

Draft Comparative Effectiveness Review

Number XX

Management of Postpartum Hemorrhage

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Prepared by:

[REDACTED]

Investigators:

[REDACTED]

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director, Center for Evidence and
Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows: <redacted for peer review>

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows: <redacted for peer review>

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

<redacted for peer review>

Management of Postpartum Hemorrhage

Structured Abstract

Objectives: To systematically review evidence addressing the management of postpartum hemorrhage (PPH), including evidence for the benefits of harms of nonsurgical and surgical treatments, interventions for anemia after PPH is resolved, and effects of systems-level interventions.

Data Sources: We searched the MEDLINE[®], Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for articles published in English since 1990.

Review Methods: We included comparative studies of nonsurgical and surgical interventions to manage PPH published in English from 1990-2014 and conducted in high resource countries. We also included case series addressing harms of interventions and benefits and harms of procedures and surgeries for PPH as these interventions are unlikely to be addressed in randomized studies. Two investigators independently screened studies against predetermined inclusion criteria (including study design, country of conduct, and outcomes addressed) and independently rated the quality of included studies. We extracted data into evidence and summary tables and summarized them qualitatively.

Results: We identified a total of 52 unique studies. Fifty studies addressed effectiveness outcomes: none of good quality, 20 fair, and 30 poor. Thirty-eight studies reported harms of interventions for PPH management: seven good quality and 31 poor. Few studies addressed pharmacologic or medical management, and evidence is insufficient to comment on effects of such interventions. The success of uterine-sparing techniques, such as uterine tamponade, embolization, uterine compression sutures, and uterine and other pelvic artery ligation, in controlling bleeding without the need for additional procedures or surgeries ranged from 36 to 98 percent; however, these data come from a limited number of studies with a small number of participants. Harms of interventions were diverse and not well-understood. Studies suggested an association between recombinant activated factor VIIa and thromboembolic events, however; sample sizes were small. Some studies with longer term followup reported adverse effects on future fertility and menstrual changes in women undergoing embolization. Studies also reported need for re-operation after hysterectomy. No study (out of two addressing such interventions) demonstrated benefits associated with transfusion or iron supplementation for anemia after PPH is stabilized. Systems-level interventions had little effect on reducing the incidence or severity of PPH or the need for transfusion or hysterectomy.

Conclusions: The literature addressing management of PPH is predominantly studies of poor quality. Diagnosis of PPH is subjective and management is emergent, often involving rapid and simultaneous initiation of interventions; therefore, comparing the severity of PPH and trajectory of care across studies is challenging. Further research is needed across all interventions for PPH management.

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Executive Summary

Introduction

Postpartum hemorrhage (PPH) is commonly defined as blood loss exceeding 500 mL following vaginal birth and 1000 mL following cesarean.¹ Definitions vary, however, and diagnosis of PPH is subjective and often based on inaccurate estimates of blood loss.¹⁻⁴ Moreover, average blood loss at birth frequently exceeds 500 or 1000 mL.⁴ PPH is often classified as primary/immediate/early, occurring within 24 hours of birth, or secondary/delayed/late, occurring more than 24 hours post-birth to up to 12 weeks postpartum. In addition, PPH may be described as third or fourth stage depending on whether it occurs before or after delivery of the placenta, respectively. Multiple studies have noted an increase in PPH in high-resource countries, including the United States, Canada, Australia, Ireland, and Norway, since the 1990s.⁵⁻⁹

PPH is a leading cause of maternal mortality and morbidity worldwide and accounts for nearly one-quarter of all maternal pregnancy-related deaths.¹⁰ Multiple studies have suggested that many deaths associated with PPH could be prevented with prompt recognition and more timely and aggressive treatment.¹¹⁻¹³ Morbidity from PPH can be severe with sequelae including organ failure, shock, edema, compartment syndrome, transfusion complications, thrombosis, acute respiratory distress syndrome, sepsis, anemia, intensive care, and prolonged hospitalization.¹⁴⁻¹⁶

The most common etiology of PPH is uterine atony (impaired uterine contraction after birth), which occurs in about 80 percent of cases. Atony may be related to overdistention of the uterus, infection, placental abnormalities, or bladder distention.¹⁷ Though the majority of women who develop PPH have no identifiable risk factors, clinical factors associated with uterine atony, such as multiple gestation, polyhydramnios, high parity, and prolonged labor, may lead to a higher index of suspicion.^{14, 15, 17, 18} Other causes of PPH include retained placenta or clots, lacerations, uterine rupture or inversion, and inherited or acquired coagulation abnormalities.^{17, 18}

Interventions to Manage PPH

Organizations and associations including the World Health Organization (WHO), International Confederation of Midwives (ICM), International Federation of Gynecologists and Obstetricians (FIGO), American College of Obstetricians and Gynecologists, and Royal College of Obstetricians and Gynaecologists (RCOG) have released guidelines for PPH prevention and management.^{10, 15, 17-20} Initial management includes identifying PPH, determining the cause, and implementing appropriate interventions based on the etiology.

Interventions to treat PPH generally proceed from less to more invasive and include compression techniques, medications, procedures, and surgeries. PPH management may also involve adjunctive therapies, such as blood and fluid replacement and/or an anti-shock garment,^{21, 22} to treat the blood loss and other sequelae that result from PPH.

Conservative management techniques such as uterotonic medications, external uterine massage, and bimanual compression are generally used as “first-line” treatments. Procedures used in PPH management include manual removal of the placenta, manual removal of clots, uterine tamponade, and uterine artery embolization.^{10, 15, 17, 18} Laceration repair is indicated when PPH is a result of genital tract trauma.

Surgical options when other measures fail to control bleeding include curettage, uterine and other pelvic artery ligation, uterine compression sutures, and hysterectomy.^{10, 15, 17, 18} More invasive procedures (e.g., uterine tamponade and uterine artery embolization) and surgical techniques are generally used after “first-line” conservative management has failed to control bleeding and can be considered “second-line” interventions.²³ Table 1 in the full report includes brief descriptions of interventions used in PPH management.

After PPH has been controlled, followup management varies and may include laboratory testing (e.g., hemoglobin and hematocrit), iron replacement therapy, and other interventions to assess and treat sequelae of PPH.

At a systems level, PPH has been the focus of perinatal care safety initiatives that attempt to improve patient outcomes by incorporating a variety of strategies, such as practice guidelines or protocols, simulation drills, and teamwork training.²⁴⁻²⁸ These systems-level interventions may influence management of PPH.

Scope and Key Questions

This systematic review provides a comprehensive review of potential benefits of PPH management (medical and surgical) as well as harms associated with treatments in women with PPH. We assess intermediate outcomes such as blood loss, hospital and intensive care unit (ICU) stay, and anemia, and longer term outcomes including uterine preservation, fertility, breastfeeding, psychological impact and harms of treatment, and mortality related to treatment.

Key Questions

We have synthesized evidence in the published literature to address the following Key Questions (KQs):

KQ1. What is the evidence for the effectiveness of interventions for management of postpartum hemorrhage?

- a. What is the effectiveness of interventions intended to treat postpartum hemorrhage likely due to atony?
- b. What is the effectiveness of interventions intended to treat postpartum hemorrhage likely due to retained placenta?
- c. What is the effectiveness of interventions intended to treat postpartum hemorrhage likely due to genital tract trauma?
- d. What is the effectiveness of interventions intended to treat postpartum hemorrhage likely due to uncommon causes (e.g., coagulopathies, uterine inversion, subinvolution)?

KQ2. What is the evidence for choosing one intervention over another and when to proceed to subsequent interventions for management of postpartum hemorrhage?

KQ3. What are the harms, including adverse events, associated with interventions for management of postpartum hemorrhage?

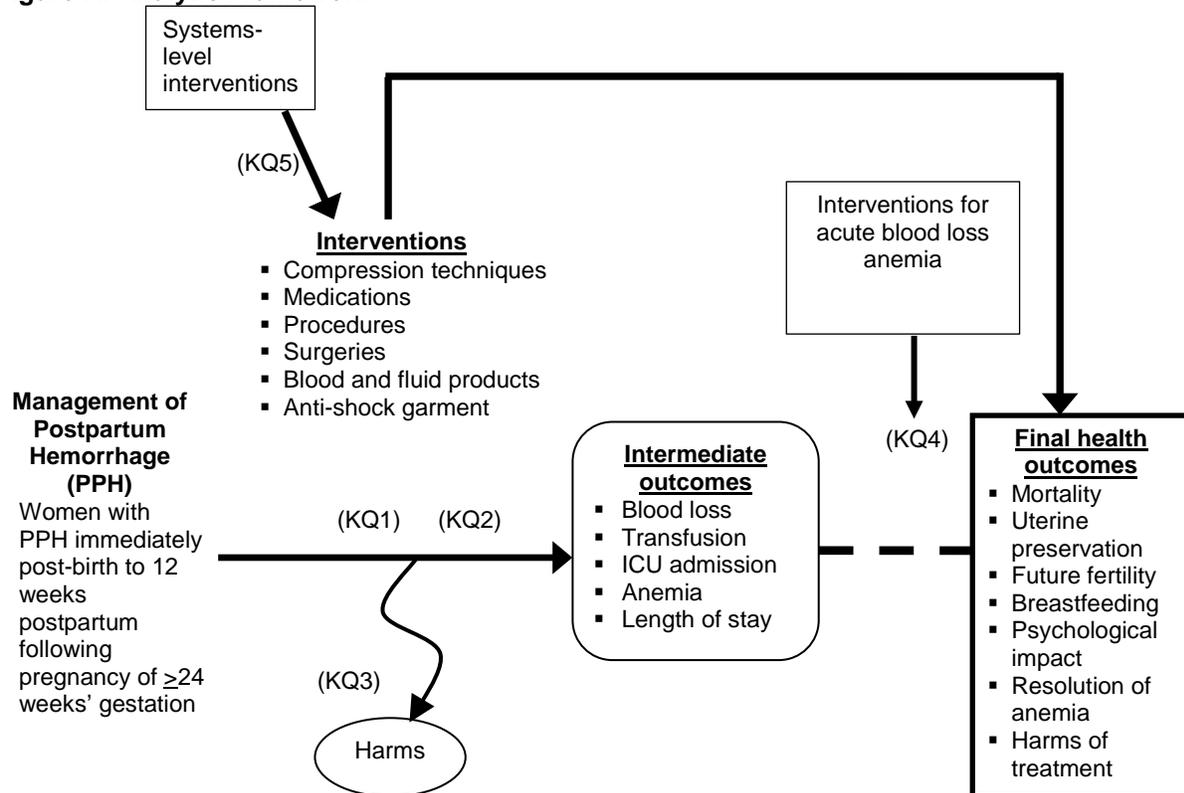
KQ4. What is the comparative effectiveness of interventions to treat acute blood loss anemia after stabilization of postpartum hemorrhage?

KQ5. What systems-level interventions are effective in improving management of postpartum hemorrhage?

Analytic Framework

The analytic framework illustrates the population, interventions, and outcomes that guided the literature search and synthesis (Figure A). The framework for management of PPH includes women with PPH immediately post-birth to 12 weeks postpartum following pregnancy of >24 weeks' gestation. The figure depicts the key questions within the context of the population, intervention, comparator, outcomes, timing, and setting (PICOTS) parameters described in the review. In general, the figure illustrates how interventions such as compression techniques, medications, procedures, surgeries, blood and fluid products, anti-shock garments or systems-level interventions may result in intermediate outcomes such as blood loss, transfusion, ICU admission, anemia, or length of stay and/or in final health outcomes such as mortality, uterine preservation, future fertility, breastfeeding, or psychological impact. Also, adverse events may occur at any point after the intervention is received.

Figure A. Analytic Framework



Abbreviations: KQ=key question; ICU=Intensive Care Unit

Methods

Literature Search Strategy

A librarian employed search strategies provided in Appendix A of the full report to retrieve research on interventions for PPH. We searched MEDLINE[®] via the PubMed[®] interface, the Cumulative Index of Nursing and Allied Health Literature (CINAHL[®]), and EMBASE (Excerpta

Medica Database). We limited searches to the English language and to studies published from 1990 to the present in order to reflect current standards of care for PPH. Our last search was conducted in September 2014. We manually searched reference lists of included studies and of recent narrative and systematic reviews and meta-analyses.

Inclusion and Exclusion Criteria

We developed criteria for inclusion and exclusion in consultation with a Technical Expert Panel (Table A). We limited studies to those published in English and conducted in Very High Human Development countries as ranked by the United Nations Development Programme Human Development Index (Table A). In the opinion of our clinical experts, processes of care and interventions available in these countries best reflect the system of health care in the United States. A considerable body of evidence addresses PPH management in developing countries; however, the limited availability of skilled clinicians and treatment options in many of these countries results in different standards of care and clinical approaches than those in the United States.

PPH is a complex condition. Treatments are selected not only by PPH etiology and severity, but also by factors related to the setting of care, the availability of medications or other therapeutic options, the availability of personnel, and the standards of care in a given treatment center. Treatment availability and feasibility of providing certain treatments differ across developed and developing nations, and even within any given nation. Because the context of care in most developing nations differs significantly from care in the United States, we instituted language and country limitations in order to identify studies that are most applicable to guiding care by clinicians in the United States, who are the intended audience for this report.

In order to provide contextual information about effectiveness and harms reported in studies conducted in developing nations, we provide summaries of recent reviews of interventions for PPH, which include studies conducted in any country, in the Discussion section (Findings in Relation to What's Known) of the main report.

Table A. Inclusion criteria

Category	Criteria
Study population	<ul style="list-style-type: none"> • KQ1-3, 5: Women with postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy >24 weeks' gestation • KQ4: Women with stabilized PPH and acute blood loss anemia • All modes of birth in any setting
Time period	1990 to present
Publication languages	English only
Country	Very High Human Development countries as indicated by the United Nations Development Programme Human Development Index. Countries as of April 2014 include: Norway, Australia, US, Netherlands, Germany, New Zealand, Ireland, Sweden, Switzerland, Japan, Canada, Republic of Korea, Hong Kong, Iceland, Denmark, Israel, Belgium, Austria, Singapore, France, Finland, Slovenia, Spain, Liechtenstein, Italy, Luxembourg, UK, Czech Republic, Greece, Brunei Darussalam, Cyprus, Malta, Andorra, Estonia, Slovakia, Qatar, Hungary, Barbados, Poland, Chile, Lithuania, United Arab Emirates, Portugal, Latvia, Argentina, Seychelles, and Croatia
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u></p> <ul style="list-style-type: none"> • KQ 1-2, 4: RCT or prospective/ retrospective cohort studies, population-based case series or registry studies with ≥50 cases of PPH treatment, case series of procedures (uterine tamponade, uterine artery embolization) or surgical approaches with ≥50 women • KQ 3: RCT or prospective/ retrospective cohort studies, case series with ≥50 cases addressing interventions for PPH • KQ 5: Pre- and post-studies related to large-scale health systems changes, RCTs, prospective/retrospective cohort studies <p><u>Other criteria</u></p> <ul style="list-style-type: none"> • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results • Studies targeting women with postpartum hemorrhage and meet the population criteria as described above • Studies that address: <ul style="list-style-type: none"> ○ Treatment modality aimed at treatment/management of PPH in a relevant population or treatment for acute blood loss anemia following stabilization of PPH ○ Outcomes related to interventions; primary outcomes of interest include blood loss, transfusion, ICU admission, anemia, length of stay, mortality, uterine preservation, future fertility, breastfeeding, and psychological impact, and harms. • Studies must include extractable data presented in text or tables (vs. solely in figures) on relevant outcomes • For KQ 5, studies must explicitly assess effects of an systems-level intervention on PPH management as a primary or secondary aim; analytic models must indicate data analysis of the effect of the strategy as it relates to PPH treatment; results data include information about effects of strategy on management of PPH; discussion interprets the strategy as potentially having value/not having value for PPH management

Abbreviations: KQ-key question; ICU-Intensive Care Unit; PPH-postpartum hemorrhage; RCT-randomized controlled trial

Study Selection

Two reviewers independently assessed each abstract. If one reviewer concluded that the article could be eligible based on the abstract, we retained it for review of the full text. Two reviewers independently assessed the full text of each included study with any disagreements adjudicated by a senior reviewer.

Data Extraction and Synthesis

We extracted data from included studies into evidence tables that report study design, descriptions of the study populations (for applicability), description of the interventions, and baseline and outcome data on constructs of interest. Data were initially extracted by one team member and reviewed for accuracy by a second. The final evidence tables are presented in Appendix D of the full report.

We completed evidence tables for all included studies, and data are presented in summary tables and analyzed qualitatively in the text. We did not conduct meta-analyses given significant heterogeneity in the study populations, interventions, and outcomes.

Quality (Risk of Bias) Assessment of Individual Studies

We used tools appropriate for specific study designs to assess quality/risk of bias of individual studies: the Cochrane Risk of Bias tool for randomized trials,²⁹ the Newcastle-Ottawa Scale for Non-Randomized Studies,³⁰ the National Heart, Lung, and Blood Institute scale for Pre-Post Studies,³¹ a tool for case series adapted from RTI Item Bank questions,³² and a four-item harms assessment instrument for cohort studies derived from the McMaster Quality Assessment Scale of Harms (McHarm) for Harms Outcomes³³ and the RTI Item Bank.³² Appendix B of the full report includes questions used in each tool.

Two team members independently assessed each included study with discrepancies resolved through discussion to reach consensus and/or adjudication by a senior reviewer. The results of these assessments were then translated to the AHRQ standard of “good,” “fair,” and “poor” quality designations as described in the full report. Quality ratings for each study are in Appendix E of the full report.

Strength of the Body of Evidence

Two senior investigators graded the body of evidence for key intervention/outcome pairs using methods based on the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.³⁴ The team reviewed the final strength of evidence (SOE) designation. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

Applicability

We assessed applicability by identifying potential PICOTS factors likely to affect the generalizability of results (i.e., applicability to the general population of women being treated for PPH). We considered factors related to the availability of interventions, severity of PPH, characteristics of the population, such as mode of birth, that may be associated with PPH, and setting of the intervention as particularly likely to affect applicability.

Results

Article Selection and Overview

We identified 2810 nonduplicative titles or abstracts with potential relevance, with 832 proceeding to full text review. We excluded 775 studies at full text review and included 52 unique studies (57 publications) in the review. We present findings by intervention and outcome area where possible under each key question. We note that for Key Question 1, we have integrated discussion of sub-questions because there was not adequate distinction in the literature to address different etiologies separately.

While a number of studies were classified as prospective or retrospective studies using our study classification algorithm (Appendix G of the full report), few cohort studies provided comparative analyses between the groups, and many were confounded by indication in that women who received interventions such as massive transfusion or hysterectomy likely had more severe cases of PPH. Additionally, initial management of PPH using first-line interventions such as uterotonics and uterine massage differed across studies and across women as each study generally included a number of patients transferred from other hospitals. Thus, populations were heterogeneous in terms of severity and level of stabilization prior to second-line interventions. Given the lack of data from randomized or controlled studies of PPH management, we present data from cohort studies and case series and note potential confounding.

The following sections summarize findings within the literature meeting our criteria. Overall, the evidence to answer questions about PPH management did not reach standards for high strength of evidence (Tables B-E). We briefly summarize strength of the evidence (SOE) findings in each section below and provide a full discussion of SOE assessment in the Discussion section of this Executive Summary and in the main report.

KQ1. Effectiveness of Interventions for Management of PPH

Forty-one unique studies examined the effectiveness of interventions for management of PPH. Some studies addressed multiple interventions. We classified these studies broadly as medical interventions, procedures, and surgical interventions and more specifically by the type of intervention including pharmacologic interventions (10 studies), transfusion as an intervention for management of acute PPH (three studies), intrauterine balloon tamponade (two studies), embolization (15 studies), uterine compression sutures (two studies), uterine artery ligation (four studies), embolization and hysterectomy (one study), hysterectomy (seven studies), and combined approaches (four studies). Studies that address transfusion as an intervention for anemia once PPH is stabilized are summarized under KQ4.

Pharmacologic Interventions

We identified few studies of pharmacologic interventions for PPH that met our review criteria (n=10). Five small studies of fair and poor quality each addressed different drugs: one RCT of TXA vs. no TXA reported significantly less blood loss, duration of bleeding, and need for transfusion in the TXA arm compared with control. A cohort study comparing misoprostol and methylergonovine reported no group differences in transfusion or need for other treatments or surgeries. Case series of sulprostone and carboprost tromethamine reported control of bleeding without additional procedures or surgeries in 83 and 88 percent of participants, respectively, and a cohort study assessing rTM reported greater D-dimer decreases in women

with PPH and disseminated intravascular coagulopathy treated with rTM than in matched controls.

Five small studies of rFVIIa had mixed results. In one retrospective cohort study, women in the rFVIIa group required more blood products and had greater blood loss than women not receiving the treatment. Differences in change in prothrombin time were not significant between women treated with rFVIIa and those who were not in a case-control study. rFVIIa used as a second-line intervention controlled bleeding without need for further procedures or surgeries in 27 to 31 percent of women in one cohort study, a rate that was similar to treatment with other second-line interventions in that study. In registry studies bleeding was considered improved after one or multiple doses of rFVIIa in 64 to 80 percent of women. No study included more than 108 women receiving rFVIIa. Strength of the evidence is insufficient for all outcomes of misoprostol, tranexamic acid, carboprost tromethamine, thrombomodulin, and rFVIIa for PPH management due to the study sizes and lack of studies addressing each agent.

Transfusion

Three studies of fair quality addressed transfusion for PPH management. Two of the studies found ICU admissions and death were higher with combined blood products versus single (whole blood or packed red blood cells) and massive transfusion versus non-massive transfusion. These differences may reflect that women in the groups with poorer outcomes had more severe PPH. A third study found that estimated blood loss, blood products transfused, and mean length of stay did not differ between cryoprecipitate and fibrinogen concentrate groups. Strength of the evidence for outcomes related to transfusion is insufficient. While there were three fair quality studies of transfusion, two of these were so confounded that we could not confidently ascertain their outcomes.

Procedures

Both of the procedures we reviewed (tamponade, embolization) showed positive results for PPH management. The median success rate (defined as control of bleeding without additional procedures or surgeries) of intrauterine balloon tamponade as the initial second-line procedure (i.e., first procedure following conservative management) was 86 percent in one study. In this study of a protocol change to add tamponade as the initial procedure after medication failure, rates of some invasive procedures (beyond tamponade) decreased in women who had vaginal births. The median success rate for embolization as the initial second-line procedure among 14 studies providing such data was 89 percent (range=58% to 98%). However, there was wide variation in the materials used for embolization, the arteries that were embolized, and the interventions that were used before and in conjunction with embolization. The availability of embolization, which is performed by an interventional radiologist, varies by hospital; therefore, this treatment modality is not available to all women with PPH. Strength of the evidence for outcomes related to uterine tamponade is insufficient given the small number of studies and small sample sizes. Strength of the evidence is low for embolization controlling bleeding without additional procedures or surgeries.

Surgical Interventions

The effectiveness of surgical interventions varied. The success rate of uterine compression sutures was 70 percent in the one study from which this could be ascertained. Ligation had a median success rate of 92 percent in three studies (range=36%-96%). The median success rate

for hysterectomy in two studies was 57% (range=20%-93%). One study compared embolization and hysterectomy and reported significantly more ICU admissions and a greater median length of stay in the hysterectomy group than the embolization group. Strength of the evidence is insufficient for the success of uterine compression sutures and hysterectomy in controlling bleeding given the few studies available. Strength of the evidence is low for the success of ligation in controlling bleeding without further procedures or surgeries.

Combined Approaches

Three studies examined a combination of medical and surgical interventions for secondary PPH. In the two studies that compared medical and surgical approaches, hospital readmission and repeat surgical evacuation occurred more frequently in women who initially received medical management versus surgical. One cohort study of women with primary PPH reported greater need for transfusion, ICU admission, and hospital length of stay in women undergoing procedures and/or surgery compared with women who were medically managed. Strength of the evidence for studies of combination interventions and length of stay was insufficient given the small sample sizes and inconsistency in interventions.

KQ2. Evidence for Choosing Interventions and Proceeding to Subsequent Interventions

We did not identify any studies addressing this question.

KQ3. Harms of Interventions for PPH

Thirty-eight studies reported harms of interventions for management of PPH. In three of the four studies that reported harms related to rFVIIa, 2 to 4 percent of women who received rFVIIa developed deep vein thrombosis or pulmonary embolism. None of the women in the two of these studies that had comparator groups had thromboembolic events; however, this may be due to the small sample sizes rather than evidence of an adverse effect of the medication. The harms reported in 14 embolization studies are diverse and few studies report the same harms. The most frequently reported adverse events were infertility (0-43%), PPH in subsequent pregnancy (5%-17%), spontaneous abortion in subsequent pregnancy (5%-15%), and hematoma at puncture site (1%-6%). The most frequently reported adverse events in seven hysterectomy studies were reoperation (6%-29%), infection (7%-21%), bladder lesion (6%-12%), and ureter lesion (0.4%-8%). Harms for other interventions were either incomparable across studies or were only reported in a single study per intervention. Strength of the evidence for harms of interventions was typically insufficient given the diversity of harms reported in single studies. Strength of the evidence was low for hematoma, infertility, and menstrual changes associated with embolization and low for a lack of association between embolization and spontaneous abortion. Strength of the evidence was also low for the association of hysterectomy and operative organ damage and reoperation due to the greater number of studies and more consistent reporting of adverse events.

KQ4. Effectiveness of Interventions for Acute Blood Loss Anemia After Stabilization of PPH

Two small, poor quality RCTs addressed interventions for acute blood loss after PPH is stabilized. In a study comparing women treated with intravenous versus oral iron

supplementation after PPH, there was no significant difference in hemoglobin level at any time point between groups. In a study that assessed differences in fatigue and quality of life between women treated with blood transfusion versus no transfusion, the difference in these outcomes between groups was minimal and possibly clinically equivalent. Strength of the evidence is insufficient for all outcomes and harms in studies of interventions for anemia after PPH given the few studies, small number of participants, and differences in intervention approaches.

KQ5. Effectiveness of Systems-Level Interventions

Across a range of systems-level interventions that range from complex multiphase project with 11 distinctive components to simple three component models for audit and feedback, findings are inconsistent about benefit. All sites, including those participating in the active sites of the null cluster randomized trial were aware of a programmatic emphasis on improving response to and outcomes of PPH. Despite this built-in bias towards finding an effect – since estimated blood loss was rarely quantitatively measured and self-report of performance would be expected to be optimistic – results of a large trial and the higher quality studies do not demonstrate ability to reduce incidence or severity of PPH, or key maternal outcomes like transfusion, hysterectomy, and ICU admission. Strength of the evidence is moderate for a lack of benefit for systems-level interventions in reducing PPH incidence or severity; preventing hysterectomy; and affecting ICU admissions. Strength of the evidence is moderate for no effect on the need for transfusion and insufficient for effects on mortality.

Discussion

Key Findings

The 52 unique studies included in the review comprise four randomized controlled trials (RCTs), two prospective and 13 retrospective cohort studies, eight pre-post studies (defined as studies that compare PPH management and/or outcomes before and after an intervention, such as introduction of a new protocol), two case-control studies, and 23 case series. Most studies were conducted in Europe (n=28), and 13 were conducted in the United States, eight in Asia, two in Australia or New Zealand, and one in Argentina. No studies were of good quality for effectiveness outcomes. We considered 20 studies as fair quality for effectiveness outcomes and 30 as poor quality. Two studies (one retrospective cohort, one case series) provided only harms data. Among the 38 studies reporting harms of interventions for management of PPH, we considered seven as good quality for harms reporting and 31 as poor quality. Five small studies of fair and poor quality addressed different pharmacologic agents. Three studies, each of different agents (TXA, sulprostone, carboprost tromethamine) reported reduced bleeding or control of bleeding. One study comparing misoprostol and methylergonovine reported no group differences in outcomes, and one of rTM to treat DIC reported greater decrease in D-dimer in the rTM arm. Five small studies of rFVIIa had mixed results related to need for transfusion and control of bleeding. The three medications most commonly used for PPH in the United States are oxytocin, methylergonovine maleate, and misoprostol. None of the studies that met our inclusion criteria focused on oxytocin; one study included methylergonovine maleate and misoprostol. Because evidence regarding first-line management, particularly pharmacologic management, is critical for decision making by clinicians and guidelines developers, we summarize findings

from other recent of studies of agents and interventions conducted in any country in the Discussion section of the main report.

