials were set in more than one country. The vast majority of the included studies (94%) were set in hospitals (Table 3). One third of included trials were conducted in high-income countries (33%; 40 trials), while more than half (58%) were undertaken in middle-income countries (39 trials in upper-middle-income and 31 trials in lower middle income). Seven trials (6%) were conducted at low-income countries. Four trials were conducted in different countries with different economic incomes. The classification of countries' income was based on the World Bank, July 2013.

The proportion of studies carried out at primary healthcare facilities (2%) was matched by the proportion of studies set at home (2%).

Table 1. Type of intervention assessed in the trials

Type of intervention	No of trials	Percentage
Pharmacological measures	106 (98 uterotonic, 6 tranexamic acid, 2 traditional Chinese medicine)	88%
Cord management	9	7%
Active versus expectant management	3	2%
Uterine manipulation	2	2%
Others (postpartum oxygen inhalation)	1	1%
Total trials	121	100%

The number of studies published every 4 years increases gradually as shown in Table 4. Most noticeable is that the number of published trials nearly doubled from between 2005 and between 2008 and 2009-2012, from 22% to 41% respectively.

A SSC was described in 68% (82/121) of the included studies (Table 8). The calculated sample size of the included studies peaked at the range 401-500 (12% of trials), (Table 5). Only two of the included studies had a sample size of more than 12,000 (12,227 and 18, 530).

Table 6 demonstrates the heterogeneity in the methods used for third stage blood measurement and diagnosis of PPH. Nearly one third of the included studies used gravimetric methods to measure blood loss (28%). The next popular method used by the trials was direct blood measurement using drape (19%). Visual estimation, despite consistently underestimating blood loss, was used in 14% of the included studied. A combination of more than one method was used by several of the included trials, as showed in Table 6.

The characteristics of the included participants are shown in Table 7. The majority of women in the included studies underwent vaginal delivery (73%). Caesarean section was the mode of delivery in over one fifth (23%) of included trials. The remaining 4% of the included studies recruited a mixed population of women i.e. both vaginal and caesarean births. A considerable proportion of the included women had no risk factors for PPH (37%), while in only 9% of the studies they were assessed as having a high risk of PPH. Many studies (46%) did not specify the risk and 8% included women with or without risk factors. The duration of pregnancy for the included mothers was known in 70% of the included studies (30% included term and preterm, 40% included term pregnancies only). Nearly one third (30%) of the included trials did not specify the duration of pregnancy for the included participants.

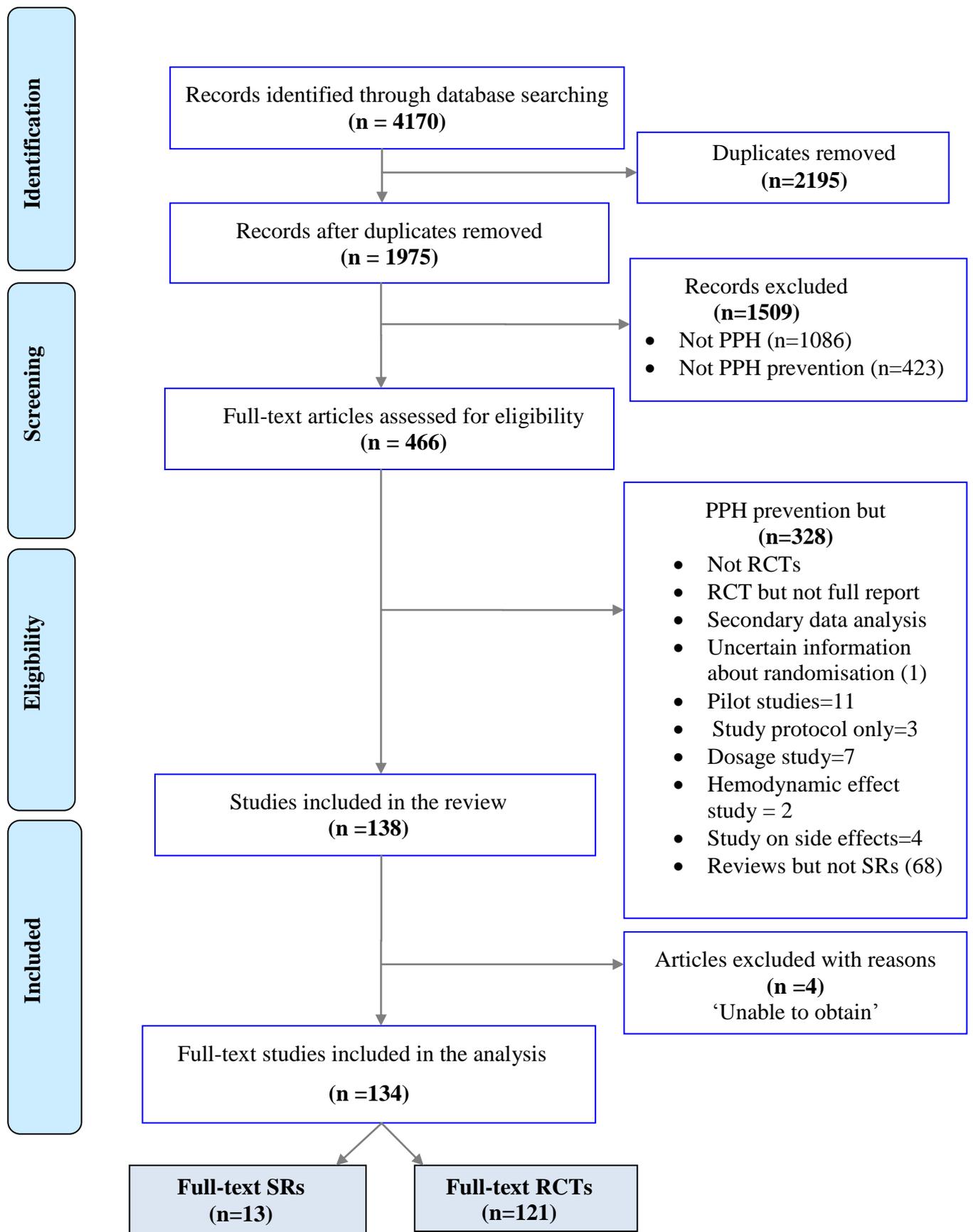


Figure 1. Flow diagram of papers throughout the systematic review according to PRISMA criteria (Liberati et al., 2009)

Table 2. Study country

Country	No of trials	Percentage
Middle East/ Asia	66	55%
Africa	20	17%
Other European countries	9	7%
USA	11	9%
Canada	6	5%
UK	4	3%
Different countries	3	2%
Latin America	1	1%
Not stated	1	1%

Table 3. Study setting

Setting	No of trials	Percentage
Hospital	114	94%
Primary healthcare centre	3	2%
Home	2	2%
Hospital and primary healthcare centre	1	1%
Not stated	1	1%

Table 4. Number of published RCTs every 4 years

Years	No of trials	Percentage
1997-2000	21	17%
2001-2004	24	20%
2005-2008	26	22%
2009-2012	50	41%

Table 5. Sample size

No of subjects	No of trials	Percentage
1-50	2	2%
51-100	13	11%
101-150	11	9%
151-200	13	11%
201-300	9	7%
301-400	12	10%
401-500	15	12%
501-600	5	4%
601-700	9	7%
701-800	2	2%
801-900	2	2%
901-1000	5	4%
1001-1500	9	7%
1501-2000	9	7%
2001-3000	3	3%
>12, 000	2	2%

Table 6. Methods used for diagnosis of PPH

Method used	No of trials	Percentage
Gravimetric method	34	28%
Direct blood measurement	23	19%
Visual estimation	17	14%
Combining direct measurement and gravimetric methods	13	11%
Not stated	11	9%
Combining gravimetric and visual estimations	6	5%
Clinical diagnosis	5	4%
Difference in haematocrit value 48 hours after delivery	4	3%
Colorimetric method	2	2%
Combining direct measured and visually estimated methods	2	2%
Combining gravimetric and haematocrit values	2	2%
More than 2 methods	2	2%

Table 7. Characteristics of participants included in the study

Mode of delivery of included women				Risk to PPH				Duration of pregnancy		
	Vaginal	Caesarean	Both	High	Low	Both	Not specified	Term	Term and preterm	Not specified
No of trials (%)	88 (73)	28 (23)	5 (4)	11 (9)	45 (37)	10 (8)	55 (46)	48 (40)	37 (30)	36 (30)

Table 8. Sample size calculation in relation to the study primary outcome

SSC stated	No of trials	Percentage
Yes	82	68%

Table 9. Clarity of stating outcomes within the trials

Outcome differentiation	No of trials	Percentage
Clear differentiation between primary and secondary outcomes	77	64%
No differentiation	44	36%

A. Outcomes reporting in clinical trials

One hundred and twenty-one RCTs were analysed with 68% (82/121) providing SSC. Seventy-seven trials clearly differentiated between primary and secondary outcomes with 92% (71/77) describing SSC. Out of these 77 trials, 46 used one primary outcome while 31 trials stated more than one primary outcome. Ten trials mentioned their outcomes as main without differentiation. In only 4 trials did we consider the ones mentioned in the objective as the key outcomes for the trials. One hundred and fifty-six different outcomes (primary and secondary) were reported by 121 RCTs; these outcomes were categorised on the basis of most commonly reported ones, primary outcomes (Appendix C.5) and secondary outcomes (Appendix C.6). The primary outcomes were not the same across all the included studies, with different endpoints used for SSC. Sixty-eight different primary outcomes were reported by 121 RCTs; 20 of these outcomes were underpinned by SSC reported by 82 trials.

Postpartum blood loss

The amount of postpartum blood loss and the incidence of PPH were the most commonly reported outcomes. Incidence of PPH \geq 500 mls was the most frequently reported primary outcome mentioned in 21% (25/121) of trials. This was used for SSC in all studies except one. This outcome was stated as a secondary endpoint in 12% (15/121) of RCTs. Postpartum blood loss was measured using different methods as showed above. The time of blood collection was either not specified or done at different time intervals (30 minutes, 1 hr, 2 hrs, 8 hrs, 24hrs, and 48hrs). There was no consensus about the definition of PPH based on the amount of blood loss. And this was true for either vaginal or caesarean delivery. The incidence of PPH was stated as an outcome in 12 of 28 articles with caesarean deliveries; the definition of PPH at caesarean delivery was not stated in 2 of them. Five of the studies, used blood loss $>$ 1000 mls to define PPH, while 3 used \geq 1000 mls, one used $>$ 500 mls and strangely one study defined PPH as blood loss \geq 400 mls. The amount of postpartum blood loss was used as an endpoint in many trials; however there were differences in the methods and times of blood collection, and different statistical measures (mean, median and percentage) were used to statistically measure this crucial outcome measure.

Maternal blood indices

Differences in pre- and post-delivery haemoglobin were the most commonly used outcome under this category. It was mentioned as a primary outcome in 16 trials (13%), 5 of which used it to calculate the study sample size, whereas it was evaluated as a secondary outcome in 29 studies (24%). However, the time of the second blood sample collection showed huge differences as 12, 20, 24, 36, and 48 hours postpartum were all used as cut-off points. This also applied to differences in pre- and post-delivery haematocrits—even though specific values of haemoglobin concentration were used as a primary or secondary outcome, different values at different time intervals were used.

Other interventions used

Under this grouping, additional uterotonics were used as a primary outcome in 22% (27/121) of RCTs. The need to treat uterine atony or PPH with uterotonics was recommended as a priority outcome measure for PPH by the WHO panel (WHO, 2007a). Two of the trials specified the use of uterotonics to treat uterine atony, while one used additional uterotonics to control PPH. The rest of the studies just stated the use of additional uterotonics without further details. Use of additional uterotonics was used for SSC in 7 studies. This important outcome was also used by 43% of trials (52/121) as a secondary outcome.

Many other outcomes under this category were evaluated. These included manual removal of placenta (primary in 3% (4/121) and secondary in 18% (22/121) of RCTs) and need for blood transfusion (primary in 3% (4/121) and secondary in 40% (48/121) of RCTs).

Duration of the third stage

The outcome related to the duration of the third stage was mentioned as a primary outcome in 9% of trials (11/121) and as a secondary endpoint in 33% (40/121). However, different statistical measures (mean, median, number and percentage) were used to assess this outcome measure. Only one of the included studies based its sample size on this outcome.

Intervention side effects

The importance of monitoring adverse events has long been recognised as an essential component of all therapeutic clinical trials (Anderson and Testa, 1994). Maternal intervention side effects, such as nausea, vomiting, shivering, metallic taste abdominal pain, hypertension and others were reported by the majority (71%) of the included studies (86/121). It was evaluated as primary in 7% (9/121) and as secondary in 64% (77/121) of RCTs.

Maternal morbidity and mortality

Only one study considered maternal mortality as one of its primary outcomes. This particularly important outcome was not used for SSC in that study. Maternal death was mentioned as a secondary outcome in 7% (8/121) of trials. A composite outcome on maternal morbidity was mentioned as a secondary outcome in 2% (2/121) of studies. No single component was common to these two composite outcomes.

Placenta-related outcomes

The outcomes under this category were mentioned as secondary outcomes only. These included the incidence of retained placenta (10/121), and the mode and timing of placental delivery (1/121).

Other maternal outcomes

Other different outcomes interested a number of researchers; for example, length of hospital stay was mentioned as a primary outcome mentioned as a main in 2% (2/121) and as a secondary outcome in 8% (10/121) of the included trials. Only one study measured women's and staff's satisfaction with the third stage management and this was used as a secondary outcome.

Neonatal outcomes

Few studies were concerned with neonatal outcomes. They were more prominent as a secondary outcome measure. Earlier establishment of breastfeeding, and less anaemia in infancy were considered as important outcomes by the WHO panel (WHO, 2007a). One study (Ceriani Cernadas et al., 2006), had the objective of determining the effect of the timing

of cord clamping on neonatal venous haematocrit and clinical outcomes in term newborns and maternal PPH. It was the only one to mention newborn venous haematocrit at 6 hours after birth as its primary outcome. This outcome was used for SSC, whereas initiation of breast feeding was mentioned only as a secondary endpoint by 2 trials.

B. Choice of primary outcomes in systematic reviews

Eighty-nine reviews were retrieved and evaluated, 69 (77%) were excluded for several reasons (Figure 2). Twenty reviews met the inclusion criteria. A further 7 reviews were excluded as they did not differentiate between primary and secondary outcomes. Thirteen reviews were therefore included in the analysis, of which the majority were Cochrane reviews (85%), and only 2 were non-Cochrane.

The types of intervention assessed by the systematic reviews are listed in Table 10. More than two thirds of the included systematic reviews (69%) assessed pharmacological measures to prevent primary PPH, in which uterotonics accounted for 89% (8 out of 9). Cord management methods were evaluated in 15 % of systematic reviews. Only 1 systematic review assessed active versus expectant management, and one looked at the effect of uterine massage in preventing PPH.

Table 10. Type of interventions assessed in the included systematic reviews

Type of intervention	Number of SRs (Total=13)	Percentage
Pharmacological measures	9	69%
Cord management	2	15%
Active versus expectant management	1	8%
Uterine massage	1	8%

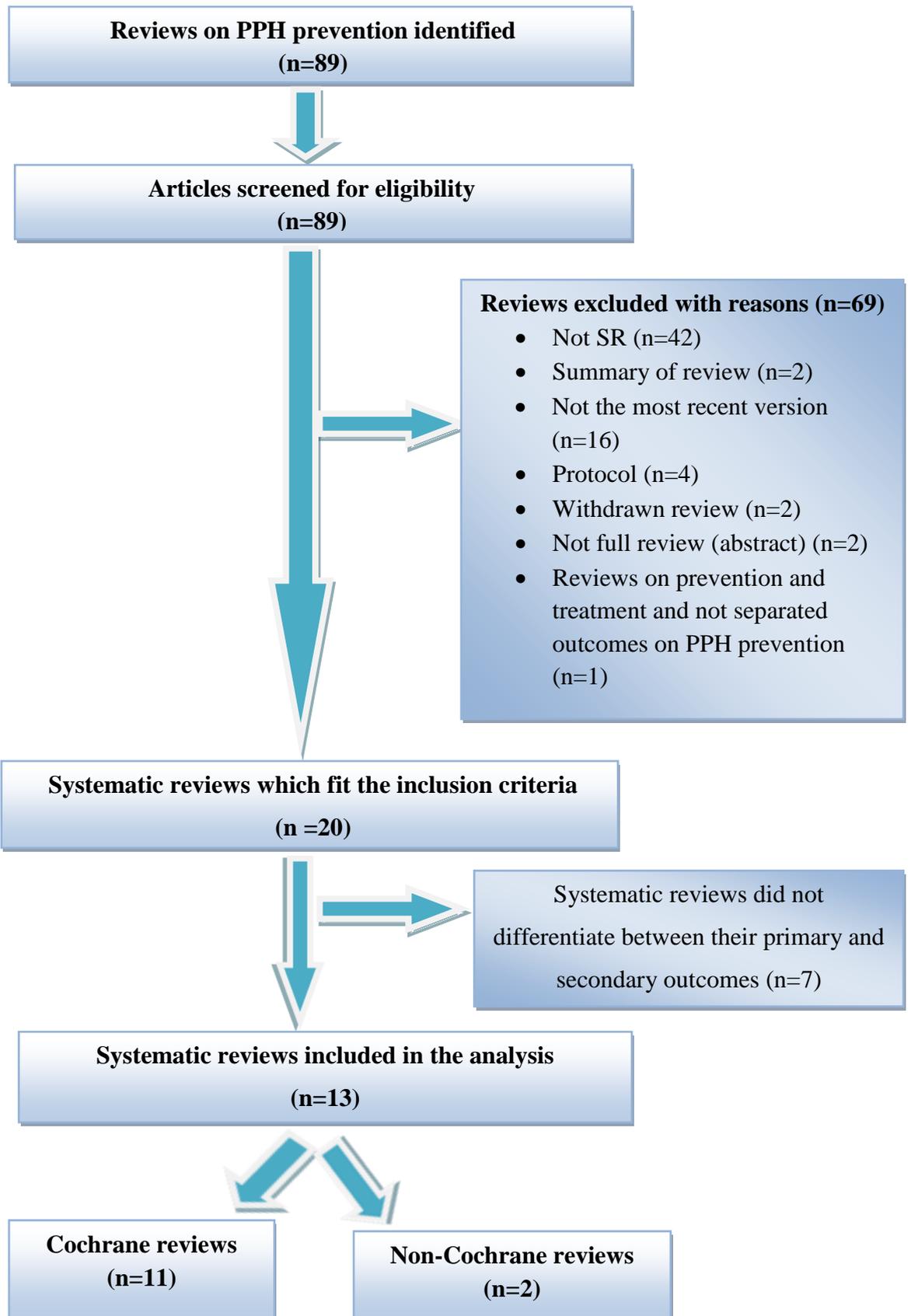


Figure 2. Flow chart of systematic review included in the review

Among 13 Cochrane and non-Cochrane reviews, 24 different primary outcomes were reported, and 85% (11/13) pre-specified more than one primary outcome (Table 11). They were categorised into maternal and neonatal. The maternal outcomes were further divided into five groups: (1) those that were related to postpartum blood loss and incidence of PPH, (2) changes in the blood indices, (3) additional interventions used (4) the length of the third stage of labour and (5), outcomes related to maternal morbidity and mortality.

The most common primary outcome reported by 10 reviews was PPH \geq 1000 mls. This had variable definitions in terms of the methods used for blood measurement. Nine studies used any clinically or estimated blood loss and one review stated clinically diagnosed blood loss \geq 1000 mls as their primary outcome. The mode of delivery of the included participants in these 10 reviews was vaginal in half of them, and caesarean in the other 5 reviews. Use of additional uterotonics and PPH \geq 500 mls (clinically estimated or measured blood loss) were the second most common primary outcomes stated by third of the included systematic reviews (5/13). Four out of the 13 reviews (31%) listed maternal mortality as a primary outcome. Only two reviews (Begley et al., 2011; Rabe et al., 2012), were concerned with neonatal outcomes and different end points were used (Table 11). However, neonatal anaemia and initiation of breast feeding, as important outcomes recommended by WHO panel, were not among the outcomes considered.

Table 11. List of primary outcomes as stated in systematic reviews

Primary outcome	Number of SRs (Total=13)	Percentage
1. Maternal outcomes		
1.a. Postpartum blood loss		
PPH \geq 1000 mls (clinically estimated or measured blood loss)	9	69%
PPH \geq 500 mls (clinically estimated or measured blood loss)	5	38%
Mean postpartum blood loss	2	15%
PPH \geq 1000 mls (clinically estimated blood loss)	1	8%
PPH \geq 500 mls (diagnosed clinically)	1	8%
PPH > 600 mls	1	8%
Very severe PPH \geq 2500 mls	1	8%
Blood loss \geq 500 mls after enrolment	1	8%
1.b. Duration of the third stage		
Third stage longer than 30 minutes	2	15%
1.c. Blood indices		
Maternal HB concentration < 9g/dl 24 to72hrs postpartum	1	8%
Maternal HB concentration 24-48 hrs. postpartum	1	8%
1.d. Interventions used		
Use of additional uterotonics	5	38%
Maternal blood transfusion	1	8%
Manual removal of placenta	1	8%
1.e. Maternal mortality and morbidity		
Maternal mortality	4	31%
Serious maternal morbidity (organ failure, hysterectomy ICU admission)	2	15%
Maternal postpartum anaemia	1	8%
2. Neonatal outcomes		
Neonatal admission to ICU	1	8%
Neonatal jaundice requiring phototherapy or exchange transfusion	1	8%
Neonatal polycythaemia treated with delusional exchange transfusion	1	8%
Neonatal death	1	8%
Death or neurosensory disability at age of 2 years	1	8%
Neonatal intraventricular haemorrhage	1	8%
Periventricular leukomalacia	1	8%

We also compared the primary outcomes from the systematic reviews with the primary outcomes that were used for SSC in the RCTs. The main findings are summarised in Tables 12 and 13.

The most common primary outcomes, reported by at least 3 trials, were compared with the primary outcomes stated in the systematic reviews (Table 12). Four out of eight of the most common primary outcomes of the RCTs were never used as primary outcomes in reviews. Similarly, maternal death was reported as a primary outcome in 31% of the systematic reviews and never mentioned as a primary outcome in the RCTs. The most common primary outcome in the RCTs was the incidence of PPH of 500 mls or more while, in addition to this outcome, systematic reviews were also more concerned with severe blood loss, use of additional uterotonic (38%) and the effect of interventions on reducing maternal death (31%).

Table 12. Most commonly reported primary outcomes underpinned by SSC in randomised trials, and proportion of systematic reviews reporting the same primary outcomes

Most common primary outcomes in RCTs*+	No of RCTs (%) (Total=82)	Primary outcome in systematic reviews (n=13)
Incidence of PPH \geq 500 mls	24 (29%)	5 (38%)
Amount of postpartum blood loss	13 (16%)	2 (15%)
Incidence of PPH > 500 mls	10 (12%)	0
Use of additional uterotonic	7 (9%)	5 (38%)
Difference in pre- and post-delivery HB	6 (7%)	0
Incidence of PPH \geq 1000 mls	5 (6%)	10 (77%)
Incidence of severe PPH > 1000 mls	3 (4%)	0
Estimated blood loss during caesarean section	3 (4%)	0

*Only outcomes used for SSC are included.