The success of uterine-sparing techniques, such as uterine tamponade, embolization, uterine compression sutures, and uterine and other pelvic artery ligation, in controlling bleeding without the need for additional procedures or surgeries ranged from 36 to 98 percent; however, these data come from a limited number of studies with a small number of participants. Harms reporting was limited to 38 studies and difficult to synthesize because diverse adverse events were reported inconsistently across studies. Only two studies addressed interventions for anemia after PPH is stabilized. Systems-level interventions (n=8 studies) showed little benefit in reducing the incidence or severity of PPH or the need for transfusion or hysterectomy.

Strength of Evidence

We included case series in our assessment of SOE for harms and success rates of procedures and surgeries, and we rated SOE for outcomes we considered to be clinically significant, consistently defined, and plausibly linked to the intervention. Overall, the evidence to answer questions about PPH management did not reach standards for high strength of evidence (Tables B-E). SOE was insufficient for all interventions/outcomes except for the SOE for the success of embolization and ligation in controlling bleeding without further procedures or surgeries, which was low.

SOE for Interventions to Manage PPH

Pharmacologic interventions. SOE was insufficient for all outcomes of misoprostol, tranexamic acid, carboprost tromethamine, thrombomodulin, and rFVIIa for PPH management due to the study sizes and lack of studies addressing each agent.

Transfusion. While three fair quality studies addressed transfusion, two of these were so confounded that we could not confidently ascertain their outcomes, thus SOE for all outcomes in insufficient.

Uterine tamponade. SOE for the success of uterine tamponade in controlling bleeding was insufficient.

Uterine artery embolization. SOE for embolization controlling bleeding without additional procedures or surgeries is low due to a lack of comparative studies and small sample sizes in studies providing data to assess success of the intervention.

Uterine compression sutures. SOE is insufficient for the success of uterine compression sutures.

Uterine and other pelvic vessel ligation. SOE is low for ligation controlling bleeding without further surgeries or procedures.

Hysterectomy. SOE is insufficient for the success of hysterectomy in controlling bleeding.

Combined interventions. SOE was insufficient for all outcomes.

As noted, we identified few studies of medications meeting our review criteria; however, a number of studies of misoprostol and oxytocin have been conducted in developing countries. Four recent systematic reviews of interventions for PPH, including two Cochrane reviews, assessed uterotonics including misoprostol. We summarize these reviews fully in the Findings in Relation to What is Known section in the main report and provide a brief summary here.

In one Cochrane review, oxytocin infusion was more effective and caused fewer side effects when used as first-line therapy for the treatment of primary PPH compared with misoprostol. When used *after* prophylactic uterotonics, misoprostol and oxytocin infusion had similar effects. The review concluded that adding misoprostol for women receiving treatment with oxytocin did not appear beneficial. In another Cochrane review differences in maternal mortality and morbidity, except for fever, did not differ significantly between misoprostol and control groups. The investigators concluded that misoprostol did not increase or decrease morbidity or mortality, with the exception of fever, and the lowest effective dose should be used. In another review of misoprostol vs. placebo, misoprostol did not reduce PPH risk significantly compared with placebo. In the fourth review and meta-analysis, higher doses of misoprostol (600 vs. 400 micrograms) were no more effective at preventing blood loss.

Table B. Summary of evidence in studies addressing the effectiveness of interventions (KQ1)

Intervention	Key Outcome(s)	Strength of the Evidence (SOE) Grade	Findings
Pharmacologic Interventions			
Tranexamic acid vs. no tranexamic acid	Anemia, transfusion, blood loss, ICU stay	Insufficient	Less blood loss, need for transfusion, and progression to severe PPH in TXA group vs. control ($p < .05$) reported in a single small, short-term cohort study with high study limitations
Misoprostol vs. methylergonovine maleate	Transfusion, uterine preservation	Insufficient for superiority of one agent over another in affecting any outcome	No group differences in need for transfusion, additional medical or surgical treatments in a single small, short-term cohort study with high study limitations
Sulprostone	Success in controlling bleeding	Insufficient	In a single, short-term study with high study limitations, bleeding was controlled in 83% of 1370 women
Carboprost tromethamine	Success in controlling bleeding	Insufficient	In a single, short-term study with high study limitations, bleeding was controlled by carboprost in 81% of 237 cases of PPH
Thrombomodulin vs. no thrombomodulin	Uterine preservation, bleeding, transfusion	Insufficient	Greater D-dimer decrease from baseline in intervention arm vs. control in a single, small, short-term cohort study with high study limitations
rFVIIa	Transfusion, anemia, uterine preservation, LOS	Insufficient	In 2 small studies with high study limitations need for transfusion was greater with rFVIIa and rates of hysterectomy, LOS were similar
Other medical interventions			
Transfusion	ICU admission, LOS	Insufficient	Inconsistency in direction of effect (greater LOS and ICU admission in transfusion or whole blood groups in 2 studies; no group differences in another study), high study limitations
Procedures			
Uterine tamponade	Success in controlling bleeding	Insufficient	Tamponade without further procedure or surgery controlled bleeding in 86% of women in one study, and tamponade plus additional intervention controlled bleeding in 98% in another but studies

			were small with high study limitations
Embolization	Success in controlling bleeding	Low for positive effect in controlling bleeding	Median success rate of 89% as initial second-line intervention in 15 studies with high limitations; conservative management and severity of PPH varied across studies. A higher SOE is not possible due to the lack of comparisons in this literature and small sample sizes
Surgeries			
Uterine compression sutures	Success in controlling bleeding	Insufficient	In a single, small study with high limitations, bleeding controlled by suture following conservative management in 70% of women with medium study limitations
Ligation	Success in controlling bleeding	Low for positive effect in controlling bleeding	92% success rate for controlling bleeding without further procedure or surgeries in 3 small studies with medium study limitations
Hysterectomy	Success in controlling bleeding	Insufficient	The median success rate for controlling bleeding was 57% in 2 small studies with medium study limitations
Combined interventions	LOS in women with primary and secondary PPH	Insufficient	Greater LOS in women with primary PPH undergoing procedures/surgeries vs. medical management in on small study with high limitations. No differences in LOS between surgical and medical management groups in 2 small studies with high limitations addressing secondary PPH

ICU-intensive care unit, LOS-length of stay, PPH-postpartum hemorrhage, TXA-tranexamic acid

SOE for Harms of Intervention

Generally SOE was insufficient given diversity of harms reported in single studies. However, SOE rose above insufficient for selected harms related to embolization and hysterectomy due to the greater number of studies and more consistent reporting of adverse events (Table C).

As noted, few studies of uterotonics met our inclusion criteria; however, harms reported in recent systematic reviews of uterotonics for PPH treatment included shivering and fever (see Findings in Relation to What’s Known section in the main report for a full summary). In one review, oral misoprostol was associated with a significant increase in vomiting and shivering compared with either oxytocin or rectal misoprostol. In another review, differences in maternal mortality and morbidity, except for fever, did not differ significantly between misoprostol and control groups. Risk of fever was increased in misoprostol groups and was highest in studies with a misoprostol dose of 600 µg or more. In another review of misoprostol vs. placebo, shivering and fever were significantly more common in misoprostol arms. A fourth review noted more adverse effects related to misoprostol vs. placebo.

While evidence in the current review was insufficient to comment on the association between rFVIIa and thrombotic events, studies in other populations have suggested increased risk of arterial events. In one review of RCTs in non-hemophilia patients, the pooled relative risk of thrombotic events across studies of prophylactic and therapeutic uses of rFVIIa was 1.45 (95% CI: 1.02 to 2.05). Another review of fertility outcomes following embolization, ligation, and sutures concluded that the techniques reviewed did not appear to compromise fertility, but the number and quality of studies was limited.

Table C. Summary of evidence in studies addressing harms of interventions (KQ3)

Intervention	Key Outcome(s)	Strength of the Evidence (SOE) Grade	Findings
Pharmacologic interventions			
Tranexamic acid	All harms	Insufficient	In one small RCT with low study limitations, serious harms did not differ between groups and mild, transient harms occurred more often in TXA group
Sulprostone	All harms	Insufficient	Insufficient SOE as only one study considered poor quality for harms reporting
Methylergonovine maleate	Acute coronary syndrome and myocardial infarction	Low SOE for lack of association of methylergonovine maleate with acute coronary syndrome and myocardial infarction	No significant difference in the incidence of these conditions in the exposed and non-exposed groups in one large cohort study with low study limitations
Carboprost tromethamine	All harms	Insufficient	Insufficient SOE as only one study considered poor quality for harms reporting
rFVIIa	Thromboembolic events	Insufficient	3 of 4 studies reported thromboembolic events (pulmonary embolus, deep vein thrombosis, myocardial infarction), but sample sizes were small and study limitations high
Other medical interventions			
Transfusion	All harms	Insufficient	Inconsistency in harms reported in 4 studies with high study limitations
Procedures			
Uterine tamponade	All harms	Insufficient	Single, small study with high limitations
Embolization	Infertility	Low SOE for negative effect of embolization on future fertility	Infertility rate among women who had embolization in these studies was greater than that of the overall population rate (range 0-43%), but few women (n=300) available for long-term followup; high study limitations and inconsistency in 5 studies with high limitations
	Spontaneous abortion in subsequent pregnancy	Low SOE for lack of association between embolization and subsequent spontaneous abortion in subsequent pregnancy	Small number of women followed-up; rates of miscarriage ranged from 5-15%, in 6 studies with high study limitations. Rates were comparable to estimates in the general population
	Menstrual changes	Low SOE for an association between embolization and subsequent menstrual changes	Rates of menstrual change including heavier, lighter, or irregular menses and amenorrhea ranged from 2% to 22% in 7 studies with high limitations
	Hematoma	Low SOE for association between embolization and hematoma	Rates ranged from 5%-15% in 5 studies with high limitations

Surgeries			
Uterine compression sutures	All harms	Insufficient	Inconsistency and limited harms reporting in studies with high limitations
Ligation	Surgical injury	Insufficient	High study limitations and imprecision in 2 studies; injuries (inadvertent ligation of the ureters and secondary hysterectomy disunion with sepsis) related to ligation reported in both studies
Hysterectomy	Bladder and ureter lesions	Low SOE for association of hysterectomy and operative organ damage	Rates of bladder and ureter lesions ranged from 6%-12% and 0.4%-8%, respectively In 5 small studies with high study limitations
	Reoperation	Low SOE for association between hysterectomy and reoperation	Rates of reoperation ranged from 6-29% in 4 small studies with high study limitations

SOE-strength of the evidence

SOE for Interventions for Anemia

There is insufficient SOE for all outcomes and harms in studies of interventions for anemia after PPH given the few studies, small number of participants, and differences in intervention approaches (Table D).

Table D. Summary of evidence in studies addressing interventions for anemia after PPH (KQ4)

Intervention	Key Outcome(s)	Strength of the Evidence (SOE) Grade	Findings
Iron supplementation	Anemia	Insufficient	No differences in groups receiving oral or intravenous iron in 1 small RCT with high study limitations and indirect outcomes
Transfusion	Fatigue	Insufficient	No significant group differences in 1 small RCT with high study limitations
	Quality of life	Insufficient	No significant group differences in 1 small RCT with high study limitations
Iron supplementation and transfusion	All harms (transfusion reactions, infections, endometritis, thromboembolic events)	Insufficient	In 2 small RCTs, harms were not pre-specified in one study. No serious adverse reactions were attributed to the study drugs in either RCT but reporting in one RCT is not clear

SOE-strength of the evidence

SOE for Systems-Level Interventions

Overall the SOE for any systems-level intervention on any outcome is insufficient or moderate as the observational data is biased and a single, very large trial suggest that at least one clearly described and implemented program did not change risk of severe hemorrhage or meaningfully modify processes of care or overall maternal outcomes. SOE is moderate that these multi-component interventions did not change specific outcomes such as severity of PPH, transfusion, hysterectomy, and ICU admission (Table E).

Table E. Summary of evidence in studies addressing systems-level interventions for PPH (KQ5)

Intervention	Key Outcome(s)	Strength of the Evidence (SOE) Grade	Findings
Systems-level approaches	Incidence of PPH	Moderate SOE for lack of benefit in reducing PPH incidence	Sites were aware of objectives with regard to reducing PPH and assessors of a somewhat subjective outcome not masked in one large cluster RCT with medium study limitations
	Severity of PPH	Moderate SOE for lack of benefit in reducing severity of PPH. Sites aware of the objectives with	Sites were aware of objectives with regard to reducing PPH and assessors of a somewhat subjective outcome not masked in one large cluster RCT with medium study limitations and 5 pre-post studies with high study limitations
	Transfusion	Moderate SOE for no effect on transfusion	Transfusion unchanged in RCT, increased in one pre-post study and unchanged in two, all with low study limitations. One with decreased use of total blood products related to decrease in risk of disseminated intravascular coagulation
	Hysterectomy	Moderate SOE for lack of benefit in preventing hysterectomy	Hysterectomy unchanged in 1 RCT with low study limitations. No significant change in 2 pre-post studies with low limitations but hysterectomies increased; risk significantly increased in one study and was similar between time periods in a third.
	ICU admission	Moderate SOE for lack of benefit	No change in 1 RCT and no change in two pre-post studies, all with low study limitations
	Mortality	Insufficient SOE for benefit	Only 1 small pre-post study with medium study limitations reported on changes in mortality

PPH-postpartum hemorrhage, RCT-randomized controlled trial, SOE-strength of the evidence

Applicability

Studies differed in terms of study population and outcome measures. Most studies did not make direct comparisons between treatments or characterize populations well in terms of severity of PPH and prior management strategies. This lack of direct comparison of treatment options hinders our ability to understand what treatments are most effective and in what order they should be used, both of which are paramount questions for clinicians. Overall, findings of studies in the review are generally applicable to the population of women who would be experiencing PPH in hospitals in high-resource nations. Most studies were conducted in Europe or the United States in tertiary care centers. Studies frequently included a number of women with PPH who were transferred from smaller or community hospitals, which can occur when women with PPH requiring additional treatment are stable enough to be moved to facilities with interventional radiology or other services. More women had PPH after cesarean birth than vaginal birth in the 38 studies reporting mode of birth (estimated 3,486 vaginal and 5,624 cesarean births among the 9,110 births for which mode was clearly reported). The most common cause of PPH was atony, which aligns with the most frequent cause of PPH in the larger community and literature. Studies of pharmacologic agents typically included women with mild to moderate to PPH while studies of procedures or surgical approaches generally included women with more severe PPH that had not been controlled with first-line therapies such as uterotonics.

The uterotonics and blood products studied are generally widely available; however, the accessibility of procedures such as embolization may be limited in smaller community hospitals. Similarly, community hospitals may lack personnel with experience with arterial ligation and

compression sutures. Comparators across studies with more than one group were typically either no specific treatment (e.g., rFVIIa or no rFVIIa) or another treatment (e.g., embolization or ligation) and are likely confounded by patient and provider characteristics that may have affected the choice of intervention. For example, patients with more severe hemorrhage likely received more aggressive treatment, and providers could only offer the options available in their facilities. Outcomes addressed across studies were appropriate and clinically relevant; however, few studies reported longer term outcomes such as future fertility or patient-centered outcomes such as quality of life.

Among studies of interventions for anemia after PPH, findings may be limited by a more selective population in one study of iron supplementation, which included predominately women with lower levels of education and lower socioeconomic status. One study of transfusion vs. no transfusion was conducted at a tertiary care center.

The populations included in the systems-level interventions both in the United States and Europe reflect those typical of similar size and type (rural, academic, etc.) current labor and delivery environments in the United States. Likewise the interventions designed and implemented in these studies were informed by processes of identifying evidence and crafting guidance that conforms to typical quality improvement and outcomes-based research. The content of the interventions is feasible to implement across a full range of settings, and the approaches to measuring outcomes are applicable to practice. Overall the systems-level interventions assessed have good applicability to current practice in the United States.

Research Gaps

Future research needs around management of PPH are both clinical and methodologic. Priorities for future research include:

- Reaching consensus on definitions and criteria for PPH and first-line management strategies to promote consistency within the literature.
- Conducting more rigorously controlled studies of all interventions for PPH management, especially medication studies in light of the fact that these are considered first-line management, and few studies in developed/high resource nations addressed agents commonly in use. While studies in this population are likely to be retrospective, studies should clearly describe first-line management to clarify the course of care. Studies must report *a priori* study size calculation to ensure that the number of subjects will be adequate to show a difference (if the study is designed for superiority). In addition, comparative studies must declare within the design and methods whether the study is a superiority trial or a non-inferiority trial.
- Conducting cluster randomized control trials of intervention bundles that address order of medications, manual interventions such as uterine massage and bimanual compression, number of times to repeat medications prior to moving on to second-line interventions, hemodynamic monitoring, and supportive care such as transfusion.
- Clearly identifying the trajectory of care, including which interventions were used and in what order.
- Conducting additional RCTs or controlled studies of treating anemia after PPH is stabilized.
- Conducting additional prospectively designed and reported studies that report data from large national databases. These studies can describe effects in larger population samples and may be valuable for identifying longer-term harms, for example, effects on breastfeeding, psychological trauma, and future fertility.

- Replicating the intrauterine balloon tamponade study that was found effective in reducing invasive interventions.
- Using and clearly reporting objective methods to diagnose PPH, including accurate measurement of blood loss. Visual estimation of blood loss is too imprecise to be used in research.
- Dedication to prospective objective measures like estimated blood loss, time course of intervention, and use of intervention components.
- Greater capture and multivariable adjustment for known risk factors and confounders to allow better understanding of the attributable impact, if any, of the intervention.
- Attention to the possibility that effect modifiers hide efficacy in some groups, which means studies will need to be powered and specify a priori stratified analyses by candidate effect modifiers, such as grand multiparity, route of birth, or infection in labor.
- Prespecifying harms, differentiating harms of interventions from sequelae of PPH wherever possible, and studying longer term effects of procedures and surgical interventions.
- The size of the study populations in systems-level interventions can clearly support multivariate modeling and could serve to drive better understanding of the general lack of effectiveness. In particular, such data are well-suited to use of risk-adjustment models that can allow comparison not only across time periods but across studies.
- The possibility exists that systems-level interventions are working against a biologically determined risk of PPH, meaning that within a specific population with particular characteristics there is an irreducible level of risk and event rates cannot be driven below that “floor”. If this were demonstrated with risk adjustment methods, this finding would fundamentally change the focus of study design and care. A floor would suggest we need very large pragmatic trials aimed not at reducing the occurrence of PPH but at diminishing associated morbidity, mortality, personal harm and distress, and costs. The systems-level intervention studies available now cannot fully inform this goal but primary meta-analyses of the highest quality cohorts with risk adjustment could determine if the evidence seen in some of the included studies that suggest benefits are worth pursuing on a larger scale, including a scale large enough to separate the influence of candidate components to determine their individual contributions to improvements in care.

Limitations of the Evidence Base

Studies included in this review are methodologically and clinically limited. There is not a universally agreed management strategy for PPH. Medications were typically used as the initial treatment; however, the specific drugs, dosages, and order varied. The selection of interventions, including which interventions were performed and in which order, was also inconsistent. Management was not well described in many studies, especially in for women who transferred from other hospitals. Overall, it was difficult to ascertain confidently the complete trajectory of care of women in many of the studies we reviewed.

Procedures and surgical interventions also differed across studies. For example, materials used for embolization varied as did the sites of embolization and ligation. There is no clear trigger for starting subsequent interventions, so success rates have limited reliability. It may be that women would have recovered after the first-line treatment if time allowed. In addition, there is the potential for cumulative effects of multiple interventions that cannot be measured. Outcomes other than control of bleeding can be difficult to assess. For example, transfusion could be an adverse outcome if treatment was not sufficient and timely to halt bleeding rapidly.

Alternately early transfusion can be the appropriate intervention; therefore, it is sometimes hard to know whether to classify transfusion as an adverse outcome. Measuring harms is similarly challenging. It can be difficult to assess in some cases if harms are due to PPH or management interventions and how much each contributed, especially to deaths. There is a significant lack of truly comparative studies and randomized studies, which would be ideal yet are complex to conduct with a life-threatening condition such as PPH. Studies were typically conducted or data collected over long time frames (median study duration = 5 years, range 6 months to 29 years), and it is likely that interventions and patient characteristics would have changed, but few studies account for secular changes such as the introduction of new interventions.

In systems-level interventions, a natural tension exists between the desire to implement robust interventions and the challenges of understanding which components may have value. In the case of these interventions, it is particularly challenging since lower quality studies with looser measures of outcomes were more likely to report intervention effects. The literature about systems-level intervention is limited by lack of analyses that seek to adjust for secular trends and changes in confounders, such as proportion of births by cesarean and trends in rising BMI. Likewise lack of multivariable modelling may obscure the influence of elements of care, such as induction of labor, and comorbidities, such as chorioamnionitis, that could identify which predictors may be exerting substantial influence and inform new approaches to diminishing risk of PPH.

Implications for Clinical and Policy Decisionmaking

A limited body of evidence addresses interventions for managing PPH. Few studies addressed medications commonly used to treat PPH, precluding our ability to draw conclusions about their effectiveness. Success rates for uterine tamponade or surgeries are typically above 60 percent (e.g., success of uterine tamponade as the initial second-line therapy in one study was 86%; success rates for ligation as the first second-line intervention to control bleeding ranged from 36 to 96%). Studies of embolization suggested that it may be associated with a median rate of successful control of bleeding without need for additional procedures or surgeries of 89 percent, with a wide range of success (58% to 98%) across studies; however, few studies clearly provided data on the success of these interventions as the initial second-line approach, so rates are based on a small number of cases. Adverse events and longer term outcomes associated with procedures and surgical interventions are also not well-understood. At this point, the evidence is insufficient to comment on the effectiveness and harms of most interventions for most outcomes.

Thus, given the mixed and insufficient evidence, clinicians will likely need to continue to make individual decisions about the care of women with PPH based on each woman's clinical situation and the management options available in the setting. This body of evidence does not provide clear answers to the key clinical questions of what interventions to use and in what order.

Conclusions

A limited body of evidence addresses interventions for managing PPH. The most effective treatments and the order in which to use treatments remain unclear. Diagnosis of PPH is subjective and management is emergent, which makes it difficult to compare the severity of PPH and how comparable participants are within and across studies. The trajectory of care, rationale for choice of intervention, and component of care ultimately responsible for controlling bleeding are also frequently unclear. Few studies addressed pharmacologic or medical management, and

evidence is insufficient to comment on effects of such interventions. The success of uterine-sparing techniques, such as uterine tamponade, embolization, uterine compression sutures, and uterine and other pelvic artery ligation, in controlling bleeding without the need for additional procedures or surgeries ranged from 36 to 98 percent; however, these data come from a limited number of studies with a small number of participants. Harms of interventions are diverse and not well-understood. Some studies reported an association between rFVIIa and thromboembolic events, however; sample sizes were small. Some studies with longer term followup reported adverse effects on future fertility and menstrual changes in women undergoing embolization. Need for re-operation was also reported after hysterectomy. Evidence is insufficient to assess the effects of interventions for anemia after PPH is stabilized, and systems-level interventions showed little benefit in reducing the incidence or severity of PPH or the need for transfusion or hysterectomy. Further research is needed across all interventions for PPH management, especially pharmacologic interventions, which as first-line therapies are the most frequently used.

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Introduction

Definition and Prevalence

Postpartum hemorrhage (PPH) is commonly defined as blood loss exceeding 500 milliliters (mL) following vaginal birth and 1000 mL following cesarean.¹ Definitions vary, however, and diagnosis of PPH is subjective and often based on inaccurate estimates of blood loss.¹⁻⁴ Moreover, average blood loss at birth frequently exceeds 500 or 1000 mL.⁴ Proposed alternate metrics for defining and diagnosing PPH include change in hematocrit, need for transfusion, rapidity of blood loss, and changes in vital signs, all of which are complicated by the emergent nature of the condition.¹ PPH is often classified as primary/immediate/early, occurring within 24 hours of birth, or secondary/delayed/late, occurring more than 24 hours post-birth to up to 12 weeks postpartum. In addition, PPH may be described as third or fourth stage depending on whether it occurs before or after delivery of the placenta, respectively.

The overall prevalence of PPH worldwide is estimated to be 6 to 11 percent of births with substantial variation across regions.^{5, 6} Prevalence differs by assessment method and ranges from 10.6 percent when measured by objective appraisal of blood loss to 7.2 percent when assessed with subjective techniques to 5.4 percent when assessment is unspecified.⁵ Multiple studies have noted an increase in PPH in high-resource countries, including the United States, Canada, Australia, Ireland, and Norway, since the 1990s.⁷⁻¹¹ In the United States, one study found that the incidence of PPH increased 26% from 1994 to 2006 (2.3% vs. 2.9%, respectively, $p < 0.001$).¹² Another U.S. study reported the incidence of severe PPH doubled from 1.9 percent in 1999 to 4.2 percent in 2008 ($p < 0.0001$).¹³ Factors underlying the increase remain unclear, and both recent U.S. studies found rising PPH rates were not explained by changes in risk factors (e.g., maternal age, cesarean birth, multiple gestation).^{12, 13}

Adverse Outcomes Associated with Postpartum Hemorrhage

PPH is a leading cause of maternal mortality and morbidity worldwide and accounts for nearly one-quarter of all maternal pregnancy-related deaths.¹⁴ Multiple studies have suggested that many deaths associated with PPH could be prevented with prompt recognition and more timely and aggressive treatment.¹⁵⁻¹⁷ Morbidity from PPH can be severe with sequelae including organ failure, shock, edema, compartment syndrome, transfusion complications, thrombosis, acute respiratory distress syndrome, sepsis, anemia, intensive care, and prolonged hospitalization.¹⁸⁻²⁰

The most common etiology of PPH is uterine atony (impaired uterine contraction after birth), which occurs in about 80 percent of cases. Atony may be related to overdistention of the uterus, infection, placental abnormalities, or bladder distention.²¹ Though the majority of women who develop PPH have no identifiable risk factors, clinical factors associated with uterine atony, such as multiple gestation, polyhydramnios, high parity, and prolonged labor, may lead to a higher index of suspicion.^{18, 19, 21, 22} Other causes of PPH include retained placenta or clots, lacerations, uterine rupture or inversion, and inherited or acquired coagulation abnormalities.^{21, 22}

Interventions

Organizations and associations including the World Health Organization (WHO), International Confederation of Midwives (ICM), International Federation of Gynecologists and

Obstetricians (FIGO), American College of Obstetricians and Gynecologists, and Royal College of Obstetricians and Gynaecologists (RCOG) have released guidelines for PPH prevention and management.^{14, 19, 21-24} Initial management includes identifying PPH, determining the cause, and implementing appropriate interventions based on the etiology. A variety of medical, procedure, and surgical interventions are available (see Table 1).

Interventions to treat PPH generally proceed from less to more invasive and include compression techniques, medications, procedures, and surgeries. PPH management may also involve adjunctive therapies, such as blood and fluid replacement and/or an anti-shock garment,^{25, 26} to treat the blood loss and other sequelae that result from PPH. Conservative management techniques such as uterotonic medications, which cause the uterus to contract, external uterine massage, and bimanual compression are generally used as “first-line” treatments.²⁷ These compression techniques encourage uterine contractions that counteract atony and assist with expulsion of retained placenta or clots. Aortic compression is another compression technique that has been used for severe PPH.^{28, 29}

The medications most commonly used in PPH management are uterotonic agents. These medications include oxytocin (Pitocin®), misoprostol (Cytotec®), methylergonovine maleate (Methergine®), carboprost tromethamine (Hemabate®), and dinoprostone (Prostin E2®).^{14, 19, 21, 22, 30} All of these medications are available in the United States. Only oxytocin, methylergonovine maleate, and carboprost tromethamine are approved by the U.S. Food and Drug Administration (FDA) specifically for PPH management; use of these other medications is off label. Typically, oxytocin is used as the initial medication for PPH management then other uterotonics are administered if oxytocin fails to stop bleeding. A recent U.S. study found wide variation in the use of these other uterotonics, which was not attributable to patient or hospital characteristics.³¹ In cases of severe blood loss from PPH, the hemostatic recombinant activated factor VIIa (NovoSeven®) and the antifibrinolytic tranexamic acid (Cyklokapron®) have been used.³²

Procedures used in PPH management include manual removal of the placenta, manual removal of clots, uterine tamponade, and uterine artery embolization.^{14, 19, 21, 22} Laceration repair is indicated when PPH is a result of genital tract trauma. Surgical options when other measures fail to control bleeding include curettage, uterine and other pelvic artery ligation, uterine compression sutures, and hysterectomy.^{14, 19, 21, 22} More invasive procedures (e.g., uterine tamponade and uterine artery embolization) and surgical techniques are generally used after “first-line” conservative management (e.g., uterotonics, uterine massage, bimanual compression, manual placenta and clot removal, and laceration repair) has failed to control bleeding and can be considered “second-line” interventions.²⁷ Procedures and surgeries can increase the risk of infection and other complications, and they may eliminate or adversely affect future fertility and pregnancy.

After PPH has been controlled, followup management varies and may include laboratory testing (e.g., hemoglobin and hematocrit), iron replacement therapy, and other interventions to assess and treat sequelae of PPH. The immediate postpartum period is a unique physiologic state with relative intravascular volume expansion with a reduction in cardiovascular demand compared to pregnancy. The physiologic anemia of pregnancy may be exacerbated by acute blood loss anemia from PPH. These physiologic realities may allow women with low hematocrits to be asymptomatic. Interventions for acute blood loss anemia include red blood cell transfusion and iron supplementation. Erythropoietin-stimulating agents (Aranesp®, Epogen®,

Procrit®) have also been used for anemia following stabilization of PPH, but they are not approved by the FDA for this use.¹⁹

At a systems level, PPH has been the focus of perinatal care safety initiatives that attempt to improve patient outcomes by incorporating a variety of strategies, such as practice guidelines or protocols, simulation drills, and teamwork training.³³⁻³⁷ These systems-level interventions may influence management of PPH.

A variety of outcomes related to PPH management are reported.³⁸⁻⁴³ Blood loss itself is measured, although often inaccurately as previously noted. Transfusion and anemia are sometimes used as markers for the amount of blood loss. The outcomes of intensive care unit (ICU) admission and extended hospitalization are used as indicators of maternal morbidity. Severe hemorrhage can lead to hysterectomy and death.

PPH can occur in any birth setting: hospital, birth center, or home. In home birth and birth center settings, severe or recalcitrant PPH can necessitate transfer for inpatient care. In considering setting, it is important to note that PPH management varies significantly according to available resources; therefore, many studies conducted in low-resource countries have limited to no applicability for higher-resource countries such as the United States.

Table 1. Brief descriptions of interventions used in PPH management

Intervention	Description
Anti-shock garment	Garment with segments that are wrapped around the woman's legs, pelvis, and abdomen then tightened with Velcro straps. The garment places pressure that forces blood to the heart, lungs, and brain to prevent or treat shock.
Aortic compression	Compressing the aorta, by applying firm pressure with a closed fist just above the umbilicus, slows bleeding.
Curettage	Insertion of a curette into the uterus to remove any retained fragments of the placenta or clots. This is most commonly performed for secondary PPH.
External uterine massage and bimanual compression	External uterine massage is performed by placing a hand on the lower abdomen. For bimanual compression, the clinician places one hand on the abdomen and the other hand inside the vagina then compresses the uterus between the two hands. These techniques cause the uterus to contract, which treats atony and assists with expulsion of retained placenta or clots.
Hysterectomy	Surgical removal of the uterus is usually performed as a last resort when other treatments fail. Hysterectomy can be total (includes removal of the cervix) or subtotal (cervix is left intact). Hysterectomy stops bleeding in most cases of PPH. It may be ineffective when placenta percreta is present, and placental implantation extends beyond the uterus.
Manual removal of the placenta and/or clots	Insertion of the clinician's hand into the uterus to remove the placenta and/or clots when they are not being expelled by contractions alone.
Recombinant activated factor VIIa (rFVIIa)	This hemostatic medication helps bleeding stop by activating the extrinsic pathway of the coagulation cascade, which is a process that causes blood to clot.
Tranexamic acid	This antifibrinolytic medication reduces blood loss by preventing clot breakdown.
Transfusion	Transfusion is the intravenous administration of blood products, including red blood cells, fresh frozen plasma, and cryoprecipitate. Red blood cells help maintain blood volume and improve the blood's capacity to carry oxygen. Fresh frozen plasma and cryoprecipitate contain coagulation factors, which are proteins that are needed to help the blood clot so that bleeding will stop.
Uterine and other pelvic artery ligation	Tying a suture around an artery to occlude blood flow. Uterine artery ligation is most commonly performed for PPH; utero-ovarian and internal iliac arteries can also be ligated.
Uterine artery embolization	Injection of one or more embolizing agents (e.g., absorbable gel particles, gelatin sponge pledgets, foam, metal coils) into the uterine arteries to reduce blood flow. This procedure is performed by an interventional radiologist.
Uterine compression sutures	Placing sutures around the uterus to compress it and stop bleeding. This surgery is performed for uterine atony that does not respond to other treatments. The most common technique for uterine compression is the B-lynch suture.

Table 1. Brief descriptions of interventions used in PPH management (continued)

Intervention	Description
Uterine tamponade	Uterine tamponade can be performed with a balloon or packing. Intrauterine balloon tamponade is performed by inserting an inflatable balloon device through the vagina or abdomen (if a cesarean was performed) into the uterine cavity and then filling it with sterile saline. For packing, gauze, which may be coated with material to enhance clotting, is used to firmly fill the uterine cavity. The balloon or packing exerts pressure on the uterine wall, which stops bleeding, and is later removed.
Uterotonic medications (oxytocin, misoprostol, methylergonovine, carboprost tromethamine)	These uterotonic medications cause contractions and increase uterine tone. These effects counter uterine atony, which is the most common cause of PPH.

PPH-postpartum hemorrhage

Scope and Key Questions

Scope of Review

This systematic review provides a comprehensive review of potential benefits of PPH management (medical and surgical) as well as harms associated with treatments in women with PPH. We assess intermediate outcomes such as blood loss, hospital and ICU stay, and anemia, and longer term outcomes including uterine preservation, fertility, breastfeeding, psychological impact and harms of treatment, and mortality related to treatment.

Key Questions

We have synthesized evidence in the published literature to address the following Key Questions (KQs):

KQ1.What is the evidence for the comparative effectiveness of interventions for management of postpartum hemorrhage?

- a. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to atony?
- b. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to retained placenta?
- c. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to genital tract trauma?
- d. What is the comparative effectiveness of interventions intended to treat postpartum hemorrhage likely due to uncommon causes (e.g., coagulopathies, uterine inversion, subinvolution)?

KQ2.What is the evidence for choosing one intervention over another and when to proceed to subsequent interventions for management of postpartum hemorrhage?

KQ3.What are the comparative harms, including adverse events, associated with interventions for management of postpartum hemorrhage?

KQ4. What is the comparative effectiveness of interventions to treat acute blood loss anemia after stabilization of postpartum hemorrhage?

KQ5.What systems-level interventions are effective in improving management of postpartum hemorrhage?

Table 2 outlines the population, intervention, comparator, outcomes, timing, and setting (PICOTS) characteristics for the Key Questions.

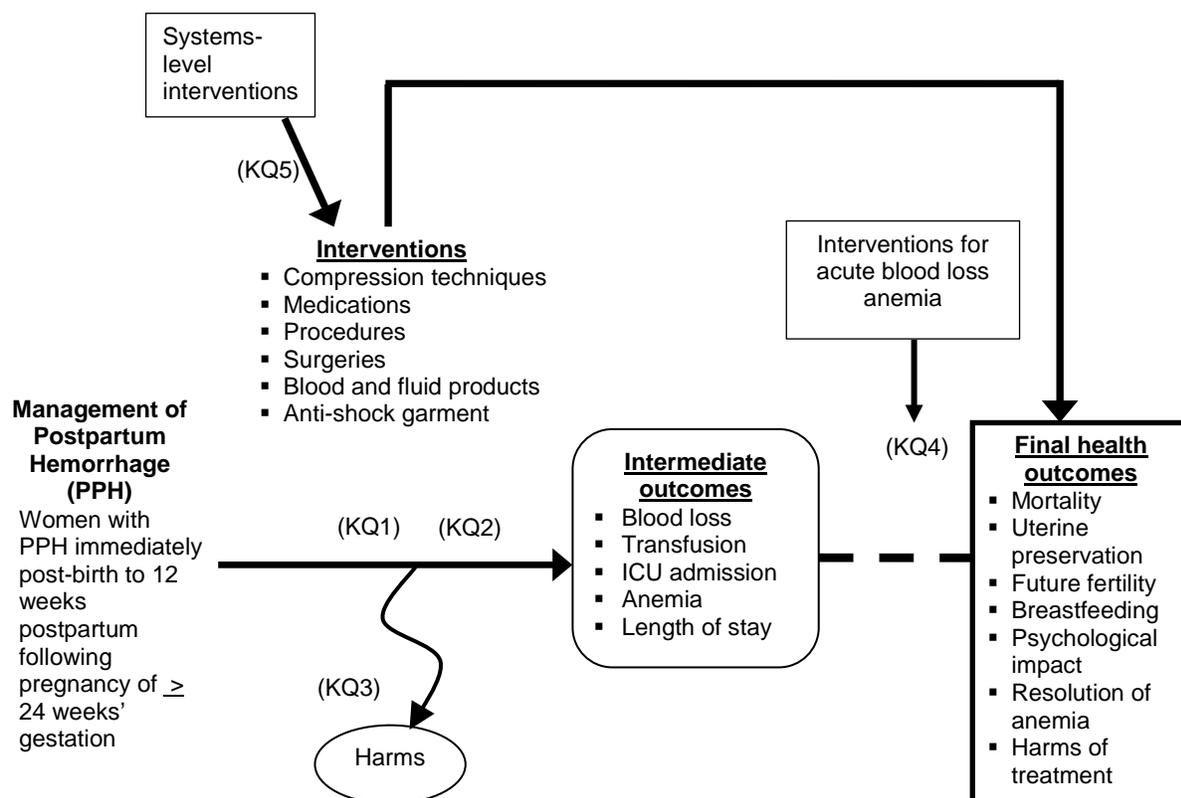
Table 2. PICOTS

PICOTS	Criteria				
Population	<ul style="list-style-type: none"> • KQ 1-3: Women with postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy > 24 weeks' gestation • KQ 4: Women with stabilized PPH and acute blood loss anemia • KQ 1-5: All modes of birth 				
Intervention(s)	<p>KQ 1-3</p> <ul style="list-style-type: none"> • Compression techniques (external uterine massage, bimanual compression, aortic compression) • Medications (oxytocin [Pitocin], misoprostol [Cytotec], methylergonovine maleate [Methergine], carboprost tromethamine [Hemabate], dinoprostone [Prostin E2], recombinant activated factor VIIa [NovoSeven], and tranexamic acid [Cyklokapron]) • Devices (Bakri postpartum balloon, Foley catheter, Sengstaken-Blakemore tube, Rusch balloon) • Procedures (manual removal of placenta, manual evacuation of clot, uterine tamponade, uterine artery embolization, laceration repair) • Surgeries (curettage, uterine and other pelvic artery ligation, uterine compression sutures, hysterectomy) • Blood and fluid products • Anti-shock garment <p>KQ 4</p> <ul style="list-style-type: none"> • Interventions for acute blood loss anemia (e.g., iron replacement, erythropoietin) <p>KQ 5</p> <ul style="list-style-type: none"> • Systems-level interventions (e.g., implementation of protocols, training) 				
Comparator	<ul style="list-style-type: none"> • Different intervention (any intervention compared with any other intervention) • Placebo 				
Outcomes	<table border="0"> <thead> <tr> <th><u>Intermediate outcomes</u></th> <th><u>Final outcomes</u></th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> • Blood loss • Transfusion • ICU admission • Anemia • Length of stay </td> <td> <ul style="list-style-type: none"> • Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms </td> </tr> </tbody> </table>	<u>Intermediate outcomes</u>	<u>Final outcomes</u>	<ul style="list-style-type: none"> • Blood loss • Transfusion • ICU admission • Anemia • Length of stay 	<ul style="list-style-type: none"> • Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms
<u>Intermediate outcomes</u>	<u>Final outcomes</u>				
<ul style="list-style-type: none"> • Blood loss • Transfusion • ICU admission • Anemia • Length of stay 	<ul style="list-style-type: none"> • Mortality • Uterine preservation • Future fertility • Breastfeeding • Psychological impact • Harms 				
Timing	<ul style="list-style-type: none"> • Immediately post-birth to 12 weeks postpartum • Primary (< 24 hours postpartum) or secondary (≥ 24 hours postpartum) 				
Setting	<ul style="list-style-type: none"> • All birth settings (hospital, birth center, home) 				

Analytic Framework

The analytic framework illustrates the population, interventions, and outcomes that guided the literature search and synthesis (Figure 1). The framework for management of PPH includes women with PPH immediately post-birth to 12 weeks postpartum following pregnancy of > 24 weeks' gestation. The figure depicts the key questions within the context of the PICOTS described in the document. In general, the figure illustrates how interventions such as compression techniques, medications, procedures, surgeries, blood and fluid products, anti-shock garments or systems-level interventions may result in intermediate outcomes such as blood loss, transfusion, ICU admission, anemia, or length of stay and/or in final health outcomes such as mortality, uterine preservation, future fertility, breastfeeding, or psychological impact. Also, adverse events may occur at any point after the intervention is received.

Figure 1. Analytic Framework



Abbreviations: KQ = key question; ICU = Intensive Care Unit

Organization of This Report

The Methods section describes the review processes including search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, methods for extraction of data into evidence tables, and compiling evidence. We also describe our approach to grading the quality of the literature and to describing the strength of the body of evidence.

The Results section presents the findings of the literature search and the review of the evidence by key question, synthesizing the findings across strategies. We present findings by intervention and outcome area where possible under each key question and focus on comparative studies of higher quality. Cohort and case-control studies, pre-post studies, case series of procedural or surgical approaches, and randomized trials are also described in more detail in summary tables for each key question. We integrate discussion of sub-questions within that for each key question because there was not adequate distinction in the literature to address them separately. We also report harms data from case series and note that harms reported in all studies of interventions for PPH are described under Key Question 3.

The Discussion section of the report discusses the results and expands on methodologic considerations relevant to each key question. We also outline the current state of the literature and challenges for future research in the field.

The report includes a number of appendices to provide further detail on our methods and the studies assessed. The appendices are as follows:

- Appendix A: Search Strategies
- Appendix B: Screening and Quality Assessment Forms

- Appendix C: Excluded Studies
- Appendix D: Evidence Tables
- Appendix E: Quality/Risk of Bias Scoring
- Appendix F: Applicability Tables
- Appendix G: Study Design Classification Algorithm

We also provide a list of abbreviations and acronyms at the end of the report.

Uses of This Evidence Report

We anticipate this report will be of primary value to organizations that develop guidelines for managing PPH and to clinicians who provide intrapartum and postpartum care for women. Interested organizations would include the American Congress of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, the American College of Nurse-Midwives, the American Academy of Family Physicians, the Association of Women's Health, Obstetric, and Neonatal Nurses, the Society of Interventional Radiology, and the Society for Obstetric Anesthesia and Perinatology.

PPH is diagnosed and treated by clinicians including obstetricians, maternal-fetal medicine physicians, midwives, family physicians, nurses, interventional radiologists, and anesthesiologists. This report supplies practitioners and researchers up-to-date information about the current state of evidence, and assesses the quality of studies that aim to determine the outcomes of treatments for PPH.

Researchers, including perinatal safety researchers, can obtain a concise analysis of the current state of knowledge of interventions in this field. They will be poised to pursue further investigations that are needed to advance research methods, develop new treatment strategies, and optimize the effectiveness and safety of clinical care for women with this potentially life-threatening condition.

This report is unlikely to be used by women and their families given that PPH is often unanticipated and requires rapid intervention due to its emergent nature.

Methods

In this chapter, we document the procedures that the Vanderbilt Evidence-based Practice Center (EPC) used to produce a comparative effectiveness review (CER) on approaches to treatment of postpartum hemorrhage (PPH). These procedures follow the methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁴⁴

Topic Refinement and Review Protocol

The topic for this report was nominated by the American College of Obstetricians and Gynecologists in a public process using the Effective Health Care website. Working from the nomination, we drafted the initial KQs and analytic framework and refined them with input from key informants representing the fields of obstetrics and gynecology, nursing, midwifery, obstetric anesthesiology, quality improvement, and perinatal safety. All members of the research team were required to submit information about potential conflicts of interest before initiation of the work. No members of the review team had any conflicts.

After review from the AHRQ, the questions and framework were posted online for public comment. No changes to the questions or framework were recommended. We also developed population, interventions, outcomes, timing, and settings (PICOTS) criteria for intervention KQs.

We identified technical experts on the topic to provide assistance during the project. The Technical Expert Panel (TEP), representing the fields of obstetrics and gynecology, midwifery, nursing, patient and perinatal safety, quality improvement, and maternal-fetal medicine, contributed to the AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included seven members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to review and provide comments as our work progressed. TEP members participated in conference calls and discussions through e-mail to:

- Help to refine the analytic framework and KQs at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria; and
- Provide input on the set of studies identified for inclusion.

The final protocol was posted to the AHRQ Effective Health Care web site and registered in the PROSPERO international register of systematic reviews (ID#: CRD42014010123).

Literature Search Strategy

Search Strategy

To ensure comprehensive retrieval of relevant studies of therapies for women with PPH, we used three key databases: the MEDLINE[®] medical literature database via the PubMed[®] interface, the Cumulative Index of Nursing and Allied Health Literature (CINAHL[®]), and EMBASE (Excerpta Medica Database), an international biomedical and pharmacological literature database via the Ovid[®] interface. Search strategies applied a combination of controlled vocabulary (Medical Subject Headings [MeSH], CINAHL medical headings, and Emtree headings) to focus specifically on management of PPH and harms of interventions. We restricted

literature searches to studies published from 1990 to the present to reflect current standards of care for PPH. Interventions such as the B-Lynch suture were introduced in the late 1990s,⁴⁵ and embolization techniques were not widely used until the mid- to late-1990s.^{46, 47} Misoprostol was initially used as a treatment for gastric ulcer and not broadly used for PPH prevention or treatment until the 2000s. The World Health Organization recommended its use for prevention of PPH in 2007.^{48, 49} Given that currently used interventions were not in widespread use prior to 1990, we set 1990 as a conservative lower bound for the search.

We only included studies published in English as a review of non-English citations retrieved by our MEDLINE search identified few studies of relevance. Appendix A lists our search terms and strategies and the yield from each database. Searches were executed in September 2014.

We carried out hand searches of the reference lists of recent systematic reviews or meta-analyses of therapies for PPH. The investigative team also scanned the reference lists of studies included after the full-text review phase for additional studies that potentially could meet our inclusion criteria.

Grey Literature

AHRQ's Scientific Resource Center requested Scientific Information Packets (SIPs) from companies that produce medications or devices with U.S. Food and Drug Administration (FDA) approval for management of uterine bleeding (oxytocin [Pitocin®], misoprostol [Cytotec®], methylergonovine maleate [Methergine®], carboprost tromethamine [Hemabate®], dinoprostone[Prostin E2®], recombinant coagulation factor VIIa [NovoSeven®], and tranexamic acid [Cyklokapron®]; and devices for PPH including Bakri™ postpartum balloon, non-pneumatic anti-shock garment [NASG], Foley catheter, Sengstaken-Blakemore tube, and the Rusch balloon) and searched for regulatory data for approved products. We also searched ClinicalTrials.gov to assess publication bias and to identify any study results that may not have been identified in our other database searches.

Inclusion and Exclusion Criteria

Table 3 lists the inclusion/exclusion criteria we used based on our understanding of the literature, key informant and public comment during the topic-refinement phase, input from the TEP, and established principles of systematic review methods.

Table 3. Inclusion criteria

Category	Criteria
Study population	<ul style="list-style-type: none"> • KQ1-3, 5: Women with postpartum hemorrhage (PPH) immediately post-birth to 12 weeks postpartum following pregnancy > 24 weeks' gestation • KQ4: Women with stabilized PPH and acute blood loss anemia • All modes of birth in any setting
Time period	1990 to present
Publication languages	English only
Country	Very High Human Development countries as indicated by the United Nations Development Programme Human Development Index. Countries as of April 2014 include: Norway, Australia, US, Netherlands, Germany, New Zealand, Ireland, Sweden, Switzerland, Japan, Canada, Republic of Korea, Hong Kong, Iceland, Denmark, Israel, Belgium, Austria, Singapore, France, Finland, Slovenia, Spain, Liechtenstein, Italy, Luxembourg, U.K., Czech Republic, Greece, Brunei Darussalam, Cyprus, Malta, Andorra, Estonia, Slovakia, Qatar, Hungary, Barbados, Poland, Chile, Lithuania, United Arab Emirates, Portugal, Latvia, Argentina, Seychelles, and Croatia

Table 3. Inclusion criteria (continued)

Category	Criteria
Admissible evidence (study design and other criteria)	<p data-bbox="505 266 716 296"><u>Admissible designs</u></p> <ul data-bbox="505 310 1435 533" style="list-style-type: none"> <li data-bbox="505 310 1435 422">• KQ 1-2, 4: RCT or prospective/ retrospective cohort studies, population-based case series or registry studies with ≥ 50 cases of PPH treatment, case series of procedures (uterine tamponade, uterine artery embolization) or surgical approaches with ≥ 50 women <li data-bbox="505 428 1435 478">• KQ 3: RCT or prospective/ retrospective cohort studies, case series with ≥ 50 cases addressing interventions for PPH <li data-bbox="505 485 1435 533">• KQ 5: Pre- and post-studies related to large-scale health systems changes, RCTs, prospective/retrospective cohort studies <p data-bbox="505 562 651 592"><u>Other criteria</u></p> <ul data-bbox="505 606 1435 1161" style="list-style-type: none"> <li data-bbox="505 606 1435 657">• Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results <li data-bbox="505 663 1435 714">• Studies targeting women with PPH and meet the population criteria as described above <li data-bbox="505 720 1435 942">• Studies that address: <ul data-bbox="602 747 1435 942" style="list-style-type: none"> <li data-bbox="602 747 1435 827">○ Treatment modality aimed at treatment/management of PPH in a relevant population or treatment for acute blood loss anemia following stabilization of PPH <li data-bbox="602 833 1435 942">○ Outcomes related to interventions; primary outcomes of interest include blood loss, transfusion, ICU admission, anemia, length of stay, mortality, uterine preservation, future fertility, breastfeeding, and psychological impact, and harms. <li data-bbox="505 949 1435 999">• Studies must include extractable data presented in text or tables (vs. solely in figures) on relevant outcomes <li data-bbox="505 1005 1435 1161">• For KQ 5, studies must explicitly assess effects of an systems-level intervention on PPH management as a primary or secondary aim; analytic models must indicate data analysis of the effect of the strategy as it relates to PPH treatment; results data include information about effects of strategy on management of PPH; discussion interprets the strategy as potentially having value/not having value for PPH management

Abbreviations: KQ = key question; ICU = Intensive Care Unit; PPH-postpartum hemorrhage; RCT = randomized controlled trial

Case series comprise much of the literature addressing treatments for PPH. We limited inclusion of case series to those with at least 50 cases of PPH in order to balance the need to identify rigorously conducted studies with identifying studies large enough to suggest effects of the interventions. We include effectiveness and harms data from case series of procedural (uterine tamponade, uterine artery embolization) and surgical (arterial ligation, uterine compression sutures, hysterectomy) approaches because they report pertinent evidence for the effects of such interventions that are unlikely to be found in randomized controlled trials (RCTs). These procedural and surgical approaches are rarely addressed in RCTs, and patients who would be receiving these second-line interventions have an unstable and emergent health status and typically are not eligible for RCTs.

We also limited studies to those published in English and conducted in Very High Human Development countries as ranked by the United Nations Development Programme Human Development Index (Table 3). In the opinion of our clinical experts, processes of care and interventions available in these countries best reflect the system of health care in the United States. A considerable body of evidence addresses PPH management in developing countries; however, the limited availability of skilled clinicians and treatment options in many of these countries results in different standards of care and clinical approaches than those in the United States.

PPH is a complex condition. Treatments are selected not only by PPH etiology and severity but also by factors related to the setting of care, the availability of medications or other therapeutic options, the availability of personnel, and the standards of care in a given treatment center. Treatment availability and feasibility of providing certain treatments differ across developed and developing nations, and even within any given nation. Because the context of care in most developing nations differs significantly from care in the United States,^{50, 51} we instituted language and country limitations in order to identify studies that are most applicable to guiding care by clinicians in the United States, who are the intended audience for this report.

In order to provide contextual information about effectiveness and harms reported in studies conducted in developing nations, we provide summaries of recent reviews of interventions for PPH, which include studies conducted in any country in the Discussion section (Findings in Relation to What's Known).

Study Selection

Once we identified articles through the electronic database searches and hand-searching, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion or exclusion, using an Abstract Review Form (Appendix B). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. Following abstract review, two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion/exclusion criteria. Disagreements between reviewers were resolved by a senior reviewer. All abstract and full text reviews were conducted using the DistillerSR online screening application (Evidence Partners Incorporated, Ottawa, Ontario). Appendix C includes a list of excluded studies and the reasons for exclusion.

Data Extraction

The staff members and clinical experts (including two nurse-midwives, three obstetrician/gynecologists, one hematologist, and two epidemiologists) who conducted this review jointly developed the evidence tables. We designed the tables to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to our key questions. Two evidence table templates were employed to facilitate the extraction of data based on study type; one form was designed for case series that reported harms data and one to accommodate all types of comparative studies and population-based case series. We based the format of our evidence tables on successful designs used for prior systematic reviews.

The team was trained to extract data by extracting several articles into evidence tables and then reconvening as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. A second team member also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. A senior reviewer reconciled disagreements concerning the information reported in the evidence tables.

The full research team met regularly during the article extraction period and discussed global issues related to the data extraction process (e.g., determining harms of treatment vs. harms of PPH itself). In addition to outcomes related to intervention effectiveness, we extracted all data available on harms. Harms encompass the full range of specific negative effects, including the

narrower definition of adverse events. The final evidence tables are presented in their entirety in Appendix D.

Data Synthesis

We considered conducting a meta-analysis, but the small number of comparative studies of any given intervention and the heterogeneity of interventions and outcomes made a meta-analysis inappropriate. We completed evidence tables for all included studies (Appendix D), and data are presented in summary tables and analyzed qualitatively in the text.

We also tabulated success rates reported in studies of procedures and surgical approaches in which we could extract data on the effectiveness of the first intervention following conservative management. We refer to these as "initial second-line interventions." Some studies reported success rates for procedures and/or surgeries only in combination or after multiple interventions; therefore, not all studies addressing a given intervention are represented in these tables. When multiple second-line interventions are combined in analysis, it is impossible to determine which of these stopped the bleeding and thus would be reasonable to use initially. We defined success for a specific intervention as control of bleeding without need for subsequent medical or surgical interventions (not including transfusion or iron supplementation). In some cases, bleeding may have ceased, but a participant ultimately died. If death was not considered to be related to the intervention but was thought to be caused by the PPH and its sequelae, we include the case in the estimate of successful control of bleeding.

Quality (Risk of Bias) Assessment of Individual Studies

We used separate tools appropriate for specific study designs to assess quality of individual studies: the Cochrane Risk of Bias tool for RCTs,⁵² the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies,⁵³ the National Heart, Lung, and Blood Institute's (NHLBI) Quality Assessment Tool for Before-After (Pre-Post) Studies,⁵⁴ and a tool adapted from questions outlined in the RTI item bank to assess case series.⁵⁵ We used questions adapted from the RTI item bank and from the McMaster McHarms⁵⁶ tools to assess reporting of harms.

The Cochrane Risk of Bias tool is designed for the assessment of studies with experimental designs and randomized participants. Fundamental domains include sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting bias. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of nonrandomized studies and assesses three broad perspectives: the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. The NHLBI tool considers questions related to study objectives, description of participants and intervention, outcome assessment, length of followup, and statistical analysis and is designed for studies without a control group. Similarly, the case series and harms tools address questions related to participant and outcome assessment and pre-specification of harms.

Quality assessment of each study was conducted independently by two team members using the forms presented in Appendix B. Any discrepancies were adjudicated by the two team members or a senior investigator. Investigators did not rely on the study design as described by authors of individual papers; rather, the methods section of each paper was reviewed to determine which rating tool to employ. The results of these tools were then translated to the Agency for Healthcare Research and Quality standard of "good," "fair," and "poor" quality as described below. Appendix E reports quality scoring for each study.