+Outcomes reported by at least 3 RCTs are listed

Table 13. Most commonly reported primary outcomes in systematic reviews and their relative frequency in randomised trials

Most common primary outcomes in systematic reviews	No systematic reviews* (%), (n=13)	Primary outcomes in RCTs (%), (n=82)
Severe PPH \geq 1000 mls (clinically estimated or measured blood loss)	10 (77%)	5 (6%)
Use of additional uterotonics	5 (38%)	5 (6%)
PPH \geq 500 mls (clinically estimated or measured blood loss)	5 (38%)	24 (29%)
Maternal mortality	4 (31%)	0

*More than one primary outcome in 11/13 reviews

5. Discussion

Well-designed clinical trials are an integral part of evidence-based medicine. Relevant and reliable outcomes play a crucial role in the correct interpretation and comparison of the results of different treatment modalities (Charman et al., 2003). Clinical trials are “only as credible as their outcomes” (Tugwell and Boers, 1993), and the decision as to which outcomes should be measured is crucial. The selection of inappropriate outcomes can lead to wasted resources or misleading information that overestimates, underestimates, or completely misses the potential benefits of an intervention (Holloway and Dick, 2002). Accurate measurement and reporting of clearly defined outcomes in RCTs and other research studies is a must in order to evaluate treatment effects and to provide health policy information (Moher et al., 2001). Information also facilitates shared decision-making, where communication between clinicians and patients about the risks and benefits of treatments allows an understanding of treatment effects and provides information on available choices (Schwartz et al., 1999; Alaszewski and Horlick-Jones, 2003). The difficulty of selecting the most appropriate outcomes for use in a clinical trial is reflected in the fact that in several fields of clinical research there is much heterogeneity between clinical trials of specific diseases regarding exactly which outcomes to select (Duncan et al., 2000; Clarke, 2007). This was also true regarding the outcomes of interventions for PPH prevention.

This systematic review has identified a wide range of outcomes which were used in PPH prevention studies. It shows inconsistency between studies in the way that outcomes are defined, measured and reported.

While there were certain similarities between studies, particularly in the selection of primary outcomes that measure the incidence of PPH, the selection, definition and measurement of this particular outcome showed a wide variability. Most investigators use their own criteria to define the condition. Moreover, all these outcomes are frequently assessed at different times across trials.

When comparing treatment effects, it is crucial that the outcomes being measured are relevant to patients, clinicians and researchers (Mease et al., 2008). Many outcomes of interventions to prevent PPH were considered critical for decision-making by the WHO panel (WHO, 2007a). These included reduction in maternal mortality and reduction in maternal morbidity as indicated by measured blood loss of 1000 mls or more, and use of blood transfusion. These critically important outcomes were stated infrequently or as only secondary outcomes in the included trials. It has been found that RCTs of PPH prevention almost always assess the amount of postpartum blood loss, but do not concentrate on maternal death and morbidity as the important consequences of PPH. Outcomes related to the duration of the third stage of labour are reported as a secondary outcome. Retained placenta and neonatal outcomes tend to be measured uncommonly across the trials. Retained placenta could occur as a consequence of drug used, or could be the only cause of atony and haemorrhage. The newborn baby may be affected by some of the interventions used such as cord clamping; therefore researchers should pay special attention to, and increase the evaluation of these important outcomes.

Although this review included only studies published after the first CONSORT statement to reduce reporting bias, a considerable number of trials showed poor reporting, including failure to differentiate between primary and secondary outcomes and not stating prior SSC.

Our findings demonstrate that the inconsistency and lack of standardisation in the selection of outcomes is prevalent not only amongst RCTs but also amongst systematic reviews. This was not surprising in the absence of a core set of outcomes. This presents authors of systematic reviews with a challenging task of bringing together, and making sense of, a variety of studies that used a variety of outcomes and outcome measures.

The challenge of comparing the findings of different trials of different interventions using different outcomes and different ways of measurement make the identification of effective, ineffective and unproven treatments for this condition especially difficult. The incidence of PPH \geq 1000 mls (clinically estimated or measured blood loss) was used as a primary outcome by 69% of included systematic reviews. However, reviewers face the problem of inconsistency in the method used to measure blood loss. Therefore they chose any clinically estimated or measured blood loss with that outcome. This was also true regarding other outcomes such as the incidence of PPH of 500 mls. There was also variability in the time of collecting the second sample for haemoglobin measurement within the trials; reviewers used the maternal haemoglobin level within 24-48 hours postpartum.

Researchers usually use outcome measures in the context of their own trial, while reviewers conducting systematic reviews usually focus on outcomes that help in making clinical decisions about the effectiveness of interventions. Therefore, Cochrane/non-Cochrane systematic reviews tend to focus on more severe blood loss (\geq 1000 mls) and maternal deaths. It is generally accepted that an important and clinically meaningful endpoint should measure how a patient feels, functions or survives (Temple, 1995). Severe haemorrhage and maternal mortality, the most common primary outcomes in PPH prevention systematic reviews, are clearly important endpoints upon which conclusions about the effectiveness of an intervention can be made. On the other hand, incidence of PPH at blood loss of 500 mls or more, the most common primary outcomes in clinical trials, is more relevant in answering the question about the effectiveness of interventions on prevention of primary PPH, particularly after vaginal delivery.

There is little evidence about the factors that influence the choice of primary outcomes in systematic reviews. Availability of data from clinical trials, previous knowledge of results, and the desire to publish positive results could potentially impact on outcomes reported (Egger and Smith, 1998). Systematic reviews are unlikely to be influenced by financial and time constraints in the same way as clinical trials, and therefore, it is not surprising that they tend to select rare endpoints that measure significant morbidity and mortality.

Many clinically important outcomes, as identified by the WHO panel (WHO, 2007a), were underrepresented in both RCTs and systematic reviews. The use of blood transfusion, one of the most important clinical outcomes, was used as a primary outcome by only one systematic review and was never used for SSC in RCTs. Although both RCTs and systematic reviews were concerned with the incidence of anaemia, they used different criteria to determine such an important outcome. It is not surprising, with the absence of a core set of outcomes, to find a huge variation in the selection of primary outcomes between RCTs and systematic reviews.

Three main problems can arise if the selection, measurement and reporting of outcomes is non-uniform across clinical trials. The first problem is that important outcomes can be overlooked. If trialists are not required to adhere to an accepted list of mandatory outcomes, it is likely that factors relating to the conduct of the trial, such as feasibility, will determine which outcomes are measured. The importance of outcomes then becomes a secondary consideration. As a result, more common outcomes that are easier to collect and interpret by researchers may be selected, but those that are most important to patients or clinicians may be overlooked.

The difficulty of research synthesis (meta-analysis) is the second problem associated with the absence of consensus on choosing outcomes. Even if the same outcomes are selected, they are often measured and analysed in different ways.

The third obstacle is the selective reporting of results. The practice of selective reporting of a subset of the original recorded outcomes, based on the results, is called outcome reporting bias (ORB) (Hutton and Williamson, 2000). In the absence of a set of core outcomes, which must be reported in all clinical trials in a given condition, trialists may decide to omit certain results from their final study report. A systematic review of studies that examined ORB in published RCTs found that statistically significant results are more likely to be fully reported than non-significant ones. It appears to be common practice to change or omit the original primary outcome, or introduce a new one, as the study progresses (Dwan et al., 2008).

The findings of this study highlight a significant lack of consensus and standardisation that exists not only amongst clinical trials but also amongst systematic reviews. The study also shows that systematic reviews are more likely to focus on rare, but clinically more meaningful endpoints such as mortality. In this study we have reviewed the available data on outcomes across a range of studies conducted both in high- and low-income countries, assessing different types of interventions used to prevent PPH. Thus any recommendations we draw will be applicable to these settings. In an attempt to reduce bias we did not apply any language restriction to the included articles. We reviewed outcomes that have been reported rather than those which were actually measured. ORB in published RCT reports is common (Chan and Altman, 2005; Dwan et al., 2008), and in order to have evaluated exactly which outcomes had been measured it would have been essential to assess trial protocols. Although ORB may lead to an underestimation of the frequency with which some outcomes were actually measured, it is unlikely that it would affect heterogeneity between studies.

We did not make a formal assessment of the quality of included studies, as this was not the primary aim of the systematic review. Our overall impression is that many studies were poorly reported and lack detail with regards to randomisation, blinding and concealment of allocation. We considered only RCTs and systematic reviews in this review, based on the assumption that in well-designed studies careful attention would be paid to the selection of outcome measures. There are however number of other study designs which also report outcomes from PPH prevention, and the inclusion of these studies may have highlighted additional important outcomes.

We have showed that there is a clear mismatch in the choice of primary outcomes between RCTs and systematic reviews. Both inappropriate selection of outcomes and a lack of standardisation of how to measure the selected outcomes make it difficult to design, interpret and meta-analyse clinical trials (Clarke, 2007) and apply their findings to clinical practice. Outcome measures used in trials and clinical practice need to provide a complete assessment of the interventions used. There is currently a movement towards the development of core outcome sets for trials of specific conditions, as detailed by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (COMET, 2012). COMET aims to standardise practice and enable comparison of the results of different treatment modalities in meta-analyses. Such initiatives increase the likelihood that important outcomes are measured, reduce non-uniformity between studies, and reduce the risk of outcome reporting bias. The

information obtained from this review will provide a basis for development of core outcome sets, and facilitate a much-needed change towards appropriate selection and standardisation of clinically important outcomes in future PPH prevention studies.

For prophylaxis trials, the best outcome measures would be incidence of PPH (blood loss of \geq 500 mls after vaginal delivery and \geq 1000 mls after caesarean delivery), total blood loss and difference in pre and post-delivery HB. These outcomes were most commonly reported in clinical trials and can be considered more practical for use in future research. Although use of additional uterotonics was one of the most commonly reported outcomes, the work in Chapter 3 demonstrates how uterotonic use in practice is often not linked with the standard 500 mls definition of PPH. Therefore, this particular outcome is not recommended unless a very clear and rigorously enforced protocol for uterotonic use is applied (which may be very difficult to follow in practice).

In research looking at the effects of treatment of PPH, the best outcome measures would be maternal mortality, amount of blood loss after uterotonic treatment received, need for additional intervention (blood transfusion, surgery (non—invasive or invasive surgeries) and hysterectomy).

Chapter 5

*Preliminary studies in developing a new device to aid
bimanual uterine compression*

1. Background

For the management of PPH, it is recommended that minimally invasive methods should be tried initially, if possible (WHO, 2009). Therefore, the initial treatment of uterine atony involves discontinuation of causative agents (inhalation anaesthetics), emptying of the bladder, uterine massage and uterotonic agents before BMC (ACOG, 2006). The treatment of PPH has for many years focused on the provision of uterotonics. However, there are frequent problems with the provision of the drugs to low-resource community settings. According to the results of a survey conducted in 37 countries between January and March 2012 to identify both national and global gaps in PPH and preeclampsia program priorities (Smith et al., 2014), 4 countries reported that oxytocin was not regularly available (Bangladesh, Liberia, South Sudan and Yemen). A further problem is that not all women respond to oxytocics. In a double-blind, non-inferiority trial, where 31,055 women using prophylactic oxytocin had blood loss measured after vaginal delivery, 809 (3%) women were diagnosed with PPH (Blum et al., 2010). Of those women with a PPH, an additional blood loss of 300 mls or greater after treatment occurred in 123 (31%) despite receiving a rapid infusion of 40 IU oxytocin.

Uterine massage is an attractive alternative to uterotonics. However, when used alone, it does not seem to be effective in reducing PPH. A trial conducted in Egypt and South Africa recruited 1964 women and examined the effect of uterine massage in prevention of PPH. It found that uterine massage alone was associated with more blood loss within 30 minutes after delivery than treatment with oxytocin with or without massage (Abdel-Aleem et al., 2010). In a Cochrane review evidence was inconclusive regarding the role of uterine massage in the treatment of PPH and the authors suggested further research (Hofmeyr et al., 2013).

The role of BMC as a treatment of PPH has been known for many years. One early version was called “bimanual kneading of the uterus” where one hand was put into the uterus and the other placed on the abdomen with counteracting pressure from fundus (Figure 1). The birth attendants used to knead the uterus bimanually until it contracted (Tweedy and Wrench, 1914). There are now two recognised methods of BMC, external BMC and internal BMC, which were described previously in Chapter 1.



Figure 1. Bimanual kneading of the uterus (Tweedy and Wrench, 1914)

Care providers in resource limited settings are often limited to physical manipulation as a form of obstetric first aid until definitive care is secured (Hussein, 2005). The technique of BMC mainly treats bleeding from an atonic uterus and cervical lacerations, but should also be effective when there is a small amount of retained placental tissue or with clotting disorders. There is no published research to provide an evidence-base for this intervention (RCOG, 2009). However, Chantrapitak and co-workers examined the efficacy of ‘lower uterine compression’ in the treatment of PPH, comparing the amount of blood loss between those treated with the ‘lower uterine compression method’ and a control group receiving conventional treatment (Chantrapitak et al., 2009). They also tested the same technique for PPH prevention. In their PPH treatment trial, both groups received PPH treatment with uterine massage, oxytocin (10-20 units in 1,000 mls of IV solution), intravenous ergometrine (methergin, 0.2 mg), a cold pack on the abdomen (fundal area), and urinary catheterisation. In addition, the experimental group received additional ‘lower uterine compression’ for 10 minutes. The lower uterine compression method comprised of two techniques. The first technique (Figure 2) was to compress the lower segment only if the abdomen was tense. If the abdomen was lax, ‘compression of lower uterine segment with counteracting pressure from fundus’ was used (the second technique; Figure 3), which sounds very much like trans-

abdominal wall (external) BMC. The authors found that the lower uterine compression method is a very effective procedure for treating PPH. The blood loss after treatment in the conventional group was statistically significantly higher than the blood loss in the group that received additional lower uterine compression ($p=0.026$). Lower uterine compression resulted in 105 mls or 47% reduction of blood loss. It also has the benefits being simple to use, safe and inexpensive. The authors state that the application of this technique could lead to a positive impact on outcomes of many PPH women over the world in either developed or developing countries (Chantrapitak et al., 2009). The result from this study shows the potential for uterine compression in the primary treatment of PPH, particularly in low-resource countries where it is a highly practical solution. In a second study the same team found that the technique was also effective for preventing PPH (Chantrapitak et al., 2011). However, the compression of lower segment of the uterus is not possible using this technique and it could be very difficult in obese women. The amount of subcutaneous fat in obese women could act as a barrier to effective compression of the lower segment of uterus against the vertebrae. The second obstacle could be the scar in women recently delivered by caesarean section, as compression at this point as demonstrated in the figures could be very painful to them.

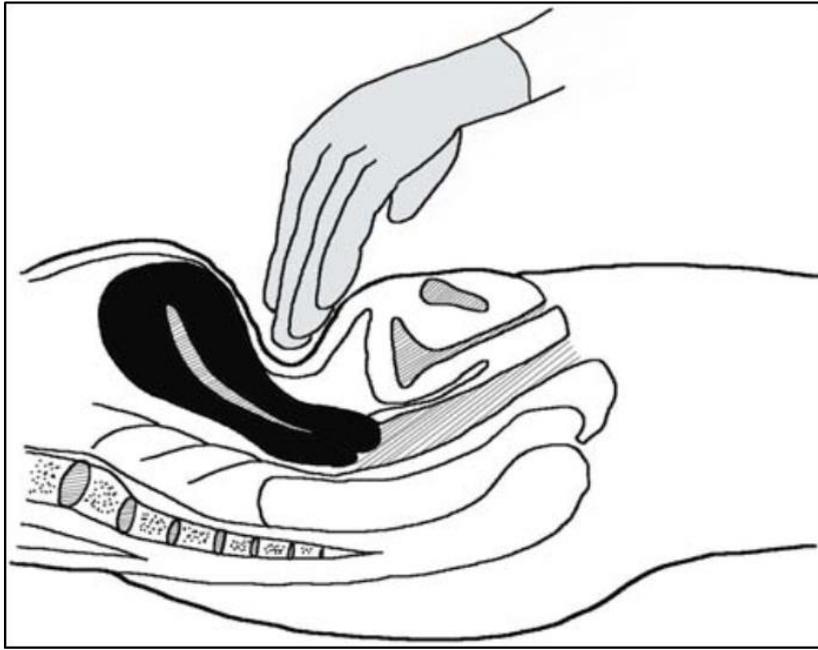


Figure 2. 'Lower uterine segment compression' method compressing the lower uterus only (Chantrapitak et al., 2009)

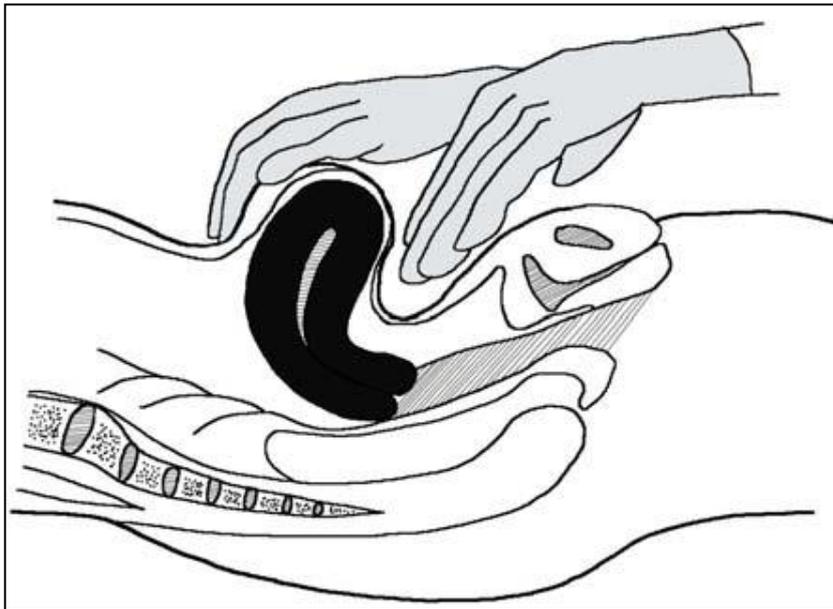


Figure 3. 'Lower uterine segment compression' with counteracting pressure from fundus (Chantrapitak et al., 2009)

The standard technique of BMC requires the insertion of a fist into the vagina, an act that is both painful and has overtones of gender-based violence (Taylor, 2015). It is therefore currently only used in extreme situations. The procedure should also be carried out under aseptic technique which is not always possible outside of healthcare facilities. Additionally, the traditional method of BMC needs to be performed correctly in order to be effective at stopping the bleeding. However, studies have found that many cannot perform it correctly. For example, in one study from Indonesia, less than 10% of skilled birth attendants (Indonesian village midwives) were able to perform BMC at an acceptable level of competency even after life-saving skill training (McDermott et al., 2001). BMC has been shown to be most effective when the attendant has been trained in how to perform the technique correctly. A trial carried out to evaluate the impact of simulation-based training on the ability of birth attendants to correctly perform BMC in response to PPH from uterine atony (Andreatta et al., 2011) showed promise. The study involved skilled (nurse- midwives and nurse midwifery students; n=111) and unskilled participants (TBA; n=14) from Ghana, where all participants significantly increased their BMC skills after training (P=0.001). Post-assessment results included a significant increase in the amount of uterine compression (number of illuminated lights; P=0.001), and an increase in the compression time (P=0.001).

If, however, BMC could be performed in a less invasive manner, then it could act as an effective low-cost first-line treatment for PPHs arising from either atony or cervical tears. This chapter reports early feasibility studies on a new device being developed in Liverpool, UK. Firstly, we conducted a survey to find out obstetric care provider's views on BMC and conducted early feasibility studies of doing BMC in an alternative manner using a platform on a handle. An evaluation of 2 commercial mannequins was also carried out to assess the optimal model for formal testing of the device. The designing team then designed a slim-line intravaginal device that could be opened within the postpartum vagina to provide a platform against which the uterus could be compressed. Studies testing the efficacy of this device on the uterus of a mannequin will be described in Chapter 6.

Each step with methodology and results will be described in the following pages, with a discussion of the whole process at the end.

2. Survey of BMC use

2.1. Introduction

BMC is a well-known first aid technique for treating PPH. The method is almost always carried out in emergency situations, and so it is understandable that there are no randomised trials evaluating this method. This survey aimed to gather the opinion of practitioners about BMC as a method of treating PPH and to explore the importance of introducing a new tool that can assist in performing the manoeuvre.

2.2. Methods

Questions were developed by NA with collaboration with AW, and are shown in Appendix D.1. The questions asked were: (1) what is your job? (2) how effective do you think BMC is at stopping bleeding? (3) how many times have you used BMC for PPH during the last year? (4) why do you not use the manoeuvre of BMC more frequently? (5) if there was a rapid test that could tell you whether bleeding was coming from lacerations anywhere in the vagina or perineum or not, how helpful would it be in your management? (6) if there was a rapid test that could tell you whether bleeding was coming from lacerations anywhere in the vagina or perineum or not, do you think that it would lead to reduction in the total blood loss?

The survey monkey online tool (www.surveymonkey.com) was used for distribution. The survey was circulated through the RCOG mailing list and midwives at Liverpool Women's Hospital in the period July-August 2012. All participants answered questions in relation to BMC and provided their view on the development of a new device that could help in treating PPH. Ethical approval was not needed as the survey was not considered research and it was anonymous and the respondents were all NHS staff (NRES., 2011).

2.3. Results

Responses were received from 111 participants; 59% of them were consultants, 28% were junior doctor and 10% were midwives.

As shown in Figure 4 the majority of participants thought that BMC is an effective procedure. Less than 1% thought it was completely ineffective. The median score was 4.

One fifth of contributors have not done BMC before (Figure 5). Eleven of those surveyed had carried out BMC more than 5 times for treating PPH during the last year. Only 4 of participated midwives had previously carried out BMC, one midwife had performed BMC 4 times and 3 midwives had done BMC once.

When asked ‘Why do you not use the manoeuvre of BMC more frequently?’ A fifth stated that it was because BMC is too invasive to the woman. Many of them also believed that drugs such as oxytocin are more effective than BMC. None of clinicians thought that BMC was ineffective. The 37 participants who answered the question as ‘other’, (Figure 6), either already did the manoeuvre frequently or had limited opportunity due to their junior position.