Determining Quality Ratings

- We required that RCTs receive a positive score (i.e., low risk of bias for RCTs) on all of the questions used to assess quality to receive a rating of good/low risk of bias. RCTs had to receive at least five positive scores to receive a rating of fair/moderate risk of bias, and studies with \leq four positive ratings were considered poor quality/high risk of bias. We considered a score of “unclear” for a question as a positive score as long as the consensus of the investigators assessing quality was that study outcomes were not likely to be biased by the factor.
- We required that case-control or cohort studies receive positive scores (stars) on all elements to receive a rating of good, ≤ 2 negative ratings for fair, and > 2 negative scores for a rating of poor quality.
- For pre-post studies we required that studies receive positive scores on all questions to receive a rating of good. We considered studies with \leq four negative ratings as fair quality and those with more than four as poor quality.
- We required that studies assessed for harms reporting receive a positive rating (i.e., affirmative response) on all four questions to receive a rating of good. Studies with at least three positive responses were considered fair quality and those with less than three positive responses as poor quality.
- Case series have inherently high risk of bias and presumptive low quality. Nonetheless, prospective case series that enroll participants consecutively and control for potentially confounding factors may provide evidence to support comparative studies. We assessed case series using questions identified in the AHRQ Effective Health Care program’s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁴⁴ The elements on which they were scored and the results are presented in Appendix E.

Strength of the Body of Evidence

We applied explicit criteria for rating the overall strength of the evidence for each key intervention-outcome pair for which the overall risk of bias is not overwhelmingly high. We established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

The strength of evidence evaluation is that stipulated in the Effective Health Care Program’s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*⁴⁴ and in the updated strength of evidence guide⁵⁷ which emphasizes five major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias. Study limitations are derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome for each comparison of interest is given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence was graded as outlined in Table 4. Two senior staff members independently graded the body of evidence; disagreements were resolved as needed through discussion or third-party adjudication. We recorded strength of evidence assessments in tables, summarizing results for each outcome. We considered case series in the assessment of

strength of the evidence for harms and for success of procedural and surgical interventions as such interventions are not likely to be represented in RCTs given the emergent nature of PPH treatment. We presumed the quality of case series providing data to assess the success of interventions to be low.

Table 4. Strength of evidence grades and definitions*

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

*Excerpted from Berkman et al. 2013³⁷

Applicability

We assessed the applicability of findings reported in the included literature to the general population of women who experience PPH by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipated that areas in which applicability would be especially important to describe would include the definition and severity of PPH, the age range and parity of the participants, and the setting in which the intervention took place. Applicability tables for each intervention are in Appendix F.

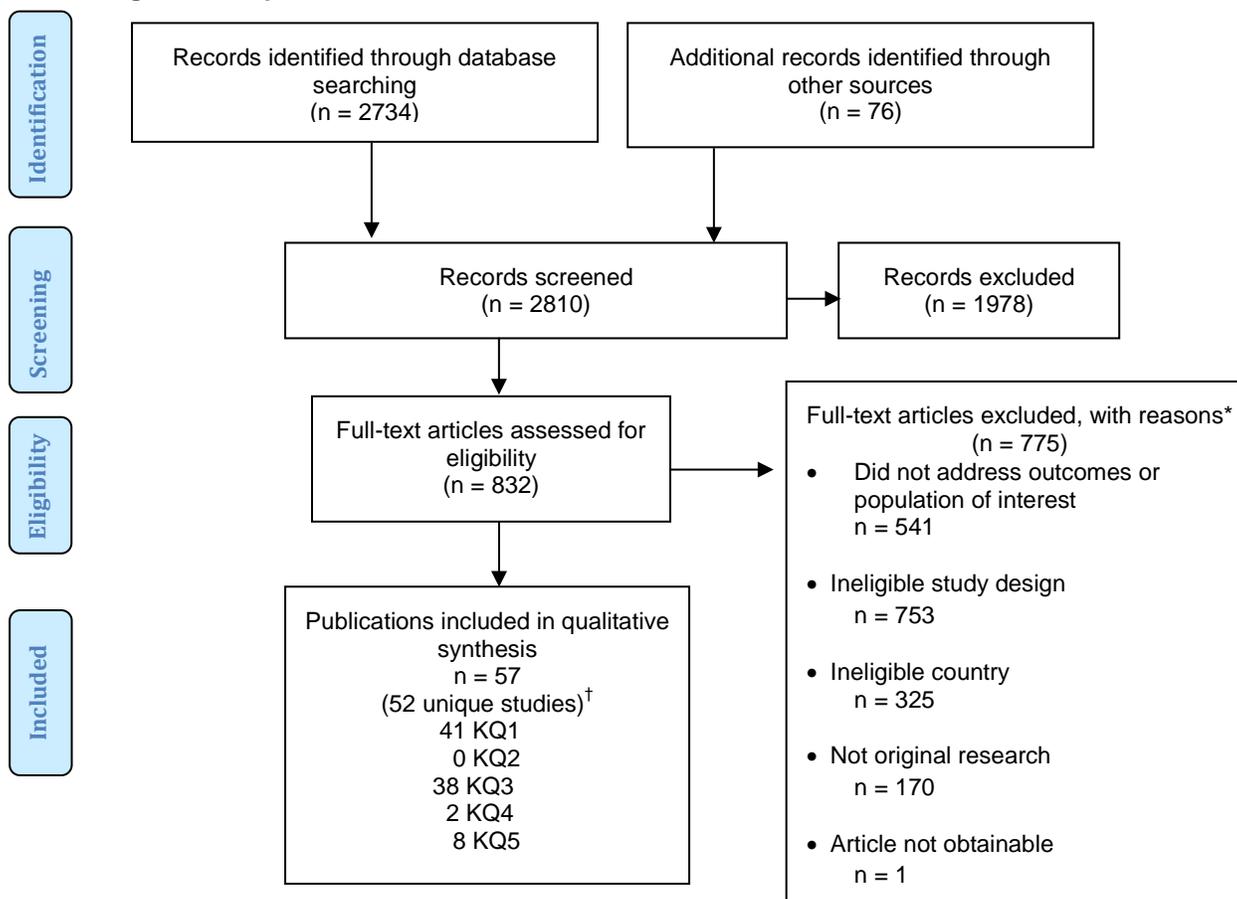
Results

Results of Literature Searches

We identified 2,810 nonduplicative titles or abstracts with potential relevance, with 832 proceeding to full text review (Figure 2). We excluded 775 studies at full text review and included 52 unique studies (57 publications) in the review. We present findings by intervention and outcome area where possible under each key question. Comparative studies and case series that provided harms or data on successful controlling of bleeding are also described in more detail in summary tables in each key question. We tabulated success rates reported in studies of procedures and surgical approaches in which we could extract data on the effectiveness of the intervention as the initial second-line intervention (i.e., first intervention following routine conservative management) and defined success as controlling of bleeding without need for additional procedures or surgeries.

We integrate discussion of sub-questions within that for each key question because there was not adequate distinction in the literature to address them separately. Harms of interventions for postpartum hemorrhage (PPH) are described under Key Question (KQ) 3. Transfusion as an intervention for anemia following stabilization of PPH is addressed under KQ4, and transfusion as an intervention to manage ongoing PPH is described under KQ1. We also briefly summarize the strength of the evidence (SOE) for interventions and key outcomes in each Key Points section and describe SOE more fully in the Discussion section.

Figure 2. Disposition of studies identified for this review



†Numbers next to each Key Question indicate number of unique studies addressing the question. Studies could address more than one Key Question.

*Numbers do not tally as studies could be excluded for multiple reasons. KQ = key question; n = number.

Description of Included Studies

The 52 unique studies included in the review comprise four randomized controlled trials (RCTs), two prospective and 13 retrospective cohort studies, eight pre-post studies (defined as studies that compare PPH management and/or outcomes before and after an intervention, such as introduction of a new protocol), two case-control studies, and 23 case series. Most studies were conducted in Europe (n = 28), and 13 were conducted in the United States, eight in Asia, and two in Australia or New Zealand and one in Argentina (Table 5). No studies were of good quality for effectiveness outcomes. We considered 20 studies as fair quality for effectiveness outcomes and 30 as poor quality (including case series, which we considered poor quality by default). Two studies (one retrospective cohort, one case series) provided only harms data.^{58, 59} Among the 38 studies reporting harms of interventions for management of PPH, we considered seven as good quality for harms reporting and 31 as poor quality.

While a number of studies were classified as prospective or retrospective studies using our study classification algorithm (Appendix G), few cohort studies provided comparative analyses, and many were confounded by indication in that women who received interventions such as massive transfusion or hysterectomy likely had more severe cases of PPH. Additionally, initial

management of PPH using first-line interventions such as uterotonics and uterine massage differed across studies and across women as each study generally included a number of patients transferred from other hospitals. Thus, populations were heterogeneous in terms of severity and level of stabilization prior to second-line interventions. Given the lack of data from randomized or controlled studies of PPH management, we present data from cohort studies and case series and note potential confounding.

Table 5. Characteristics of included studies

Characteristic	RCTs[†]	Prospective Cohort Studies	Retrospective Cohort Studies	Pre-post Studies	Case-control Studies	Population-based Case Series	Retrospective Case Series	Total Literature[*]
Intervention								
Pharmacologic	1	1	4	0	1	3	0	10
Transfusion	0	0	3	0	0	2	0	5
Uterine tamponade	0	0	0	1	0	0	1	2
Uterine artery embolization	0	2	4	0	1	0	9	16
Uterine and other pelvic artery ligation	0	1	1	0	0	0	2	4
Uterine compression sutures	0	1	0	0	0	0	1	2
Hysterectomy	0	1	2	0	0	4	1	8
Combined interventions	0	0	2	0	0	0	2	4
Interventions for anemia	2	0	0	0	0	0	0	2
Systems-level interventions	1	0	0	7	0	0	0	8
Population Characteristics								
Study population								
U.S./Canada	0	0	3	3	0	4	3	13
Europe	3	2	6	5	2	4	6	28
Asia	0	0	4	0	0	0	4	8
Other	1	0	0	0	0	1	1	3

Table 5. Characteristics of included studies (continued)

Characteristic	RCTs [†]	Prospective Cohort Studies	Retrospective Cohort Studies	Pre-post Studies	Case-control Studies	Population-based Case Series	Retrospective Case Series	Total Literature [*]
Initial Management[‡] (N studies explicitly reporting component)								
Uterotonics/Prostaglandins	1	1	5	1	1	5	9	23
Uterine massage or compression	0	0	3	0	1	1	7	12
Manual exploration and/or placenta removal	0	1	2	0	0	3	5	11
Suture of lacerations	0	0	1	0	0	0	5	6
Transfusion (any blood product)	1	2	2	0	0	4	2	11
Total N participants	737	477	142218^{††}	2198^{**}	65	3585	2275	152197

rFVIIa-recombinant activated factor VIIa; RCT-randomized controlled trial

[†]Does not include N participants in one systems-level RCT.³⁶

^{*}Total across interventions exceeds 52 as some interventions were addressed in multiple studies.

[‡]N studies reporting a specific component out of 24 studies that explicitly reported components of initial management.

^{††}One cohort study using data from a utilization database includes 139,617 women exposed to methylergonovine during hospitalization for birth.

^{**}Ns from post periods.

Key Question 1. Effectiveness of Interventions for Management of PPH

Studies of Medical Interventions

Pharmacologic Interventions

Key Points

- Five small, single studies of fair and poor quality addressed various pharmacologic interventions not including recombinant activated factor VIIa (rFVIIa) with mixed results.
- In one RCT of tranexamic acid (TXA), blood loss, progression to severe PPH, and need for transfusion were reduced in the TXA arm compared with the non-TXA control arm, but need for further interventions did not differ.
- Need for transfusion or further interventions did not differ in a retrospective cohort study comparing misoprostol and methylergonovine maleate.
- In a small, population-based case series, sulprostone stopped bleeding in 83 percent of participants without need for further intervention.
- Carboprost tromethamine controlled bleeding in 88 percent of women in a small, population-based case series.

- Blood loss and transfusion in women with PPH and disseminated intravascular coagulation (DIC) did not differ in a retrospective study comparing women who received recombinant thrombomodulin with matched controls who did not receive the drug.
- Five small studies of rFVIIa also had mixed results. In one retrospective cohort study, women in the rFVIIa group required more blood products and had greater blood loss than women not receiving the treatment. Differences in change in prothrombin time were not significant between women treated with rFVIIa and those who were not in a case-control study. rFVIIa used as a second-line intervention controlled bleeding without need for further procedures or surgeries in 27 to 31 percent of women in one cohort study, a rate that was similar to treatment with other second-line interventions in that study. In registry studies bleeding was considered improved after one or multiple doses of rFVIIa in 64 to 80 percent of women. No study included more than 108 women receiving rFVIIa.
- Strength of the evidence is insufficient for all outcomes of misoprostol, tranexamic acid, carboprost tromethamine, thrombomodulin, and rFVIIa for PPH management due to the study sizes and lack of studies addressing each agent.

Overview of the Literature

Ten studies addressed pharmacologic agents for the treatment of PPH:⁶⁰⁻⁶⁹ one RCT,⁶⁰ four cohort studies,^{63, 64, 68, 69} one case-control study,⁶⁵ and four population-based case series or registry studies.^{61, 62, 66, 67} Studies were conducted in France,^{60, 61} the United States,^{62, 69} Finland,⁶⁴ Ireland,⁶⁵ Japan,⁶³ the United Kingdom,⁶⁸ and Australia and New Zealand.⁶⁷ One registry study reported data from various northern European countries.⁶⁶

Five of these studies (two cohort studies,^{64, 68} one case-control,⁶⁵ and two registry studies^{66, 67}) addressed rFVIIa. The studies included a total of 320 women, and atony accounted for many of the cases of PPH in studies reporting etiology (range = 18 to 56% of cases).

Other agents were each addressed in one study: tranexamic acid (one RCT, n = 144),⁶⁰ misoprostol compared with methylergonovine maleate (one retrospective cohort, n = 58),⁶⁹ sulprostone (one population-based case series, n = 1,370),⁶¹ carboprost tromethamine (one registry study, n = 236),⁶² and recombinant human soluble thrombomodulin (rTM; one cohort study, n = 36).⁶³ Two studies included only women with atonic PPH,^{61, 62} and, where reported, atony accounted for 36 to 65 percent of cases. In total these studies included 1,844 women with PPH. We rated the RCT as poor quality for all effectiveness outcomes and the five cohort and case-control studies as fair quality. The case series were considered poor quality by default. Table 6 provides an overview of key outcomes.

Detailed Analysis

Tranexamic Acid

A single RCT (rated poor quality for all efficacy outcomes) with 144 participants reported reduction of blood loss in women with PPH treated with high-dose TXA (n = 72).⁶⁰ The RCT was an open-label trial at multiple centers in France and included women with PPH > 800 mL following vaginal birth. All women received packed red blood cells (PRBCs) and colloids as ordered by clinicians. The use of additional procoagulant treatments was permitted only in cases involving intractable bleeding. The treatment group received TXA in a loading dose of 4 g over 1 hour, then infusion of 1 g/hour over 6 hours. Women in the control group did not receive TXA, and groups did not differ on maternal or obstetric characteristics at baseline. The primary

outcome was efficacy of TXA in the reduction of blood loss as measured using collection pouches. The volume of blood loss between enrollment and 6 hours later was significantly lower in the TXA group (median = 173 mL; first to third quartiles, 59 to 377) than in the control group (median = 221 mL; first to third quartiles 105 to 564, $p = 0.041$).

Secondary outcomes included PPH duration, anemia, transfusion, and the need for invasive interventions. In the TXA group, bleeding duration was shorter and progression to severe PPH and PRBC transfusion was less frequent than in the control group ($p < 0.03$). PPH stopped after only uterotonics and PRBC transfusion in 93 percent of the women who received TXA versus 79 percent of the women in the control group ($p = 0.016$). There was no significant difference between the groups in the ratio of invasive interventions performed.

Misoprostol versus Methylergonovine Maleate

A fair quality retrospective cohort study compared intramuscular methylergonovine maleate versus rectal misoprostol for patients who had a clinical diagnosis of PPH and were treated between 2000 and 2005.⁶⁹ Inclusion criteria were gestational age at birth of 37 to 42 weeks, singleton pregnancy, a “clinical diagnosis of PPH” in the medical record, and the patient “required something more than standard oxytocin.” Fifty-eight records were included for review. Forty patients received misoprostol, and 18 received methylergonovine maleate. The study reported no differences between the groups in age, gestational age, or type of birth. There were no differences in the need for blood transfusion, “third-level” medical treatment, or surgical interventions. However, the number of participants was small; therefore, the apparent lack of difference in outcomes could be due to Type II error. Furthermore, the assignment to intervention was by provider choice, which introduced selection bias.

Sulprostone

One retrospective population-based case series reports outcomes following sulprostone administration in women with PPH (defined as blood loss of ≥ 500 mL of blood loss necessitating manual placenta removal and/or uterine examination) who were treated at one of 106 French maternity hospitals.⁶¹ Outcomes related to a multifaceted educational intervention conducted in these hospitals with the aim of lowering PPH rates are described under KQ5.^{36, 70} Among the 9,365 cases of PPH occurring in the study period (2004-2006), 4,038 women had clinically assessed atonic PPH, of whom 1370 received sulprostone (995 after vaginal birth, 375 after cesarean birth). Women received additional treatments including uterine cavity or genital tract examination ($n = 1634$), oxytocin ($n = 1297$), and vascular volume expansion ($n = 653$). Among women who received sulprostone, bleeding stopped without the need for additional procedures or surgeries in 83.4 percent. Need for a third-line intervention was more common after cesarean birth compared with vaginal birth (26.1% vs. 13%, $p < .01$).

Carboprost Tromethamine

A retrospective population-based case series reviewed carboprost tromethamine for PPH in 236 women (237 cases of PPH) at 12 U.S. obstetrics units.⁶² The women (mean age 25.3 ± 5.7 years) were given either 125 micrograms or 250 micrograms of carboprost tromethamine (range one to five doses), preceded in 96 percent of cases by oxytocics. The decision to administer carboprost tromethamine was made at the discretion of independent practitioners. Hemorrhage was controlled in 208 of 237 cases (87.8%). In 17 cases, PPH was controlled with additional oxytocics. Second-line treatments in the 12 women in which carboprost tromethamine failed included nine arterial ligations (followed by hysterectomy in four cases) and immediate

hysterectomy in three women. Twenty-seven percent of women received transfusions, but the timing of transfusion (pre- or post-carboprost tromethamine) is not clear.

Recombinant Human Soluble Thrombomodulin (rTM)

A fair quality retrospective cohort of the use of rTM in 10 consecutive patients with severe PPH complicated by DIC reported no significant difference in total blood loss or transfusion requirements between those treated with rTM and matched controls.⁶³ All 36 patients were admitted to a single tertiary center. The primary outcome was the efficacy of recombinant human soluble thrombomodulin (rTM) in disseminated intravascular coagulation (DIC) associated with severe PPH. Ten consecutive patients with DIC associated with severe PPH were treated with rTM. Twenty-six patients with DIC associated with severe PPH were chosen for comparison. The baseline characteristics of the control group were described as “similar” to the treated group. On day 2 following treatment, D-dimer decrease from baseline was significantly greater in the rTM group compared with the control group ($p < .05$). The intervention is targeted for DIC, and is not a treatment for PPH without the presence of DIC.

Table 6. Key outcomes in comparative studies of pharmacologic agents

Author, Year Country Groups (n) Quality	Age, Years Parity	Key Outcomes
Ducloy-Bouthers et al. 2011 ⁶⁰ France G1: Tranexamic acid (78) G2: Control (74) Quality: Poor/High risk of bias for all outcomes	Age, mean \pm SD G1: 29 \pm 4 G2: 28.5 \pm 5 Primipara, n (%) G1: 46 (64) G2: 50 (69)	<ul style="list-style-type: none"> • Blood loss for G1 was significantly lower vs G2 (G1: median 170 mL vs G2: median 221 mL) • Bleeding duration was shorter for G1: n = 28 (36%) with persistent bleeding after 6 hours vs G2: n = 37 (50%), p = 0.03
Baruah et al., 2008 ⁶⁹ US G1: Misoprostol (40) G2: Methylergonovine maleate (18) Quality: Fair	Age, n (%) Under 20 G1: 6 (15) G2: 1(5.5) 20-29 G1: 14 (35) G2: 9 (50) 30-39 G1: 19 (47.5) G2: 8 (44.4) \geq 40 G1: 1(2.5) G2: 0 Primipara, n (%) G1: 14 (35) G2: 6 (33)	<ul style="list-style-type: none"> • 5 women in G1 needed transfusion and none in G2, p = 0.11 • Need for third line medical or surgical therapy was comparable G1: 27 (67.5%) vs G2: 14 (77.8%) • One woman in each group had hysterectomy

Table 6. Key outcomes in comparative studies of pharmacologic agents (continued)

Author, Year Country Groups (n) Quality	Age, Years Parity	Key Outcomes
Sugawara et al. 2013 ⁶³ Japan G1: Recombinant thrombomodulin (10) G2: No thrombomodulin (26) Quality: Fair	Age, Mean ± SEM G1: 33.2 ± 1.7 G2: 31.7 ± 1.1 Parity NR	<ul style="list-style-type: none"> • Participants did not differ at baseline on blood loss, transfusions, obstetrical complications; shock index (PPH severity) significantly greater in G1 vs. G2 (p < .05) • G1 received 380 U/kg/day thrombomodulin for 3.0 ± 0.6 days + blood products as needed; incidence of undefined bleeding symptoms was not significantly less in G1 vs. G2 (22.2% vs. 42.3% at day 1 and 11.1% vs. 19.2% at day 2, p = .28) • No adverse events associated with either group were reported

G-group; NR-not reported; SEM-standard error of the mean

Recombinant Activated Factor VIIa (rFVIIa)

A fair quality retrospective cohort study in Finland compared the effectiveness of rFVIIa versus standard management (no rFVIIa) among women with PPH (defined as loss of 1.5 times patient's blood volume).⁶⁴ Eligible participants were identified using medical records at a single tertiary referral hospital. Of the 48 women identified, 26 were treated with rFVIIa and 22 were not. There were no statistically significant differences in age, body mass index (BMI), obstetrical course (cause of PPH, mode of birth, length of hospital stay after birth), lowest hemoglobin, or lowest platelet count between the two groups. Activated partial thromboplastin time, liters of total bleeding (11.3 vs. 8.0, p = 0.005), units of RBC (20 vs. 13, p = 0.003), units of platelets (23 vs. 14, p = 0.014), and number with fibrinogen concentrate transfused (15 vs. 5, p = 0.014) were significantly greater among women treated with rFVIIa than among untreated women. There was no statistical comparison of maternal or fetal outcomes between the groups.

A retrospective case-control study in Ireland compared the effectiveness of rFVIIa in reversing coagulopathy associated with massive PPH versus standard management (no rFVIIa) between 2003 and 2006.⁶⁵ Twenty-eight women with massive PPH (defined as transfusion of > 5 units of PRBC in 24 hours) were identified using medical records at a single Irish hospital. Of these, six women who were treated with rFVIIa and had a prolonged prothrombin time (PT) were matched with six women with the largest number of PRBC units transfused and prolonged PTs who were not treated with rFVIIa. There were no statistically significant differences in age, obstetrical factors (gestation, parity, cause of massive PPH, or number of hysterectomies), or coagulopathy factors (PRBC, platelets, fresh frozen plasma [FFP], or cryoprecipitate transfused, or worst PT or fibrinogen levels) between the two groups. The PT improved with management in both groups, and there was no significant difference in the magnitude or absolute value of improvement (p = 0.9). There was no statistical comparison of maternal or fetal outcomes between the groups.

One fair quality cohort study used data from the U.K. Obstetric Surveillance System (UKOSS). The UKOSS includes all hospitals with a consultant-led maternity unit in the United Kingdom. Clinicians in these hospitals reported data on PPH cases and treatment to the UKOSS using case notification cards completed monthly. UKOSS personnel also followed up with hospitals to identify potential missed cases. In this study, 31 women received rFVIIa as the first second-line therapy after failure of conservative PPH management approaches. Sixteen received

rFVIIa after uterotonic failure, and 15 received it after failure of uterotonics plus intrauterine tamponade (either with balloon or packing). Among the 16 who had received only uterotonics plus rFVIIa, 11 had successful cessation of bleeding. One required compression sutures, two had ligations, one had interventional radiology, and seven required hysterectomy to control bleeding. Thus, the success rate (control of bleeding without further procedures or surgeries) for rFVIIa was 31 percent. Among the 15 who had rFVIIa after intrauterine tamponade plus uterotonics, seven required hysterectomy while interventional radiology controlled bleeding after rFVIIa in four (27% success rate for rFVIIa plus tamponade).⁶⁸

Two registry studies also assessed use of rFVIIa. A voluntary registry study described outcomes of treatment of PPH with rFVIIa in nine Northern European countries.⁶⁶ Eligible women (128 total identified, 108 included in the analysis) were identified differently in each country, with most identified by physicians or pharmacists who responded to requests for information about use of rFVIIa for treatment of PPH. In Finland and the Netherlands, information was collected for national surveys prior to initiation of this study, and those data were provided to the study group. Information on study endpoints was gathered retrospectively via standardized surveys completed by local practitioners in some instances and via national survey data in others. The registry gathered information on hematologic parameters after the use of rFVIIa as the primary treatment for PPH and as secondary prophylaxis if other interventions were used prior to rFVIIa. Clinicians noted improvements in bleeding after a single dose in 80 percent of the 92 women receiving rFVIIa to treat PPH and in 75 percent of the 16 women receiving it as secondary prophylaxis. Clinicians judged rFVIIa as failing to control bleeding in 15 cases overall (13.8%) Hemoglobin increased in 51 percent of cases in which bleeding was reduced after rFVIIa and showed no significant change in 32 percent of cases. Hemoglobin levels dropped post-administration in 17 percent of cases.

A comprehensive registry study was performed to describe outcomes of off-label use of rFVIIa for treatment of PPH in Australia and New Zealand.⁶⁷ Cases were identified between 2002 and 2008 from the Australian and New Zealand Haemostasis Registry (ANZHR), representing approximately 50 percent of hospitals in those countries. Data were collected via standardized data forms from 105 case medical records and treating clinicians of women with acute obstetric hemorrhage who received rFVIIa. Overall, bleeding stopped or decreased in 76 percent of women. Most (78%) women received a single dose of rFVIIa, and 64 percent of these women had decrease or cessation of bleeding. Median dose of rFVIIa was 92 micrograms/kg (range 9 to 139). Most women (76%) required < 6 units PRBC transfusion after receiving rFVIIa, and 13 women (21%) required hysterectomy after rFVIIa failed to control bleeding.

Table 7 outlines key outcomes.

Table 7. Key outcomes in comparative studies of rFVIIa

Author, Year Country Groups (n) Quality	Age Parity	Key Outcomes
Ahonen et al., 2007 ⁶⁴ Finland G1: rFVIIa (26) G2: control (22) Quality: Fair	Age, mean ± SD G1: 33 ± 4 G2: 35 ± 4 Nulliparous, n (%): G1: 12 (46) G1: 12 (54.5)	<ul style="list-style-type: none"> • Response to rFVIIa was considered good (n = 17, 65%), moderate (n = 3, 12%), and poor (n = 6, 23%) • Blood loss (liters) was significantly greater in G1 (mean 11.3 ± 4.5) vs G2 (mean 8.0 ± 3.1)
McMorrow et al., 2008 ⁶⁵ Ireland G1: rFVIIa (6) G2: control (6) Quality: Fair	Age, mean ± SD G1: 34 ± 2.8 G2: 31 ± 4.6 Parity, mean ± SD: G1: 2 ± 0.5 G1: 1 ± 0.75	<ul style="list-style-type: none"> • Prothrombin time improved in both groups with no significant differences between the groups (p = 0.09) • Women in both groups received uterotonics (oxytocin, ergometrine, misoprostol, carboprost tromethamine), and uterine massage • The number of hysterectomies performed was comparable in G1: 50% and G2: 67%
Kayem et al. 2011 ^{68, 71} UK G1: Uterine compression sutures (199) G2: Pelvic vessel ligation (20) G3: Interventional radiology (embolization, arterial balloon) (22) G4: rFVIIa (31) Quality: Fair	Age < 35, n (%) G1: 128 (64) G2: 12 (60) G3: 12 (55) G4: 21 (68) > 35, n (%) G1: 71 (36) G2: 8 (40) G3: 10 (45) G4: 10 (32) Nulliparous, n (%) G1: 92 (46) G2: 3 (15) G3: 6 (27) G4: 9 (29)	<ul style="list-style-type: none"> • Among all women receiving these second-line therapies, 205 had prior uterotonic therapy (oxytocin, ergometrine, carboprost tromethamine, misoprostol) alone, 67 had prior uterotonics and intrauterine tamponade • rFVIIa was successful in controlling bleeding in 5/16 women who received only uterotonics and in 4/15 who had uterotonics and tamponade as a first-line therapy • 14 women who received rFVIIa ultimately required hysterectomy

G-group, rFVIIa-recombinant activated factor VIIa

Studies of Other Medical Interventions

Transfusion

Key Points

- No good quality studies addressed transfusion.
- In one retrospective cohort study, women receiving combination blood products compared with whole blood or PRBC only had a greater level of transfusion, greater likelihood of intensive care unit (ICU) stay, and greater risk of adverse outcomes.
- Estimated blood loss, blood products transfused, and mean length of stay did not differ between groups in a retrospective cohort study comparing outcomes following cryoprecipitate or fibrinogen transfusion.
- Strength of the evidence for outcomes related to transfusion is insufficient. While there were three fair quality studies of transfusion, two of these were so confounded that we could not confidently ascertain their outcomes.