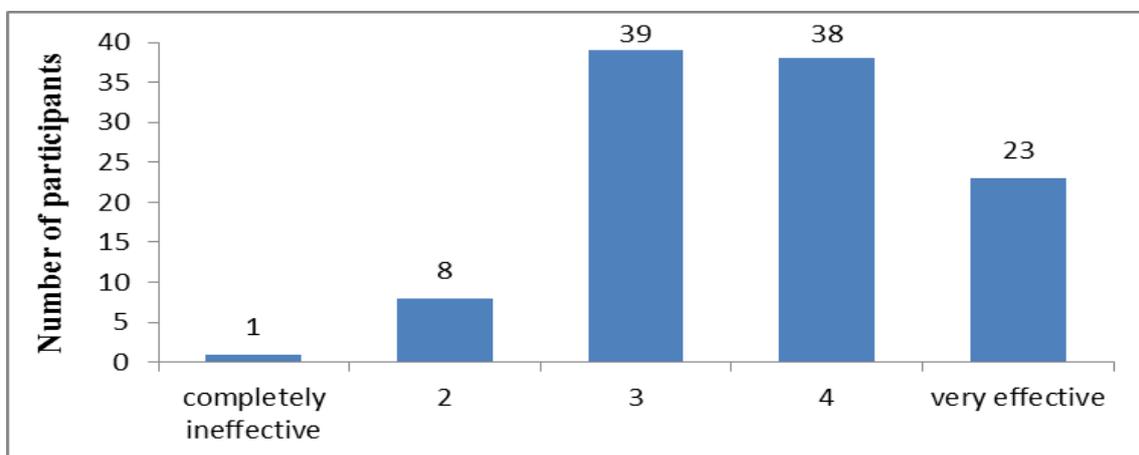


Figure 4. How effective do you think BMC is at stopping bleeding (score 1-5)?(1= completely ineffective, 5= very effective)

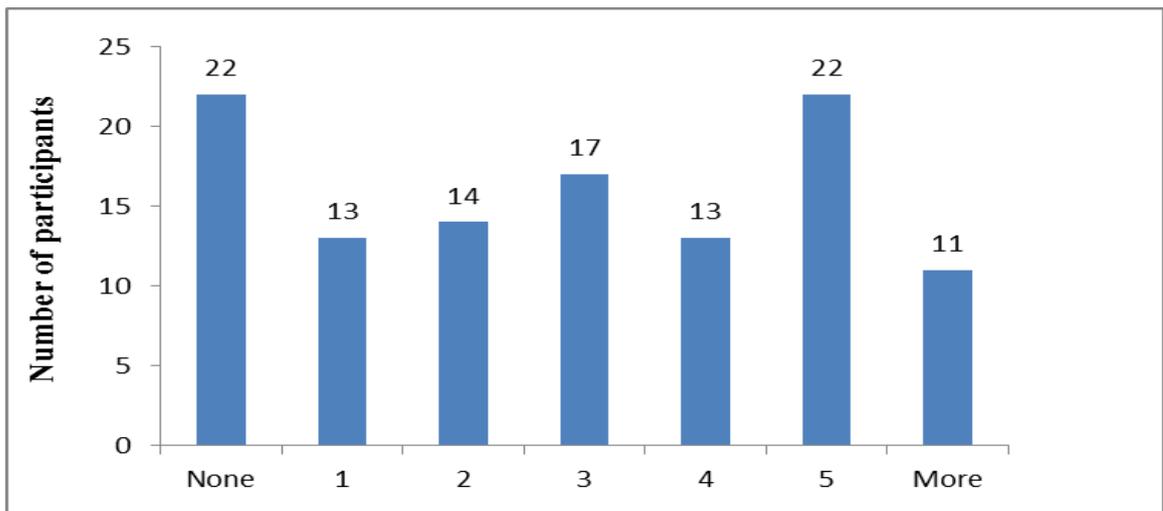


Figure 5. How many times have you used BMC for PPH during the last year?

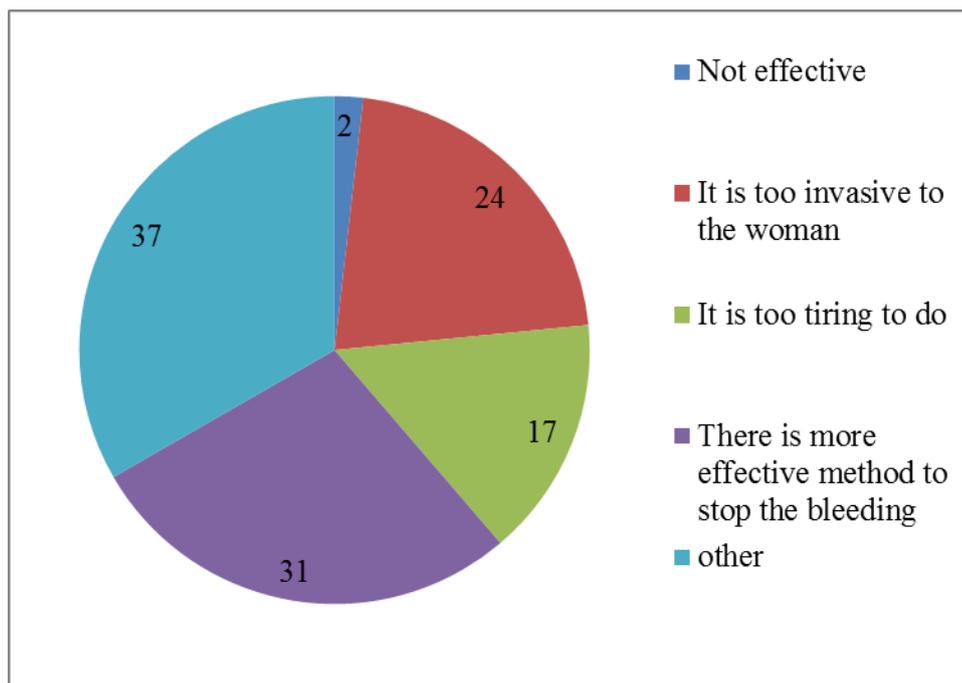


Figure 6. Why do you not use the manoeuvre of BMC more frequently? [Tick all that apply]

Figure 7 shows the participant's views on the introduction of a new method that could help in diagnosis of the source of bleeding in PPH and control the blood loss. More than half of contributors thought that it would be very helpful to know the source of bleeding and the majority (36%) believed that the test could assist in reducing the bleeding. However, there were a few participants who were unenthusiastic about the introduction of a new method and its role in helping in the management (14%) and reduction of the total blood loss (19%).

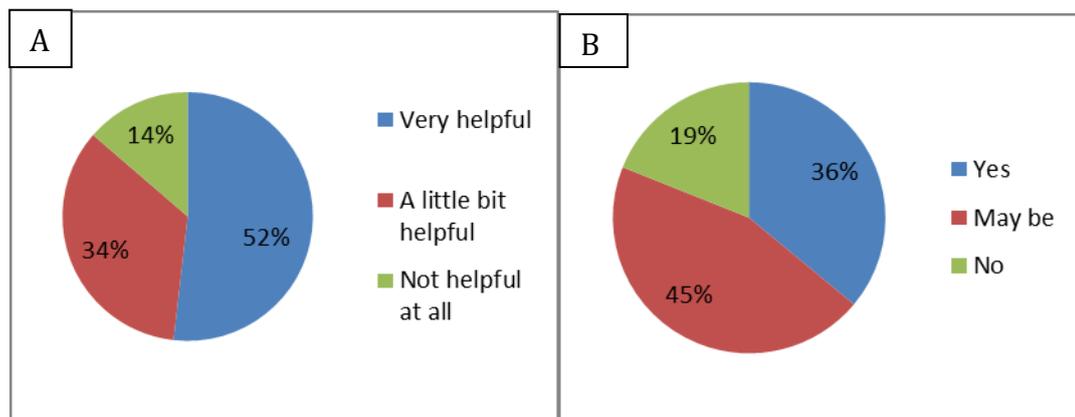


Figure 7. If there was a rapid test that could tell you whether bleeding was coming from lacerations anywhere in the vagina or perineum or not (A) how helpful would it be in your management? and (B) do you think that it would lead to a reduction in total blood loss?

3. Feasibility study

3.1. Introduction

The feasibility of using a mounted platform on a mannequin to generate intrauterine pressure was assessed in a small study. The aims were (1) to assess the suitability of a commercial mannequin, (2) to assess whether the placement of a pneumatic intrauterine pressure sensor could measure intrauterine pressures, and (3) to assess the likely pressures generated by both BMC and a PPH Butterfly prototype.

3.2. Materials and methods

The commercial mannequin (SimMom, Limbs and Things Ltd, Bristol, UK) was supplied with an atonic uterus (Figure 8). A pneumatic pressure sensor (RS Components Ltd, Corby) was inserted into the uterus and connected to a personal computer via a data logger (Picolog 1012 Data Logger, Pico Technologies Ltd, St Neots (Figure 8)).

The equipment was assessed in May 2012 by 5 clinical academics at Liverpool Women's Hospital, Liverpool, UK. They all had at least 5 years of obstetric practice and had conducted BMC several times in real clinical scenarios. The ethics committee at Liverpool Women's Hospital stated that ethical approval was not required for this study as it involved NHS staff only and no patient contact. However, informed verbal consent was obtained from all participants who volunteered for this study.

The participants were asked to perform uterine compression twice: first in the classic fashion using an intra-vaginal fist, and secondly using an appropriately sized platform mounted on a handle and inserted into the vagina. We used a commercial produced potato masher (John Lewis, Ltd, UK; Figure 9). Each participant was asked to carry out uterine compression on the mannequin model as if they were in a clinical setting for five minutes in each occasion, with a rest period of 5 minutes in-between. The intrauterine pressure generated by each participant were recorded and displayed in graphic form using the supplied Pico software (Picoscope 6). After finishing the procedure, the obstetrician filled in a feedback form (Appendix D.2).

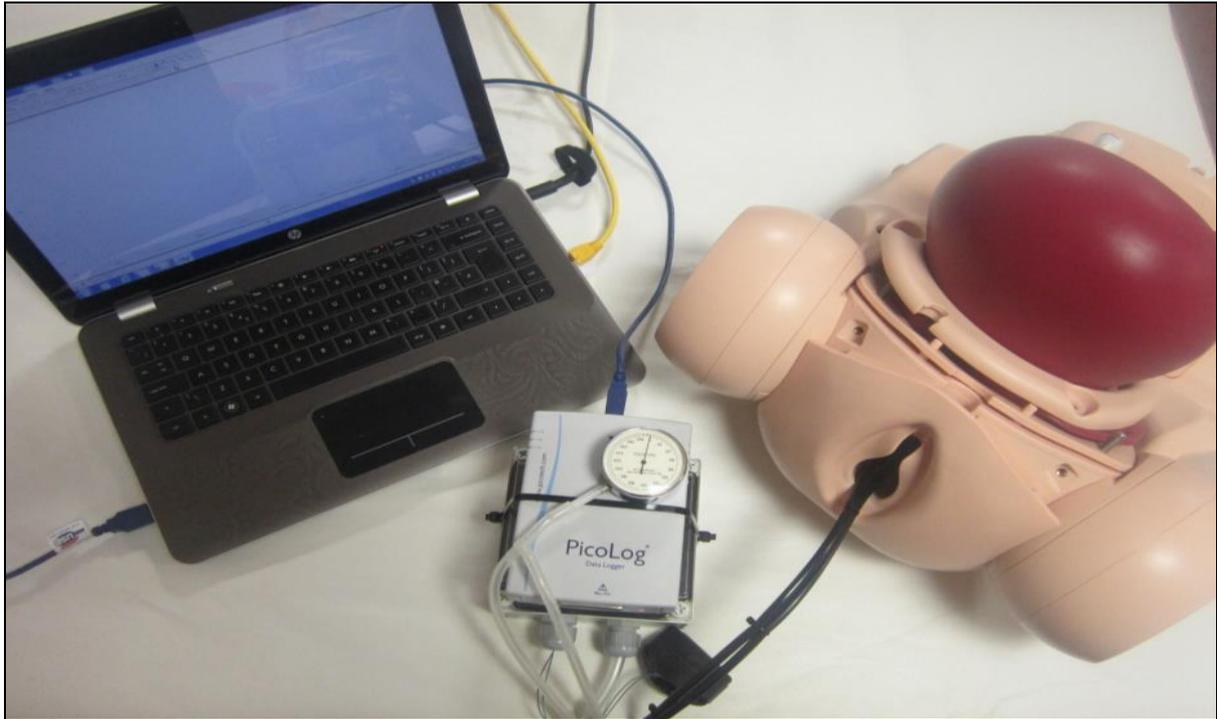


Figure 8. Material used for the feasibility study, SimMom, Limbs and Things Ltd, Bristol, UK)



Figurer 9. Picture of mounted platform (John Lewis, Ltd, UK)

3.3. Results

All 5 clinicians completed the study. Typical graphic outputs are shown below, (Figure 10 and 11). The graphs showed that the equipment was able to reliably provide a measurement of the intrauterine pressure and record it over a period of 5 minutes. With the classic method of BMC, initial pressures were good, but they rapidly decreased over time as the practitioner became tired (Figure 10). In contrast, the pressures could be maintained for longer when the PPH Butterfly was in place (Figure 11). Note that the Y-axis values are voltage and not pressure. They do however allow comparison of pressure between methods and over time.



Figure 10. Using the classic method of BMC

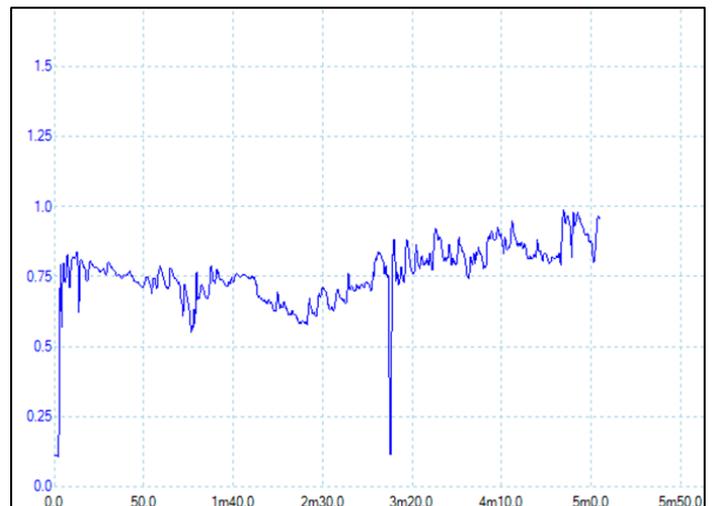


Figure 11. Uterine compression with the mounted platform

Written feedback was also gathered from the participants regarding the mannequin and the idea of using the device. Two open questions were asked to all participants. The first was on the acceptability of the mannequin and the second was on the participant view of the idea of the device. The majority of participants (3 out of 5) like the idea of the device. A typical response was that “using the device was more comfortable than the traditional way of doing BMC and will maximise the effect of uterotonic”. The staff were less enthusiastic about the mannequin however, and many felt that it did not give the same feel as in real life. It was felt that the mannequin’s vagina was too short and inflexible making the insertion of the hand very difficult. One stated “difficult to get hand through the vagina, does not give the same feel as the *in vivo* situation”. Furthermore, the tone of the supplied uterus was very firm in comparison with the real postpartum atonic ones. A participant commented that “the uterus feels a bit too resistant to compress when compared to usual atonic uterus”.

4. Internal uterine compression on a mannequin model: a pilot study

4.1. Introduction

The first evaluation of uterine compression *in vitro* using the mounted platform documented considerable problems with the mannequin used. We therefore obtained further commercial mannequin models, each provided with an ‘atonic uterus’. The supplied uteruses were large but with different degrees of tone. They also varied in their anatomy, especially those areas relating to BMC. After several meetings and discussions with the research team, we ended up with 2 birthing simulators that were suitable for use in our study. The first model is Noelle[®], (Figure 12), and the second model is Mama Natalie[®] (Figure 13). Noelle[®] is a product of Gaumard Ltd a company based in Miami, Florida. It is a comprehensive teaching system designed to provide a complete birthing experience, before, during and after delivery. One important application of Noelle[®] is PPH simulation. The mannequin is supplied with an ‘atonic uterus’ to mimic PPH. The mannequin is computerised and has a refillable internal blood reservoir and programmable bleeding levels to simulate postpartum bleeding. Noelle’s uterus has a cavity to teach the method of inserting and inflating a Bakri Balloon. This is surrounded by an air-filled sealed cavity that can be inflated to mimic an atonic uterus.

This study was designed to determine which of the two models to use in a formal randomised trial of mannequin uterine compression. The two models were assessed in terms of their anatomical accuracy, realism when simulating BMC, and ability to conduct pressure measurements. The data from the appropriate model were also used to calculate the sample size needed for the randomised trial, and to assess the likely pressures generated by BMC on the mannequin. The average pressure generated in this study was used as the cut-off point for the later study.

4.2. Materials and methods

The two mannequins selected were Noelle[®] (Gaumard, Ltd) and Mama Natalie (Laerdal). The uterus in both models contained an air-filled pressure sensor connected to a uterine pressure inflator to record the intrauterine pressure. This was connected to a personal computer via a data logger (Picolog 1012 Data Logger; (Figure 12)).

Noelle[®] already has a sealed cavity on the outside of the uterus and so the air supply tube was cut, and connector inserted, and a pressure sensor was connected. Natalie however had no cavity present and so an air-filled pressure pad was inserted into the uterine cavity for assessment.

Mama Natalie is produced by Laerdal, a major manufacturer of medical equipment and medical training products based in Stavanger, Norway. As with Noelle[®], the main function of Mama Natalie[®] is to provide realistic simulations in maternal and newborn care. Since obtaining these 2 models, we have modified them and inserted pressure sensors, so as to enable the measuring of intrauterine pressure, generated by BMC. We also made some changes to Noelle's uterus so as to make it more realistic. In the commercial product, the pressure tubes entered the uterus at the fundus, thus restricting BMC. Furthermore, the abdominal wall was very firm (in contrast to the postpartum abdomen). We therefore contacted Gaumard Ltd who adapted the mannequin, moving the pressure connectors from the fundus to the sides of the uterus. They also supplied us with an alternative, more lax abdominal wall.

After discussion with Research and Development Department, it was decided that ethical approval was not required for this study as it involved NHS staff only and no patient contact. The decision on ethical approval when involving NHS staff was based on published advice from the National Research Ethics Service (NRES) (NRES., 2011). However, informed verbal consent was obtained from all participants.

Ten experienced obstetricians at Liverpool Women's Hospital were invited to participate in the study. They all had at least 5 years of obstetric practice and had conducted BMC several times in real clinical scenarios. Participants were randomised to the order in which they conducted compression on the models. A commercial randomisation programme was used to produce a random list of allocations to the two mannequins (www.sealedenvelope.com). The allocations list (consultant's names and allocation) was developed by research staff not involved in the study.

Each participant was asked to carry out BMC on each mannequin model for five minutes, with a rest period of 5 minutes in-between. The pressure generated over a 5 minute period for each participant was recorded and saved. The mean pressure for each participant was then calculated, and an overall mean calculated out of the 10 participants' mean pressure. After completing the procedure, the obstetrician filled in a feedback form related to the procedure and the acceptability of the mannequin models (Appendix D.3).

Responses were recorded on a 10 point Likert scale (ranging from 0 (highly disagree) to 10 (highly agree)). The following aspects were evaluated:

- Anatomical accuracy of vagina and cervix
- Feel of uterus
- Realism of conducting BMC

After the optimal mannequin was chosen, data from that mannequin was analysed so as to device baseline data for future research.

Data analysis was performed using statistical software Graphpad Prism version 6 (GraphPad Prism Software, Inc. San Diego, California, USA). Data from the mannequins were compared. The statistical significance of difference between the medians was assessed using the Mann–Whitney test with $P < 0.05$ considered significant.

The main outcomes were the mean amount of uterine pressure generated by the all participants and the percentage of time over average for each participant and the mean of that value (Table 2).

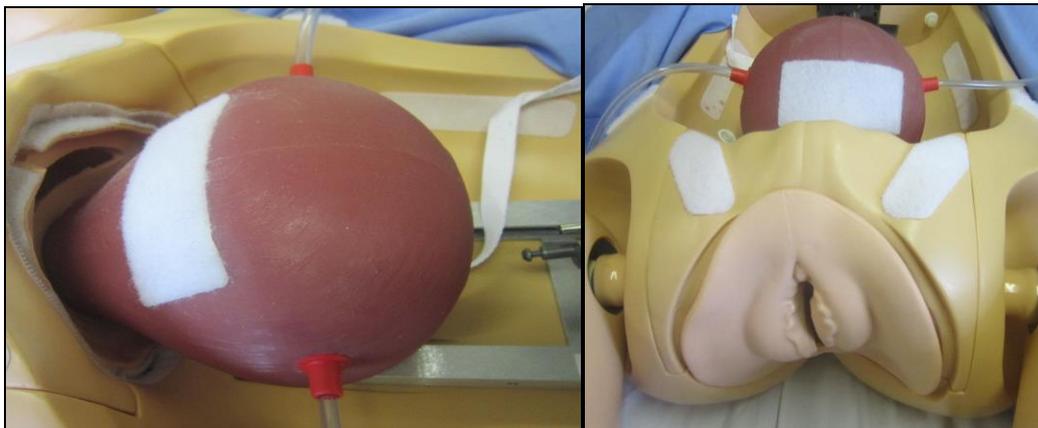


Figure 12. Noelle[®] mannequin



Figure 13. Mama Natalie mannequin

4.3. Results

The rating of different anatomical parts and realism of BMC on both mannequins is presented in Table 1. The Noelle[®] model was superior in all variables compared with Mama Natalie, but, the only statistical significant difference was between the vagina of the two models.

Table 1. Quality assessment in both mannequins (0= highly disagree, 10 = highly agree)

Variable	Noelle [®]	Mama Natalie	P-value
Anatomical accuracy			
• Vagina	8 (2-8)	4 (2-6)	0.005
• Cervix	7 (2-9)	4 (2-8)	0.07
Feel of uterus	7 (2-8)	4 (0-7)	0.19
Realism of BMC	7 (2-9)	4 (1-9)	0.34

*Data are presented as median (Range)

Analysis of data from the preferred mannequin (Noelle[®])

The mean pressure from the Noelle[®] mannequin was equal to 34 mmHg with a standard deviation of 10.05. The mean percentage of time over 34 mmHg was then calculated, Table 2.

Table 2. Expert percentage of time over mean pressure (34 mmHg)

Participant No	1	2	3	4	5	6	7	8	9	10
% of time over 34 mmHg	94	93	91	53	35	31	19	11	0.2	0
Average of % of time over 34 mmHg (SD)	43% (38%)									

Sample size calculation

There is no previous data on the correct pressure for BMC. We therefore used the information we obtained from the experts in this study, considering that they would have the best assessment of the correct pressure needed to compress the uterine blood vessels. It can be seen from Table 2 that the percentage of time over average has an extreme value (0-94) and it is not known what the 'correct value' is. After discussion we decided that an increase of 17% (up to 60%) would be a clinically important improvement that would demonstrate the benefit of a new device to compress the uterus.

In the expert group the percentage of time over 34 mmHg was 43% (SD=38%). A sample size of 42 participants is needed to improve time over average by 17% at alpha equal to 0.05 and beta equal to 0.8.

5. Discussion

There are no previous human studies on the effectiveness of BMC for treating PPH. There have been, however; a number of simulation based studies on BMC (Andreatta et al., 2011; Andreatta et al., 2012). The first study evaluated the ability of simulation to train birth attendants to correctly perform BMC as obstetric first aid. The 2012 study examined the impact of team-based BMC for managing PPH from uterine atony.

This new device to aid uterine compression to treat primary PPH was evaluated in several steps. This was first done by exploring maternity care providers' view of BMC and this new tool to help provide effective uterine compression. The survey reveals that a cross section of maternity care providers believe that BMC is an effective method for controlling PPH. This fits with experts' view - BMC is recommended in guidelines by WHO, NICE and RCOG. As expected; however, their use of the procedure is limited by concerns that it is too invasive for the women and too tiring for the clinicians. The vast majority of clinicians also believe that a tool to diagnose the site of the bleeding would be very helpful in the management of PPH and would probably reduce overall blood loss. This survey provides evidence of the clinician's need for a less invasive device that will facilitate uterine compression.

We believed that the above mentioned problems of BMC could be overcome by the insertion of a small vaginal device - the PPH Butterfly based on the shelf pessary. Initial designs were already in place and the survey data was used to obtain the National Institute for Health Research (NIHR) grant funding for formally develop the device for clinical use.

The feasibility of using a mannequin model for testing the PPH Butterfly *in vitro* was evaluated. The first feasibility study of measuring uterine pressure produced by the participants doing uterine compression revealed that there was enthusiasm from the participants about the value of a PPH Butterfly prototype device. The majority of staff agreed that the device seems to help and that the approach is sensible as BMC can control the bleeding and maximise the effect of uterotonics. Furthermore, the compression using the device produced firm and sustained pressure on the uterus, and prevented clinician fatigue. Some of the practitioners using the PPH Butterfly prototype chose to let go of the handle of the device mid-way through and lean on the abdominal hand to prevent fatigue. This was made possible by wedging the handle of the PPH Butterfly prototype on the surface upon which the mannequin was placed. This led to a modification to the device so that it could be wedged into the bed.