Overview of the Literature

Three retrospective cohort studies addressed transfusion as a therapy for management of PPH. Studies that address transfusion as an intervention for anemia once PPH is stabilized are summarized under KQ4. Cohort studies were conducted in the United States,⁷² Ireland,⁷³ and Korea⁷⁴ and included a total of 1,700 women. Causes of PPH, where reported, included atony (range = 2.5 to 38%), placental abruption or placenta previa (8%), chorioamnionitis (21%), and placenta accreta (14%). Studies assessed different aspects of transfusion: whole blood vs. PRBC vs. a combination of products,⁷² massive transfusion vs. no massive transfusion,⁷⁴ and cryoprecipitate vs. fibrinogen concentrate.⁷³ We rated all cohort studies as fair quality.

Detailed Analysis

A fair quality, single-center, retrospective cohort study conducted in the United States compared complication rates between whole blood transfusion, PRBC transfusion alone, and combination blood product transfusion.⁷² Eligible participants with PPH (defined as hypovolemia sufficient to provoke hemodynamic instability) were identified using a database of obstetric and neonatal outcomes for all women who gave birth at a single hospital. Of 1,540 women identified, 659 received whole blood transfusion, 593 received PRBC only, and 288 received a combination of blood products. There were no statistically significant differences between groups in age, race, or parity, but women in the combination blood product group were more likely to have perineal trauma, placenta previa or abruption, and hysterectomy than the other groups. Mean units of blood product transfused was significantly greater among women getting a combination of blood products when compared with women receiving whole blood or PRBC only (5.5, 2.2, and 2.3 units in the combination blood products, whole blood, and PRBC groups, respectively, $p < 0.001$). Women in the combination transfusion group were also significantly more likely to be transferred to the ICU (23%, 4%, and 7% in the combination blood products, whole blood, and PRBC alone groups, respectively, $p < 0.05$) and to die (2%, 0%, and 1% in the combination blood products, whole blood, and PRBC alone groups, respectively, $p = 0.03$) than women in the other two groups.

Another fair quality, single-center, retrospective cohort study used electronic medical records at a Korean academic hospital to determine whether patients with an elevated shock index at the

time of presentation with PPH would be more likely to require massive transfusion.⁷⁴ Women with PPH (defined as blood loss \geq 500 mL) were identified as part of the massive transfusion group (defined as receiving transfusion of \geq 10 units PRBC within 24 hours of birth) or the non-massive transfusion group. There were 26 women in the massive transfusion group and 100 in the non-massive transfusion group. There were no significant differences in several baseline characteristics (age, parity, mode of birth, bleeding time) between groups. Significantly fewer women in the massive transfusion group had an alert mental status (18 vs. 95, $p < 0.01$) and underwent embolization (22 vs. 36, $p < 0.01$), and significantly more women in this group required ICU stay (11 vs. 5, $p < 0.01$) and died (3 vs. 0, $p < 0.01$). Additionally the median systolic and diastolic blood pressures and hemoglobin levels were significantly lower (5.9 vs. 9.5, $p < 0.01$), and the median shock index (1.3 vs. 0.8, $p < 0.01$) and length of hospital stay (4.0 vs. 2.0, $p < 0.01$) were significantly higher in the massive transfusion group than in the non-massive transfusion group. Transfusion requirements were significantly higher in the first 24 hours and during the hospitalization among the massive transfusion group than the non-massive transfusion group (18.0 units and 3.0 units in the first 24 hours, respectively, and 20.0 units and 4.0 units during the hospitalization, respectively). These findings are confounded by indication as the massive transfusion group was presumably experiencing more severe PPH given their lower median hemoglobin and lower median systolic and diastolic blood pressures than the non-massive transfusion group.

Finally, one fair quality, single-center, retrospective cohort study from Ireland compared the effectiveness of transfusion with cryoprecipitate ($n = 14$) versus fibrinogen concentrate ($n = 20$).⁷³ Women were identified for inclusion in a major obstetric hemorrhage database if they experienced PPH (defined as blood loss of ≥ 2.5 L, transfusion of ≥ 5 units PRBC, or treatment of a coagulopathy in the acute event). Eligible participants from the database were women treated with either cryoprecipitate or fibrinogen concentrate between 2009 and 2011. There were no statistically significant differences between groups in age, race, BMI, parity, gestation at birth, birth weight, or cause of PPH, but women in the cryoprecipitate group were more likely to have a previous cesarean birth. There was no statistically significant difference between groups in mean estimated blood loss; number of units of PRBC, Octaplas/fresh frozen plasma, or platelets transfused; medical and surgical treatments administered; and mean length of hospital stay. Table 8 outlines key outcomes.

Table 8. Key outcomes in comparative studies of transfusion

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Alexander et al., 2009 ⁷² US Groups: G1: Whole blood only (659) G2: PRBC only (593) G3: Combinations of blood products (208)	Age, year, n (%): 17 or less G1: 54 (8) G2: 39 (7) G3: 28 (10) 35 or older G1: 66 (10) G2: 54 (9) G3: 34 (12) Nulliparous, n (%) G1: 333 (51) G2: 306 (52) G3: 135 (47)	<ul style="list-style-type: none"> • Mean units of blood transfused was 2.2 units for G1, 2.3 units for G2, and 5.5 units for G3 (p < 0.001) • G3 more likely than G1 and G2 to be transferred to the ICU (23%, 4%, and 7%, respectively, p < 0.05) and to die (2%, 0%, and 1%, respectively, p = 0.03)
Sohn et al. 2013 ⁷⁴ Korea G1: Massive transfusion requiring 10 or more units of PRBCs (26) G2: Received < 10 units PRBCs (100)	Age, median (IQR range) G1: 31 (29.8-34.5) G2: 31 (29-34) Primiparous, n (%) G1: 17 (65.4) G2: 56 (56) Multiparous, n (%) G1: 9 (34.6) G2: 44 (44)	<ul style="list-style-type: none"> • Women in G1 had greater length of stay and need for ICU care compared with G2 (p < 0.01) • Findings confounded by indication
Ahmed et al., 2012 ⁷³ Ireland G1: Cryoprecipitate (14) G2: Fibrinogen (20)	Age, mean G1: 32.8 G2: 31.0 Nulliparous, n (%) G1: 6 (43) G2: 6 (30)	<ul style="list-style-type: none"> • Cryoprecipitate was used prior to July 2009 and then replaced with fibrinogen • Hypofibrinogenaemia was resolved with both treatments • The two groups had comparable hemoglobin, hematocrit, and platelet counts

G-group; ICU-Intensive care unit; IQR-interquartile range; PRBC-packed red blood cells

Studies of Procedures

Uterine Tamponade

Key Points

- No good quality studies addressed uterine tamponade.
- In one fair quality pre-post study, 86% of women who had tamponade did not require further procedures or surgeries.
- One population-based case series reported a decrease or cessation of bleeding in 98% of patients treated with a novel dual balloon tamponade device, with and without prior or subsequent surgeries or procedures.
- Strength of the evidence for outcomes related to uterine tamponade is insufficient given the small number of studies and small sample sizes.

Overview of the Literature

Two studies, one pre-post study and one population-based case series, addressed the use of intrauterine balloon tamponade for the management of PPH.^{75, 76} The pre-post study was conducted in France and the case series in the United States. Most of the women in these studies had atony (100% in pre-post study and 73% in case series). A total of 94 women had intrauterine balloon tamponade, 43 in the pre-post study and 51 in the case series.

Detailed Analysis

One fair quality pre-post study examined the rate of invasive procedures (embolization and surgery) after adding balloon tamponade to the protocol for PPH management in a maternity unit at a tertiary care university hospital in France.⁷⁵ The new protocol required that intrauterine balloon tamponade be performed prior to any invasive intervention in cases of PPH due to uterine atony that were nonresponsive to sulprostone. Data were collected prospectively for 30 months after implementation of the new protocol. The patients in the control group (n = 290, none of whom had tamponade) were identified from electronic medical records as women admitted to the hospital with PPH due to atony requiring sulprostone therapy in the 30 months prior to the new protocol implementation. During the study period, 395 women with PPH required sulprostone therapy, which was unsuccessful in 72 women. Of these women who needed additional procedures or surgeries, 43 had intrauterine balloon tamponade as the initial second-line therapy. No additional procedures or surgeries were required after tamponade in 92% (11/12) of the women who had cesarean births and 84% (26/31) of the women who had vaginal births. Among the six women for whom tamponade was unsuccessful, three had embolization, two had conservative surgical interventions (defined as artery ligations and/or uterine compression sutures), and one had hysterectomy. The overall success rate of tamponade was 86% (37/43 women). Adding tamponade to the protocol decreased the rates of arterial embolization (8.2% pre vs. 2.3% post, p = 0.006, OR 0.26, 95 percent CI: 0.09-0.72) and conservative surgical procedures (5.1% pre vs. 1.4% post, p = 0.029, OR 0.26, 95% CI: 0.07-0.95) among women with vaginal births. Hysterectomy and transfusion rates were unchanged. Rates of invasive interventions and transfusion were unchanged among women with cesarean births (Table 9).

One population-based case series examined the outcomes of women with PPH treated with a novel dual-balloon catheter tamponade device, the Belfort-Dildy Obstetrical Tamponade System, using postmarketing surveillance data from medical records and clinician interviews at 11 hospitals in the United States.⁷⁶ During the study period (September 2010 – October 2012), 51 women with PPH were treated with the tamponade device. Of these, 28 women had vaginal births and 23 had cesarean births. The median time interval between birth and insertion of the balloon was 2.2 hours (range 0.3-210 hours). Estimated median blood loss was 2000mL (range 855-8700). Thirty-nine (77%) patients required PRBC transfusion, and 12 (24%) were admitted to the ICU. Bleeding was considered to be decreased in 22 (43%) women and stopped in 28 (55%). Eight patients (16%) required additional procedures or surgeries after the balloon placement including hysterectomy (n = 4), uterine artery embolization (n = 4), and surgical repair (n = 3); some required more than one intervention. The overall success rate of tamponade in controlling or decreasing bleeding was 98% (50/51 women, who also had prior medical or surgical interventions). Table 9 outlines key outcomes in studies of uterine tamponade.

Table 9. Key outcomes in studies of uterine tamponade

Author, year, country Groups (N) Study quality	Age, years Parity	Key outcomes
Laas et al. 2012 ⁷⁵ France G1: Women with PPH due to atony and nonresponsive to sulprostone admitted to the maternity service after implementation of new protocol using intrauterine balloon tamponade as first-line therapy after medication failure (395) G2: Control group, had PPH requiring sulprostone during the 30 months before implementation of new protocol (290) Quality: Fair	Age, median (range) G1: 30 (27-34) G2: 31 (26-34) Nulliparous, n (%) G1: 212 (53.7) G2: 160 (55.2)	<ul style="list-style-type: none"> • In G1, 72 women required interventions beyond medication and 43 of these had intrauterine balloon tamponade • No additional procedures or surgeries were required after tamponade in 92% (11/12) of women who had cesareans and 84% (26/31) of women who had vaginal births • The rates of invasive interventions among women who had vaginal births were significantly lower after introduction of new protocol
Dildy et al. 2013 ⁷⁶ US G1: Dual-balloon tamponade (51)	Age, median (range) G1: 33 (19-47) Parity NR	<ul style="list-style-type: none"> • 77% required red blood cell transfusion • 24% were admitted to the ICU • Bleeding was considered to be decreased or stopped in 98% of cases • 16% required surgical interventions after balloon tamponade

G-group; ICU-intensive care unit; NR-not reported; PPH-postpartum hemorrhage

Embolization

Key Points

- No good quality studies addressed embolization.
- Embolization materials, arteries embolized, and interventions used prior to and concomitantly with embolization varied across studies.
- Success (control of bleeding without further procedures or surgeries) rates for embolization as the initial procedure after conservative management ranged from 58 to 98 percent (success in 1155/1325 women), with a median rate of 89 percent.
- Strength of the evidence is low for embolization controlling bleeding without additional procedures or surgeries.

Overview of the Literature

Fifteen studies addressed embolization to treat PPH. Six studies had explicit comparison groups: one poor quality case-control study⁷⁷ and five fair quality cohort studies (reported in multiple publications), four of which were retrospective^{47, 78-82} and one prospective.⁶⁸ Four studies were conducted in France in tertiary care hospitals,^{77, 78, 81, 82} one in Korea,⁴⁷ in a hospital that serves Jehovah's Witnesses, and one in the United Kingdom,⁶⁸ which reported data collected via the UKOSS (described in the section on rFVIIa). These six studies included a total of 342 cases of embolization. Ten women in one cohort study also had concomitant vessel ligation and/or uterine compression sutures,⁷⁸⁻⁸⁰ one woman in each of two studies had prior or

concomitant artery ligation,^{47, 81} and three in another study⁶⁸ also had intra-arterial balloon placement along with embolization. Eighty-one percent of the cases of PPH reported in the case-control study were due to atony.⁷⁷ Rates of atony in the cohort studies ranged from 9 to 69.5 percent. Other causes in all populations included placenta accreta, percreta, and/or previa (range: 9.4 to 22%); thrombus, vascular anomaly, or coagulopathy (range: 2 to 10%); and genital tract lacerations or uterine tears (range: 1 to 14%). The case-control study and two retrospective cohort studies reported primarily on longer-term fertility with followup of participants at ≥ 12 months post-embolization (fertility data reported in KQ3).^{77, 78, 81} The prospective cohort study reported primarily success of embolization and the need for additional second-line interventions⁶⁸ as did one retrospective cohort study.⁸² Remaining studies also reported primarily on the rate of success (i.e., controlling bleeding without further procedures or surgical interventions) of embolization.

Nine retrospective case series also addressed embolization.⁸³⁻⁹¹ Studies were conducted in France (n = 4), Asia (n = 4), the United States (n = 1) and included a total of 1174 women undergoing embolization. Most cases of PPH were due to atony (range = 43 to 100%), and most studies reported primarily on rates of success.

Detailed Analysis

One fair quality retrospective cohort study reported in three publications⁷⁸⁻⁸⁰ included all 101 women who had pelvic artery embolization for PPH from 1994 to 2007 at a tertiary care facility in France. Embolization failed to control bleeding in 11 of 101 women, seven of whom required a postpartum hysterectomy. Failure was associated with increased blood loss as 100 percent of failed cases had blood loss greater than 1500 ml (p < .001). Failure was also associated with increased rate of transfusion with 90 percent of women in whom embolization failed receiving more than 5 units PRBC compared with 43 percent of the successful embolizations (p < .004). Cases of failed embolization were more likely to be complicated by wound infection (27% vs. 6% in the success group, p < .04).

A second fair quality retrospective cohort study conducted in France assessed outcomes in 52 women undergoing selective embolization using gelfoam (n = 41, mean age = 29.2 \pm 4.65 years, 9 primiparous, 11 vaginal births), hysterectomy (n = 6, mean age = 30.1 \pm 4.11, 2 primiparous, 2 vaginal births), or both embolization and hysterectomy (n = 5, mean age = 36.6 \pm 4.56, 0 primiparous, 0 vaginal births).⁸¹ All women were treated between 1996 and 2005, and atony was the most frequent cause of PPH across groups (69.5%). All women had medical management (oxytocin, manual placenta removal, uterine massage, prostaglandins, transfusion) prior to embolization or hysterectomy. Embolization successfully stopped bleeding in 41 of 46 cases (89.1%). Five women required additional embolization procedures (insertion of coil to correct injury sustained in cesarean birth, ovarian artery embolization, embolization beyond gluteal artery, embolization of internal iliac artery, embolization of ligated hypogastric arteries). Among five women proceeding to hysterectomy following failed embolization, two women had placenta accreta, one had percreta, and one had sustained arterial injury during embolization. The study also assessed fertility in women who had had embolization (n = 37 available for followup) 2 to 11 years earlier: of the 16 women who desired a future pregnancy, all became pregnant 1 to 11 months following the decision to try to conceive (total of 19 pregnancies in the followup period).

In one fair quality retrospective cohort study reporting outcomes after embolization, ligation, or hysterectomy (see full study description in Ligation section), eight of 61 women with PPH underwent embolization using gelatin sponge or coils as the first secondary procedure.⁸² Embolization failed in three cases: one woman undergoing embolization also required

methotrexate, one required subsequent ligation, and one required hysterectomy (63% success rate for embolization alone). This study also reported intervention by cause of PPH: among eight cases treated with primary embolization, three women had PPH due to atony (one cesarean birth). Embolization failed in one case, which resulted in hysterectomy and subsequent death. Embolization was successful in two cases of PPH due to accreta (one cesarean birth) and in one case due to placental abruption (vaginal birth). The procedure failed in one case of PPH due to genital tract laceration (instrumented vaginal birth), leading to subsequent ligation, and successfully controlled bleeding in another case following lacerations.⁸²

One poor quality case-control study conducted in France assessed the effects of embolization on fertility in 53 women exposed to embolization following PPH and 106 women who had not undergone embolization and were matched on date of birth, age, gravidity and parity, fertility assistance, and mode of birth.⁷⁷ Women (mean age = 34.3, range 19-44) had undergone embolization (78.5% using absorbable gelatin, 1.8% using coils, 7.1% using microparticles, 12.6% using gelatin+other) between 2000 and 2006, and the primary cause of PPH was atony (81.1%). Embolization successfully controlled bleeding in 100 percent of women, but three required more than one embolization procedure.

One fair quality prospective cohort study reported UKOSS data collected between 2007 and 2009.⁶⁸ The study reported an analysis of outcomes of second-line therapies (i.e., interventions received after uterotonics alone or with intrauterine tamponade via balloon or packing). Second-line interventions included interventional radiology (defined as embolization or occlusion with an intra-arterial balloon), ligation (of any of the internal iliac, uterine, hypogastric, or ovarian arteries), compression sutures (including B-lynch, modified B-lynch, multiple vertical or horizontal sutures, squared compression sutures, and others), or rFVIIa. Among an estimated 1,237,385 births in the study period, 272 women had PPH treated with the interventions of interest as a second-line intervention. More than 50 percent of PPH cases (53%) were primarily due to atony. Other causes included placenta previa (9%), placenta accreta (10%), uterine tears (13%), and other (15%, includes placental abruption, genital bleeding, amniotic fluid embolism, infection, clotting abnormalities, undetermined causes). Women who had a cesarean birth (n = 230) were treated with a surgical method in 199 (87%) of the cases, and those who gave birth vaginally (n = 42) were more likely to be treated by interventional radiology or rFVIIa (52%, $p < 0.001$). Among the 272 cases of PPH, 205 women received uterotonics alone, and 67 had uterotonics plus intrauterine tamponade as first-line procedures. Data for each of the second-line therapies addressed in the study are reported under the appropriate intervention type (suture, etc.). Among the 22 women treated with interventional radiology, 19 had embolization alone, two had embolization plus balloon, and one had balloon only. Fourteen of the 22 women received uterotonics prior to interventional radiology. The interventional radiology procedures failed to control bleeding in two women (14%; 95% CI: 0 to 43), who required hysterectomy. Among the eight of 22 women who received uterotonics and intrauterine tamponade prior to interventional radiology, bleeding was controlled in seven cases, and one woman (12%, 95% CI: 0 to 53) required an additional (unstated) intervention. The study does not report the success of embolization alone but only the success of both interventional radiology procedures together.

One fair quality retrospective cohort conducted at a hospital that treated Jehovah's Witnesses in Korea reported results from women treated with embolization or hysterectomy between 2002 and 2009 (see Hysterectomy section for results from that arm).⁴⁷ All women were initially treated with uterotonics (oxytocin, ergots, prostaglandins), uterine massage, transfusion (in patients who were not Jehovah's Witnesses), and fluid replacement. Among the 124 women

(eight Jehovah's Witnesses) experiencing primary PPH, 60 (mean age 31.0 ± 4.8 years, 17 primiparous, 23 vaginal births) underwent selective embolization using gelfoam. PPH was most frequently due to atony (92.4%), and mean blood loss prior to embolization was 676.7 ml. Embolizations were performed by the same two interventionists across the study period. Mean ICU stay in the embolization group was 5 days (mean overall LOS = 8.6 days). Two women in the embolization group required hysterectomy due to continued bleeding from the cesarean uterine wound and from vaginal and cervical lacerations after vaginal birth. In case series, rates of success (control of bleeding after embolization without further procedures or surgeries) ranged from 58 to 98 percent. In some cases, women had a procedure such as ligation or tamponade prior to embolization. Five studies also reported on resumption of menses and/or pregnancies achieved (see discussion in KQ3).

One retrospective case series included 56 women (median age = 33 years, median gravida = 2, median para = 2) with severe PPH (defined as $\geq 1000\text{mL}$ blood loss via clinical estimation or weighing of blood collecting bag; $\geq 500\text{mL}$ blood loss with poor clinical signs; continued bleeding; need for transfusion; or DIC) undergoing embolization at a French tertiary care hospital between 1995 and 2005.⁸³ All women received initial medical treatment including suturing of vaginal or cervical lesions, oxytocin, uterine massage, and sulprostone. Thirty births were vaginal without instrumentation (54.5%), nine were instrumented vaginal (16.5%), and 16 were cesarean (29%). All women had atony, and 36 required transfusion (64.3%). Embolization was performed with gelfoam or sponge. Embolization successfully stopped bleeding in 55 cases (98% success rate). One woman required a second embolization session to control bleeding, and none needed further surgical interventions for bleeding.

Another French retrospective case series including 113 women (mean age = 31 years, 67 cesarean births) reported on menses and fertility outcomes and success of the embolization procedure.⁸⁴ PPH was most frequently due to atony (75% of cases), and all women received medical management prior to embolization. Embolization materials included gelatin sponge, powder, and microparticles. Eighteen women required surgery prior to embolization (sutures, $n = 11$; ligation, $n = 7$). Embolization successfully controlled bleeding in 111 cases (results not reported for women who had embolization without a prior surgical procedure). Two women required hysterectomy post-embolization.

In a Korean retrospective case series reporting on 251 women with primary PPH (mean age 32 ± 4 years, 139 nulliparous, 141 vaginal births), most cases of PPH were due to atony (78.9%).⁸⁷ The study reviewed data from women treated between 2000 and 2011. All women had medical management prior to embolization, and 22 had surgical interventions prior to embolization (hysterectomy, $n = 15$; uterine artery ligation, $n = 2$; laparotomy, $n = 2$; suture or uterine wall repair, $n = 2$; dilatation and curettage, $n = 1$). Embolization was performed with gelatin sponge or multiple particles. Embolization successfully controlled bleeding in 201 of the 229 women for whom embolization was the first second-line procedure (88%). Among all 251 women, embolization successfully controlled bleeding in 217 (87%). Twelve women required a repeat embolization (success in nine cases, one hysterectomy, one laparotomy, one death), nine required hysterectomy, six required laparotomy (one death), three required additional conservative management, one required uterine artery ligation, and three died after the first embolization session. Successful embolization was associated with vaginal birth, absence of DIC, and absence of need for transfusion of > 10 PRBC units (p values $< .05$).

A retrospective review of embolization for PPH conducted at two Korean hospitals between 2006 and 2011 included data from 176 women (mean age = 33.9 years, 105 vaginal births, 73

primiparous) undergoing 189 embolization procedures.⁹¹ Women who had cesarean births were significantly older than those with vaginal births ($p = 0.035$). Twenty-five cases of PPH were secondary, and overall, PPH was most frequently due to atony (57.6% of cases). Embolizations were done with gelatin sponge, particles, coils, or a combination. Bleeding successfully stopped after embolization in 158 cases (89.7%). Twelve women needed a repeat embolization, 11 needed a surgical procedure (five hysterectomies), and one needed vascular ligation.

One retrospective case series reporting data from a U.S. tertiary care hospital included 76 women (mean age = 33 years, 18 cesarean births) who had PPH.⁸⁵ Ten women were excluded from analysis because they had interventions prior to or concomitant with embolization or had an ectopic pregnancy. Embolization (performed with gelfoam and/or coils) successfully controlled bleeding without further procedures or surgeries in 63 of 66 women (95%). Three women required a subsequent hysterectomy. Embolization was successful in 98% (49/50) of the women with primary PPH and 88% (14/16) of the women who had secondary PPH (presentation 4 to 72 days post-birth, mean = 25 days). Women required a mean 0.4 units PRBC after embolization, and the mean hospital stay overall was 3.5 days (range 1-12 days). Among those with primary PPH, mean hospital stay was 3.9 days and was 2 days in the secondary PPH group.

One Japanese retrospective case series included data from 55 women (median age 33 years, 34 vaginal births, median parity = 1, range 0-3) with PPH treated with embolization between 2003 and 2013.⁹⁰ Most cases of PPH were due to atony ($n = 41$), and all women had initial conservative management including uterine massage, packing, and uterotonics. The embolization material was gelatin sponge, and embolization successfully stopped bleeding without an additional intervention in 46 women (84%). Bleeding stopped in two women who went on to hysterectomy after embolization due to uterine necrosis. The study does not report the interventions performed for the other seven women who required another procedure after embolization. Advanced maternal age and retained placenta were independent risk factors for failure of embolization (OR 1.46, 95% CI: 1.12 to 2.18 and OR 15.48, 95% CI: 2.04 to 198.12, respectively).

One French retrospective case series reported outcomes among 102 women (mean age 31.8 ± 5.9 years, 82 vaginal births, mean parity 2.01 ± 1.11) undergoing embolization at an academic medical center between 1998 and 2002.⁸⁹ Women may have had medical management including uterine massage and oxytocin prior to embolization. PPH was due to atony in 43 percent of women. Mean ICU stay was 2.07 ± 1.2 days, and units of whole blood, platelets, and fresh frozen plasma transfused ranged from 0 to 31. Embolization was successful without further surgical procedure in 59 women. Fourteen women required a second embolization to control bleeding, and 29 required surgery (nine laparotomies, two uterine artery ligations, seven hysterectomies, 11 genital tear repairs plus subsequent embolization). Embolization was more successful in women with vaginal births (success in 63/81 vaginal births) compared with cesarean (success in 11/21 cesarean births, $p = 0.017$; OR for poor outcome associated with cesarean birth: 0.16, 95% CI: 0.04 to 0.5). Atony as the cause of PPH was also associated with greater success (success in 39/44 women; OR 4.13, 95% CI: 1.35 to 12.6).

Another retrospective case series conducted in a French tertiary care hospital reported on success rates for embolization in 98 women with PPH (33 considered “major” PPH, defined as change in peripartum hemoglobin level of ≥ 4 g/dL and/or hemodynamic instability and/or hypovolemic shock).⁸⁸ All women had treatment (resuscitation, uterotonics, manual placenta removal, surgical repair of tears as indicated) prior to embolization, and most cases of PPH were due to atony. Forty-five women had vaginal births, 14 had instrumented vaginal births, and 28

had cesarean births. Embolization was performed with gelatin sponge pledgets and coils as needed. Twenty-six women had a surgical procedure prior to embolization (vaginal or cervical suture, n = 17; uterine suture, n = 1; artery ligation, n = 3; hysterectomy, n = 9; packing, n = 2). Embolization successfully controlled bleeding in 90 of the 98 cases of PPH. Women in whom PPH failed to control bleeding required subsequent uterine suture (n = 4), laparotomy for vessel ligation (n = 2), and repair of genital tears (n = 2). Embolization plus uterine sutures failed in three cases, leading to hysterectomy.

In another large retrospective case series from Korea, 257 women (mean age = 32 years, 162 primiparas, 112 cesarean births) underwent embolization for PPH between 2004 and 2011.⁸⁶ PPH was most often caused by atony (n = 156 cases), and embolization materials included gelatin sponge, N-butyl-cyanoacrylate, or both. Nineteen cases of PPH were secondary. Nine women had a surgical procedure prior to embolization (eight hysterectomies, one artery ligation). Embolization successfully stopped bleeding in 233 women overall (91%). In the 248 women for whom embolization was the first second-line procedure, embolization was successful in 226 (91%). Women for whom embolization failed to control bleeding were more likely to have DIC (OR 6.57, 95% CI: 1.60 to 26.9, p = .009), and the rate of major complications was significantly greater among failed embolizations vs. successful (9.4% vs. 37.5%, p < .01). Table 10 outlines key outcomes.

Table 10. Key outcomes in studies of embolization

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Sentilhes et al. 2010 ⁷⁸⁻⁸⁰ France G1: Embolization alone (58 at followup) G2: Embolization + vessel ligation and/or suture (10 at followup) Quality: Fair	Age NR Parity NR	<ul style="list-style-type: none"> • Bleeding not controlled by embolization in 11/101 women • 7 women required hysterectomy • 100% percent of failed cases had blood loss greater than 1500 ml (p < .001) • 90% of women in whom embolization failed received more than 5 units PRBC compared with 43% of successful embolizations (p < .004). • Cases of failed embolization were more likely to be complicated by wound infection (27% vs. 6 % in the success group, p < .04)
Chaleur et al. 2008 ⁸¹ G1: Embolization (41) G2: Hysterectomy (6) G3: Embolization and hysterectomy (5) Quality: Fair	Age, mean ± SD G1: 29.2 ± 4.65 G2: 30.1 ± 4.11 G3: 36.6 ± 4.56 Primiparous, n (%) G1: 9 (21.9) G2: 2 (33) G3: 0	<ul style="list-style-type: none"> • All patients had had medical management prior to procedure • 5 second-line hysterectomies (G3) were performed due to embolization failure • Among 16 women in G1 desiring future pregnancy, all were able to conceive 1-11 months after beginning to try to conceive
Ledee et al. 2001 ⁸² France G1: Hysterectomy (10) G2: Bilateral hypogastric artery ligation (48) G3: Embolization (9) Quality: Fair	Age NR Parity NR	<ul style="list-style-type: none"> • All women underwent bimanual compression, oxytocin and prostaglandin IV administration, and resuscitation before further intervention • Embolization was primary procedure in 8 cases and secondary in 1. In 3 cases, an additional intervention was needed to control bleeding

Table 10. Key outcomes in studies of embolization (continued)

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
<p>Hardeman et al. 2010⁷⁷ France</p> <p>G1: Embolization (53) G2: No embolization (106)</p> <p>Quality: Poor</p>	<p>Age, mean (range) G1: 34 (19-44) G2: NR</p> <p>Parity, mean (range) G1: 2.02 (1-5)</p>	<ul style="list-style-type: none"> • 43 cases of PPH due to atony • Embolization successful in controlling bleeding without additional procedure or surgery in 50/53 cases • Three women required a second embolization, which was successful in all cases
<p>Kayem et al. 2011^{68, 71} UK</p> <p>G1: Uterine compression sutures (199) G2: Pelvic vessel ligation (20) G3: Interventional radiology (embolization, arterial balloon) (22) G4: RFVlla (31)</p> <p>Quality: Fair</p>	<p>Age < 35, n (%) G1: 128 (64) G2: 12 (60) G3: 12 (55) G4: 21 (68)</p> <p>> 35, n (%) G1: 71 (36) G2: 8 (40) G3: 10 (45) G4: 10 (32)</p> <p>Nulliparous, n (%) G1: 92 (46) G2: 3 (15) G3: 6 (27) G4: 9 (29)</p>	<ul style="list-style-type: none"> • Among all women receiving these second-line therapies, 205 had had prior uterotonic therapy (oxytocin, ergometrine, carboprost tromethamine, misoprostol) alone, 67 had had uterotonics and intrauterine tamponade • 19 women had embolization only, 2 had occlusion with intra-arterial balloon and embolization, and 1 had balloon only • Interventional radiology after uterotonics alone was successful as first second-line therapy in 12/14 women; 2 went on to hysterectomy. • Interventional radiology was successful as first second-line therapy after uterotonics+tamponade in 7/8 cases. 1 women required an additional (unstated) intervention • Overall, 71 women had hysterectomy(47 after failure of second-line therapy, 24 after failure of uterotonics/tamponade and subsequent treatments)
<p>Kim et al. 2013⁴⁷ Korea</p> <p>G1: Embolization (60) G2: Hysterectomy (61)</p> <p>Quality: Fair</p>	<p>Age, mean ± SD G1: 31.0 ± 4.8 G2: 31.8 ± 4.0</p> <p>Primiparous, n G1: 17 G2: 22</p>	<ul style="list-style-type: none"> • Primary cause of hemorrhage in both groups = atony • 8 women in study were Jehovah's Witnesses-4 in each group • All women in G1 and G2 received uterotonics (G1: oxytocin = 100%, sulprostone = 68%, Ervin = 36%; G2: oxytocin = 100%, sulprostone = 60.6%; Ervin = 19.6%). 25 women in G1 and 36 in G2 required transfusion prior to procedure • Embolization was successful in 96% of G1; 2 women required hysterectomy due to continued bleeding from cesarean uterine wound and vaginal and cervical lacerations • Mean days in ICU in G1 = 5 days (5 women). ICU days not reported in G2 but 39 women required ICU care; LOS in hospital was 8.60 days in G1 and 11.5 in G2

Table 10. Key outcomes in studies of embolization (continued)

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Case series		
Lee et al. 2012 ⁸⁷ Korea G1: Embolization (251)	Age, mean ± SD G1: 32 ± 4 Nulliparous, n (%) G1: 139 (55)	<ul style="list-style-type: none"> • 22 women had surgical procedure before embolization; embolization successful in controlling bleeding as the first second-line procedure in 201/229 women (88%) • Success rate among all 251 women = 86.5% • Success associated with vaginal birth, absence of DIC, absence of massive transfusion (all p values < .05) • Among 113 women with ≥ 6 months followup, 110 had regular menses
Fiori et al. 2009 ⁸³ France G1: Embolization (56)	Age, median G1: 33 Parity, median (range) G1: 2 (1-4)	<ul style="list-style-type: none"> • Embolization successful in 55/56 cases (98%) • Regular menses in 30/34 available for followup
Gaia et al. 2009 ⁸⁴ France G1: Embolization (113)	Age, mean G1: 33 Parity NR	<ul style="list-style-type: none"> • Embolization successfully controlled bleeding in 111 cases; 2 women required hysterectomy post-embolization • 99/107 with available fertility data had resumed menses, normal menses in 66 (menorrhagia = 10, oligomenorrhea = 23, amenorrhea = 6) • 29 women desired future pregnancy, 18 conceptions (mean conception delay 11 months from decision to try to conceive)
Lee et al. 2009 ⁹¹ Korea G1: Embolization (176)	Age, mean G1: 33.9 Primiparous, n G1: 73	<ul style="list-style-type: none"> • Bleeding successfully stopped after embolization in 158 cases (89.7%) • 12 women had repeat embolization, 11 had surgical procedure (5 hysterectomies), and 1 had vascular ligation (some women had more than 1 procedure)
Ganguli et al. 2011 ⁸⁵ US G1: Embolization (66)	Age, mean G1: 33 Parity, mean (range) G1: 1.8 (0-9)	<ul style="list-style-type: none"> • Embolization successfully controlled bleeding without further procedures or surgeries in 63 of 66 women overall (95%). • Embolization successful in 14/16 women with secondary PPH (88%) • Embolization successful in 49/50 cases of primary PPH (98%) • Women required a mean 0.4 units PRBC after embolization • Mean hospital stay overall was 3.5 days (range 1-12 days)
Touboul et al. 2008 ⁸⁹ France G1: Embolization (102)	Age, mean ± SD G1: 31.8 ± 5.9 Parity, mean ± SD G1: 2.01 ± 1.11	<ul style="list-style-type: none"> • Embolization successful without further surgical procedure in 59/102 cases • Embolization more successful in women with vaginal births (success in 63/81) compared with cesarean (success in 11/21, p = 0.017; OR for poor outcome associated with cesarean birth: 0.16, 95% CI: 0.04 to 0.5) • Atony associated with greater success (success in 39/44 women; OR 4.13, 95% CI: 1.35 to 12.6) • Mean ICU stay 2.07 ± 1.2 days • Units of whole blood, platelets, and fresh frozen plasma transfused ranged from 0 to 31

Table 10. Key outcomes in studies of embolization (continued)

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Yamasaki et al. 2013 ⁹⁰ Japan G1: Embolization (55)	Age, mean G1: 33 Parity, median (range) G1: 1 (0-3)	<ul style="list-style-type: none"> • Successful controlling of bleeding without further procedures or surgeries in 46/55 • Bleeding stopped in two women who went on to hysterectomy after embolization due to uterine necrosis • Advanced maternal age (OR 1.46 95% CI: 1.12 to 2.18) and retained placenta were independent risk factors for failure of embolization (15.48 95% CI: 2.04 to 198.12)
Poujade et al. 2012 ⁸⁸ France G1: Embolization (98)	Age, mean ± SD Successful embolization: 32.3 ± 5.7 Failed embolization: 31.2 ± 6.4 Parity, mean ± SD Successful embolization: 2.1 ± 1.3 Failed embolization: 2.1 ± 1.7	<ul style="list-style-type: none"> • Embolization successfully controlled bleeding in 90 of the 98 women, 26 of whom also had surgical procedure prior to embolization • Women in whom PPH failed to control bleeding required subsequent uterine suture (n = 4), laparotomy for vessel ligation (n = 2), and repair of genital tears (n = 2). Embolization plus uterine sutures failed in three cases, leading to hysterectomy
Kim et al. 2013 ⁸⁶ Korea G1: Embolization (257)	Age, mean G1: 32 Primiparous, n G1: 162	<ul style="list-style-type: none"> • Embolization successful in 233/257 women overall • Success rate in the 248 women for whom embolization was the first second-line procedure = 91% • Overall, women for whom embolization failed to control bleeding were more likely to have DIC (OR 6.57, 95% CI: 1.60 to 26.9, p = .009)

DIC-disseminated intravascular coagulation; G-group; ICU-intensive care unit; LOS-length of stay; NR-not reported; PPH-postpartum hemorrhage

Embolization Success Rates

As noted earlier, we tabulated success rates reported in studies of embolization in which we could extract data on the effectiveness of the procedure as the initial second-line procedure (i.e., women routinely had first-line conservative management prior to the procedure). Some studies only reported rates in combination with other procedures/interventions or after an initial procedure or intervention, thus not all studies addressing embolization are represented. Success rates for embolization, which was performed using different materials and on different arteries across studies, ranged from 58 to 98 percent (success in 1155/1325 women), with a median rate of 89 percent (Table 11).

Table 11. Success rates after embolization as the initial second-line procedure

Study Country	Quality	Total N Treated	Total N Successful*	% Success
Cohort Studies				
Kim 2013 ⁴⁷ Korea	Fair	60	58	96.67
Zwart 2010 ⁹² Netherlands	Fair	114	94	82.46
Chaleur 2008 ⁸¹ France	Fair	46	41	89.13
Ledee 2001 ⁸² France	Fair	8	5	62.50
Case-Control				
Hardeman 2010 ⁷⁷ France	Poor	53	50	94.34
Case Series				
Yamasaki 2013 ⁹⁰ Japan	NR	55	46	83.64
Lee 2013 ⁹¹ Korea	NR	176	158	89.77
Kim 2013 ⁸⁶ Korea	NR	248	226	91.13
Sentilhes 2011 ⁸⁰ France	NR	100	89	89.00
Ganguli 2011 ⁸³ US	NR	66	63	95.45
Lone 2010 ⁹³ U.K.	NR	229	201	87.77
Fiori 2009 ⁸³ France	NR	56	55	98.21
Touboul 2008 ⁸⁹ France	NR	102	59	57.84
Total	NA	1354	1175	Range: 58-98% Median Success Rate: 89.13%

Note: Success = control of bleeding without further procedure or surgery

*Outcomes of this study described in section on embolization and hysterectomy

NA-not applicable, NR-not rated

Studies of Surgical Interventions

Uterine Compression Sutures

Key Points

- No good quality studies addressed uterine compression sutures.

- In one fair-quality prospective cohort study, sutures were effective in controlling bleeding without further procedures or surgeries in 140 of 199 women, all of whom received uterotonics and/or intrauterine tamponade prior to sutures (70% success rate).
- Strength of the evidence is insufficient for the success of uterine compression sutures in controlling bleeding given the few studies available.

Overview of the Literature

Two studies addressed uterine compression sutures, one prospective cohort study (reported in two publications) and one retrospective case series.^{68,71,94} The cohort study, rated as fair quality, reported data collected via the UKOSS.^{68,71} Two-hundred and eleven cases of PPH were treated with sutures in the study period. The case series reported data from interventions performed by a single surgeon in Argentina.⁹⁴ The study reports on 539 cases of PPH treated with ligation or suture and does not clarify how many women received each technique.

Detailed Analysis

One fair quality prospective cohort study reported UKOSS data collected between 2007 and 2009.⁶⁸ The study reported an analysis of outcomes of second-line therapies (i.e., interventions received after uterotonics alone or with intrauterine tamponade via balloon or packing. Among women who were initially treated with uterotonics alone, 161 went on to require compression sutures, which were successful in controlling bleeding in 120 cases (74.53% success rate). Twenty-five women required hysterectomy (without another intervening procedure) after sutures. Three women had ligation after suture; seven had either embolization or balloon placement (three of these went on to require hysterectomy); and six had rFVIIa (four ultimately required hysterectomy). Thus, compression sutures with or without subsequent procedures failed to control bleeding in 32 women, leading to hysterectomy. Among 38 women who required sutures after failure of uterotonics plus intrauterine tamponade, 14 went on to require hysterectomy (eight immediately, two after ligation and/or rFVIIa, two after interventional radiology and/or rFVIIa, and two after rFVIIa alone). Overall (among women who received uterotonics and intrauterine tamponade), sutures successfully controlled bleeding in 70 percent of cases (n = 140/199 cases)⁶⁸

Another publication from this study,⁷¹ which includes data from the majority (n = 199/211) of the participants who received sutures described above,⁶⁸ reported on 211 women receiving compression sutures (B-lymph, n = 79; modified B-lymph, n = 48; other, including square sutures or combination sutures, n = 32; unspecified, n = 52) to treat PPH in the study period. The most common reason for the hemorrhage was uterine atony (n = 129, 61%). As in the first study, all women had prior uterotonic treatment either for prophylaxis or treatment of PPH. Ten women had embolization or ligation, 41 had uterine balloon or packing, and two had rFVIIa prior to sutures. Embolization or ligation following sutures was required in 18 cases, rFVIIa in nine, and uterine packing or balloon in 25. Overall, sutures as the initial second-line therapy failed to control bleeding, leading to subsequent hysterectomy, in 46 cases and successfully controlled hemorrhage in 153 cases (sutures were not the initial second-line therapy in 12 cases). Fifty-two women (25%) of all women (those who received sutures as the initial second-line therapy and those who received sutures in combination with or after another second-line procedure) required hysterectomy to control bleeding. More women who required an additional second-line intervention went on to require hysterectomy (OR 3.09, 95% CI: 1.46 to 6.56).

One retrospective case series reported data on 539 cases of PPH treated with either uterine sutures or arterial ligation in hospitals in Argentina between 1989 and 2009.⁹⁴ Sutures were placed by a single surgeon, and suture types included B-lynch, Cho, Hayman, and Pereira. The number of sutures compared with ligations, and potential overlap between interventions, is not clear. Overall, the study reports cessation of bleeding in 499 cases. Forty women required hysterectomy, but whether this occurred after suture or ligation or a combination is not clear. B-lynch sutures were reported as successful in 81 of 86 cases, Hayman sutures in 34 of 37, Cho sutures in 281 of 313 cases, and Pereira in 11 of 11 cases, but again, prior or subsequent interventions are not clear.

Because the number of women who received sutures as the initial second-line intervention is clearly reported in only one study,^{68, 71} we do not include a success rate table for uterine compression sutures. Table 12 outlines data from studies with comparison groups.

Table 12. Key outcomes in studies of uterine compression sutures

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Kayem et al. 2011 ^{68, 71} UK G1: Uterine compression sutures (199) G2: Pelvic vessel ligation (20) G3: Interventional radiology (embolization, arterial balloon) (22) G4: rFVIIa (31) Quality: Fair	Age < 35, n (%) G1: 128 (64) G2: 12 (60) G3: 12 (55) G4: 21 (68) > 35, n (%) G1: 71 (36) G2: 8 (40) G3: 10 (45) G4: 10 (32) Nulliparous, n (%) G1: 92 (46) G2: 3 (15) G3: 6 (27) G4: 9 (29)	<ul style="list-style-type: none"> • Among all women receiving these second-line therapies, 205 had had prior uterotonic therapy (oxytocin, ergometrine, carboprost tromethamine, misoprostol) alone, 67 had had uterotonics and uterine tamponade • Compression sutures used more often in PPH caused by atony (63%, interventional radiology used more often for cases related to genital or ligament bleeding or clotting abnormalities) • Sutures as the first second-line therapy were successful in 120/161 women who received prior uterotonics only; 25 required immediate hysterectomy, 3 required ligation (no subsequent hysterectomy), 7 interventional radiology (3 subsequent hysterectomies), 6 rFVIIa (4 subsequent hysterectomies). In total 32 went on to hysterectomy • Among women who received uterotonics plus intrauterine tamponade, sutures were successful in 20/38 cases • Overall (across all groups) 71 women had hysterectomy (47 after failure of second-line therapy, 24 after failure of tamponade and subsequent treatments)
Palacios-Jaraquemada 2011 ⁹⁴ Argentina G1: Arterial ligation or uterine suture (539)	Age NR Parity NR	<ul style="list-style-type: none"> • Review of 539 cases of ligation or suture for PPH conducted by single surgeon • Techniques successful in controlling bleeding in 499 cases; 40 women required subsequent hysterectomy • Suture (B-lynch, Hayman, Cho, Pereira) appears to have been successful in 431 cases but denominator not clearly presented, nor are procedures received prior to or in conjunction with sutures clearly reported

G-group; PPH-postpartum hemorrhage; rFVIIa-recombinant activated factor VIIa

Uterine and Other Pelvic Artery Ligation

Key Points

- No good quality studies addressed uterine and other pelvic artery ligation (hereafter, ligation).
- Rates of successful control of bleeding without further procedures or surgeries ranged from 36 to 96 percent with a median of 92 percent in three studies.
- Strength of the evidence is low for ligation controlling bleeding without further procedures or surgeries.

Overview of the Literature

Four studies reported data on ligation.^{68, 82, 94, 95} Studies include two fair quality cohort studies, one conducted in the U.K.⁶⁸ and one in France.⁸² In the prospective study, 25 percent of cases of PPH were due to atony, 30 percent due to uterine tears, 20 percent due to accreta, and 25 percent due to other causes, and most women were under age 35 (60%).⁶⁸ Nearly 40 percent of cases of PPH in the retrospective cohort study were due to atony, and participant age was not reported. Studies primarily reported rates of success for ligation. Two retrospective case series, one reporting cases performed by a single surgeon in Argentina⁹⁴ and one reporting on outcomes over 30 years in a U.S. center,⁹⁵ also report data on ligation. Case series primarily report success rates and provide little data on participant characteristics.

Detailed Analysis

Outcomes of ligation were reported in a fair quality UKOSS cohort study described fully above.⁶⁸ Fourteen women required vessel ligation as second-line procedure following uterotonics alone. Ligation successfully controlled bleeding in five women, and five required sutures (followed by hysterectomy in three), two required rFVIIa (followed by hysterectomy in one), and two required hysterectomy immediately after ligation. Six women had ligation after uterotonics and intrauterine tamponade failure, and three went on to hysterectomy to control bleeding (two after sutures plus rFVIIa, one after sutures alone).⁶⁸

Another fair quality retrospective cohort study reported data from women with PPH admitted to a French ICU between 1983 to 1998 and included some data on future fertility.⁸² Sixty-one cases of PPH occurred in the time period, 48 of which were treated with bilateral ligation of the hypogastric arteries, eight with embolization using gelatin sponge or coils, and five with hysterectomy as the primary procedure. Across groups, 39 women required transfusion of four or more blood units. Most of the 56 women requiring either ligation or embolization as a primary procedure had cesarean births (n = 41). The women requiring primary hysterectomy all had hemorrhagic shock. The primary procedure failed in eight cases (described under each intervention). Among the 48 women undergoing primary ligation, four required hysterectomy to correct bleeding (92% success rate for primary ligation). This study also reported intervention by cause of PPH: 20 women had PPH due to atony and received ligation as the primary intervention. Nineteen of these 20 had cesarean births (elective or emergency). Ligation was successful in controlling bleeding in 18 of 20 cases, with two women requiring subsequent hysterectomy (one vaginal birth and one cesarean birth). Eleven women (10 cesarean births) had PPH due to accreta. Ten ligations were successful in this group; one woman who had a cesarean birth required hysterectomy and subsequently died. Seven women had PPH due to genital tract

laceration (seven vaginal births, 4 instrumented), and ligation was successful in all cases. Six women had placental abruption (six cesarean births), and ligation was successful in all cases. Two women had uterine rupture or pre-rupture (two cesarean births) with bleeding controlled successfully by ligation in both cases. Two women had PPH due to uterine artery injury, presumably incurred during cesarean birth. Ligation successfully controlled bleeding in one case, and the other women died. Finally, one woman with a cesarean birth had PPH related to placenta previa. Ligation failed to control bleeding, leading to subsequent hysterectomy.⁸²

One retrospective case series reported data on 539 cases of PPH treated with either uterine sutures or arterial ligation in hospitals in Argentina between 1989 and 2009.⁹⁴ Interventions were conducted by a single surgeon. The number of sutures compared with ligations, and potential overlap between interventions, is not clear. Overall, the study reports cessation of bleeding in 499 cases. Forty women required hysterectomy, but whether this occurred after suture or ligation or a combination is not clear. Ligation was reported as successful in 68 of 105 cases, but again, prior or subsequent interventions are not clear.

Another retrospective case series reviewed data from 29 years (1963-1992) of ligations performed in a U.S. hospital.⁹⁵ Women received initial medical therapy including uterotonics, and 265 underwent bilateral uterine artery ligation after cesarean birth. Atony accounted for most cases of PPH across the study period (n = 135), and the rate of PPH treated with ligation declined across decades (n = 124, 60, 81 per each decade from 1963-1992). Overall, ligation failed to control bleeding in 10 women, eight of whom had abnormal placentation. Six of these 10 women had total hysterectomies, three had sutures, and one had ovarian artery ligation. Most treatment failures (n = 7) occurred in the first decade reviewed. The study reports that menstrual flow was not affected, but method and timing of followup is not clear. Table 13 outlines key outcomes of studies.

Table 13. Key outcomes in studies of uterine and other pelvic artery ligation

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Cohort Studies		
Kayem et al. 2011 ^{68, 71} UK G1: Uterine compression sutures (199) G2: Pelvic vessel ligation (20) G3: Interventional radiology (embolization, arterial balloon) (22) G4: rFVIIa (31) Quality: Fair	Age < 35, n (%) G1: 128 (64) G2: 12 (60) G3: 12 (55) G4: 21 (68) > 35, n (%) G1: 71 (36) G2: 8 (40) G3: 10 (45) G4: 10 (32) Nulliparous, n (%) G1: 92 (46) G2: 3 (15) G3: 6 (27) G4: 9 (29)	<ul style="list-style-type: none"> • Among all women receiving these second-line therapies, 205 had had prior uterotonic therapy (oxytocin, ergometrine, carboprost tromethamine, misoprostol) alone, 67 had had uterotonics and intrauterine tamponade • Ligation as the initial second-line therapy was successful in 5/14 women, 2 went on to immediate hysterectomy, 5 required sutures (3 subsequent hysterectomies), 2 required rFVIIa (1 subsequent hysterectomy). In total, 6 women had hysterectomies. • Overall, 71 women had hysterectomy (47 after failure of second-line therapy, 24 after failure of uterotonics/ tamponade and subsequent treatments)
Ledee et al. 2001 ⁸² France G1: Hysterectomy (10) G2: Bilateral hypogastric artery ligation (48) G3: Embolization (9) Quality: Fair	Age NR Parity NR	<ul style="list-style-type: none"> • All women underwent bimanual compression, oxytocin and prostaglandin IV administration, and resuscitation before further intervention • Ligation was primary procedure in 48 women and secondary in 1; ligation failed to control bleeding in 4 cases, which all required hysterectomy
Case Series		
Palacios-Jaraquemada 2011 ⁹⁴ Argentina G1: Arterial ligation or uterine suture (539)	Age NR Parity NR	<ul style="list-style-type: none"> • Review of 539 cases of ligation or suture for PPH conducted by single surgeon • Techniques successful in controlling bleeding in 499 cases; 40 women required subsequent hysterectomy • Ligation appears to have been successful in 68 cases but denominator not clearly reported, nor are procedures received prior to or in conjunction with ligation •
O'Leary 1995 ⁹⁵ US G1: Uterine artery ligation (265)	Age NR Parity NR	<ul style="list-style-type: none"> • 265 cases of PPH treated over 30 years; ligation failed in 10 cases leading to hysterectomy (6 cases), placental site ligation (3 cases), ovarian artery ligation (1 case) • Menstrual flow reportedly not affected but followup not clearly described

G-group; NR-not reported; PPH-postpartum hemorrhage; rFVIIa-recombinant activated factor VIIa

Ligation Success Rates

Ligation was performed on multiple sites (e.g., internal iliac, uterine arteries) within and across studies, and rates of successful control of bleeding ranged from 36 to 96 percent with a median of 92 percent (Table 14).

Table 14. Success rates after uterine and other pelvic artery ligation as the initial second-line procedure

Study Country	Quality	Total N Treated	Total N Successful*	% Success [*]
Cohort Studies				
Kayem 2011 ⁶⁸ UK	Fair	14	5	35.71
Ledee 2001 ⁸² France	Fair	48	44	91.67
Case Series				
O'Leary 1995 ⁹⁵ US	NR	265	255	96.23
Total	NA	422	372	Range: 36-96% Median success rate: 91.67%

*Success = control of bleeding without further procedure or surgery
NA-not applicable, NR-not rated

Embolization and Hysterectomy

Key Points

- One study compared embolization and hysterectomy.
- Embolization failed to control bleeding in 20 cases (18%), leading to 17 hysterectomies.
- Women in the hysterectomy group had significantly more ICU admissions compared with the embolization group (RR 1.6, 95% CI: 1.1 to 2.4) and had a greater median length of stay (LOS, 10 days vs. 7 days).
- Strength of the evidence was low for embolization controlling bleeding without additional procedures or surgeries and insufficient for the effects of hysterectomy.

Overview of the Literature

One fair quality prospective cohort study conducted in the Netherlands⁹² compared outcomes following embolization or hysterectomy. The 205 women in the study most frequently had PPH related to atony (33%), and 43.4 percent were age 40 or older.

Detailed Analysis

One fair quality cohort study (Table 15) conducted in the Netherlands (LEMMoN: Nationwide Study into Ethnical Determinants of Maternal Morbidity in the Netherlands) prospectively collected data on severe maternal morbidity from all 98 Dutch maternity hospitals between 2004 and 2006 using a standardized collection form.⁹² Two hundred and five women required either embolization (n = 114) or hysterectomy (n = 108) or both (n=17) during the study period. More than 40 percent (43.4%) of women in both groups were age 35 or older, 39.5 percent were nulliparous, and 49.8 percent had cesarean births. The most frequent cause of PPH in the embolization arm was atony (33%) and disorders of placentation (placenta previa, morbidly adherent placenta) in the hysterectomy group (35%). Women in both arms had other interventions prior to either embolization or hysterectomy including oxytocin (> 80% of both groups); sulprostone (> 50% of both groups); plasma replacement, frozen plasma, or red blood cell transfusion (> 78% of both groups); and other surgical interventions including arterial ligation, B-lynch suture, inspection (6 women in embolization and 11 in hysterectomy groups).