This study also showed that the use of a mannequin linked to a pressure sensor was suitable for testing uterine compression. However, the mannequin used was not a good model with respect to female anatomy. This drove us to look at different mannequin models and conduct a pilot randomised study included the best 2 models we have obtained. Both models were compared by experience clinicians in many anatomical and clinical aspects. The user acceptance of Noelle[®] was an added benefit. The data obtained from Noelle[®] was considered as a base-line and used for calculating the sample size for the next PPH Butterfly *in vitro* testing study.

From the ten experts we noticed that there were wide variations in the pressure produced. It seems that there are different interpersonal factors that affect the amount of pressure. This could be explained by gender, age, and strength of the participants which were not assessed in the study. An additional point that could clarify this diversity is the lack of a standardised method of BMC. As has been noted previously participants differ in their BMC technique with some clinicians combining uterine massage and BMC as one procedure when asked to carry out BMC.

The studies in this chapter have strengths and limitations. Firstly, although the survey was simple and gave an overview of BMC practice amongst obstetric caregiver, it was conducted among clinicians in the UK only. The result could differ if obstetric care providers from low-income settings were included. This is particularly important in the results relating to the effectiveness and frequency of conducting BMC. The procedure is expected to be carried out more in low-resourced places where other interventions are less readily available.

With regard to the survey questions we included only 6 questions so as to maximise the response rate. However, an additional question on how long the participants carry out BMC for a real clinical scenario? knowledge of this would have aided the future studies where 5 minutes was used without prior knowledge of usual practice.

The simulation studies included in the chapter show that the mannequin can be used to measure uterine pressure bimanually or with using a platform on a handle. The SimMom mannequin used in the first simulation study was neither representative nor acceptable to the participants. The genital parts of the mannequin bear little resemblance to a real postpartum woman. The study was not randomised - all participants conducted BMC followed by uterine compression using the device. Additionally, both forms of uterine compression were done on the same day. However, neither the lack of randomisation nor the same day compression are likely to have introduced bias to the study. This is because there was good quality compression using the device from most of the participants. However, the pressure readings from the simulation could not be used as the design and the materials were not the ideal one for the final PPH Butterfly design. The device material (stainless steel) could have contributed to the strength of the compression produced by the participants in this study.

The second simulation experiment used the preferred mannequin of Noelle[®]. The model is very expensive (£26,500), but should be off-set by its use for clinical training. The allocation of participants in this study was made before the verbal consent was obtained. We admit from the methodological point of view that it is not the right way to allocate participants. However, in this situation it is less likely to introduce bias to the study. The participants in both studies were not blinded due to the nature of intervention but they were blinded to the pressure produced by each mode of compression (bimanually or using the device).

In summary, these feasibility studies have led to the identification and modification of the mannequin that is not only highly rated by clinicians but which also gives uterine pressure measurements. The clinicians' survey has shown that there is the clinical need for a less-invasive method for conducting BMC and has contributed to the development of the PPH Butterfly. The next phase will be a device testing stage through a formal randomised cross-over study comparing using the PPH Butterfly device with the standard way of doing BMC using the preferred mannequin (Noelle[®]).

Chapter 6

A randomised cross-over study of a novel device for the management of postpartum haemorrhage

The efficacy of the PPH Butterfly to facilitate uterine compression: a randomised cross-over study

1. Introduction

Reports from the confidential enquiries into maternal deaths (2009-2012) showed that most PPH deaths involved substandard care in the diagnosis and management of haemorrhage (Knight M et al., 2014). Up to 80% of cases are estimated to have received substandard care (ACOG, 2006; Rath, 2011). Examples include underestimation of blood loss, lack of local protocols, lack of adequate education and training (Bohlmann and Rath, 2013), poor communication, and deficiencies in organisation, such as staff shortages, inadequate equipment and insufficient teamwork and coordination (Upadhyay and Scholefield, 2008; Driessen et al., 2011; Rath, 2011). Much of this relates to the deficiency in organising transfer and complex, multi-disciplinary care at the health unit. A low-cost, effective intervention that can be used by first level maternity services providers could be a major advance in reducing maternal mortality from PPH, especially in low-resource settings where the majority of deaths occur.

A vital step in the physiological prevention of PPH is achieving immediate contraction and retraction of myometrial muscle fibres during and after the third stage of labour. Uterine atony is a condition characterised by the inability of the uterus to contract adequately after the placenta has separated from the uterus. This condition is thought to be the most common cause of PPH (Combs et al., 1991a; Maughan et al., 2006). There are many recognised risk factors for uterine atony including an over-distended uterus (due to polyhydramnios, multiple pregnancies, or a large fetus), prolonged labour, chorioamnionitis, tocolytics and general anaesthesia (RCOG, 2009). Despite the attempts that have been made to identify women at risk of uterine atony, it has been found to occur unpredictably in women with no risk factors (Breathnach and Geary, 2009). The most common clinical signs of uterine atony in women are a flaccid, boggy uterus and genital tract bleeding. An engorged, atonic uterus can contain many litres of blood, and may go unrecognised except for signs of haemodynamic instability secondary to hypovolaemic shock (Chestnut et al, 2009).

The PPH Butterfly

The PPH Butterfly is a simple, low cost, newly invented medical device that is designed to work as a management tool to assist in the diagnosis and treatment of primary PPH. The device was invented by Professor Andrew Weeks and the intellectual property is held by the University of Liverpool. The prototypes were developed in the Clinical Engineering Department of the University of Liverpool. The initial concept is loosely based upon the existing shelf pessary that is used to treat utero-vaginal prolapse. The addition of a handle enables the user to easily insert the device and align it into its correct position. The handle is large so as to limit the depth of insertion. When folded, the device can be slipped longitudinally into the vagina with minimal trauma. Once inserted, the device is unfolded by sliding the two arms of the device over each other so that the uterine platform pivots into a horizontal position facing into the maternal abdomen. Thus the surface of the platform ends up perpendicular to the axis of the uterus. Upon sliding back the handle, the device will return to its original folded state, allowing the device to be removed without discomfort or trauma. The insertion process is demonstrated graphically in Figure 1.

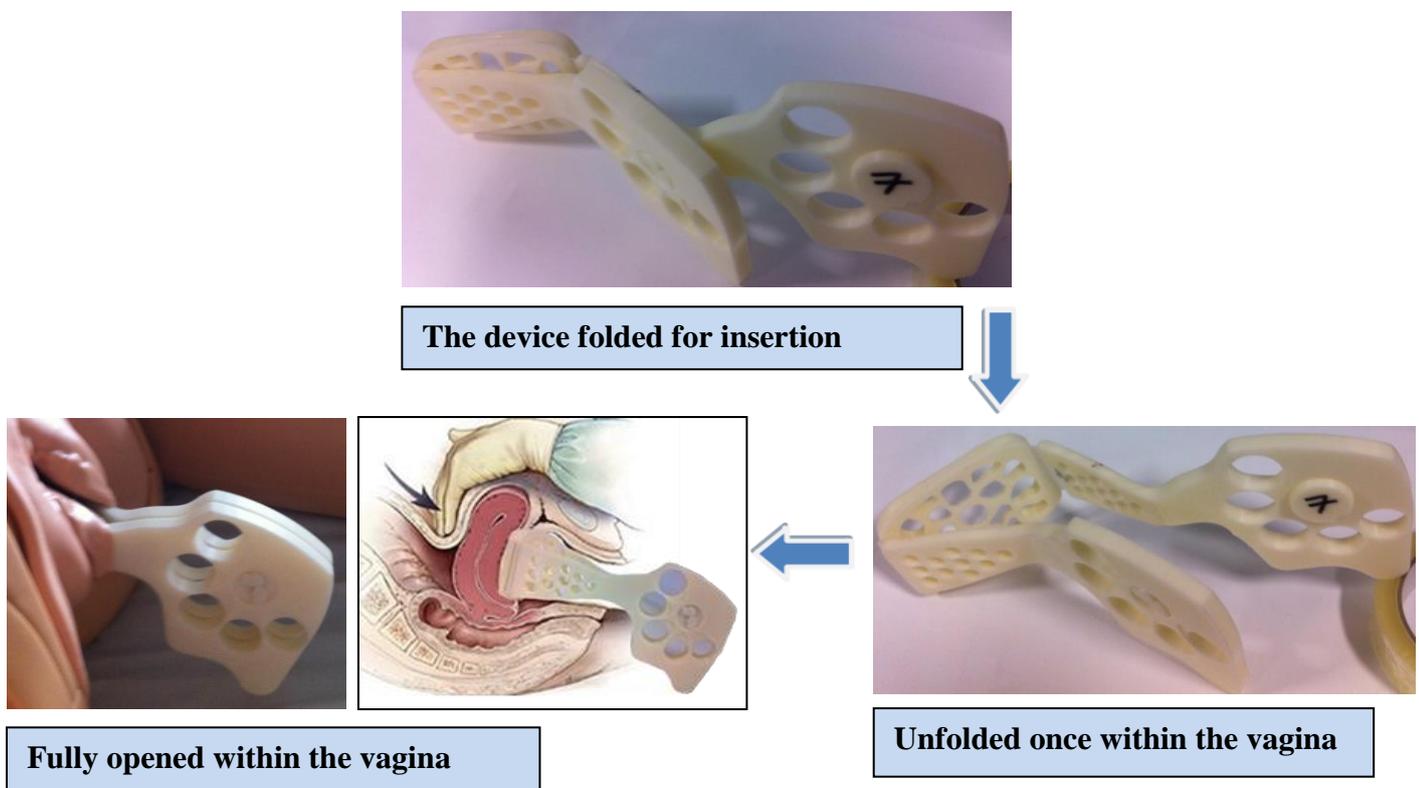


Figure 1. PPH Butterfly prototype - the insertion process

The theory behind the device

The idea of the device was to achieve the benefits of BMC without being so invasive, thus allowing it to be more widely used. The PPH Butterfly has been designed to be a slim, easily insertable replacement to a fist in the vagina (as occurs in BMC), thus increasing acceptability of uterine compression to both women and clinicians. This will make uterine compression available for use at a much earlier stage in the PPH treatment process, and provide an effective treatment without the need for medicines or advanced diagnostic skills. Once inserted, the uterus is compressed against the PPH Butterfly by a hand pushing against the woman's abdomen. The device will be held in place by its handle, which can be wedged against the bed allowing the uterine compression to be achieved with one hand on the maternal abdomen, or be held by the clinician or an assistant. The compression of the uterus can therefore be provided by either an individual clinician, two clinicians, or it will be possible to alternate between the two. This will allow the clinicians to share the task of uterine compression, and also prevent the rapid fatigue that occurs when conducting BMC. The PPH Butterfly is also designed to work as a management tool that assists in the diagnosis of primary PPH. Using the PPH Butterfly to immediately stop bleeding coming from the uterus will assist clinicians in determining the cause and source of postpartum bleeding.

Once the device is in the correct position, this can assist in the diagnosis of the source of the bleeding. If compressing the uterus against the device causes the blood loss to stop, then the user can be confident that the haemorrhage was uterine in origin and can continue uterine compression along with systemic oxytocics. Assessment of the bleeding will be made by releasing the pressure on the uterus. If the bleeding restarts, then the uterine compression can be continued and further oxytocics given. If, on the other hand, blood loss visibly continues whilst the uterus is being compressed then the user can be confident that the source of the haemorrhage is vaginal tears. This will allow a rapid diagnosis of the source of the bleeding so that appropriate steps can be taken. The surface of the platform of the device resembles a grill, with multiple holes. This gives a surface against which to compress the uterus, whilst preventing the entrapment of blood above it.

The three phases of the project were completed sequentially beginning with the designing phase, followed by the choosing and development of a usable device, and ending with an evaluation of the developed device. The device evaluation involved conducting a prospective randomised cross-over observational study at Liverpool Women's Hospital. This current study tested the use of the PPH Butterfly in a mannequin model when used by delivery suite staff, and examined the amount of compression that can be exerted on the uterus and the percentage of time over the 'effective pressure' (34 mmHg) by the PPH Butterfly and by standard BMC. The choice of a level of 34 mmHg for "effective pressure" is described in Chapter 5. The role of PPH Butterfly in diagnosing the source of the bleeding was not tested in this study.

Study type: randomised crossover study.

Study hypotheses

Three research hypotheses were examined: (1) use of the PPH Butterfly produces an equivalent amount of uterine pressure to standard BMC (2) uterine pressure from the PPH Butterfly can be sustained for a longer time than BMC, and (3) there will be no difference in effectiveness of uterine compression between experienced and inexperienced maternity care providers using PPH Butterfly.

Primary outcome measures

Hypothesis 1 primary outcome: the mean area under an intrauterine pressure curve over 5 minutes.

Hypothesis 2 primary outcome: the percentage of time in each group for which there was effective compression in minutes 4 and 5 of compression.

Hypothesis 3 primary outcomes: the percentage of time in each group for which there was effective compression.

Secondary outcome measures

- The maximum intrauterine pressure achieved in each group.
- The mean uterine pressure over time (0-1, 1-2, 2-3, 3-4 and 4-5 minutes).
- The percentage of time in each group during which there was effective compression during the first minute and minutes 2-3.
- The percentage of time during which there was inadequate uterine pressure (24 mmHg) over a period of 5 minutes in each group. Inadequate pressure was defined as 'expert mean – 1 SD' (34 mmHg -10 mmHg).

Materials

The commercial mannequin (Noelle[®]-Gaumard) was supplied with a rubber uterus to mimic the postpartum atonic uterus; (see Figure 12 in Chapter 5). Some modifications were made to Noelle[®] to facilitate BMC; and a full description of these is in Chapter 5. The uterus was supplied with air-filled pressure sensor which was connected to the uterine pressure inflator to record the intrauterine pressure, and connected to a personal computer via a data logger (Picolog 1012 Data Logger; (Figure 2)). Pressure from the uterus of the mannequin Noelle[®] is delivered to a piezoelectric pressure transducer ADP51A11 (Panasonic Electric Works Co., Ltd, Tokyo, Japan) via plastic tubing, where it is converted it into an electrical signal. The electrical output is directly proportional to the pressure. There is a small offset voltage at the output of the transducer at pressure 0 mmHg that is subtracted from the output value for analysis. The system includes a pressure gauge and hand pump (taken from a sphygmomanometer), initially pump air into the pressure pad. To calibrate the transducer, the tap is opened, pressure is pumped up to 10 mmHg and the value of the output noted. The pressure is then increased to 300 mmHg and the output value again noted. Because of the direct proportionality of the output to pressure, the actual pressure for any given voltage can be calculated. The tap to the hand pump was opened; the pressure in the pad increased to 10 mmHg and the tap was closed.

The output signal is then fed into a data logger that digitises it. The data logger has a USB interface to allow connection to a laptop and an associated computer program (Picoscope 6; Pico Technology, Cambridgeshire, UK). This receives the data and converts it into both graphical and numerical form. The program allows mathematical manipulation and storage of the data so that the calibration values can be inserted into it to produce a graphical representation as well as and a spreadsheet of absolute pressure (mmHg) versus time. The pressure sensor set up and calibration was done by Mr John Porter at Electronic Product Supplies Ltd, Irby, Wirral, UK.

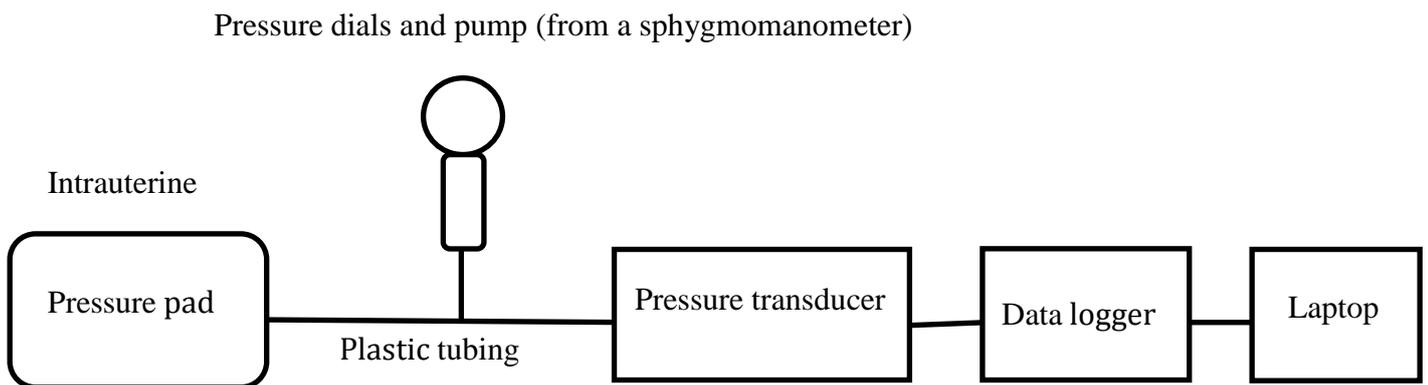


Figure 2. Uterine pressure system

Setting

The study was carried out at Liverpool Women's Hospital, Liverpool, UK.

Participants

The 'expert' group consisted of obstetric care providers at Liverpool Women's Hospital, senior obstetricians and trainees (ST3 onward) who had conducted human BMC several times before. The 'novice' group consisted of midwives who had no prior experience of conducting BMC. Any midwife who had previously conducted BMC was excluded.

Ethical consideration and consent

According to the ethics committee at Liverpool Women's Hospital, ethical approval was not required for this study as it involved NHS staff only and was performed on a mannequin model. The decision on ethical approval when involving NHS staff was based on NRES advice (NRES., 2011). However, informed verbal consent was obtained from all participants who volunteered for this study prior to their participation.

Sample size

A pilot study amongst 10 experienced clinicians doing BMC on Noelle[®] showed that the mean percentage of time over 'effective pressure' was 43% (SD=38%) (The study is reported in Chapter 5). It was agreed that an absolute increase of 17% to 60% would be clinically significant at alpha 0.05 and beta 0.8. A sample size of 42 pairs was therefore required for this study. The sample size calculation was done using StatsDirect software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

Randomisation

A statistical software programme (StatsDirect version 2.8.0, Cheshire, UK) was used to randomly allocate staff to the two methods of uterine compression. The allocations were written on cards and placed in consecutively numbered, sealed opaque envelopes by staff not involved in the study. We stratified this according to the participant experience (i.e. two separate randomisation lists were created for 'novice' and 'expert' providers).

2. Methods

Experienced delivery suite doctors (ST3 onwards) and midwives were informed about the study and invited to participate. After each participant gave verbal consent, participants were divided into 2 groups: the expert group and the novice group according to their expertise in BMC. The group of midwives who had not undertaken BMC before were shown a picture illustrating BMC by the principal investigator (NA) before they started. Each participant was then asked to carry out two forms of uterine compression on a mannequin model: traditional BMC and uterine compression using the PPH Butterfly. As previously mentioned, the participants were randomised as to which form of uterine compression they undertook first. Some of the participants performed the standard BMC technique first, while others started with uterine compression using the PPH Butterfly device. This was to control the effect of fatigue. The participants compressed the uterus for 5 minutes on each occasion, with a minimum of 5 minutes rest in-between. All users were asked not to wedge the PPH Butterfly handle into the bed.

The mannequin was supplied with an atonic uterus containing a pressure sensor. The sensor recorded the amount of uterine pressure produced by the participants compressing the uterus, and displayed it in the form of a graph.

The researcher then translated the reading in the form of the time (in seconds) in which the participant had produced pressure of > 34 mmHg, for the whole 5 minutes. This was repeated with each member in each group (expert and novice group), as well as with each form of compression (traditional BMC, and uterine compression with the PPH Butterfly). GraphPad Prism version 6 software (GraphPad Prism Software, Inc. San Diego, California, USA) was used for data analysis.

The percentage of time in each group when the pressure sensors recorded >34 mmHg was calculated for each group. The novice and the expert group were treated as sub-groups for the compression of BMC and PPH Butterfly compression. The Mann-Whitney test was used to compare the results within each group as well as a comparison between the 2 groups. The differences were considered statistically significant if the p value was ≤ 0.05 .

The research was funded by NIHR Invention for Innovation (i4i) programme, but they had no direct involvement in the study.

3. Results

The study was conducted during June 2014 and lasted for three months. Forty two participants (20 doctors and 22 midwives) were enrolled and completed the study.

1. Mean uterine pressure (area under the curve)

There was no statistical difference between the two groups in the amount of uterine pressure produced over the period of 5 minutes, both between the two groups and between the subgroups. The mean uterine pressure produced by each group is shown in Table 1 and is represented graphically in Figures 3 and 4. The mean pressure for the overall data (expert and novice together) was 29.02 (SD=8.17) and 27.23 (SD=8.18) for the BMC and PPH Butterfly respectively. There were also no differences within the subgroups. The pressures were equivalent among the experts with the two techniques (BMC mean 28.47 (SD=8.67), PPH Butterfly mean 27.28 (SD=9.40)). The pressure produced by the novice group was also very similar when using BMC or the PPH Butterfly (P=0.34), (Figure 3).