Embolization failed to control bleeding in 20 cases (18%): 17 women in the embolization group also ultimately required hysterectomy to control PPH (two of these were due to uterine necrosis) and one case was resolved with balloon tamponade. In sub-analyses of these failed cases, embolization had a failure rate of 25 percent following cesarean birth. Women in the hysterectomy group required more transfusions (median 14 vs. 10, $p = 0.002$) and more massive transfusions (\geq eight units of red blood cells) compared with women undergoing embolization (RR 1.5, 95% CI: 1.1 to 2.1); however, timing of transfusion (i.e., pre- or post-embolization or hysterectomy) is not clear. Women in the hysterectomy group also had significantly more ICU admissions compared with the embolization group (RR 1.6, 95% CI: 1.1 to 2.4) and had a greater median LOS (10 days vs. 7 days).⁹²

Table 15. Key outcomes in studies of embolization and hysterectomy

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Zwart et al. 2010 ⁹² G1: Embolization (114) G2: Hysterectomy (108) Quality: Fair	Age, greater than 35, % G1+G2: 43.4 Nulliparity, % G1+G2: 39.5 Parity \geq 3: G1+G2: 7.3	<ul style="list-style-type: none"> • Women in both groups had additional interventions including misoprostol (13% in both groups), sulprostone (G1: 67%, G2: 86%), transfusion (98% of both groups), balloon therapy G1: 21%, G2: 30%), ligation or suture (G1: 10%, G2: 6%) • 17 women in G1 went on to have hysterectomy, 1 went on to tamponade after embolization • Women in G2 required more massive transfusions (\geq 8 units red blood cells) than G1 (RR:1.5, 95% CI: 1.1 to 2.1) but the timing of transfusion (pre- or post-procedure) is not clear • Women in G2 more often admitted to ICU than women in G1 (RR: 1.6, 95% CI: 1.1 to 2.4); 67 women in G1 admitted to ICU (number NR for G2) • Median length of hospitalization for G1 = 7 days (range 1-38) vs. 10 days (range 2-65) for G2

G-group; ICU-intensive care unit

Hysterectomy

Key Points

- Two of seven studies reported data to calculate success rates (control of bleeding without additional procedures or surgeries). In these two studies the median success rate for hysterectomy as the initial second-line intervention was 57 percent.
- In one case series analyzing data by hospital volume, there was no difference in transfusion, intraoperative injury, length of stay, or medical complications based on hospital volume after adjusting for age, race, hospital size, year of diagnosis, and hospital type.
- Strength of the evidence is insufficient for the success of hysterectomy in controlling bleeding given the few studies available.

Overview of the Literature

Seven studies reported outcomes of hysterectomy. Studies included two retrospective cohort studies of fair quality conducted in France⁸² and Korea (total $n = 71$).⁴⁷ Atony accounted for 75 percent of the 61 cases in one study,⁴⁷ while PPH in the 10 women undergoing hysterectomy in the second was due to genital tract lacerations in three cases, atony in three cases, placenta accreta or previa or placenta abruption in three cases, and uterine rupture in the final case. Four

population-based case series also reported on outcomes following hysterectomy. Case series were conducted in Canada,⁹⁶ Denmark,⁹⁷ the U.K.,⁹⁸ and the United States⁹⁹ and included data from 2,763 cases of PPH collected in regional or countrywide databases/registries. Participant ages ranged from 18 to 50 years in the studies reporting age,^{96,99} and PPH was typically due to atony (range 30 to 53% of cases) or placenta previa or accreta (range: 34 to 38% of cases). Finally, one retrospective case series conducted at a university hospital in the U.K. and including data from 52 cases of PPH also reported risk factors for hysterectomy.⁹³

Detailed Analysis

In one fair quality cohort study including women undergoing embolization (results described in embolization section) or hysterectomy, all women were initially treated with uterotonics (oxytocin, ergots, prostaglandins), uterine massage, transfusion (in patients who were not Jehovah's Witnesses) and fluid replacement.⁴⁷ Among the 124 women (eight Jehovah's Witnesses) experiencing primary PPH, 61 (mean age 31.8 ± 4.0 years, 22 primiparous, 33 vaginal deliveries) underwent hysterectomy. PPH was most frequently due to atony (75.4%), and mean blood loss prior to procedure was 1288.3 ml. Significantly more women in the hysterectomy group had DIC, hypotension, elevated heart rate, greater blood loss before intervention, and greater total transfusion requirements than in the comparison arm of women undergoing embolization (all p values < 0.001). Mean total LOS was 11.5 days. Thirty-nine women in the hysterectomy group required ICU care; however, the study does not report mean ICU stay. Fifty-seven women in the hysterectomy group required transfusion after surgery, and four also required embolization post-hysterectomy.

In another fair quality retrospective cohort study reporting outcomes after embolization, ligation, or hysterectomy (see full study description in Ligation section above), five of 61 women received hysterectomy as the primary procedure. The women requiring primary hysterectomy all had hemorrhagic shock, and the procedure was not successful at controlling bleeding in four cases. One woman also required subsequent embolization. This study also reported intervention by cause of PPH: hysterectomy was the primary procedure in three cases of PPH due to genital tract laceration (three vaginal births). As noted, one woman required subsequent embolization, and the other two died. Similarly, one woman who had a cesarean birth died after hysterectomy for PPH due to uterine rupture. Hysterectomy successfully controlled bleeding in one case of PPH due to placental abruption.⁸²

One population-based case series reported on outcomes following peripartum hysterectomy due to PPH.⁹⁸ In this study there were 315 cases of PPH that resulted in hysterectomy identified via UKOSS between 2005 and 2006. The median ICU stay was 2 days. Sixty-two women had a return to the operating room for a second surgery after hysterectomy. Fourteen percent of these women had a second surgery due to continued bleeding and 6 percent had return due to damage to other organs during hysterectomy. The median number of blood units transfused ranged from nine to 12 depending on etiology of transfusion.

Another population-based case series from the United States was conducted with data from a nationwide validated database that collected quality and resource utilization data (Perspective) data from 500 facilities in the United States.⁹⁹ The main hypothesis of this study was that hospital volume affects outcomes of postpartum hysterectomy. Among the 2,209 patients identified, overall maternal mortality was 1.2 percent among low, intermediate, and high volume facilities, reoperation rates were 3.2 to 6.4 percent (p = 0.02). Intensive care use rates were 45 percent, 39.6 percent and 27.4 percent for low, medium and high-volume institutions,

respectively ($p < 0.001$). The mean length of stay was 3.5 to 4.1 days. After adjusting for age, race, hospital size, year of diagnosis and hospital type, there was no difference in transfusion or length of stay based on hospital volume. Perioperative death was higher at low volume facilities (1.8% compared with 0.9 and 0.8% at medium and high volume hospitals, $p = 0.02$). Adjusted OR for perioperative death was 0.22 at high volume facilities.

A population-based case series in Denmark collected peripartum hysterectomy data from 1995 to 2004 using the Danish Medical Birth Register, which records information on all births in the country since 1973.⁹⁷ Peripartum hysterectomy was defined in this study as a hysterectomy taking place immediately after and up to one month after birth. Out of 653,482 births, there were 152 peripartum hysterectomies to control hemorrhage; thirty percent of cases of PPH were due to atony. Prior to hysterectomy, 80 percent of women received oxytocin, 73 percent prostaglandins, 43 percent misoprostol, and 43 percent ergot alkaloid. Ligation was performed in 21 percent of patients and B-lynch suture was also done in 21 percent prior to hysterectomy. Hysterectomy was more often performed after cesarean birth ($n = 101$, RR for hysterectomy after cesarean compared with vaginal birth = 11.1, 95% CI: 7.9 to 15.6, $p < .0001$). Sixteen women (11%) needed reoperation.

An additional population-based case series reported on all cases of postpartum hysterectomy done between 1999 and 2006 in a Canadian hospital.⁹⁶ All obstetric care in the region is linked to a regional database. Investigators identified all hysterectomies that occurred within 24 hours of birth. A total of 87 peripartum hysterectomies were performed in the study period, a rate of 0.8 per 1,000 births. Thirty-four percent of women in the series had placenta previa or accreta. All women received uterotonics prior to hysterectomy, and 86 percent received blood transfusion. Pelvic vessels were ligated in 33 percent of cases. B-lynch suture was done 3 times. Forty-six women (53%) were admitted to the ICU, and mean length of stay after birth was 6 days (range 2 to 16). Eighty-one percent of hysterectomies took place after cesarean birth ($n = 70$). Table 16 outlines outcomes.

A final case series reported on emergency hysterectomy outcomes at one U.K. hospital over 20 years.⁹³ Most ($n=50$) women had primary PPH and all had numerous interventions, including uterotonics, packing, tamponade, and sutures, prior to hysterectomy to control bleeding. In multivariate analyses, multiparity, placenta previa, primary PPH, and failed induction were significant risk factors for hysterectomy (all p values $< .02$).

Table 16. Key outcomes in studies of hysterectomy

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Cohort studies		
Kim et al. 2013 ⁴⁷ Korea G1: Embolization (60) G2: Hysterectomy (61) Quality: Fair	Age, mean ± SD G1: 31.0 ± 4.8 G2: 31.8 ± 4.0 Primiparous, n G1: 17 G2: 22	<ul style="list-style-type: none"> • Primary cause of hemorrhage in both groups was atony • 8 women in study were Jehovah's Witnesses-4 in each group • All women in G1 and G2 received uterotonics (G1: oxytocin = 100%, sulprostone = 68%, Ervin = 36%; G2: oxytocin = 100%, sulprostone = 60.6%; Ervin = 19.6%). 25 women in G1 and 36 in G2 required transfusion prior to procedure • Embolization was successful in 96% of G1; 2 women required hysterectomy due to continued bleeding from cesarean uterine wound and vaginal and cervical lacerations • Hysterectomy was successful in 93% of G2. 4 women required embolization following hysterectomy for extrauterine vaginal bleeding or continued bleeding of ligated vessels • 57 women required transfusion post-hysterectomy in G2 • Mean days in ICU in G1 = 5 days (5 women). ICU days not reported in G2 but 39 women required ICU care; LOS in hospital was 8.60 days in G1 and 11.5 in G2
Ledee et al. 2001 ⁸² France G1: Hysterectomy (10) G2: Bilateral hypogastric artery ligation (48) G3: Embolization (9) Quality: Fair	Age NR Parity NR	<ul style="list-style-type: none"> • All women underwent bimanual compression, oxytocin and prostaglandin IV administration, and resuscitation before further intervention • Hysterectomy was the primary procedure in 5 women (all with hemorrhagic shock) and secondary in 5 • Hysterectomy as a primary procedure failed to control bleeding in 4 cases—3 deaths, 1 subsequent embolization
Case Series		
Lone et al. 2010 ⁹³ UK G1: Hysterectomy (52)	Age, mean (range) G1: 29.4 (14-54) Parity, mean G1: 1.35	<ul style="list-style-type: none"> • Most women had multiple interventions prior to hysterectomy: bimanual compression, n = 46; oxytocin, n = 52; arterial ligation, n = 28; uterine packing, n = 18; intrauterine balloon, n = 17; B-lynch suture, n = 15; rVlla, n = 2 • Primary PPH, induction, placenta previa were significant risk factors for hysterectomy in multivariate analyses
Wright et al. 2010 ⁹⁹ US G1: Hysterectomy (2209)	Age, n (%) < 30 years: 673 (30.5) ≥ 30 years: 1536 (69.5) (overall median = 33, range = 14 to 50) Parity NR	<ul style="list-style-type: none"> • 35% of cases of PPH due to atony, 35% due to placenta accreta • Reoperation rates were 3.2% to 6.4% (p = 0.02 among low, intermediate, high volume hospitals) • Intensive care use was 45%, 39.6%, and 27.4% for low, medium and high-volume institutions, respectively (p < 0.001), mean length of stay was 3.5 to 4.1 days • No difference in transfusion, intraoperative injury, length of stay, or medical complications based on hospital volume in adjusted analyses • Perioperative death was higher at low volume facilities (1.8% compared with 0.9% and 0.8% at medium and high volume hospitals, p = 0.02). Adjusted OR for perioperative death was 0.22 at high volume facilities

Table 16. Key outcomes in studies of hysterectomy (continued)

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Case series		
Glaze et al. 2008 ⁹⁶ Canada G1: Hysterectomy (87)	Age, mean ± SD 34 ± 5 Primiparous, n (%) 37 (43)	<ul style="list-style-type: none"> All women received uterotonics prior to hysterectomy; 86% had blood transfusion; 33% had pelvic vessel ligation 53% admitted to ICU Mean LOS 6 days (SD = 3, range = 2-16)
Knight et al. 2008 ⁹⁸ UK G1: Hysterectomy (315)	Age NR Parity NR	<ul style="list-style-type: none"> Median ICU stay = 2 days Need for further procedure or surgery in 62 cases; 14% due to continued bleeding, 6% due to organ damage incurred during hysterectomy Median number of blood units transfused ranged from 9 to 12 depending on etiology
Sakse et al. 2007 ⁹⁷ Denmark G1: Hysterectomy (152)	Age NR Nulliparous, n 36	<ul style="list-style-type: none"> Most hysterectomies performed after cesarean birth (n = 101); RR for hysterectomy after cesarean birth compared with vaginal = 11.1, 95% CI: 7.9 to 15.6, p < .0001 Women generally received initial medical management Ligation was performed in 21% and B-lynch suture in 21% prior to hysterectomy 16 women (11%) needed reoperation

G-group; ICU-intensive care unit; LOS-length of stay; NR-not reported; PPH-postpartum hemorrhage; rFVIIa-recombinant activated factor VIIa

Hysterectomy Success Rates

Data on success rates (control of bleeding without further procedure) of hysterectomy as the initial second-line procedure were only extractable from two studies. Four women died after hysterectomy⁴⁷ in one study and five (two after another intervention plus hysterectomy) died in the second,⁸² so “success” rates may include some women who ultimately died. The median success rate was 57% in these two studies (Table 17).

Table 17. Success rates after hysterectomy as the initial second-line procedure

Study Country	Quality	Total N Treated	Total N Successful*	% Success
Cohort Studies				
Kim 2013 ⁴⁷ UK	Fair	61	57	93.44
Ledee 2001 ⁸² France	Fair	5	1	20.00
Total	NA	66	58	Range: 20-93% Median success rate: 56.72%

*Success = control of bleeding without further procedure or surgery; death may have occurred after hysterectomy

NA-not applicable

Studies of Combined Approaches

Key Points

- One cohort study of women with primary PPH reported greater need for transfusion, ICU admission, and hospital length of stay in women undergoing procedures and/or surgery compared with women who were medically managed.
- In three studies of women with secondary PPH, interventions included medical and surgical interventions. In one study, curettage resolved bleeding in 92 percent of women.
- Strength of the evidence for studies of combination interventions and length of stay was insufficient given the small sample sizes and inconsistency in interventions.

Overview of the Literature

Four studies addressed combination approaches and reported data in such a way that findings for individual interventions could not be isolated.¹⁰⁰⁻¹⁰³ Studies included two fair quality retrospective cohort studies^{100, 101} and two case series^{102, 103} that were conducted in France,¹⁰⁰ Israel,¹⁰¹ the United States,¹⁰³ and the United Kingdom.¹⁰² Three studies included women with secondary PPH, typically defined as bleeding occurring ≥ 24 hours after birth and up to 12 weeks later.¹⁰¹⁻¹⁰³ Studies of secondary PPH included a total of 413 women, and all studies typically reported on success of interventions to control bleeding.

Detailed Analysis

One fair quality French retrospective cohort study compared outcomes in women initially treated for PPH medically (n = 147) or using “advanced interventional procedures” (n = 110), which included uterine artery embolization (n = 85), embolization plus surgery (n = 11), or surgery alone (n = 14; surgery included peritoneal packing, arterial ligation, hysterectomy, or combination of all three).¹⁰⁰ Women (median age = 31 years) were treated between 2004 and 2005. Twelve women required hysterectomy: four in the medically managed group and eight in the advanced procedures group (p = NS). Both groups required transfusion, with the procedures group requiring significantly more units of RBC (2.8 vs. 1.2, p = 0.0004) and fresh frozen plasma (1.6 vs. 0.6, p = 0.003). Six women in the medical group and 31 in the advanced group were admitted to the ICU (p < 0.0001), and the median length of stay in the hospital was significantly greater in the procedures group (3.2 days vs. 1.0, p < .0001). However, the procedures group was likely experiencing more severe PPH given their lower median hemoglobin and systolic and diastolic blood pressures than the medically managed group. The study identified five factors that predicted the need for an advanced procedure: abnormalities of placental implantation, prothrombin time < 50 percent, fibrinogen < 2 g/l, troponin detectable, and heart rate > 115 beats per minute.

Three studies, one fair quality retrospective cohort study and two case series, focused on secondary PPH.¹⁰¹⁻¹⁰³ The cohort study, conducted in Israel and including data from 1990 to 2002, compared initial surgical evacuation of the uterus (n = 50, mean age = 29.9, 4 cesarean births) or primary medical treatment (n = 118, mean age = 28.5, 16 cesarean births) with regard to immediate complications and future reproduction.¹⁰¹ The study defined secondary PPH as occurring 24 hours after the end of the third stage of labor and up to 12 weeks later. More women in the medical group also had primary PPH compared with the surgical group (15 vs. 14, p = .03), and more women in the surgical group had manual separation of the placenta than did women in the medical group (8 vs. 5, p = .02). Need for blood transfusion, antibiotics,

hysterectomy, uterine perforation, readmission, hospitalization > 2 days, and hemoglobin drop of > 20g/L did not differ significantly between groups. One woman in the surgical group required a hysterectomy (0 in the medical group, $p = \text{NS}$). More women in the medical group required a secondary surgical evacuation than in the surgical group (31 vs. 4, $p = .01$).

A case series conducted in the U.K. reported on 132 women with secondary PPH (excessive vaginal blood loss or lochial discharge occurring ≥ 24 hours after the end of third stage of labor and up to 6 weeks following), 33 of whom had had primary PPH.¹⁰² More than half of the women presented with secondary PPH in the first two weeks postpartum (19% at ≤ 7 days after birth, 41% at 8-14 days, 23% at 15-21 days, 12% at 22-28 days, and 5% at > 28 days). Initially, 57 women had conservative management and 75 women had uterine evacuation. Most women (97%) received antibiotics as an initial treatment, 17% had blood transfusion, and overall 63% had uterine evacuation. The majority of the women were hospitalized (84%), and the mean length of stay was 3.5 ± 2.3 days. Women who were initially managed conservatively were more likely to be readmitted to the hospital than women who had surgical evacuation (OR 7.8, 95 per CI: 1.2-28.8) One woman required a hysterectomy after uterine perforation.

The second case series reports on cases of secondary PPH (defined as vaginal bleeding post-discharge severe enough to require readmission or surgery) over a 10-year period (1981-1991) at two tertiary hospitals in the United States.¹⁰³ One-hundred and thirteen women had secondary PPH (mean age = 26, range = 16-39, 10 cesarean births, 22 cases of prior PPH) occurring at a mean of 18 days postpartum. Eleven percent of bleeding occurred > 6 weeks after birth. Two-thirds of the women required hospitalization (67%, mean LOS = 4 days) and one-third had transfusion (35%, mean PRBC = 3 units). Bleeding resolved in 12% of women with conservative management. The majority of women (88%) had curettage, which was successful for 92%. Of the nine women who required additional surgical intervention to control bleeding, six had hysterectomy, one had ligation, and one had laparotomy. Table 18 outlines outcomes.

Table 18. Key outcomes in studies of combined interventions

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Gayat et al. 2011 ¹⁰⁰ France G1: Advanced interventions (embolization, ligation, surgery, packing, hysterectomy) (110) G2: Medical management (147) Quality: Fair	Age, median (first to third quartile) G1: 32 (30-36) G2: 31 (27-35) Primiparous, n (%) G1: 32 (29) G2: 57 (39)	<ul style="list-style-type: none"> • Women in both groups received transfusion, sulprostone (> 80% in each group) prior to procedure • Women in G1 received embolization (n = 85), surgery only (n = 14), or embolization + surgery (n = 11). Surgery included one or combination of peritoneal packing, ligation of arteries, hysterectomy. 12 women had a hysterectomy and 11 women had ligation before transfer to study hospital. 14 of these women were still actively bleeding on arrival to study hospital • ICU and LOS in obstetric unit significantly longer in G1 vs. G2 (ICU: median 31 days vs. 6 days, p < .0001, LOS in unit: median 3.2 vs. 1.0 days, p < .0001)
Feigenberg et al. 2009 ¹⁰¹ Israel G1: Initial medical treatment for secondary PPH(118) G2: Surgical evacuation of uterus for secondary PPH (50) Quality: Fair	Age, mean G1: 28.5 G2: 29.9 Parity, mean pregnancies prior to PPH G1: 3 G2: 2.7	<ul style="list-style-type: none"> • All women had secondary PPH—mean time to admission post-birth was 16.8 days in G1 and 27.9 days in G2 (p = .0003) • 48 women in G1 and 22 in G2 required > 2 days hospitalization, p = ns • 1 woman in G2 required hysterectomy (0 in G1), p = ns
Hoveyda et al. 2001 ¹⁰² UK G1: Medical and surgical management for secondary PPH (132)	Age NR Nulliparous, n (%) G1: 56 (42.4)	<ul style="list-style-type: none"> • Initial management of women with secondary PPH was conservative (n = 57) or surgical evacuation (n = 75); 84% were hospitalized • More women initially treated conservatively required readmission compared with women initially treated with evacuation (OR 7.8, 95% CI: 2.1 to 28.8) • Mean LOS = 3.5 ± 2.3 days
Boyd et al. 1995 ¹⁰³ US G1: Medical and surgical management for secondary PPH (113)	Age, mean (range) G1: 26 (16-39) Nulliparous, % G1: 39	<ul style="list-style-type: none"> • Bleeding resolved in 91/99 women treated with curettage; 6 had hysterectomy, 1 had ligation, 1 had laparotomy • Bleeding resolved in 12/99 treated conservatively • Mean LOS = 4 days, range 1-19 days

G-group; ICU-intensive care unit; LOS-length of stay; NR-not reported; PPH-postpartum hemorrhage; rFVIIa-recombinant activated factor VIIa

KQ2. Evidence for Choosing One Intervention Over Another and Proceeding to Subsequent Interventions

We did not identify any studies addressing this question.

KQ3. Harms of Interventions for Management of PPH

Key Points

- Thirty-eight studies reported harms of interventions for management of PPH. Seven of these were assessed as good quality for harms reporting and the remainder as poor quality.
- In three of the four studies that reported harms related to rFVIIa, 2 to 4 percent of women who received rFVIIa developed deep vein thrombosis or pulmonary embolism (PE). None of the women in the two of these studies that had comparator groups had thromboembolic events; however, this may be due to the small sample sizes rather than evidence of an adverse effect of the medication.
- Fourteen studies reported harms in women who underwent embolization; however, the harms reported in these studies are diverse and few studies report the same harms. The most frequently reported adverse events were infertility (0-43%), PPH in subsequent pregnancy (5%-17%), spontaneous abortion in subsequent pregnancy (5%-15%), and hematoma at puncture site (1%-6%).
- Seven studies reported diverse harms among women who had hysterectomy. The most frequently reported adverse events were reoperation (6%-29%), infection (7%-21%), bladder lesion (6%-12%), and ureter lesion (0.4%-8%).
- Multiple studies reported harms of transfusion (four studies), uterine compression sutures (two studies), uterine and other pelvic artery ligation (two studies), curettage (two studies), and combined approaches (two studies); however, they did not report comparable adverse events.
- Harms for tranexamic acid, sulprostone, methylergonovine maleate, carboprost tromethamine, and intrauterine balloon tamponade were only reported in one study per intervention. Most side effects were mild.
- Strength of the evidence for harms of interventions was typically insufficient given the diversity of harms reported in single studies. Strength of the evidence was low for hematoma, infertility, and menstrual changes associated with embolization and low for a lack of association between embolization and spontaneous abortion. Strength of the evidence was also low for the association of hysterectomy and operative organ damage and reoperation due to the greater number of studies and more consistent reporting of adverse events.

Overview of the Literature

Thirty-eight unique studies (reported in 43 publications) reported harms of interventions for management of PPH.^{36, 47, 58-62, 64-68, 70, 71, 72, 73, 75, 77-99, 101-103} These include two RCTs,^{36, 60, 61, 70} with harms data from one RCT reported in subsequent case series publications; two prospective cohort studies;^{68, 92} nine retrospective cohort studies;^{47, 58, 64, 72, 73, 78-82, 101} two case-control studies;^{65, 77} one pre-post study;⁷⁵ eight population-based case series;^{59, 62, 66, 67, 96-99} and 14 retrospective case series.^{83-91, 93-95, 102, 103} Seven studies were assessed as good quality for harms reporting;^{58, 60, 67, 86, 91, 99, 101} the remaining were of poor quality. Twelve studies were conducted in France,^{36, 59-61, 70, 75, 77-84, 88, 89} seven in the United States,^{58, 62, 72, 85, 95, 99, 103} four in Korea,^{47, 86, 87, 91} four in the United Kingdom,^{68, 93, 98, 102} two in Ireland,^{65, 73} and one each in Canada,⁹⁶ Argentina,⁹⁴ Australia and New Zealand,⁶⁷ Japan,¹⁰⁴ Israel,¹⁰¹ Finland,⁶⁴ the Netherlands,⁹² Denmark,⁹⁷ and multiple European countries.⁶⁶

In most studies, authors differentiated harms that seemed to be related to the intervention from those that were thought to be due to complications of PPH. When that is the case, we report only those harms attributed to the intervention. When that distinction was not made, we report all harms listed in the study. In almost all cases of maternal mortality, the authors provided detailed explanations that made it clear that the deaths were due to the PPH and its sequelae rather than the intervention. In this section, we have only reported deaths for which there was no detail about the cause and thus we could not distinguish if it was attributable to the intervention, the hemorrhage, or some other etiology.

Detailed Analysis

Pharmacologic Interventions

Tranexamic acid. In an RCT that compared women who received tranexamic acid with women who did not ($n = 72$ per group), serious side effects did not differ between the two groups. Two women in the tranexamic acid group and one in the control group had deep vein thrombosis ($p = 0.37$). None of the women experienced renal failure, seizures, or death. Mild, transient adverse effects occurred more often in the tranexamic acid group than in the control group (24% vs 6%, $p = 0.03$). These side effects included nausea and vomiting (15% vs 2%, $p = 0.002$), phosphenes (11% vs 3%, $p = 0.02$), and dizziness (6% vs 4%, $p = 0.28$). The trial was not adequately powered to report safety but was good quality for harms reporting.⁶⁰

Sulprostone. In one population-based case series of 1,370 women treated with sulprostone, 51 women (3.7%) experienced at least one side effect.⁶¹ These side effects included digestive effects ($n = 34$), hyperthermia and chills ($n = 7$), cardiac effects ($n = 5$), high blood pressure ($n = 2$), respiratory effects ($n = 2$), and dizziness ($n = 2$). The cardiac side effects (tachycardia, $n = 1$; atypical chest pain, $n = 1$; ischemia, $n = 3$) were considered severe by the investigators and resolved with cessation of sulprostone. Other severe harms included acute hypertension in one woman and acute cyanosis in a woman with asthma, both of which also resolved with cessation of sulprostone. This study, which is part of family of studies reporting on a systems-level intervention for PPH,^{36, 61, 70} was rated as poor quality for harms reporting.

Methylergonovine maleate. One cohort study (rated good quality for harms reporting) used data from U.S. hospital admissions collected over 4 years to identify women who had been given methylergonovine maleate during hospitalization for birth ($n = 139,617$) and those who had not ($n = 2,094,013$).⁵⁸ The study compared rates of myocardial ischemia and infarction in the exposed and unexposed women. Six women in the methylergonovine maleate group and 52 in the non-methylergonovine maleate group had an acute coronary syndrome (composite of acute myocardial infarction and unstable angina). The adjusted relative risk of developing an acute coronary syndrome associated with methylergonovine maleate exposure was 1.67 (95% CI: 0.40 to 6.97), and the risk difference was 1.44 per 1000,000 patients (95% CI: -2.56 to 5.45). Four women in the methylergonovine maleate group and 44 in the non-exposed group had an acute myocardial infarction (RR for infarction associated with methylergonovine maleate = 1.00m 95% CI: 0.20 to 4.95, risk difference per 100,000 patients = 0, 95% CI: -3.47 to 3.47).

Carboprost tromethamine. One-fifth (n = 48/237) of the participants in a population-based case series experienced a side effect attributed to the drug. Harms reported included diarrhea (11.4%), elevated blood pressure (6.8%), vomiting (6.8%), elevated temperature (2.1%), flushing (1.7%), and tachycardia (1.7%). Quality for the reporting of harms was assessed as poor.⁶²

Recombinant Activated Factor VIIa (rFVIIa). Four studies with rFVIIa as an intervention reported harms. Two women who received rFVIIa in a retrospective cohort study⁶⁴ (n = 26) experienced adverse events that may be related to the medication. These included pulmonary edema (n = 1) and PE (n = 1). Neither of these events occurred in women who did not receive rFVIIa (n = 22), but this may be due to the small sample size rather than evidence of an effect of the medication.⁶⁴ One case-control study reported one case of ARDS among the six women who received rFVIIa. There were no long term sequelae, though exact long term complications of interest were not described.⁶⁵ In a population-based case series, adverse events potentially related to rFVIIa in the 92 women to whom it was administered included thromboembolism (n = 4; 2 had PE, one had bilateral ovarian vein thrombosis, and one had a thrombus involving the jugular and subclavian vein, upper arm, and axilla that was not thought to be related to rFVIIa), myocardial infarction (n = 1), and allergic reaction (n = 1). None of these events occurred in women who did not receive rFVIIa (n = 16), but this may be due to the small sample size.⁶⁶ In another population-based case series rated as good quality for harms reporting (n = 105) adverse events potentially related to rFVIIa included cerebrovascular accident (n = 1), deep venous thrombosis (n = 1), and pulmonary embolism (n = 1).⁶⁷ We considered the other three studies as poor quality for harms reporting.