Table 1. Study outcomes

Outcome		BMC	PPH Butterfly	P value
Hypothesis 1: Mean uterine pressure of a period of 5 minutes (SD)	All	29.02 (8.2)	27.23 (8.2)	0.26
	Expert	28.47 (8.7)	27.28 (9.4)	0.51
	Novice	29.52 (7.9)	27.18 (7.1)	0.34
Hypothesis 2: % of time over 34 mmHg over minutes 4 and 5 (Mean, SD)	All	22.55 (38)	17.21 (32.2)	0.50
	Expert	21(37.8)	17.4 (34.1)	0.63
	Novice	24 (24.1)	17.1 (31.2)	0.15
Hypothesis 3: % of time over effective pressure (34 mmHg) of a period of 5 minutes (Median, IQR)	All	14.5 (0-53.8)	9 (1-41)	0.73
	Expert	13 (0-49.3)	8.5 (0.25-32.3)	0.51
	Novice	14.5 (0.75-64)	9 (1-52)	0.62
Secondary outcomes: % of time over 34 mmHg in minute 1(Mean, SD)	All	47.19 (42.8)	40.33(41.1)	0.78
	Expert	38.5 (41.1)	38 (39.6)	0.83
	Novice	55 (43.6)	43(43.1)	0.58
% of time over 34 mmHg in minutes 2 and 3 (Mean, SD)	All	30.26 (37.4)	27.43(37.7)	0.54
	Expert	28 (37.9)	26 (39.5)	0.78
	Novice	32 (37.7)	25 (34.4)	0.45
Maximum pressure (Median, IQR)	All	41.15 (34.2-53.8)	35.4 (28.1-446)	0.008*
	Expert	41.5 (34.7-53.5)	38 (29.6-44.7)	0.20
	Novice	41.15 (33.8-55.1)	33.11(27.9-41)	0.02*
% of time over of inadequate pressure (24 mmHg) of a period of 5 minutes (Mean, SD)	All	35.8 (37.4)	43.2 (37)	0.52
	Expert	44 (41)	48 (36.7)	0.79
	Novice	28.3 (32.9)	39 (37.8)	0.52

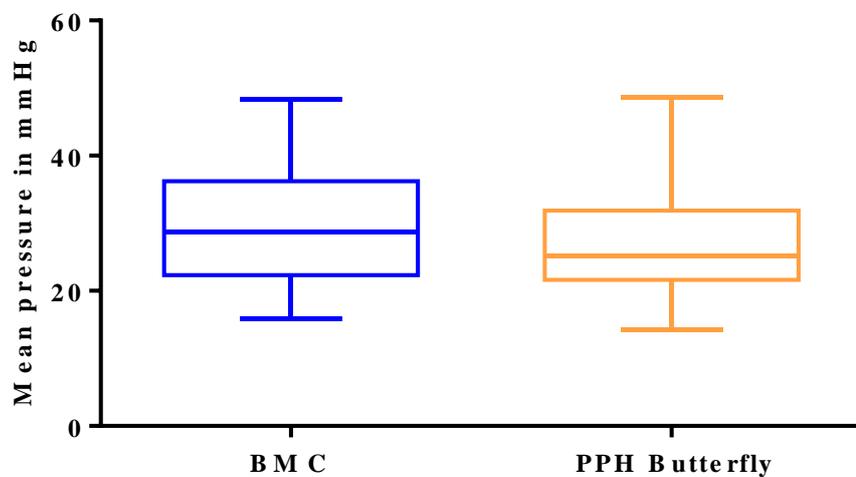


Figure 3. Mean pressure produced by each method

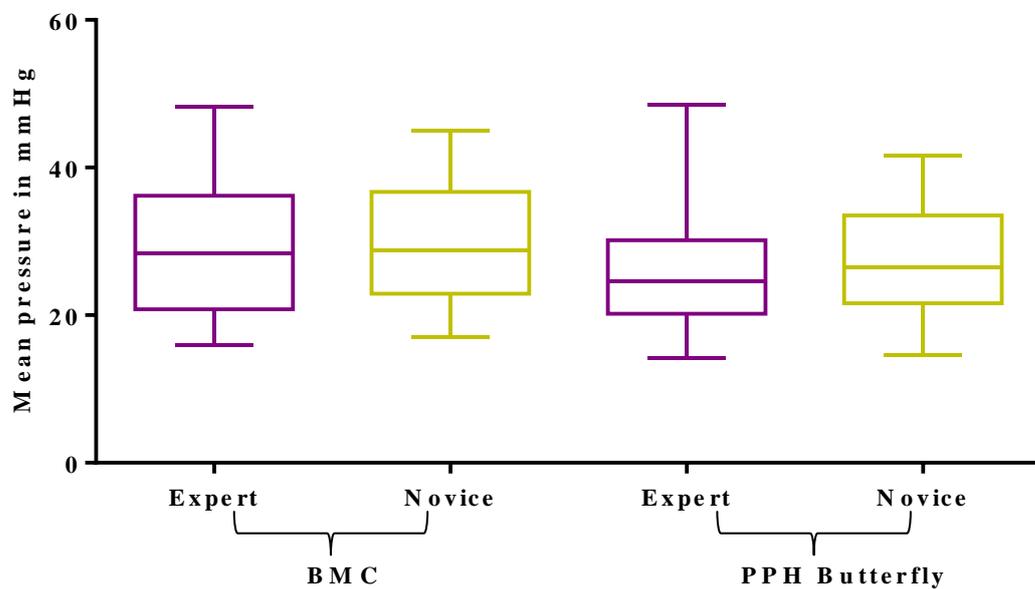


Figure 4. Mean pressure produced by the subgroups

2. The percentage of time in each group over recommended pressure (34 mmHg) during minutes 4 and 5.

The percentage of time that each group was over the recommended pressure (34 mmHg) was slightly lower when comparing the last 2 minutes with time minutes 2 and 3. The trend of a decrease in the amount of time above the recommended pressure was observed in both groups, but was more considerable with PPH Butterfly compression. However, these differences were not statistically significant. Both groups kept the pressure over 34 mmHg for exactly the same duration with the PPH Butterfly. The values for this outcome are summarised in Table 1.

3. Percentage of time of effective pressure (34 mmHg)

The percentage of time that the participants achieved effective pressure over a period of five minutes was calculated. This was then compared according to the method of compression and the experience of the participants, and between the groups. This is explained below.

A. Effect of technique

There was no statistical difference in the percentage of effective pressure within each group over a period of 5 minutes, (expert and novice), when looking at both of the methods of uterine compression. The median percentage of time over effective pressure during period of 5 minutes was 14.5 (IQR=0-53.8) in the BMC group (expert and novice) and 9 (IQR=1-41) in the PPH Butterfly group (expert and novice), $P=0.73$. In the expert group the median percentage of time over effective pressure was 13 (IQR=0-49.25) with BMC and 8.5 (IQR=0.25-32.25) with the PPH Butterfly ($P=0.96$). Whereas in the novice group the median percentage of time over effective pressure was 14.5 (IQR=0.75-64) with BMC and 9 (IQR=1-52) with the PPH Butterfly ($P=0.55$).

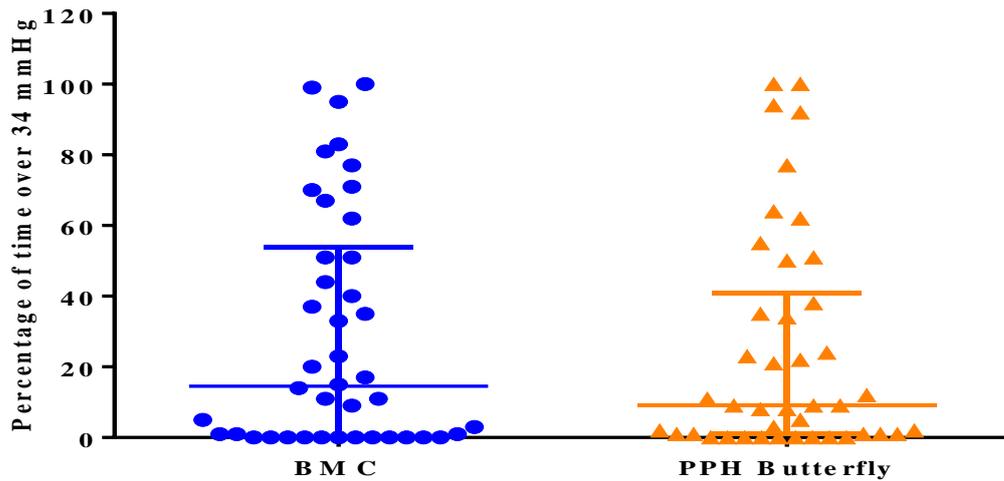


Figure 5. Percentage of time over recommended pressure over 5 minutes in subgroups

B. Effect of experience

There was no statistical difference between the experts and novices when performing each method of uterine compression. Both groups were able to keep the pressure over the recommended 34 mmHg at the same level regardless of experience. The majority of participants kept the pressure over the recommended value for only 20-25% of time. The median percentage of time over effective pressure during a period of 5 minutes was 13 (IQR=0-49.25) among expert and 14.5 (IQR=0.75-64) amongst novice doing BMC, $P= 0.52$. Expert using PPH Butterfly produced a median of 8.5 (IQR=0.25-32.25) versus 9 (IQR=1-52) in the novice PPH Butterfly group ($P=0.84$).

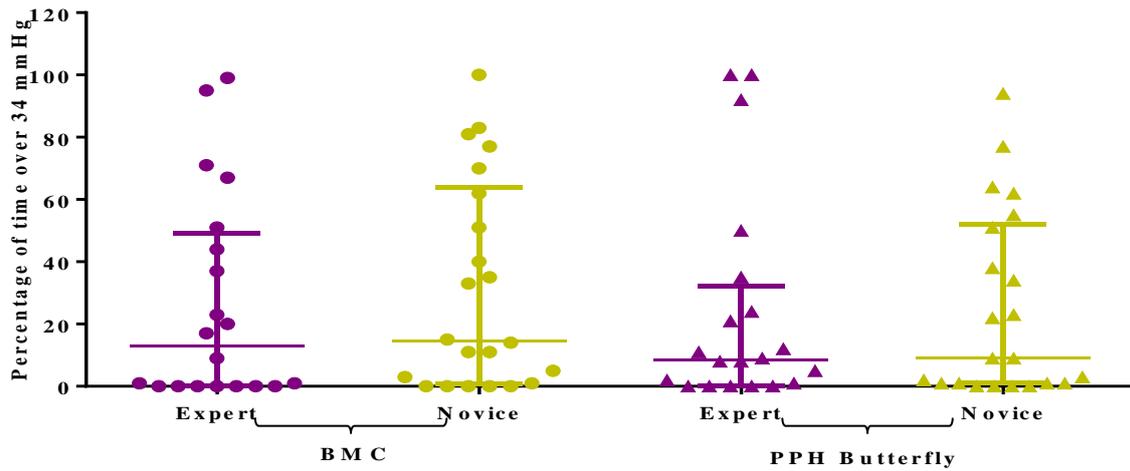


Figure 6. Percentage of time over recommended pressure over 5 minutes in subgroups

4. Maximum uterine pressure produced

Figure 7 demonstrates the maximum amount of uterine pressure produced by the two methods. The participants were able to produce a higher amount of uterine pressure with BMC than PPH Butterfly ($P=0.008$). The maximum value of uterine pressure in the BMC group was 88 mmHg and this was produced by one of the expert group. The maximum value of uterine pressure in the PPH Butterfly group was 65 mmHg, and again was among the expert group. The maximum pressure produced by a novice was 79 mmHg and 51 mmHg using BMC and PPH Butterfly respectively, (Figure 8). There was no difference among experts using either method of compression in relation to this outcome ($P=0.20$). The maximum uterine pressure produced by the two methods of compression was significantly different in the novice group ($P=0.02$).

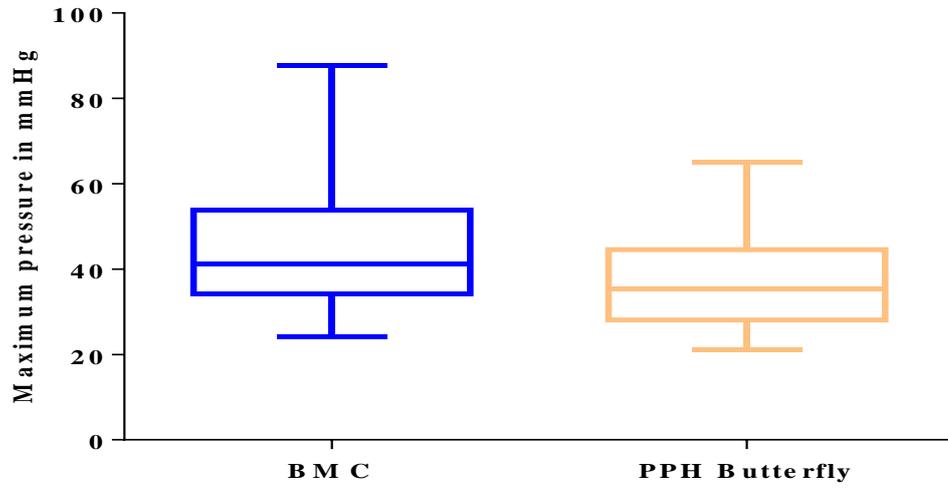


Figure 7. Maximum uterine pressure produced

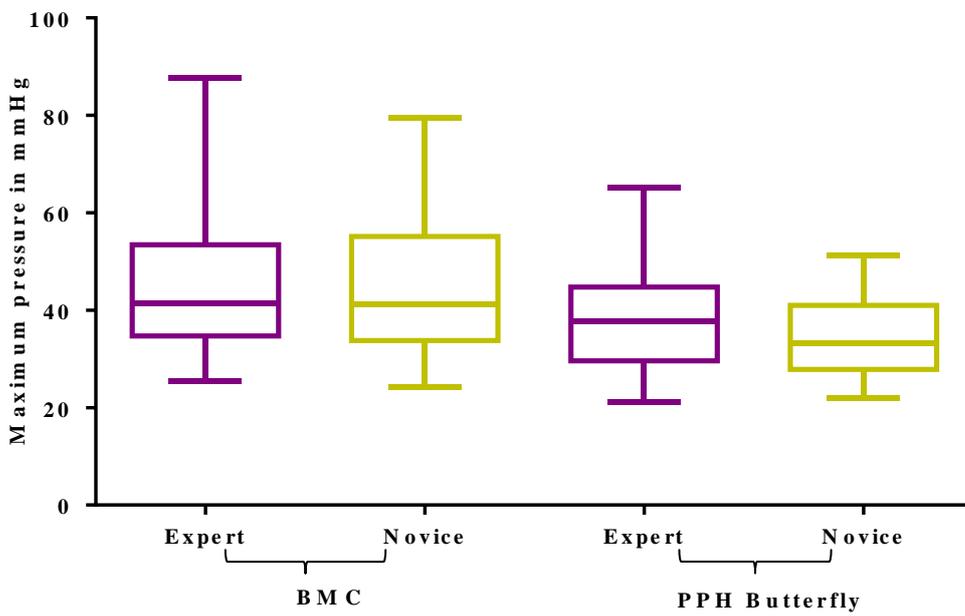


Figure 8. Maximum pressure produced in subgroups

5. The percentage of time in each group over recommended pressure (34 mmHg) during minute 1 and minutes 2 and 3.

The percentage of time that each group was over the recommended pressure (34 mmHg) over the initial 2 time intervals (minute 1 and minutes 2 and 3) was sustained at a similar level among the expert using either method of compression. Midwives kept the pressure over 34 mmHg for a slightly higher duration with the BMC than the PPH Butterfly. The values of this outcome are summarised in Table 1.

6. Mean pressure over time

Participants were unable to maintain the same level of pressure over 5 minute periods, using either form of compression. It can be noted from Figures 9 and 10 that the mean uterine pressure produced by the participants reduced slowly over the 5 minutes.

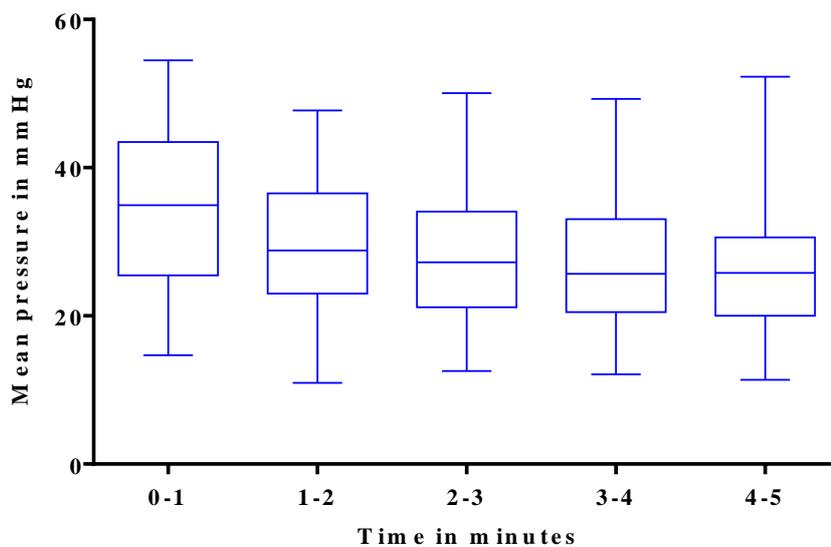


Figure 9. Mean pressure over time in the BMC group

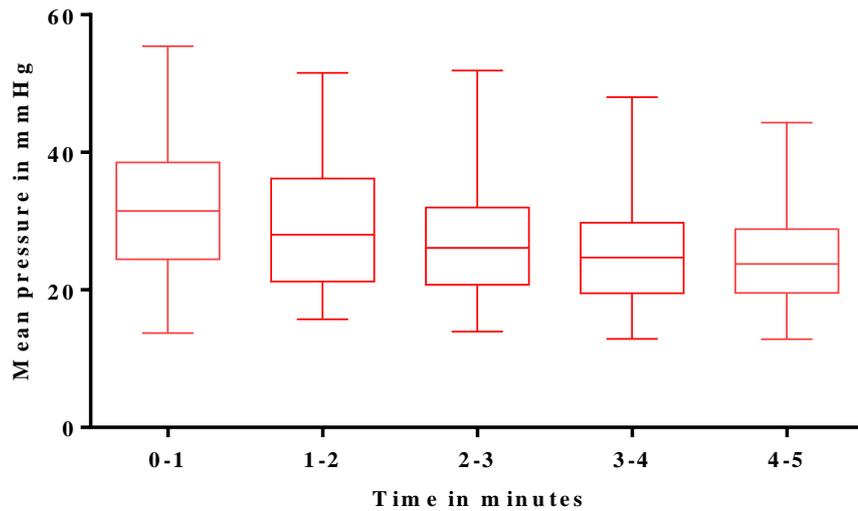


Figure 10. Mean pressure over time in the PPH Butterfly group

7. Percentage of time of inadequate pressure (< 24 mmHg)

The percentage of time of ineffective pressure over a period of 5 minutes was also calculated and presented in Figures 11 and 12. In the BMC group the mean was 35.8 (SD=37.4), in the PPH Butterfly group the mean was 43.2 (SD=37.1). Generally, using either method of uterine compression, both groups had almost the same percentage of time below the ineffective pressure of 24 mmHg, Figure 11. Novices were able to keep the pressure in the effective zone more than the expert, and this was more with BMC (Figure 12).

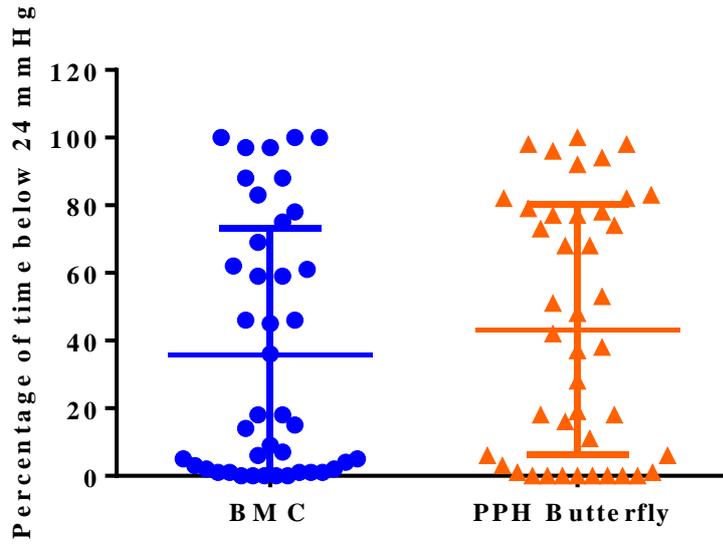


Figure 11. Percentage of time of inadequate pressure (< 24 mmHg) with the two methods

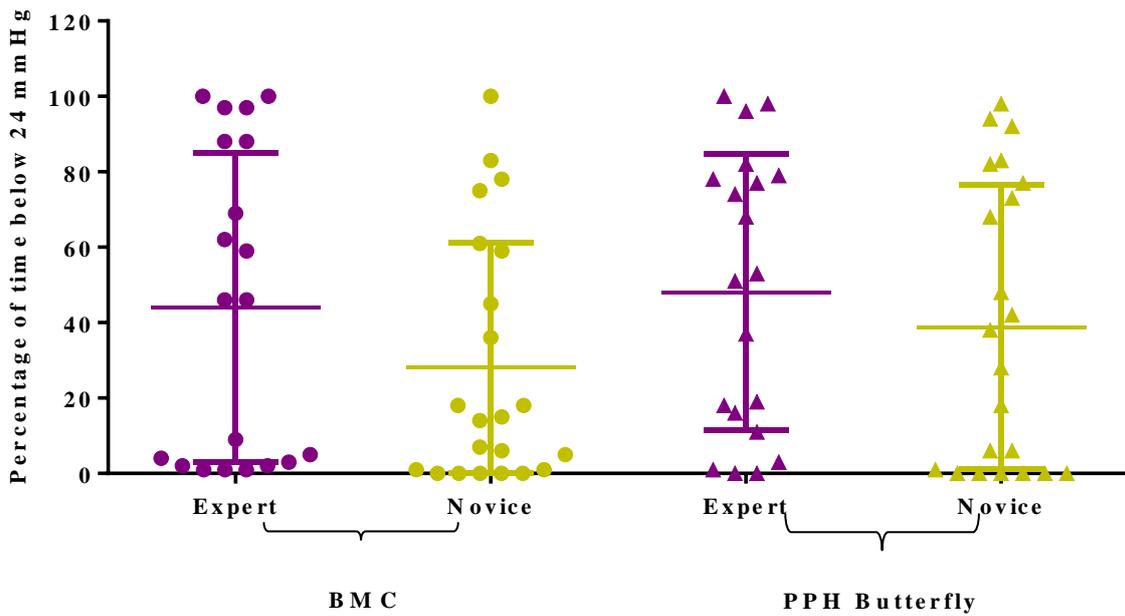


Figure 12. Percentage of time of inadequate pressure (< 24 mmHg) in the subgroups

Informal verbal feedback from the two groups on the use of the PPH Butterfly (ease of use, comfort, fatigue) during the time of performing uterine compression was varied. The majority of participants, especially the midwives, felt comfortable when holding the device, and stated that the compression was much easier using the PPH Butterfly and less tiring. Many of the clinicians felt comfortable with the device size but some felt that, it needed to be smaller. Following participant feedback the device was subsequently reduced in size with the platform reduced in size from 76.5 x 43.5 x 90 mm to 65 x 40 x 90 mm. Some doctors felt that when using the device they lost the tactile sensation that they had with traditional BMC.

4. Discussion

As countries strive to meet the MDGs before the 2015 deadline, rapid and urgent action is needed to ensure that communities, particularly women, have equitable access to high-quality health supplies and services. Whilst the goal of MDG 5 to improve maternal health has witnessed impressive reductions in the global number of maternal deaths (Fathalla, 2012; WHO et al., 2012). BMC is one of the emergency methods used to control PPH and prevent maternal mortality. The ICM, FIGO, and WHO all have recommended its inclusion as a treatment alternative of atonic PPH (Lalonde, 2012; WHO, 2012). The PPH Butterfly is designed to be as effective as BMC, but to be less invasive, easily used by less experienced health workers and to be more easily sustained for longer period. However, there have been concern raised about the ‘violence’ of the technique and suggestions that this may violate human rights (Taylor, 2015).

There are no previous human studies on the effectiveness of BMC in treating PPH. There are only 2 mannequin studies, and these evaluate the ability of simulation to train birth attendants to correctly perform BMC as obstetric first aid (Andreatta et al., 2011) and examined the impact of team-based BMC for managing PPH from uterine atony (Andreatta et al., 2012).

In this study we have found that the PPH Butterfly is simple to use on a mannequin model, even among obstetric care providers with little experience. It produces an equivalent amount of pressure to BMC, but feedback from focus group (data not shown) suggested an appropriate size and this would be less invasive than the standard BMC. It has also demonstrated the feasibility of using a mannequin model for teaching and performing BMC. However, uterine compression is not sustainable by the majority of participants.

There was a huge diversity within the group in all measured outcomes. Experts were able to produce the same amount of uterine pressure using either method of uterine compression. Novices produced a slightly higher pressure with BMC. This was a surprising finding, but it may relate to the lack of previous BMC experience. Those inexperienced in uterine compression will not be aware of how hard to compress the uterus in order to stop the bleeding and so will simply compress as hard as possible. Those experienced in compression may understand that the amount of pressure needed is only enough to compress the intramyometrial arterioles. This may have led to the experienced group not using too much pressure. It could also relate to the build of the participants. It has been suggested that a large body mass is required to produce effective pressure, as it has been found on a feasibility study that the level of pressure reached through compression was directly proportional to the clinician's body weight (Douma and Brindley, 2014). Finally, it may relate to the way doctors conducted BMC. This was not constant and some carried out BMC and uterine massage at the same time.

The majority of participants (experts and novices) kept the pressure over the recommended value for only around 10% of time. It seems that BMC is poorly taught and more attention should be paid to training on the correct way of carrying BMC. From the study we noted that BMC is easy to teach but the amount of pressure produced by the compression is difficult to standardise. Standardisation of pressure is possible on a mannequin model but would not be easy in human subjects. In one evaluation of simulation-based training on the ability of birth attendants to correctly perform BMC as obstetric first aid, researchers used six light pressure sensors to give biofeedback on the amount of uterine compression. The better level of uterine compression would be achieved the more lights were lit up (Andreatta et al., 2011). The authors found significant differences in the post-assessment quality of compression ($P= 0.04$) and the length of sustained compression ($P= 0.001$). All these studies are affected by a lack of knowledge about what the 'correct' pressure is when BMC is performed. In this study we used the pressure produced by (10) clinical academics as gold standard (see Chapter 5). However, these levels of compression were rarely achieved again, even by experienced practitioners, and retrospect they may have over-estimated the amount of force needed.

Almost all participants verbally indicated how tiring and hard it was to maintain uterine compression by either method. Use of the new handle of the device to wedge into the bed when a woman is lying in lithotomy may help to maintain pressure as it will allow practitioners to 'lean' on the uterus whilst merely stabilising the device with the other hand. This should be less tiring. It has also been suggested that BMC is more effective when performed by a team, with a primary attendant maintaining internal lower uterine segment pressure and monitoring the patient's condition, and a partner applying external pressure to the uterine fundus (Andreatta et al., 2012). This could also be true when using the PPH Butterfly. However, researchers need to be very careful when testing this on humans, as the amount of pressure produced using this method could harm the uterus if the compression was too high.

One drawback of using the device would be losing the vaginal hand as a 'biosensor'. This limitation could be lessened by vaginal examination before insertion of the device to assess the area of insertion, presence of injuries and for removal of blood clots.

The risk of trauma cannot be eliminated until the device is assessed *in vivo* and its safety is evaluated in women immediately after delivery. However, as protective measures, the edges of the device that will be used in the human study will be round in shape in order to reduce the risk of injuries to lower genital tract. Additionally, lubricant will be used to facilitate the process of insertion.

The study is strengthened by being a randomised trial, but does have several limitations related to the simulation method. Firstly, even the modified abdominal wall of the mannequin was much firmer than a postnatal woman's abdominal wall, making external compression hard to do. Participants may have under/overestimated their maintainable and maximum effort in the absence of clinical urgency. That is, given the absence of a conscious, haemorrhaging woman, participants were able to undertake uterine compression in whatever position they felt comfortable, without the potential restrictions of a conscious woman. This may have affected how long they were able to sustain the uterine pressure, and thus what level of pressure they were able to achieve. Also, the lack of clinical feedback in response to uterine compression in the form of amount of bleeding and uterine tone could have contributed to the value of the pressure produced by the participants. Another limitation is that we needed to limit the time that participants were asked to maintain compression to just 5

minutes. Human studies need to be conducted to assess how long the clinician can sustain the pressure. Because of the nature of the intervention, staff could not be blinded to the group allocation, although they were blinded to the amount of uterine pressure they produced. We had to ask the participant to perform both methods of uterine compression on the same day. This was tiring however, and having the compression methods carried out on two separate days could possibly have given a better result, especially in term of sustainability. The results from this study are transitional in nature and may not apply in actual clinical settings. We did not formally collected feedback from the participants on the device usage, fatigue and comfortability. Having a structured questionnaire would have allowed us to gain further information on the device shape, size and ease of usage, and to formally assess this. However, the PPH Butterfly project has other focus group meetings that dealt with such feedback and assessment.

BMC is performed by applying external pressure to the uterine fundus with one hand and internal lower uterine pressure with the other hand in order to compress the uterus. Finding that the uterine pressure produced by both the PPH Butterfly and BMC was not sustained and BMC is easy to teach, one may argue that using two hands to compress the uterus rather than the device is still cheaper. However; from the feminine point of view the use of device rather than insertion a fist would be more acceptable and less invasive. Additionally, the traditional method of BMC requires clinicians to come in direct contact with maternal blood which may increase the risk of transmission of blood borne diseases, namely HIV. It also may increase the potential introduction of infection to the mother. Although wearing gloves may allay some of these concerns, the availability of sterile gloves may be a problem in low-resource settings. In clinical practice, BMC often needs to be carried out for long periods of time. This is very tiring and it is impossible for the same person to maintain an effective level of pressure. With traditional BMC the tiredness would make the clinician need to remove their hand and this would make the pressure drop to zero. Using the PPH Butterfly will allow the clinician to alter their position more easily, whilst allowing the pressure to be maintained. The device has also the capability to be wedged into the bed and this would add more sustainability to the compression.

One advantage to using the device in low-resource countries is that a re-usable device will be of low cost compared to the other available early use PPH therapies such as balloon technologies. In these countries it is envisaged that the device will be reusable as opposed to

disposable, and thus will reduce the cost, as an individual device will not be required for each haemorrhaging woman. The new device will be available for only the cost of re-sterilisation. Also by using the device as a first line of defence, the costs of other later stage interventions such as additional drugs and theatre-based interventions could also be substantially diminished.

It will be importance to assess the efficacy of the PPH Butterfly *in vivo* studies, especially in the developing world. Human studies are needed to ascertain with more precision the size and efficacy of the PPH Butterfly, and also its effectiveness in the presence and the absence of injectable uterotonics. This intervention, if efficacious, may become a vital tool to be implemented in all public healthcare centres, and could especially have applicability in under-resourced areas of developing nations.

Chapter 7

General discussion and future research

1. Final discussion

This thesis is devoted to critical evaluation of the standard methods available to prevent and early treat PPH mainly due to uterine atony. Failure of the uterus to contract and retract following childbirth has for centuries been recognised as the most important cause of PPH. In the developing world, PPH is responsible for ten maternal deaths every hour. For more than 50 years AMTSL has been proposed for the prevention of PPH and is still recommended in current guidelines. The 3 key components of AMTSL have been the prophylactic administration of oxytocin, clamping and cutting of the umbilical cord and CCT, and the combination has been shown to reduce the rate of severe PPH by 70%. However, it has taken 50 years to become clear that prophylactic oxytocin is the most important component of AMTSL.

1. Bimanual uterine compression

While primary PPH can occur in spite of AMTSL, maternal death from PPH is an unforgivable tragedy. In order to optimise the prevention and treatment of PPH, different approaches have been introduced and modified over the last century. The importance of BMC in treating PPH has increased gradually, moving from third to first treatment option in the PPH treatment process (Chapter 2).

Physical measures are thought to be important in the early treatment of PPH. However, with a lack of research into the effectiveness of BMC, the procedure is rarely used by clinicians (Chapter 5). Whilst BMC is thought to be effective, obstetric care providers consider BMC to be tiring and too invasive to the women (Chapter 5). A commercial mannequin was therefore used to evaluate a new intervention that might contribute to the early physical management of PPH by making uterine compression available at very early stages of management. The PPH Butterfly is a new low cost device that is designed to make uterine compression simpler, less tiring and less invasive (Chapter 6). The device was initially compared to standard BMC. The study revealed that the PPH Butterfly is simple to use on a mannequin model, even among obstetric care providers with little experience. It also demonstrates the feasibility of using a mannequin model for teaching and performing BMC.

If proven efficient, using the PPH Butterfly would replace many of today's first aid measures. In comparison with anti-shock garment, the device would be much simpler and cheaper to use. Additionally, the effect of device can be seen immediately by assessing the patient's responsiveness through the amount of blood loss and uterine contractility.

One potential disadvantage of the device in comparison with the garment would be the invasiveness of the PPH Butterfly that can result in genital trauma but using lubricated appropriate sized device would reduce this risk.

2. Choosing the right outcomes for PPH clinical trials

The first step in reducing maternal morbidity and mortality associated with PPH is to improve methods of prevention. PPH prevention is an important subject and research is going on all over the world to improve the current management and medications. Historically, PPH care is not evidence based (Chapter 2). Studies commonly use PPH of 500 mls or additional uterotonic use (Chapter 4) as their primary outcome, but the evidence from the histogram study suggested that these do not correlate in the research context (Chapter 3). In a systematic review including 121 studies conducted to identify the outcome measures for prevention of PPH, there was a huge diversity in choice of outcomes (Chapter 4). There is strong need for development of a clear core set of outcomes in clinical trials. This would best be done through a Delphi technique or other methods, so as to reach a consensus around the optimal outcomes. This, however, is very challenging especially when it related to PPH outcomes. The dilemma around PPH definition, varying maternal haemoglobin at the time of delivery, differences in the time of postnatal haemoglobin measurement and methods of blood measurement make it very difficult to to produce a core set. In their 2009 PPH guidelines, WHO attempted to reach consensus around optimal postpartum care (WHO, 2009). WHO staff drafted questions on interventions and listed all possible outcomes for the treatment of atonic PPH and retained placenta. The draft questions and list of outcomes relating to the treatment of PPH and management of retained placenta were sent to 144 experts from all over of the world. They included a multidisciplinary panel of international health workers and consumers (including physicians, midwives, and non-clinicians (policy-makers, researchers and consumers)). The WHO team applied a similar methodology on various interventions described for the prevention of atonic PPH (WHO, 2007a).

3. How effective are uterotonics for PPH treatment?

Clinical trials evaluating the efficacy of uterotonics in treating PPH are rare. Where present they usually compare two uterotonics with an absence of control group, as it is unethical to leave a bleeding woman untreated. Historically, uterotonics use were taught as first line in PPH pathway of care (Chapter 2), but evidence for their use as a treatment largely came from PPH prevention studies. With the lack of placebo-controlled randomised trials the effectiveness of uterotonics in treatment of PPH is still questioned. Although treatment studies are very difficult, repeated doses of uterotonics appear to be ineffective (Widmer et al., 2010; Sheehan et al., 2011; Weeks et al., 2014). A recent innovation is to model the likely outcomes in the absence of uterotonic therapy through histograms (Weeks et al., 2014). This worked well in the presence of a clearly defined and implemented pathway for PPH diagnosis and treatment. Examination of 4 other PPH datasets from PPH prophylaxis studies however found that histogram analysis was unhelpful – largely due to the fact that women were given PPH treatment at a wide variety of blood losses (Chapter 3). Based on this evidence it is clear now that a new methodology is required. This could be either by conducting cluster RCTs or reviewing ‘large data’. All of these solutions are not without obstacles including lack of power and consent issues.

2. Future research

It is well-recognised phenomenon that whenever research questions are answered, more questions arise. This increases the researchers’ interest and may lead them to continue their investigations and improve the methodology, or to replicate their previous findings. The work in this thesis is no different and opens new avenues in several aspects of research.

The third stage blood loss histogram study, in Chapter 3, could be replicated using datasets from large RCTs with a clearly defined treatment point and policy. This would result in a clearer picture of the benefit of using uterotonics for treating PPH at a blood loss > 700 mls and give adequate power to confirm or contradict the findings. From reviewing the data from the included studies in the histogram study in Chapter 3, it is clear that there is massive heterogeneity with a lack of consistency in methods used for data collection, abbreviations and code using. The production and use of a predefined data extraction sheet with standard code and definitions for use in all clinical trials would be highly beneficial.

The work in Chapter 4 about the clinical outcomes of PPH prevention studies has already been taken further by Dr. Shireen Meher, Clinical Lecturer in Obstetrics and Gynaecology University of Liverpool. The development of core outcome sets for PPH future studies will help in reaching a clear conclusion on the effect of intervention. A study is ongoing to examine the status of outcomes within PPH treatment trials to facilitate the development of COS. As mentioned above, different aspects of PPH (including its definition and method of blood loss measurements) need to be agreed at least in the context of research.

The work in Chapter 2 could be linked to other sources of evidence based such as RCOG and CEMD recommendations.

PPH remains a major cause of maternal mortality especially in low resource settings, where the majority of deaths take place. Providing affordable and effective intervention is essential for reducing maternal mortality from PPH. Although BMC is a well-known first aid procedure in treating PPH more research is required to establish its efficiency. This may also include research on how long it should be conducted for. The invention of the PPH Butterfly could help in treating PPH and preventing the tiredness caused by the standard method of BMC. However, this device now needs to be tested in women; first to test the device size and acceptability, and then to test its efficacy *in vivo*.

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Appendixes

FEATURE

CHRISTMAS 2012: EVOLUTION OF PRACTICE

Push, pull, squeeze, clamp: 100 years of changes in the management of the third stage of labour as described by Ten Teachers

Should we look back at historical methods to see if we are missing a trick? Aflaifel and Weeks trace the history of managing the third stage of labour

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The third stage of labour (between the delivery of the baby and the placenta) is the most dangerous time of childbirth for the mother. Many of today's obstetricians were taught that "active management" of this stage (oxytocics, early cord clamping, and controlled cord traction) was the only safe way to deliver the placenta. Recent studies have shown that although prophylactic oxytocics are beneficial, early cord clamping is of no benefit (and could be harmful) and controlled cord traction has little benefit.¹ We sought to place these changes in context through a historical study of obstetric practice over the last century.

The undergraduate textbook *Obstetrics by Ten Teachers* has been a favourite with students for many generations. First published in 1917 as *Midwifery by Ten Teachers*,² the book was renamed in 1966³ and is now in its 19th edition. Each edition is written by 10 leading obstetricians from the British Isles with the authors chosen by the senior editor. With a complete absence of references in the text, the series provides an excellent example of "eminence based" medicine and gives an insight into changes in labour ward practice over the past century.

We reviewed the regimens for the third stage of labour between 1917 and 2011 as described in the successive editions of the books. Copies were obtained from the University of Liverpool's Harold Cohen library and from interlibrary loans as necessary.

Routine third stage management

Routine third stage management focuses on reducing blood loss and achieving rapid and complete delivery of the placenta. Figure 1 and appendix 1 show details of changes over the past century. Although uterotonic drugs (drugs that enhance the contraction of the uterine muscle) in various forms have been used ever since the first edition, the practices of early cord

clamping and controlled cord traction were taught only after the "active management of the third stage of labour" package was popularised in the 1960s.

Successive authors seem to have had reservations about the practice of early cord clamping, however, and have described its use as "an option" with use of the active management package or if the baby requires resuscitation. Oddly, the first mention of its routine use appears in the 2011 edition, just as national and international evidence based guidelines were dropping it as part of their recommendations, demonstrating the well recognised disconnect between "evidence based" and "eminence based" medicine.

The treatment of atonic postpartum haemorrhage

Atonic postpartum haemorrhage is the most common cause of bleeding after childbirth and results from poor contraction of the uterine muscle. See appendix 1 for details of its management since 1917.

The Ten Teachers series has always taught that uterotonic drugs are the best initial treatment for atonic postpartum haemorrhage. The standard drug has been ergot, but other early options included transabdominal intramyometrial ergometrine (1961-72) and oxytocin (1948). From 1995 onwards the choice of uterotonic drugs increased to include intravenous syntometrine, oxytocin infusion, prostaglandin F_{2α} (intramuscular or directly into the uterine muscle), and misoprostol.

Aside from drug treatment, uterine massage (sometimes in combination with squeezing the uterus through the abdominal

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Appendix 1: Additional details of the interventions over time

EDITORIALS

Active management of the third stage of labour

Oxytocin is all you need

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The original description of active management of the third stage of labour had three components—delivery of a prophylactic uterotonic drug, early cord clamping and cutting, and controlled cord traction.¹ When randomised trials in the 1980s found that this package reduced the risk of severe postpartum haemorrhage by 70%,² active management was adopted widely. It was thought to be especially important in low resource settings, where more than 20 000 deaths occur each year as a result of haemorrhage.³ In these settings, active management of the third stage has almost become a mantra for the safe motherhood movement.

But in the half century since active management was described, we have never known which component is the most important. Guidelines from around the world have varied widely in their selection of oxytocic agent, early cord clamping, cord traction, uterine massage, and cord drainage.⁴ Controlled cord traction became popular only when it was incorporated into the active management package in 1962, and, although there were no major randomised trials of cord traction, it was thought to decrease the incidence of postpartum haemorrhage and retained placenta.⁵

The required evidence on cord traction appeared in March this year.⁶ Gulmezoglu and colleagues from the World Health Organization's maternal health research network conducted a large multicentre controlled trial to examine the effect of active management of the third stage of labour with and without cord traction in more than 24 000 women.⁶ All women received oxytocin (10 IU intramuscularly immediately after delivery) and had "delayed" cord clamping at one to three minutes. Participants then either underwent cord traction at the time of the first uterine contraction or the placenta was allowed to deliver with the aid of gravity and maternal effort only. The study had a non-inferiority design, and the team decided a priori that the two groups would be equivalent if the 95% confidence interval of the relative risk did not include a 30% or more increase in severe postpartum haemorrhage in the controlled traction group over the simplified regimen.

Compliance with the protocol was good, but in the simplified package group 6% of women still needed cord traction to deliver the placenta. The researchers found that omission of cord traction from the active management package had no significant effect on the rate of severe haemorrhage (risk ratio 1.09, 95%

confidence interval 0.91 to 1.31), but the difference in the risk of haemorrhage of more than 500 mL was of borderline significance (1.07, 1.00 to 1.14). Furthermore, given that the upper 95% confidence interval limit just crossed the pre-stated non-inferiority margin of 1.30, the authors had not proved that the two were equivalent. The time to placental delivery was halved in those having cord traction from 12 to six minutes (difference 6.5, 6.2 to 6.8), and this reduced the need for manual removal (1.45, 1.14 to 1.86). Further analysis of the results, however, showed that the difference in manual removal occurred in one country only. That country had experienced difficulty with recruitment and one of the two sites had been giving a combination of oxytocin and ergometrine for prophylaxis (in contravention of the study protocol). When the data were analysed without the results from that country (81% of all recruits were still included) no effect on the need for manual removal was seen (0.97, 0.68 to 1.37).

This study therefore showed that during active management of the third stage of labour cord traction has little, if any, part to play in reducing severe postpartum haemorrhage. It also showed that in sites using oxytocin alone for prophylaxis, cord traction reduced the length of the third stage by six minutes but had no effect on manual removal rates. The same may not be true when the combined oxytocin-ergometrine preparation is used.

The study is good news for maternity care providers, especially in low resource settings. Although cord traction is straightforward, it is often poorly done. If traction is performed before a contraction occurs it can result in uterine inversion or haemorrhage, and if the cord is pulled too vigorously it cause the cord to snap. In settings where the training of birth attendants is brief and continuing support minimal, trainers are therefore likely to err on the side of caution and omit the cord traction step from the standard "oxytocin alone" active management package. The method will, however, still need to be taught because about one in 20 women who use maternal effort will require the procedure, and it may be important in settings that still use ergometrine based prophylaxis.

In settings where providers are confident that cord traction will be performed correctly, it will probably remain part of the package because it does no harm and could still have a small beneficial effect on blood loss.

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Appendix B.1.Third stage management prophylaxis as stated in ‘Obstetric by Ten Teachers’ editions

Year	Edition	Third stage management prophylaxis			
		Drug	Placental delivery	Cord clamping	Other
1917	1	E oral liquid extract one teaspoonful in a wine-glass of water or hypodermic injection of some ergot preparation after delivery of placenta (Good practice not essential)	Maternal straining	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward
1920	2	E oral liquid extract one teaspoonful in a wine-glass of water or hypodermic injection of some ergot preparation after delivery of placenta (Good practice not essential)	Maternal straining	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward
1925	3	E oral (liquid extract) one teaspoonful in a wine-glass of water or hypodermic injection of ergtin after delivery of placenta (good practice not essential)	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward then directly downward
1931	4	E oral(liquid extract) one teaspoonful in a wine-glass of water or hypodermic injection of ergtin after delivery of placenta (good practice not essential)	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward then following the curve of genital canal direct the pressure downward and forward toward the vulval outlet
1935	5	E oral(liquid extract of ergot) one teaspoonful in a wine-glass of water or hypodermic injection of ergtin after delivery of placenta (good practice not essential)	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward then following the curve of genital canal direct the pressure downward and forward toward the vulval outlet

1938	6	E oral (liquid extract of ergot) one teaspoonful in a wine-glass of water or intramuscular injection of ergometrine 0.25 mg after delivery of placenta (good practice not essential)	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward then following the curve of genital canal direct the pressure downward and forward toward the vulval outlet
1942	7	E oral(liquid extract of ergot) one teaspoonful in a wine-glass of water or intramuscular injection of ergometrine, 0.25 mg after delivery of placenta (good practice not essential)	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward then following the curve of genital canal direct the pressure downward and forward toward the vulval outlet
1948	8	E oral or IM or OX IM	Maternal effort	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward gently and steady
1955	9	E 0.5 mg, IM immediately after delivery of baby	Maternal straining	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (after few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward gently and steady
1961	10	E IM 0.5 mg after delivery of baby If patient had anaesthesia E IV 0.3mg after head is crowned	Maternal effort or cord traction if the placenta not delivered (some clinics)	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (few minutes)	If the mother not able to expel the placenta, grasp the uterus with left hand, make it contract by stimulation with the tip of fingers and then press the uterus downward and backward gently and steady

1966	11	<u>Physiological method:</u> NM	Maternal effort/obstetrician pressing on the fundus of contracted uterus/CT/ B-A method	Until baby cried vigorously and pulsation stop and the umbilical vein collapse (few minutes) Placing the baby below the level of placenta to facilitate blood flow by the aid of gravity	Divide third stage management to conservative and active method (first mentioned) If the mother not able to expel the placenta, grasp the uterus with left hand, wait for a contraction then press the uterus downward and backward gently and steady
		<u>Active method:</u> E 0.5 mg IV or IM after delivery of anterior shoulder E/OX IM	Combination of fundal pressure and CT or by B-A method	Early	
1972	12	E 0.5 mg IV or IM after delivery of anterior shoulder or E/OX IM (in the active method)	Maternal effort (conservative method) if mother fail the placenta will be delivered by B-A method	Until baby cried vigorously and pulsation stop and the umbilical vein collapse. Placing the baby below the level of placenta to facilitate blood flow by the aid of gravity Immediately in active method	Divide third stage management to conservative and active method
1980	13	E 0.5 mg IV after delivery of anterior shoulder or E/OX IM	B-A method	If baby well: Until baby cried vigorously and pulsation, keep the baby same level as the placenta, no milking, not to hold the baby too low or too high If resuscitation needed immediate (early) cord clamping	Active management advocated by nearly all obstetricians

1985	14	(Preferred) OX, IM 5 units within the delivery of anterior shoulder in primigravida While the head is crowing in multipara or E/OX	B-A method	If baby well: Until baby cried vigorously and pulsation, keep the baby same level as the placenta or a little low but not o held high If resuscitation needed immediate (early) cord clamping	Can be treated by simple observation but, active management advocated by nearly all obstetricians Mention side effects of erogmetrine nausea vomiting and high blood pressure
1990	15	OX 5 units IM or IV with the delivery of anterior shoulder in primigravida While the head is crowing in multipara or E/OX	B-A method/NM	If baby well: Until baby cried vigorously and pulsation, keep the baby same level as the placenta or a little low but not to held high If resuscitation needed immediate (early) cord clamping	Can be treated by simple observation but, active management advocated by nearly all obstetricians
1995	16	OX 5 units IM or IV with the delivery of anterior shoulder in primigravida While the head is crowing in multipara or E/OX	B-A method/NM	If baby well: Until baby cried vigorously and pulsation, keep the baby same level as the placenta or a little low but not o held high If resuscitation needed immediate (early) cord clamping	Can be treated by simple observation but, active management advocated by nearly all obstetricians
2000	17	OX 10 IU or E/OX, IM after delivery of anterior shoulder	CCT	Delayed (until cord pulsation cease), baby between the mother's legs	Active management Suckling to simulate oxytocin release E/OX contraindicated in hypertension
2006	18	OX 10 IU or E/OX, IM after delivery of anterior shoulder	CCT	Delayed, baby between the mother's legs	Active management Suckling to simulate oxytocin release

2011	19	Active management: OX, 10 IU IM with the delivery of anterior shoulder or immediately after delivery of baby	CCT	Early , baby between mother's legs	Active or physiological management Recommended active management to all women
		Physiological management: no uterotonic	Maternal effort		

Appendix B.2. Summary on PPH treatment as stated in ‘Obstetric by Ten Teachers’ editions

Year	Edition	Drug Type/dose	Expulsion of the placenta/Crede’s manoeuvre	Bimanual compression	Aortic compression	Uterine massage	Surgery	Other
1917	1	Ergot glass ampoules containing one dose IM (Ergotin) and pituitary extract IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail manual removal	<u>Third:</u> Yes but if case of severe flooding start with it	Yes (difficult in obese women, may cause damage to intestines)	<u>First:</u> Squeezing the uterus	<u>Last resource:</u> Plugging the uterus using gauze (Surgical non-invasive)	<u>Second:</u> Intrauterine douche at a temperature 180° F
1920	2	Ergot glass ampoules containing one dose IM (Ergotin) and pituitary extract IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail manual removal	<u>Third:</u> Yes but if case of severe flooding start with it	Yes (difficult in obese women, may cause damage to intestines)	<u>First:</u> Squeezing the uterus	<u>Last resource:</u> Plugging the uterus using gauze (Surgical non-invasive)	<u>Second:</u> Intrauterine douche at a temperature 180° F
1925	3	Ergot glass ampoules containing one dose IM (Ergotin) and pituitary extract IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail manual removal	<u>Third:</u> Yes but if case of severe flooding start with it	Yes (difficult in obese women, may cause damage to intestines)	<u>First:</u> Squeezing the uterus	<u>Last resource:</u> Plugging the uterus using gauze (Surgical non-invasive)	<u>Second:</u> Intrauterine douche at a temperature 180° F
1931	4	Ergot glass ampoules containing one dose IM (Ergotin) and pituitary extract IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail manual removal	<u>Third:</u> Yes but if case of severe flooding start with it	Yes (difficult in obese women, may cause damage to intestines)	<u>First:</u> Squeezing the uterus	<u>Last resource:</u> Plugging the uterus using gauze (Surgical non-invasive)	<u>Second:</u> Intrauterine douche at a temperature 180° F
1935	5	Ergot glass ampoules containing one dose IM (Ergotin) and pituitary extract IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail manual removal	<u>Third:</u> Yes but if case of severe flooding start with it	Yes (difficult in obese women, may cause damage to intestines)	<u>First:</u> Squeezing the uterus	<u>Last resource:</u> Plugging the uterus using gauze (Surgical non-invasive)	<u>Second:</u> Intrauterine douche at a temperature 180° F

1938	6	E, glass ampoules containing one dose IM (Ergometrine) and pitocin IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted,(<u>first time mention and description of Cred's manoeuvre</u>), if fail manual removal	<u>Second:</u> Yes but if case of severe flooding start with it	NM	Yes, <u>First:</u> Squeezing the uterus (mentioned the word uterine massage)	NM	<u>Third: (after uterus gained contractility):</u> Intrauterine douche at a temperature 180° F of dettol, or inject sterile glycerine intrauterine
1942	7	IM or IV 0.5 mg E (asap) E, glass ampoules containing 0.5 mg IM (Ergometrine) and pitocin IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail expression under anaesthesia if not manual removal(Ergot 8 hr for 3-4 days)	<u>Second:</u> Yes but if case of severe flooding start with it	NM	Yes, <u>First:</u> Squeezing the uterus	NM	<u>Third:(if the uterus unable to maintain tone):</u> Intrauterine douche of dettol, at a temperature 180° F
1948	8	<u>Before the birth of placenta</u> 0.5 mg E, IM <u>After the birth of placenta</u> 5 units OX IM or E 0.5 mg IM	<u>Before the birth of placenta</u> Fundal squeezing while uterus contracted, if fail expression under anaesthesia if not manual removal	<u>Second:</u> Yes but if case of severe flooding start with it	NM	Yes, <u>First:</u> Squeezing the uterus In addition to drug	NM	<u>Third:</u> Repeat ergot if uterine contractility not achieved
1955	9	<u>After the birth of placenta and patient not received E</u> E 0.5 mg IV	<u>Before the birth of placenta</u> One attempt of Crede's manoeuvre, fundal squeezing while uterus contracted, if fail and in hospital expression under anaesthesia if not manual removal, If patient in poor facility place: E 0.5MG IV	<u>Second:</u> Yes but if case of severe bleeding start with it	NM	Yes, <u>First:</u> Rub the uterus	NM	<u>Divide the treatment according to:</u> 1. Placenta delivered or not 2. Patient received E or not 3. Available facility such as anaesthesia and blood transfusion

			if failed transfers to hospital for manual removal					Third: Repeat ergot or give 10 IU OX if uterine contractility not achieved with bimanual compression
1961	10	<u>After the birth of placenta and patient not received</u> E E 0.5 mg IV	<u>Before the birth of placenta</u> Crede's manoeuvre, (become unpopular) , cord traction if fail manual removal	Second: Yes but if case of severe bleeding start with it while waiting for E to act	NM	Yes, First: Rub the uterus	NM	Third: Repeat E IMM, transabdominally if uterine contractility not achieved with bimanual compression
1966	11	<u>After the birth of placenta and patient not received</u> E E 0.5 mg IV	<u>Before the birth of placenta</u> <u>If separated:</u> Backward and downward pressure or CT <u>If not separated:</u> B-A method Crede's manoeuvre if uterus contracted one attempt if failed manual removal	Second: Yes but if case of severe bleeding start with it	NM	Yes, First: Rub the uterus,	Hysterectomy if sever bleeding	Third: Repeat E injection if uterine contractility not achieved with bimanual compression
1972	12	<u>After the birth of placenta and patient not received</u> E E 0.5 mg IV	<u>Before the birth of placenta</u> <u>If separated:</u> Backward and downward pressure or CT <u>If not separated:</u> B-A method, if uterus contracted one attempt if failed manual removal (Crede's manoeuvre NM)	Second: Yes but if case of severe bleeding start with it	NM	Yes, First: Rub the uterus	Hysterectomy if sever bleeding	Third: Repeat E injection if uterine contractility not achieved with bimanual compression

1980	13	After the birth of placenta First: E 0.5 mg IV even the patient received E	Before the birth of placenta Manual removal under GA	Second: Yes	NM	NM	Last resource: Hysterectomy	Divide treatment of PPH into 2 principles arrest the bleeding restore blood volume) Taking in consideration bleeding disorders
1985	14	After the birth of placenta First: E 0.5 mg IV	Before the birth of placenta <u>If separated:</u> B-A method, if uterus contracted <u>If not separated:</u> Manual removal under GA.	Second: Yes	NM	Yes, First: with fundal pressure	Last resource: Hysterectomy	
1990	15	After the birth of placenta First: E 0.5 mg IV	Before the birth of placenta <u>If separated:</u> B-A method, if uterus contracted <u>If not separated:</u> Manual removal under GA.	Second: Yes	NM	Yes, First: with fundal pressure	Last resource: Hysterectomy, in case of uncontrolled bleeding	
1995	16	After the birth of placenta First: E/OX 0.5 mg IV	Before the birth of placenta <u>If separated:</u> B-A method, if uterus contracted <u>If not separated:</u> Manual removal under GA.	Second: Yes	NM	Yes, First: with fundal pressure	Last resource: In case of uncontrolled bleeding, internal iliac artery ligation or hysterectomy,	
2000	17	First : 1. E 0.5 mg IM(repeat with IV if bleeding continue) 2. OX 100 IU in 1 litre of normal saline, 20 drops/min (these as first line),		NM	NM	Yes, First	Third: Arterial ligation if possible To avoid hysterectomy: -Uterine packing	Treatment of atonic PPH

		Second: PGF2 alpha(second line) IM or intramyometrial					-Balloon tamponade (Sengstaken-blahemore tube) -Embolisation of pelvic vasculature	
2006	18	E and OX IV (to maintain contraction) PGF2 alpha(second line) IM or IMM		Yes, First	NM	Yes, First	If medical treatment fail Balloon tamponade (Rusch urological catheter) -Rarely, bilateral IIAL or hysterectomy	Treatment of atonic PPH Empty the bladder
2011	19	First: OX bouls, E/OX And OX 40 IU IN 500 ml saline over 4 hr Or E, PGF2 alpha or PG E2		Yes, First	NM	Yes, First	If medical treatment fail Balloon tamponade Radiological occlusion of uterine vessels Laporatomy for bilateral IIA ligation Uterine compression sutures Last resource: Hysterectomy	Empty the bladder as an empty bladder aid uterine contraction

Appendix C.1. Search strategy

(Same search strategy was used for all databases (Cochrane library, the Embase, the Ovid version of Midline, the Web of Knowledge and Scopus)

A. Any intervention used

- **Pharmacological**

- #1 oxytocin
- #2 pitocin
- #3 misoprostol
- #4 ergometrine
- #5 ergonovine
- #6 methergine
- #7 ergot alkaloid
- #8 methyl ergometrine
- #9 syntometrine
- #10 prostaglandin
- #11 tranexamic acid
- #12 traditional Chinese medicine
- #13 oxytocin agonist
- #14 carbetocin

- **Cord management**

- #15 cord clamp
- #16 placental cord drainage
- #17 controlled cord traction
- #18 umbilical cord injection

- **Uterine manipulation**

- #19 uterine massage
- #20 fundal pressure

- **Others**

- #21 nipple stimulation
- #22 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)

B. Third stage labour/ postpartum haemorrhage

- #23 postpartum h?emorrhage
- #24 third stage labo?r
- #25(#23 or#24)

C. (#22 and #25)

Appendix C.2. Translation form

To be completed by the translator.

Please note: full translations of papers are not necessary. The following questions are designed to assist in the extraction of necessary information for the inclusion of randomised controlled trials in a systematic review.

Date of translation:

Translator:

Language of the paper:

A. Publication details:

1. Authors:

2. English title

3. Original title:

4. Journal Name:

5. Year:

Volume:

Issue:

Pages:

B. Introduction/abstract

1. What is the objective of the study?

C. Materials and methods

2. Is this study described as being a randomised control trial?

If Yes, please continue with Sections C-D below.

If No – we do not need any further information, but please give a description of the study (e.g. a review article, a case-controlled study, a cohort study, a letter to a journal, a controlled before and after study, etc).

3. What is the total number of patients participating in the trial?

4. Were the participant described as low or high risk to postpartum haemorrhage?

5. Stage of pregnancy (in weeks)

6. Mode of delivery (vaginal or caesarean)

7. In which country the study was conducted?

8. Where were the patients recruited from (e.g. community centre, hospital, outpatients clinic, emergency department, city, rural setting)?

9. What were the inclusion criteria?

10. What were the exclusion criteria?

11. Is there any information on the measurement of blood loss? if yes, (What method used to measure it, when they start measuring it and for how long)

12. What was the definition of postpartum haemorrhage in the paper?
13. Is there any outcome that clearly stated as primary? If NO go to Q 16
14. Did the authors clearly differentiate between primary and secondary outcomes?
 - If Yes (please answer Q 15)
 - If No (go to Q16)
15. What were the primary outcome measures?
16. What were the secondary (other) outcome measures?
17. Is there any outcomes that mentioned as main or key outcomes?(If yes please list them)
18. If the haemoglobin or the haematocrit level were mentioned in the outcome measures, when was (in hours) the second postpartum sample of blood taken?
19. Is there any information on sample size calculation? If yes, what outcome is used for sample size calculation?

D. Results

20. Were the results reported in tables/graphs? If so, please indicate if the term primary or secondary outcomes used for the table title or subtitle and list the outcomes that considered as primary and the one that considered as secondary within the result table?

E. Is there any additional information which you consider significant?

Appendix C.3. RCT data extraction form

Serial No	Extractor	Nasreen	Year of publication	
Reference				
Number of participants included				
Type of intervention				
Setting				
Location				
Type of participants				
Study objective				
Primary outcomes	Not pre-specified Explicitly pre-specified Not explicitly pre-specified Primary outcome (define)			
SSC	Not pre-specified pre-specified based on primary outcomes pre-specified not based on primary outcomes			
Outcome used for SSC if different				
Secondary outcomes				
Does the outcomes stated clearly in the abstract and/or the main text				
How was the blood loss measured				
Subgroups	Mode of delivery: Duration of pregnancy: Risk of women for PPH :			

ID= identification number; SSC= sample size calculation; PPH= postpartum haemorrhage.

Appendix C.4. Systematic review data extraction form

Serial No	Extractor	Nasreen
Reference		
What is the type of review?	<input type="checkbox"/> Cochrane review <input type="checkbox"/> Non-Cochrane review	
What was the type of intervention assessed?		
Dose the study differentiate between primary and secondary outcomes? <input type="checkbox"/> Yes <input type="checkbox"/> No (exclude)		
Primary outcomes		

Appendix C.5. RCTs primary outcomes

	Number of trials (n=121)					
	SSC/ clearly stated	SSC/ not clearly stated	clearly stated/no SSC	Mentioned as main	Mentioned as objective	Total (%) (n=121)
A. Maternal outcomes						
1. Blood loss						
1. 1. Incidence of Postpartum haemorrhage						
1.1.1 Incidence of PPH > 500 mls						
Incidence of PPH > 500 mls (time of blood collection not defined)	5	3		2		10 (8%)
Incidence of PPH > 500 mls, 48hrs after delivery	1		1			2 (2%)
Incidence of PPH > 500 mls within 24 hrs. after delivery	1					1 (0.8%)
1.1.2. Incidence of PPH ≥ 500 mls						
Incidence of PPH ≥ 500 mls (time of blood collection not defined)	7					7 (6%)
Incidence of PPH ≥ 500 mls up to 1 hr. after delivery	6	1				7 (6%)
Incidence of PPH ≥ 500 mls within 2 hrs. after delivery	1	2	1			4 (3%)
Incidence of PPH ≥ 500 mls within 24 hrs. after delivery	4					4 (3%)
Incidence of PPH ≥ 500 mls up to 1 hr. after delivery of placenta	2					2 (2%)
Incidence of PPH ≥ 500 mls (until active bleeding stop for minimum of 1 hr. after delivery)	1					1 (0.8%)
1.1.3. Incidence of PPH >1000 mls						
Incidence of PPH > 1000 mls (time of blood collection not defined)	2			1		3 (2%)
Incidence of PPH > 1000 mls (up to 2hrs after delivery of baby)	1					1(0.8%)
Incidence of PPH > 1000 mls within 24 hrs. of delivery			1			1(0.8%)
A.1.1.4. Incidence of PPH ≥ 1000 mls						
Incidence of PPH ≥ 1000 mls within 1 hr. after delivery	3		1			4 (3%)
Incidence of PPH ≥ 1000 mls (time of blood collection not defined)	1		2			3 (2%)
Incidence of PPH ≥ 1000 mls within 2 hrs. after delivery	1					1(0.8%)

1.1.5. Other incidence of PPH						
Incidence of PPH (amount and time of blood collection not defined)	1		2			3 (2%)
Incidence of PPH > 800 mls (time of blood collection not defined)	1					1(0.8%)
Incidence of primary PPH (amount not defined) within 1 hr. of delivery			1			1(0.8%)
Incidence of PPH (> 500 mls OR 10% drop in haematocrit value [24 hrs. after delivery])	1					1(0.8%)
Delayed haemorrhage within the first 24hrs			1			1(0.8%)
1. 2. Amount of blood loss						
1.2.1. Measured blood loss						
Mean measured blood loss up to 1 hrs. post delivery	3		2		1	6 (5%)
Mean measured postpartum blood loss within 24hrs of delivery	1		1	1	1	4 (3%)
Mean measured postpartum blood loss (time of blood collection not defined)			2	2		4 (3%)
Mean measured blood loss (within 2hrs after delivery of baby)	3				1	3 (2%)
Mean measured blood loss, total before and after placental delivery (time of blood collection not defined)				1		1(0.8%)
Amount of measured blood loss (1-2 hrs. after delivery) (median)	1					1(0.8%)
Median measured postpartum blood loss over 72hrs		1				1 (0.8%)
Mean measured blood loss (2 hours after delivery of placenta)					1	1 (0.8%)
Measured blood loss of 300 mls or more within 30 minutes after delivery	1					1(0.8%)
1.2.2. Estimated blood loss						
Estimated blood loss during caesarean section	3		1			4 (3%)
Mean estimated blood loss (time of blood collection not defined)	2				1	3 (2%)
Mean estimated blood loss 2hrs. after delivery	1					1 (0.8%)
Mean estimated blood loss for 8 hrs. post delivery	1					1 (0.8%)
Mean estimated blood loss within 48hrs post-delivery	1					1 (0.8%)
Median estimated blood loss (4 hours post-operative)	1					1 (0.8%)
2. Maternal blood indices						
Difference in pre and post-delivery HB (24 hrs.)	1		4	2		7 (6%)

Difference in pre and post-delivery HB (12 hrs.)	3					3 (2%)
Difference in pre and post-delivery HB (72 hrs.)		1		1		2 (2%)
Decrease in HB and haematocrit from baseline to 24hrs after delivery	1		1			2 (2%)
Drop in HB > 2 g/dl from before to 3 -5 days post- delivery			1			1 (0.8%)
Postpartum anaemia (HB < 8 g/dl) 3-5 days post-delivery			1			1 (0.8%)
Postpartum HB < 10 g/dl				1		1 (0.8%)
Changes in HB and haematocrit during postpartum period (at 24 and 36 hrs.)				1		1 (0.8%)
Difference in pre and post-delivery haematocrit (time of blood collection not defined)			1			1 (0.8%)
Difference in pre and post-delivery HB time of blood collection not defined)		1				1 (0.8%)
Difference in pre and post-delivery haematocrit (24 hrs.)				1		1(0.8%)
Difference in pre and post-delivery haematocrit (48hrs.)	1					1 (0.8%)
Haematocrit drop 10% or greater 24 hrs postpartum			1			1 (0.8%)
Postpartum HB \geq 2 g/dl lower than pre-delivery HB			1			1 (0.8%)
3. Maternal assessment/ intervention side effect						
Maternal side effect of intervention				8	1	9 (7%)
Change in blood pressure				2		2 (2%)
Atony or haemorrhage requiring treatment (medical or surgical) (composite outcome)	1					1 (0.8%)
4. Other interventions used						
Use of additional uterotonics	4	1	12	6		23
Manual removal of placenta		1	2	1		4(3%)
Need for blood transfusion			3	1		4 (3%)
Proportion of patient requiring additional uterotonic for uterine atony (48hrs.)	1		1			2(2%)
Additional uterotonic to control PPH			1			1 (0.8%)
Need for additional uterotonic in the first 24 hrs.	1					1(0.8%)

Number of women need uterine massage			1			1 (0.8%)
5. Duration of the third stage						
Mean duration of the third stage of labour	1		2	4	2	9 (7%)
Duration of the third stage (median)				1		1 (0.8%)
Duration of the third stage (number, percentage)			1			1 (0.8%)
Third stage equal to or > 30 minutes			1			1 (0.8%)
6. Maternal mortality and morbidity						
Maternal mortality			1			1 (0.8%)
Endometritis				1		1 (0.8%)
7. Others						
Length of hospital stays for the mother.				2		2 (2%)
Consumption of paracetamol				1		1 (0.8%)
B. Neonatal outcomes						
Newborne venous haematocrit 6 hrs. after birth	1					1 (0.8%)

Appendix C.6. RCTs secondary outcomes

Secondary outcome	Number of trails (%) (n=121)
A. Maternal outcomes	
A.1. Blood loss	
A.1.1. Incidence of postpartum haemorrhage	
A.1.1.1 Incidence of PPH > 500 mls	
PPH > 500 mls (time of blood collection not defined)	6 (5%)
PPH > 500 mls within 2 hrs. after delivery	2 (2%)
PPH > 500mls (within the first hr. after delivery)	1(0.8%)
A.1.1.2 Incidence of PPH ≥ 500 mls	
Incidence of PPH ≥ 500 mls within 24hrs after delivery	4 (3%)
Incidence of PPH ≥ 500 mls (time of blood collection not defined)	4 (3%)
Incidence of PPH ≥ 500 mls within 2 hrs. after delivery	3 (2%)
Incidence of PPH ≥ 500 mls up to 1 hr. after delivery of baby	2 (2%)
Incidence of PPH ≥ 500 mls in 30 minutes	1(0.8%)
Incidence of PPH ≥ 500 mls up to 1 hr. after delivery of placenta	1(0.8%)
A.1.1.3 Incidence of PPH > 1000 mls	
Sever haemorrhage > 1000 mls (time of blood collection not defined)	5 (4%)
A.1.1.4 Incidence of PPH ≥ 1000 mls	
Incidence of PPH ≥ 1000 mls within 2 hrs. of delivery of baby	8 (7%)
Incidence PPH ≥ 1000 mls (time of blood collection not defined)	4 (3%)
Incidence of PPH ≥ 1000 mls within 1 hr. after delivery	4 (3%)
Incidence of PPH ≥ 1000 mls within 1 hrs. from delivery of placenta	2 (2%)
Incidence of PPH ≥ 1000 mls in 30 minutes	1(0.8%)
A.1.1.5 Other incidence of PPH	
Incidence of primary PPH (amount not defined) within 1 hr. of delivery	4 (3%)
Delayed haemorrhage within the first 24hrs	4 (3%)
Clinical diagnosis of PPH (visually estimated blood loss, amount of blood loss and time of diagnosis not defined)	2 (2%)
Incidence of blood loss ≥ 1500 mls within 1 hr. after delivery	1(0.8%)
Intermediate and severe PPH (≥ 750 and ≥ 1000 mls; until active bleeding stop for minimum of 1 hr. after delivery)	1(0.8%)
Intermediate and severe PPH (≥ 750 and ≥ 1000 mls) 1 hr. after delivery	1(0.8%)
Incidence of blood loss ≥ 1500 mls within 1 hr. after delivery	1(0.8%)
Incidence of PPH defined as blood loss of > 400 mls within 2 hrs. after birth	1(0.8%)

Severe haemorrhage (amount not defined) in 48hrs	1 (0.8%)
A.1.2. Amount of blood loss	
A.1.2.1. Measured blood loss	
Mean measured blood loss (within 2hrs of delivery)	11 (9%)
Mean measured blood loss (time of blood collection not defined)	7 (6%)
Mean measured blood loss up to 1 hrs. after delivery of baby	6 (5%)
Mean measured blood loss up to 1 hrs. after delivery of placenta	4 (3%)
Mean measured postpartum blood loss over 72hrs	2 (2%)
Mean and median measured blood loss within 1 hr. postpartum	1 (0.8%)
Mean measured blood loss (until active bleeding stop for minimum of 1 hr. after delivery)	1 (0.8%)
Mean measured blood loss within 24hrs of delivery	1 (0.8%)
Measured blood loss of from \geq 500-999 mls	1 (0.8%)
A.1.2.2. Estimated blood loss	
Mean estimated blood loss (time of blood estimation not defined)	12 (10%)
Mean estimated blood loss within 24hrs post-delivery	2 (2%)
Amount of blood loss from placental delivery to end of CS	1 (0.8%)
Estimated blood loss (%) (time not defined)	1 (0.8%)
Estimated blood loss during caesarean section	1 (0.8%)
Median estimated blood loss (time not defined)	1 (0.8%)
Median estimated blood loss (4 hours post-operative)	1 (0.8%)
Amount of blood loss from end of CS to 2hrs. after delivery	3 (2%)
A. 2. Maternal blood indices	
Difference in pre and post-delivery HB (24 hrs.)	14 (12%)
Difference in pre and post-delivery HB (48 hrs.)	11 (9%)
Haemoglobin concentration 24hrs postpartum	7 (6%)
Difference in pre and post-delivery haematocrit (48 hrs.)	5 (4%)
Difference in pre and post-delivery haematocrit (24 hrs.)	4 (3%)
Change in HB concentration in pre and 12 hrs. post-delivery	3 (2%)
Incidence of a 10% decrease in HB between pre and 24 hrs. post-delivery	2 (2%)
Difference in pre and post-delivery haematocrit (12 hrs.)	1 (0.8%)
Difference in pre and post-delivery HB (20 hrs.)	1 (0.8%)
Haemoglobin < 9g/dl and < 11g/dl (3-5 days post-delivery)	1 (0.8%)
Haemoglobin < 8 g/dl and < 10g/dl (12-24 post-delivery)	1(0.8%)
Decline of 6% unit or more in haematocrit (8-24 hrs.) post-delivery	1 (0.8%)

HB concentration < 6 g/dl 24 hrs. after delivery	1 (0.8%)
HB concentration 24-48hrs postpartum	1 (0.8%)
Haematocrit drop 10% or greater 24hrs postpartum	1 (0.8%)
Mean drop in HB (3-5 days post-delivery)	1 (0.8%)
Percentage of women with >10% decline in postpartum HB (12-48 hrs.)	1 (0.8%)
Reduction in HB > 20% (severe anaemia) 48hrs after delivery	1 (0.8%)
A haemoglobin drop of 30 mg/L or greater(24-36hrs)	1 (0.8%)
Postpartum HB \geq 2g/dl lower than pre-delivery HB	1 (0.8%)
Drop in haemoglobin concentration (time not defined)	1 (0.8%)
Difference in postoperative blood chemistry (creatinine, alkaline .phos. Na)	1 (0.8%)
A. 3. Assessment of mother/Intervention side effect	
Maternal side effect of intervention	77 (64%)
Change in blood pressure	8 (7%)
Uterine tone	6 (5%)
Change in clinical parameter (pulse, T, BP)	5 (4%)
Uterine fundal position over time	2 (2%)
Frequency of postpartum pain	2 (2%)
Severity of maternal side effect of intervention	1 (0.8%)
Vital signs during and after the operation	1 (0.8%)
Acceptability of misoprostol sublingually my the women	1 (0.8%)
Postpartum uterine involution over 24hrs	1 (0.8%)
General health at 6 weeks	1 (0.8%)
A. 4. Duration of the third stage	
Mean duration of the third stage of labour	30 (25%)
Duration/length of the third stage (median)	5 (4%)
Duration/length of the third stage (number, percentage)	5 (4%)
Third stage > 30 minutes	3 (2%)
Third stage equal to or > 30 minutes	1 (0.8%)
A. 5. Intervention used	
Use of additional uterotonic	52 (43%)
Need for blood transfusion	48 (40%)
Manual removal of placenta	22 (18%)
Subsequent evacuation of uterus	7 (6%)
Surgical intervention to control PPH	5 (4%)
Maternal admission ICU	2 (2%)

Need to transfer to high facility	2 (2%)
Need for uterine massage	2 (2%)
Additional uterotonic to treat uterine atony	1 (0.8%)
Additional uterotonic to control PPH	1 (0.8%)
Other procedure to treat PPH	1 (0.8%)
Other procedure to treat uterine atony	1 (0.8%)
Bimanual compression	1 (0.8%)
Exploration under general anaesthesia	1 (0.8%)
Infused fluid volume	1 (0.8%)
A. 6. Placenta-related outcomes	
Frequency / incidence of retained placenta	10 (8 %)
Time from bolus/ injection to delivery of placenta	2 (2%)
Mode and timing of delivery of placenta	1 (0.8%)
Percentage of placenta remained undelivered beyond 15 minutes	1 (0.8%)
Placenta delivered spontaneously	1 (0.8%)
A. 7. Maternal mortality and morbidity	
Maternal mortality	8 (7%)
Hysterectomy	3 (2%)
Maternal morbidity (e.g. admission to ICU, prolonged hospitalisation)	1 (0.8%)
Maternal morbidity (composite outcome, hysterectomy, blood loss \geq 2000 mls, uterine inversion)	1 (0.8%)
Morbidity requiring admission	1 (0.8%)
Endometritis	1 (0.8%)
Laporatomy	1 (0.8%)
Frequency of haemorrhagic shock	1 (0.8%)
Number of patient with major complication (not defined)	1 (0.8%)
Third and fourth degree tear	1 (0.8%)
A. 8. Others	
Length of hospital stays for the mother.	10 (8 %)
Cost of oxytocic	2 (2%)
Women and staff satisfaction with the third stage management	1 (0.8%)
Duration of surgery (minutes)	1 (0.8%)
Delay before need for additional uterotonic	1 (0.8%)
Safety outcomes (e.g. fluid overload requiring diuretics)	1 (0.8%)

B. Neonatal outcomes	
Neonatal outcomes(Apgar score, arterial blood pressure, heart rate, oxygen saturation)	2 (2%)
Initiating breastfeeding	2 (2%)
Birth weight	2 (2%)
Apgar score	1 (0.8%)
Admission to special baby unit	1 (0.8%)
Infant health (admission to intensive care unit, Phototherapy for jaundice, no problem reported)	1 (0.8%)
Neonatal haematocrit at 24-48 hr. of age	1 (0.8%)
Early neonatal morbidity and mortality (e.g. jaundice, sepsis, necrotizing colitis and death)	1 (0.8%)
Admission to neonatal ICU	1 (0.8%)
Newborn length of hospital stay	1 (0.8%)
Any neonatal disease that occurred between birth and one month of age	1 (0.8%)
Type of feeding at 1 month of age	1 (0.8%)
Neonatal side effect of intervention	1 (0.8%)
Need for supplement lactation	1 (0.8%)

Appendix.C.7. Reference of RCTs included in Chapter 4

Abdel-Aleem 2010

Abdel-Aleem, H., Singata, M., Abdel-Aleem, M., Mshweshwe, N., Williams, X. & Hofmeyr, G. J. (2010). Uterine massage to reduce postpartum hemorrhage after vaginal delivery. *Int J Gynaecol Obstet*, 111, 32-36.

Acharya 2001

Acharya, G., Al-Sammarai, M. T., Patel, N., Al-Habib, A. & Kiserud, T. (2001). A randomized, controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during cesarean section. *Acta Obstet Gynecol Scand*, 80, 245-50.

Afolabi 2010

Afolabi, E. O., Kuti, O., Orji, E. O. & Ogunniyi, S. O. (2010). Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour. *Singapore Med J*, 51, 207-11.

Amant 1999

Amant, F., Spitz, B., Timmerman, D., Corremans, A. & Van Assche, F. A. (1999). Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. *Brit J Obstet Gynaecol*, 106, 1066-70.

Andersen 1998

Andersen, B., Andersen, L. L. T. & Sørensen, T. (1998). Methylergometrine during the early puerperium; a prospective randomized double blind study. *Acta Obstet Gynecol Scand*, 77, 54-57.

Askar 2011

Askar, A. A., Ismail, M. T., Abo, A. & Rabie, N. H. (2011). Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. *Arch Gynecol Obstet* 84, 1359-1365.

Attilakos 2010

Attilakos, G., Psaroudakis, D., Ash, J., Buchanan, R., Winter, C., Donald, F., et al. (2010). Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG*, 117, 929-36.

Badejoko 2012

Badejoko, O. O., Ijarotimi, A. O., Awowole, I. O., Loto, O. M., Badejoko, B. O., Olaiya, D. S., et al. (2012). Adjunctive rectal misoprostol versus oxytocin infusion for prevention of postpartum hemorrhage in women at risk: a randomized controlled trial. *J Obstet Gynaecol Res*, 38, 1294-1301.

Balki 2008

Balki, M., Dhumne, S., Kasodekar, S., Kingdom, J., Windrim, R. & Carvalho, J. C. A. (2008). Oxytocin-ergometrine co-administration does not reduce blood loss at caesarean delivery for labour arrest. *BJOG*, 115, 579-584.

Bamigboye 1998

Bamigboye, A. A., Hofmeyr, G. J. & Merrell, D. A. (1998a). Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. *M J Obstet Gynecol*, 179, 1043-6.

Bamigboye 1998

Bamigboye, A. A., Merrell, D. A., Hofmeyr, G. J. & Mitchell, R. (1998b). Randomized comparison of rectal misoprostol with syntometrine for management of third stage of labor. *Acta Obstet Gynecol Scand*, 77, 178-81.

Baskett 2007

Baskett, T. F., Persad, V. L., Clough, H. J. & Young, D. C. (2007). Misoprostol versus oxytocin for the reduction of postpartum blood loss. *Int J Gynaecol Obstet*, 97, 2-5.

Bellad 2012

Bellad, M. B., Tara, D., Ganachari, M. S., Mallapur, M. D., Goudar, S. S., Kodkany, B. S., et al. (2012). Prevention of postpartum haemorrhage with sublingual misoprostol or oxytocin: a double-blind randomised controlled trial. *BJOG*, 119, 975-82.

Bhullar 2004

Bhullar, A., Carlan, S. J., Hamm, J., Lamberty, N., White, L. & Richichi, K. (2004). Buccal misoprostol to decrease blood loss after vaginal delivery: a randomized trial. *Obstet Gynecol*, 104, 1282-8.

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Biswas, A., Bal, R., Kundu, M. K., Kyal, A. & Halder, M. (2007). A study of prophylactic use of 15-methyl prostaglandin F₂alpha in the active management of third stage of labour. *J Indian Med Assoc*, 105, 506, 508-9.

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Borruto, F., Treisser, A. & Comparetto, C. (2009). Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. *Arch Gynecol Obstet*, 280, 707-12.

Boucher 1998

Boucher, M., Horbay, G. L., Griffin, P., Deschamps, Y., Desjardins, C., Schulz, M., et al. (1998). Double-blind randomised comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing caesarean section. *J Perinatol*, 18, 202-7.

Boucher 2004

Boucher, M., Nimrod, C. A., Tawagi, G. F., Meeker, T. A., Rennicks, R. E. & Varin, J. (2004). Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynaecol Can*, 26, 481-488.

Bugalho 2001

Bugalho, A., Daniel, A., Faundes, A. & Cunha, M. (2001). Misoprostol for prevention of postpartum hemorrhage. *Int J Gynaecol Obstet*, 73, 1-6.

Caliskan 2003

Caliskan, E., Dilbaz, B., Meydanli, M. M., Ozturk, N., Narin, M. A. & Haberal, A. (2003). Oral misoprostol for the third stage of labor: a randomized controlled trial. *Obstet Gynecol*, 101, 921-8.

Caliskan 2002

Caliskan, E., Meydanli, M. M., Dilbaz, B., Aykan, B., Sonmezer, M. & Haberal, A. (2002). Is rectal misoprostol really effective in the treatment of third stage of labor? a randomized controlled trial. *Am J Obstet Gynecol*, 187, 1038-1045.

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Carbonell, I. J. L. E., Hernandez, J. M. R., Piloto, M., Setien, S. A., Texido, C. S., Tomasi, G. et al. (2009). Active management of the third phase of labour plus 400 mug of sublingual misoprostol and 200 mug of rectal misoprostol versus active management only in the prevention of post-partum haemorrhage: arandomised clinical trial. *Progresos de Obstetricia y Ginecologia*, 52, 543-551.

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Ceriani Cernadas, J. M., Carroli, G., Pellegrini, L., Otano, L., Ferreira, M., Ricci, C., et al. (2006). The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. *Pediatrics*, 117, e779-86.

Chandhiok 2006

Chandhiok, N., Dhillon, B. S., Datey, S., Mathur, A. & Saxena, N. C. (2006). Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India. *Int J Gynaecol Obstet*, 92, 170-5.

Chantrapitak 2011

Chantrapitak, W., Srijuntuek, K. & Wattanaluangarun, R. (2011). The efficacy of lower uterine segment compression for prevention of early postpartum hemorrhage after vaginal delivery. *J Med Assoc Thai*, 94, 649-56.

Chaudhuri 2010

Chaudhuri, P., Banerjee, G. B. & Mandal, A. (2010). Rectally administered misoprostol versus intravenous oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss. *Int J Gynaecol Obstet*, 109, 25-9.

Chaudhuri 2012

Chaudhuri, P., Biswas, J. & Mandal, A. (2012). Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women. *Int J Gynaecol Obstet*, 116, 138-42.

Choy 2002

Choy, C. M. Y., Lau, W. C., Tam, W. H. & Yuen, P. M. (2002). A randomised controlled trial of intramuscular syntometrine and intravenous oxytocin in the management of the third stage of labour. *BJOG*, 109, 173-177.

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Cook, C. M., Spurrett, B. & Murray, H. (1999). A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. *Aust Nz J Obstet Gyn*, 39, 414-9.

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Dabbaghi Gale, T., Elmizadeh, K. H., Moradi, S. D. & Rashvand Melli, E. (2012). Comparison of intravenous oxytocin and oral misoprostol in reduction of postpartum hemorrhage. *ZUMS Journal*, 20, 1-8.

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Dansereau, J., Joshi, A. K., Helewa, M. E., Doran, T. A., Lange, I. R., Luther, E. R., et al. (1999). Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol*, 180, 670-6.

De Bonis 2012

De Bonis, M., Torricelli, M., Leoni, L., Berti, P., Ciani, V., Puzzutiello, R., Severi, F. M. & Petraglia, F. (2012). Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage. *J Matern Fetal Neonatal Med*, 25, 732-5.

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Derman, R. J., Kodkany, B. S., Goudar, S. S., Geller, S. E., Naik, V. A., Bellad, M., et al. (2006). Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet*, 368, 1248-1253.

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Eftekhari, N., Doroodian, M. & Lashkarizadeh, R. (2009). The effect of sublingual misoprostol versus intravenous oxytocin in reducing bleeding after caesarean section. *J Obstet Gynaecol*, 29, 633-6.

El-Refaey 2000

El-Refaey, H., Nooh, R., O'brien, P., Abdalla, M., Geary, M., Walder, et al. (2000). The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. *BJOG*, 107, 1104-10.

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El Tahan, M. R., Warda, O. M., Rashad, A., Yasseen, A. M., Ramzy, E. A., Ahmady, M. S., et al. (2012). Effects of preoperative sublingual misoprostol on uterine tone during isoflurane anesthesia for cesarean section. *Revista brasileira de anesthesiologia*, 62, 625-635.

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Elsedeek, M. S. E. A. (2012). Impact of preoperative rectal misoprostol on blood loss during and after elective cesarean delivery. *Int J Gynaecol Obstet*, 118, 149-152.

Enakpene 2007

Enakpene, C. A., Morhason-Bello, I. O., Enakpene, E. O., Arowojolu, A. O. & Omigbodun, A. O. (2007). Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor. *J Obstet Gynaecol Res*, 33, 810-7.

Fararjeh 2003

Fararjeh, C., Gezer, A., Çepni, I., Benian, A., Öcal, P. & Kösebay, D. (2003). The efficacy of rectal misoprostol in preventing postpartum Bleeding *Jinekoloji ve Obstetrik Dergisi*, 17, 218-223.

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Fawole, A. O., Sotiloye, O. S., Hunyinbo, K. I., Umezulike, A. C., Okunlola, M. A., Adekanle, D. A., et al. (2011). A double-blind, randomized, placebo-controlled trial of misoprostol and routine uterotonic for the prevention of postpartum hemorrhage. *Int J Gynaecol Obstet*, 112, 107-11.

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Fekih, M., Jnifene, A., Fathallah, K., Ben, L., Memmi, A., Bouguizene, S., et al. (2009). Benefit of misoprostol for prevention of postpartum hemorrhage in cesarean section: a randomized controlled trial. *J Gynecol Obst Bio R*, 38, 588-593.

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Fujimoto, M., Takeuchi, K., Sugimoto, M. & Maruo, T. (2006). Prevention of postpartum hemorrhage by uterotonic agents: comparison of oxytocin and methylergometrine in the management of the third stage of labor. *Acta Obstet Gynecol Scand*, 85, 1310-4.

Gai 2004

Gai, M. Y., Wu, L. F., Su, Q. F. & Tatsumoto, K. (2004). Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. *Eur J Obstet Gynecol Reprod Biol*, 112, 154-157.

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Gerstenfeld, T. & Wing, D. (2001). Rectal misoprostol versus oxytocin for prevention of postpartum hemorrhage following vaginal delivery. *Am J Obstet Gynecol*, 184, S120-S120.

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Giocalone, P. L., Vignal, J., Daures, J. P., Boulot, P., Hedon, B. & Laffargue, F. (2000). A randomised evaluation of two techniques of management of the third stage of labour in women at low risk of postpartum haemorrhage. *BJOG*, 107, 396-400.

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Guelmezoglu, A. M., Lumbiganon, P., Landoulsi, S., Widmer, M., Abdel-Aleem, H., Festin, M., et al. (2012). Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. *Lancet*, 379, 1721-1727.

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Gul, A., Zeteroglu, S., Karayel, M., Sahin, G., Kocar, M. & Surucu, R. (2000). The comparison of misoprostol and oxytocin efficacy in the prevention of postpartum hemorrhage related to uterine atony. *Jinekoloji ve Obstetrik Dergisi*, 14, 20-23.

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Gülmezoglu, A. M., Villar, J., Ngoc, N. N., Piaggio, G., Carroli, G., Adetoro, L., et al. (2001). WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet*, 358, 689-695.

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Gungorduk, K., Asicioglu, O., Celikkol, O., Olgac, Y. & Ark, C. (2010). Use of additional oxytocin to reduce blood loss at elective caesarean section: a randomised control trial. *Aust N Z J Obstet Gynaecol*, 50, 36-9.

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Gungorduk, K., Asicioğlu, O., Yildirim, G., Ark, C., Tekirdağ, A. & Besimoglu, B. (2012). Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? a randomized controlled study. *Am J Perinatol*, 30, 407-13.

Güngördük 2011

Güngördük, K., Asicioğlu, O., Yildirim, G., Gungorduk, O. C., Besimoglu, B. & Ark, C. (2011). Is post-partum oxygen inhalation useful for reducing vaginal blood loss during the third and fourth stages of labour? a randomised controlled study. *Aust N Z J Obstet Gynaecol*, 51, 441-445.

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Gungorduk, K., Yildirim, G., Asicioglu, O., Gungorduk, O. C., Sudolmus, S. & Ark, C. (2011). Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. *Am J Perinatol*, 28, 233-239.

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Gungorduuk, K., Asicioglu, O., Besimoglu, B., Guungorduuk, O. C., Yildirm, G., Ark, C. et al. (2010). Using intraumbilical vein injection of oxytocin in routine practice with active management of the third stage of labor: a randomized controlled trial. *Obstet Gynecol*, 116, 619-624.

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Hamm, J., Russell, Z., Botha, T., Carlan, S. J. & Richichi, K. (2005). Buccal misoprostol to prevent hemorrhage at cesarean delivery: a randomized study. *Am J Obstet Gynecol*, 192, 1404-6.

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Harriott, J., Christie, L., Wynter, S., Dacosta, V., Fletcher, H. & Reid, M. (2009). A randomized comparison of rectal misoprostol with syntometrine on blood loss in the third stage of labour. *W Indian Med J*, 58, 201-6.

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Hofmeyr, G. J., Fawole, B., Mugerwa, K., Godi, N. P., Blignaut, Q., Mangesi, L., et al. (2011). Administration of 400 mug of misoprostol to augment routine active management of the third stage of labor. *Int J Gynaecol Obstet*, 112, 98-102.

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Hoj, L., Cardoso, P., Nielsen, B. B., Hvidman, L., Nielsen, J. & Aaby, P. (2005). Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. *BMJ*, 331, 723.

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Jackson, K. W., Jr., Allbert, J. R., Schemmer, G. K., Elliot, M., Humphrey, A. & Taylor, J. (2001). A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. *Am J Obstet Gynecol*, 185, 873-7.

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Jangsten, E., Mattsson, L. A., Lyckestam, I., Hellstrom, A. L. & Berg, M. (2011). A comparison of active management and expectant management of the third stage of labour: a Swedish randomised controlled trial. *BJOG*, 118, 362-369.

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Jiang, Q., Wang, P. & Cao, W. (2001). Effect on different doses of misoprostol to prevent postpartum hemorrhage. *Chi Nurs Res*, 15, 313-314.

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Jin, L. J. & Zhou, L. (2000). Application of anus misoprostol to decrease the volume of postpartum hemorrhage. *J Pract Nurs*, 16, 9-10.

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Karkanis, S. G., Caloia, D., Salenieks, M. E., Kingdom, J., Walker, M., Meffe, F. et al. (2002). Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. *J Obstet Gynaecol Can*, 24, 149-54.

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Kashanian, M., Fekrat, M., Masoomi, Z. & Ansari, N. S. (2010). Comparison of active and expectant management on the duration of the third stage of labour and the amount of blood loss during the third and fourth stages of labour: a randomised controlled trial. *Midwifery*, 26, 241-245.

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Khan, G. Q., John, I. S., Wani, S., Doherty, T. & Sibai, B. M. (1997). Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. *Am J Obstet Gynecol*, 177, 770-4.

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Khurshid, R., Fatima, K., Parveen, S., Ul, I. & Salman, R. (2010). A comparison between intramuscular PGF2 a125 mG and intravenous methyl ergometrine 0.2 Mg in the active management of third stage labor. *Int J Gynaecol Obstet*, 14.

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Appendix D.1. Survey on bimanual uterine compression

1. What is your job?
2. How effective do you think bimanual compression is at stopping bleeding (score 1-5)?

[1= completely ineffective, 5= very effective]

3. How many times have you used bimanual compression for PPH during the last year?

None

1

2

3

4

5

More

4. Why do you not use the manoeuvre of bimanual compression more frequently? (Tick all that apply)

- Not effective
- It is too invasive to the woman
- It is too tiring to do
- There are more effective methods to stop the bleeding
- Fear of harming the woman
- Other

5. If there was a rapid test that could tell you whether bleeding was coming from lacerations anywhere in the vagina or perineum or not, how helpful would it be in your management?

- a) Very helpful
- b) A little bit helpful
- c) Not helpful at all

6. If there was a rapid test that could tell you whether bleeding was coming from lacerations anywhere in the vagina or perineum or not, do you think that it would lead to reduction in the total blood loss?

- a) Yes
- b) May be
- c) No

Appendix D.3. Feedback sheet for the feasibility study on BMC

1. Noelle®

What do you think of Noelle®?

0= highly disagree 10 = highly agree

- Anatomical accuracy of vagina and cervix (0-10)
- Feel of uterus (0-10)
- Realism when conducting BMC (0-10)

Would you suggest any modification to the uterus?

2. Mama Natalie

What do you think of Mama Natalie?

0= highly disagree 10 = highly agree

- Anatomical accuracy of vagina and cervix (0-10)
- Feel of uterus (0-10)
- Realism when conducting BMC (0-10)

Would you suggest any modification to the uterus?