Other Medical Interventions

Transfusion. Four studies reported harms of transfusion for PPH management. One retrospective cohort study included 659 women who received whole blood transfusion, 593 who received packed red blood cells (PRBC) only, and 288 who received a combination of blood products. There was a significant difference in the number of women who experienced acute tubular necrosis (0.3% whole blood only vs 2% PRBC only vs 4% combinations), acute respiratory distress (0.5% vs .3% vs 2%), pulmonary edema (7% vs 4% vs 14%), and hypofibrinogenemia (0.2% vs 0.3% vs 16%).⁷² In another retrospective cohort study, there were no thrombotic complications or adverse reactions to cryoprecipitate or fibrinogen concentrate among 34 women receiving either treatment.⁷³ In a population-based case series addressing the thromboembolic risk associated with severe PPH and blood replacement therapies in 317 women with severe PPH (defined as uterine bleeding in the first 24 hours after birth, persisting after manual exploration of the uterine cavity and requiring IV uterotonics with a decrease of hemoglobin > 40g/l⁻¹, or > 4 U RBCs, hemostatic intervention or death), none of the women developed symptomatic deep vein thrombosis (DVT) or PE.⁵⁹ Three women developed superficial venous thrombosis (SVT). Severe PPH or packed RBC unit transfusions were found to be a risk factor for SVT. Other variables, such as cesarean birth, absence of low molecular weight heparin use, pre-eclampsia, severe pre-eclampsia, HELLP syndrome, placenta abruption, pregnancy loss, unexplained pregnancy loss, or F12C46T polymorphism were found to be significant risk factors for SVT. In one report from a larger, systems-level RCT^{36, 61, 70} that included 660 women who received a transfusion, five transfusion-related adverse events (not

described) occurred. The investigators considered one case of pulmonary edema to be a severe harm.⁷⁰ All four of these studies were assessed as poor quality for harms reporting.

Procedures

Uterine tamponade. Only one adverse event was reported among 43 women who had intrauterine balloon tamponade in a pre-post study with poor quality for harms reporting. One woman was diagnosed with endometritis, which was successfully treated with antibiotics.⁷⁵

Embolization. Fourteen studies (in multiple publications) reported harms in women who underwent embolization (Table 19);^{47, 77-81, 83-92} however, the harms reported in these studies are diverse and few studies report the same harms. Table 20 summarizes adverse events of embolization that are comparably reported in two or more studies. The most frequently reported adverse events (four studies for each) were hematoma at puncture site (1%-6%), infertility (0-38%), spontaneous abortion in subsequent pregnancy (5%-15%), and PPH in subsequent pregnancy (5%-17%). Although authors report PPH in subsequent pregnancy, it is likely related to history of PPH, which increases risk of recurrence, rather than the intervention.^{105, 106}

Table 19. Harms reported in embolization studies

Author Date Country Study Design	Quality	n	Follow-up n Duration	Reported Harms
Kim et al., 2013 ⁸⁶ Korea Retrospective case series	Good	257	257 NR	<ul style="list-style-type: none"> • Paresthesia in the posterior thigh (n = 10, 4%) • Uterine abscess (n = 3, 1%) • Postembolization syndrome (n = 2, 1%)
Lee et al., 2013 ⁹¹ Korea Retrospective case series	Good	176	148 Mean: 22.4 months (range: 2-58)	<ul style="list-style-type: none"> • Postembolization syndrome (n = 13, 9%) • Hematoma at the arterial puncture site (n = 3, 2%) • Heavier menses (n = 5, 3%) • Lighter menses (n = 17, 11%) • Dysmenorrhea (n = 1, 0.7%) • Uterine infarctions (n = 0) • Ischemic injuries (n = 0) • Neurologic complications (n = 0) • Major complications, not specified (n = 0) • Complications in subsequent pregnancies: preterm birth (n = 2/13, 15%)
Zwart et al., 2010 ⁹² Netherlands Prospective cohort	Poor	114	114 NR	<ul style="list-style-type: none"> • Infection (n = 9, 8%) • Acute respiratory distress syndrome (n = 1, 1%) • Laparotomy (n = 3, 3%) • Ischemic complaints (n = 2, 2%) • Maternal death (n = 3, 3%), no details provided
Chaleur et al., 2008 ⁸¹ France Retrospective cohort	Poor	46	46 Range: 2-11 years	<ul style="list-style-type: none"> • Allergy to iodine (n = 1, 2%) • Acute pulmonary edema related to massive volume expansion (n = 1, 2%) • Hematoma from the puncture site resulting in cardiovascular instability (n = 1, 2%) • Major hemoperitoneum related to dissection of the epigastric artery (n = 1, 2%) • Infertility (n = 0/16 desiring pregnancy) • Death from methotrexate-related nephrotoxicity in one woman with placenta percreta given methotrexate in conjunction with embolization; death appears to be related to treatment but not to embolization • Complications in subsequent pregnancies: spontaneous abortion (n = 1/19, 5%), twin pregnancy with preterm birth and fetal growth restriction (n = 1/19, 5%), PPH (n = 1/19, 5%)

Table 19. Harms reported in embolization studies (continued)

Author Date Country Study Design	Quality	n	Follow-up n Duration	Reported Harms
Kim et al., 2013 ⁴⁷ Korea Retrospective cohort	Poor	60	60 2 years	<ul style="list-style-type: none"> • Transient fever > 38.5°C (n = 11, 18%) • Infection per blood culture findings (n = 0) • Ovarian failure (n = 1, 2%)
Sentilhes et al., 2011 ⁷⁸⁻⁸⁰ France Retrospective cohort	Poor	101	68 (fertility and psychological outcomes) Mean: 71.4 months (range: 12-152 months)	<ul style="list-style-type: none"> • Buttock necrosis requiring debridement (n = 1, 1%) • Pulmonary embolism (n = 1, 1%) • Postpartum myocarditis (n = 1, 1%) • Puncture site hematoma (n = 1, 1%) • Postpartum fever (n = 22, 22%) • Endometritis (n = 14, 14%) • Wound infection (n = 8, 8%) • Increased menstruation (n = 11, 16%) • Amenorrhea or decreased menstrual flow (n = 15, 22%) • Synechia (n = 8, 12%) • Ovarian insufficiency (n = 7, 10%) • Infertility (13/30 desiring pregnancy, 43%) although the authors state there was no secondary infertility • Complications in subsequent pregnancies: miscarriage (n = 4/26, 15%), ectopic pregnancy (n = 1/26, 4%), uteroplacental insufficiency (1/19, 5%), recurrent PPH (n = 6/19, 32%) <p>Psychological outcomes (may be due to PPH or PPH+treatment)</p> <ul style="list-style-type: none"> • Symptoms requiring psychological care post-PPH (n = 2, 3%) • Fear of death post-PPH (n = 24, 35%) • Negative memory of pain post-PPH (n = 13, 19%) • Negative memory of separation from baby post-PPH (n = 6, 9%) • Complete amnesia about the birth (n = 3, 4%) • Think about event at least once/month (n = 16, 24%) • De novo phobia post-PPH (n = 5, 7%) • Persistent fear of death (n = 5, 7%) • Impossible to have sexual intercourse for ≥ 12 months (n = 4, 6%) • Marital problems considered related to event (n = 3, 4%) • Fear of PPH recurrence that lead to decision to avoid further pregnancy (n = 14, 21%) • Partners' negative feelings about PPH lead to decision to avoid further pregnancy (n = 13, 19%) • Anxiety or depression in subsequent pregnancy related to prior PPH (n = 16, 24%)

Table 19. Harms reported in embolization studies (continued)

Author Date Country Study Design	Quality	n	Follow-up n Duration	Reported Harms
Hardeman et al., 2010 ⁷⁷ France Case-control	Poor	53	53 Range:12-70 months	<ul style="list-style-type: none"> • Pain and fever (n = 19, 36%) • Hematoma/inguinal pain (n = 3, 6%) • Metrorrhagia (n = 2, 4%) • Amenorrhea (n = 3, 6%) • Infertility (2/14 desiring pregnancy, 14%) • Complications in subsequent pregnancies: late miscarriage (n = 1/14, 7%), recurrent PPH (n = 2/12, 17%)
Fiori et al., 2009 ⁸³ France Retrospective case series	Poor	56	34 Median 44.4 months (range: 8.3-118.2)	<ul style="list-style-type: none"> • Hypomenorrhea due to partial corporeal uterine synechiae: (n = 1, 3%) • Irregular menstrual bleeding (n = 1, 3%) • Infertility (n = 2/15 desiring pregnancy, 13%) • Complications in subsequent pregnancies: spontaneous abortion (n = 3/20, 15%) and ectopic pregnancy (n = 1/20, 5%), preterm birth (n = 1/12, 8%), PPH (n = 1/12, 8%)
Gaia et al., 2008 ⁸⁴ France Retrospective case series	Poor	113	107 Mean \pm SD: 46.4 \pm 21.8 months (range: 12-84)	<ul style="list-style-type: none"> • Pulmonary embolism (n = 2, 2%) • Acute pulmonary edema (n = 1, 1%) • Myocardial infarction (n = 1, 1%) • Femoral vein thrombosis (n = 5, 4%) • Urinary disorders (n = 8, 7%) • Vaginal dryness (n = 11, 10%) • Hot flushes (n = 13, 12%) • Dyspareunia (n = 14, 13%) • Menorrhagia (n = 10, 10%) • Oligomenorrhea (n = 23, 21%) • Amenorrhea and diffuse uterine synechiae (n = 6, 6%) • Infertility (n = 11/29 desiring pregnancy, 38%) • Complications in subsequent pregnancies: spontaneous abortion (n = 1/19, 5%), PPH (n = 3/18, 17%)
Ganguli et al., 2011 ⁸⁵ US Retrospective case series	Poor	66	66 NR	<ul style="list-style-type: none"> • Lower extremity DVT (n = 1, 2%) • Pancreatitis (n = 1, 2%) • Endometritis (n = 1, 2%) • Minor complications, not specified (n = 0)
Lee et al., 2012 ⁸⁷ Korea Retrospective case series	Poor	251	113 Mean: 30 \pm 23 months (range 6-99)	<ul style="list-style-type: none"> • Dissection of the uterine arteries (n = 2, 0.8%) • Transient numbness of the lower extremities (n = 2, 1%) • Edema of the lower legs (n = 1, 0.4%) • Hematoma at the puncture site (n = 3, 1%) • Irregular menses (n = 2, 2%)
Poujade et al., 2012 ⁸⁸ France Retrospective case series	Poor	98	98 NR	<ul style="list-style-type: none"> • Pulmonary edema (n = 1, 1%) • Uterine necrosis (n = 1, 1%) • Hysterectomy due to UAE-associated uterine necrosis (n = 1, 1%) • Endometritis (n = 11, 11%) • Wound infection (n = 1, 1%)

Table 19. Harms reported in embolization studies (continued)

Author Date Country Study Design	Quality	n	Follow-up n Duration	Reported Harms
Touboul et al., 2008 ⁸⁹ France Retrospective case series	Poor	102	102 NR	<ul style="list-style-type: none"> • Ischemia of the lumbar plexus (n = 1, 1%) • Gluteal pain (n = 1, 1%)
Yamasaki et al., 2013 ⁹⁰ Japan Retrospective case series	Poor	55	55 NR	<ul style="list-style-type: none"> • Fever (n = 6, 11%) • Lower limb neuropathy (n = 1, 2%) • Uterine necrosis (n = 2, 4%) • Hysterectomy due to UAE-associated uterine necrosis and infection (n = 2, 4%)

DVT-deep vein thrombosis; NR-not reported; PPH-postpartum hemorrhage; UAE-uterine artery embolization

Table 20. Adverse events reported in multiple embolization studies

Adverse Event	Number of Studies	Incidence
Infertility	5 ^{77, 78, 81, 83, 84}	0-43%
Spontaneous abortion in subsequent pregnancy	5 ^{77, 78, 81, 83, 84}	5%-15%
Hematoma at puncture site	5 ^{77, 80, 81, 87, 91}	1%-6%
PPH in subsequent pregnancy	4 ^{77, 81, 83, 84}	5%-17%
Fever	3 ^{47, 80, 90}	11%-22%
Amenorrhea	3 ^{77, 78, 84}	6%-22%
Lighter menses	3 ^{83, 84, 91}	3%-21%
Heavier menses	3 ^{78, 84, 91}	3%-20%
Preterm birth in subsequent pregnancy	3 ^{81, 83, 91}	5%-15%
Endometritis	3 ^{80, 85, 88}	2%-14%
Infection, not defined or wound infection	3 ^{80, 88, 92}	1%-8%
Irregular menses	3 ^{77, 83, 87}	2%-4%
Thromboembolic event (DVT or PE)	3 ^{80, 84, 85}	1%-4%
Lower extremity neuropathy, including numbness or paresthesia	3 ^{86, 87, 90}	1%-4%
Pulmonary edema	3 ^{81, 84, 88}	1%-2%
Ischemia	3 ^{89, 91, 92}	0-2%
Postembolization syndrome	2 ^{86, 91}	1%-9%
Ectopic pregnancy in subsequent pregnancy	2 ^{83, 97}	4%-5%
Uterine necrosis	2 ^{88, 90}	1%-4%

DVT-deep vein thrombosis; PE-pulmonary embolism

Surgical Interventions

Uterine compression sutures. A retrospective case series described 265 women who underwent uterine artery ligation to treat PPH after a cesarean.⁹⁵ Two of the women who had uterine artery ligation had small broad ligament hematomas. None of the women experienced a major complication or long-term adverse effects. This study was rated poor quality for harms reporting.

Uterine and other pelvic artery ligation. One retrospective cohort (poor quality for harms) reported a case of “secondary hysterectomy disunion with sepsis” (not clearly described) following ligation.⁸² This study also reports fertility outcomes for an unstated number of women who had ligation: among the number followed, 10 planned another pregnancy and seven were able to conceive 1 to 4 years post-ligation.

Uterine compression sutures and uterine and other pelvic artery ligation. In a retrospective case series of poor quality for harms reporting, 539 women underwent a variety of surgeries involving uterine compression sutures and arterial ligation. Five women had inadvertent ligation of the ureters, and one woman developed uterine necrosis. At 6 to 12 months after surgery, 404 women had a hysteroscopy (n = 100) or MRI (n = 304). Endometrial adhesions were present in three of the women who had hysteroscopy. None of the women who had MRI had endometrial adhesions or uterine morphological alterations. The study also notes 116 successful, spontaneous pregnancies in the study period, but the number desiring pregnancy and the method and timing of followup is not clear.⁹⁴

Hysterectomy. Seven studies reported harms of hysterectomy.^{47, 92, 93, 96-99} In a prospective cohort study, complications among 108 women who underwent hysterectomy included urinary tract lesions (n = 11, including 8 bladder and 3 ureter lesions), ovarian removal (n = 8), infection/abscess (n = 8), relaparotomy (n = 15, including one case of burst abdomen), Sheehan syndrome (n = 4), paralytic ileus (n = 3), DVT/PE (n = 3), and other (n = 2, exact harm not reported).⁹²

Harms reported in a retrospective cohort study of 61 women who had a hysterectomy included 14 cases of transient fever and two skin wounds. Blood cultures did not identify any infections.⁴⁷

Reported harms in a retrospective case series of 52 women who had an emergency hysterectomy included ureteric injury (n = 4 women), bladder injury (n = 3), small bowel injury (n = 2), urinary tract infection (n = 4), septicemia (n = 3), wound infection (n = 4), ARDS (n = 9), renal failure (n = 2), DIC (n = 11), repeat surgery (n = 15), and cardiac arrest (n = 2).⁹³ This authors did not distinguish which harms were specific to hysterectomy, but some of the adverse events (e.g., ARDS and renal failure) are likely unrelated to the surgical intervention.

In one population-based case series reporting data from the UKOSS, 18 of 315 women (6%) undergoing hysterectomy had a return to the operating room for a second surgery due to damage to other organs during hysterectomy.⁹⁸ Damage to organs such as ovaries (n = 28), bladder (n = 38) or ureters (n = 14) was reported in 67 women (21%).

In one U.S. population-based case series reporting on 2,209 peripartum hysterectomies, 715 hysterectomies were performed at low volume, 867 at intermediate volume, and 627 at high volume hospitals.⁹⁹ Harms included intraoperative injury and surgical and medical complications. Rates of bladder injury ranged from 7 to 9 percent across hospital types; ureteral injury ranged from 2 to 3 percent; intestinal injury from 3 to 4 percent; and vascular and “other” (not defined) injures from 0 to 10.7 percent. Rates of intraoperative injuries did not vary significantly across hospital types. Wound complications were higher in low volume hospitals (9.9%, 6.8%, 6.7% in low, intermediate, and high volume hospitals, respectively). Postoperative hemorrhage rates were 4.3 percent at intermediate volume, 5.9 percent at high volume, and 6.9 percent at low volume hospitals (p = ns). Rates of venous thromboembolism ranged from 0.8 to 2.2 percent (p = ns). Pulmonary complications were lowest in high volume hospitals (9.7%) compared with intermediate (12.6%) and low volume hospitals (14.1%), p = .05. Cardiovascular, gastrointestinal, and infectious complications ranged from 4.3 to 6.4 percent, 7.3 to 8.8 percent, and 11.6 to 12.4 percent, respectively and did not differ significantly across hospital types. Volume was not associated with rates of intraoperative injuries or medical complications in analyses adjusted for age, race, year of diagnosis, insurance status, hospital type, and hospital

size. The incidence of perioperative surgical complications, however, was lower in high volume hospitals compared with low volume (OR 0.66, 95% CI: 0.47 to 0.93).

A population-based case series from Denmark with 152 women reported the following complications after hysterectomy: reoperation (n = 16), infection (n = 13), bladder lesion (n = 10), oophorectomy (n = 8), ureter lesion (n = 3), abscess (n = 3), death (n = 2), and pulmonary embolism (n = 1).⁹⁷ No details are provided about the women who died.

Finally, one Canadian population-based case series reports postoperative complications in 87 women undergoing peripartum hysterectomy: anemia (n = 32), DIC (n = 17), ileus (n = 8), fever (n = 7), depression (n = 1), hematoma (n = 1), and pneumonia (n = 1).⁹⁶ This study also did not distinguish which adverse events were thought to be related to hysterectomy versus other causes.

All seven of these studies were assessed as poor quality for reporting harms. Table 21 outlines harms reported in more than one study. Reoperation is included in the harms for hysterectomy (and not for other procedures or surgical interventions) because it is typically considered the final surgical intervention and no further procedural or surgical intervention should be expected.

Table 21. Harms reported in multiple hysterectomy studies

Harm	N studies reporting	Incidence
Bladder lesion	5 ^{92, 93, 97-99}	6%-12%
Ureter lesion	5 ^{92, 93, 97-99}	0.4%-8%
Reoperation	4 ^{92, 93, 97, 98}	6%-29%
Any Infection	4 ^{92, 93, 97, 99}	7%-21%
DVT/PE	3 ^{92, 97, 99}	1%-3%
Fever	2 ^{47, 96}	8%-23%
DIC	2 ^{93, 96}	20%-21%
Ileus	2 ^{92, 96}	3%-9%

DIC-disseminated intravascular coagulation; DVT-deep vein thrombosis; PE-pulmonary embolism

Curettage. Two retrospective case series, both of poor quality for harms reporting, described women who were treated with curettage for secondary PPH.^{102, 103} In a series of 99 women, two had documented cases of Asherman syndrome on follow-up and one had uterine perforation from curettage that required repair via laparotomy.¹⁰³ In a series of 85 women, three had uterine perforation, one of whom underwent hysterectomy.¹⁰² These were the only harms reported in these studies.

Combined interventions. One prospective cohort study of 272 women addressing multiple second-line therapies (embolization, uterine compression sutures, ligation, and rFVIIa) reported ARDS (five cases), pulmonary edema (11 cases), and cardiac arrest (six cases). The study also reports six instances of the following harms but does not clarify the number of cases of each: hypoxic brain injury, renal failure, pulmonary embolism, and bladder damage after hysterectomy. The study also does not clarify if any of the reported harms were due to intervention or the PPH itself. This study was assessed as poor quality for harms reporting.⁶⁸

In a retrospective cohort study including 168 women with secondary PPH treated initially with either medical approaches or surgical evacuation, two women in the surgical group had uterine perforation.¹⁰¹ At followup, 12.1 percent of the medical group (n = 90, mean 88.3 months after PPH) and 30.8 percent of the surgical group (n = 41, mean 81.6 months after PPH) had secondary infertility. (p = .06). The majority of the women (74% of medical group and 65% of surgical group) desired a subsequent pregnancy. More women in the surgical group (28%) than medical group (11%) required infertility treatments, but this difference was not significant. The

mean number of births among those who conceived was 1.5 in the medical arm and 2.8 in the surgical arm ($p = .004$) Miscarriages did not differ between groups, and 3 percent of women in the medical group and 16 percent in the surgical arm required adhesiolysis ($p = .003$) in the followup period. We rated this study as good quality for harms reporting.

KQ4. Effectiveness of Interventions to Treat Acute Blood Loss Anemia in Women With Stabilized PPH

Key Points

- One small RCT reported elevations in hemoglobin in women with anemia after PPH receiving either oral or intravenous iron with no significant between group differences.
- One small RCT reported a decrease in fatigue and improvements in quality of life among women with asymptomatic anemia after PPH treated with transfusion, but differences between groups were not significant.
- Strength of the evidence is insufficient for all outcomes and harms in studies of interventions for anemia after PPH given the few studies, small number of participants, and differences in intervention approaches.

Overview of the Literature

We identified few studies addressing anemia after PPH is stabilized. Two studies addressed iron supplementation and transfusion. We did not identify studies of erythropoietin stimulating agents or other interventions. The two RCTs addressing interventions for post-PPH anemia were both rated as poor quality for all effectiveness outcomes and good¹⁰⁷ and poor¹⁰⁸ quality for harms.^{107, 108} Studies were conducted in Australia¹⁰⁸ and the Netherlands¹⁰⁷ and assessed transfusion and iron supplementation in women with stabilized hemorrhage. The RCTs included a total of 593 women followed for 6 weeks post-birth.

Detailed Analysis

A randomized non-inferiority trial, rated as poor quality for all effectiveness outcomes and good quality for reporting of harms, conducted in the Netherlands compared the effect of PRBC transfusion versus no intervention on quality of life among women with anemia due to PPH at 37 Dutch university and general hospitals.¹⁰⁷ Eligible women were enrolled between 12 and 24 hours after birth, and had a hemoglobin concentration between 4.8 and 7.9 g/dl after experiencing PPH (defined as blood loss of ≥ 1000 mL and/or decrease hemoglobin concentration of ≥ 1.9 g/dl). Women with severe symptoms of anemia were excluded from the study. In total, 521 women were randomized to receive transfusion with PRBC (259 women) or no intervention (262 women). There were no significant differences in baseline characteristics between groups (no p-value reported), and there was no significant difference between baseline hemoglobin concentration (7.3 vs. 7.4 in the transfusion vs non-intervention groups, $p = 0.56$). The hemoglobin at discharge was significantly higher among women receiving transfusions than those that did not (9.0 g/dL vs 7.4 g/dL in the transfusion vs non-intervention groups, $p < 0.001$), but there was not a statistically significant difference in hemoglobin concentration between groups at 6 weeks (12.1 g/dL vs 11.9 g/dL in the transfusion vs non-intervention groups, $p = 0.18$). The non-intervention group had greater mean fatigue, but the difference in mean physical

fatigue between groups did not meet pre-specified non-inferiority parameters and was negligible overall. There was no significant difference in health-related quality of life between groups after removing questions not answered within the study timeframe. There was no difference between the groups in rates of breastfeeding at 6 weeks (64% vs 71% in the transfusion vs. non-intervention groups, $p = 0.30$). There was no difference between the transfusion and no transfusion groups in length of stay or in complications (transfusion reactions, thromboembolic events, urinary tract infections, infected surgical wound, infected episiotomy/rupture, endometritis, and total infectious complications [10.5% vs 11.4% in the transfusion vs non-transfusion groups, $p = 0.90$]).

An Australian RCT (rated as poor quality for all outcomes) compared the effectiveness of intravenous versus oral iron supplementation among anemic women with PPH.¹⁰⁸ Eligible participants were women with iron-deficiency anemia (hemoglobin < 110 g/L and ferritin < 12 $\mu\text{g/L}$) after PPH. Women were identified within 72 hours of cesarean or vaginal birth with blood loss > 500mL. Women (74 total) were enrolled over a 2-year period, and were randomized to either two intravenous infusions of 200 mg of iron sucrose (31 women) or daily oral ferrous iron sulfate tablets (43 women, total 160 mg iron daily) for a six-week period following enrollment. Hemoglobin and ferritin levels were measured at baseline and on days 1, 14, and 42, and transfusion of PRBC and drug reactions were documented. There was no statistically significant difference in mean hemoglobin levels at any time point between the intravenous and oral iron supplementation groups (baseline hemoglobin 96 vs 95, $p = 0.5$; hemoglobin on day fourteen 115 vs 118, $p = 0.2$, and hemoglobin on day forty-two 124 vs 127, $p = 0.7$ in the IV intravenous iron vs oral iron groups, respectively). Ferritin was significantly higher on days 14 and 42 among women in the intravenous iron repletion group than the oral iron repletion group (ferritin on day fourteen 101 vs 37, $p < 0.001$; ferritin on day forty-two 46 and 19 and $p = 0.01$). There was no statistically significant difference in rate of red blood cell transfusion between the treatment groups. The study reports arrhythmia in one participant and notes that no other adverse reactions occurred. Table 22 summarizes key outcomes in these studies.

Table 22. Key outcomes in studies in women with stabilized PPH and anemia

Author, Year Country Groups (n) Quality	Age, years Parity	Key Outcomes
Prick et al. 2014 ¹⁰⁷ Netherlands G1: Red blood cell transfusion following resolved PPH (258) G2: No transfusion (261) Quality: Poor for all outcomes	Age, mean ± SD G1: 30.7 ± 5.0 G2: 30.9 ± 5.3 Nulliparous, n (%) G1: 152 (59) G2: 143 (55)	<ul style="list-style-type: none"> • 13% of G2 also received transfusion for anemic symptoms, blood loss, endometritis, inability to tolerate parenteral iron • G1 received a median of 2 red blood cell units and at discharge had a median Hb concentration of 9.0 g/dl (range: 8.5-9.5) vs. 7.4 (range: 6.8-7.7) in G2, p < .001 • Hb concentration at 6 weeks was not significantly different between groups (12.1 vs. 11.9 g/dl) • LOS did not differ between groups (median 2 days) • Physical fatigue scores were statistically significantly higher in G2 vs. G1 at all time points though the differences were not clinically significant • Harms in both groups included transfusion reactions, infections, endometritis, thromboembolic events; group differences were not significant
Froessler et al. 2013 ¹⁰⁸ Australia G1: IV iron sucrose (31) G2: Oral iron sulfate (43) Quality: Poor for all outcomes	Age, median (range) G1: 28 (26-32) G2: 30 (26-34) Parity NR	<ul style="list-style-type: none"> • Hb increased significantly in both groups by Day 14 and remained elevated at Day 42; G1: mean at baseline 96 g/dL (range: 87-102) and at Day 42 124 g/dL (118-132); G2: mean at baseline 95 g/dL (range: 89-106) increased to 127 g/dL (range:120-132) • No differences in Hb levels between the groups at any time point • Increased levels of ferritin in both groups, however time course of changes differed by treatment; levels were significantly increased for G1 from baseline 18 mg/L (range: 11-32), at Day 14 mean 101 (range:82-114) and Day 42 mean 46 (range: 24-64) while levels for G2 baseline mean 21 (range:24-52) were increased only at Day 14 37 (range: 24-52), and had dropped to by day 42 19 (range: 13-33). • Ferritin levels were significantly higher for G1 vs G2 at Day 14 and Day 42 • Blood loss at birth was comparable for both groups (mean 775 mL for G1 and 800 mL for G2) • No serious drug reactions observed (one patient excluded due to arrhythmia during first iron transfusion but since she had prior occurrence it was deemed not related)

G-group; Hb-hemoglobin; LOS-length of stay; NR-not reported; PPH-postpartum hemorrhage; rFVIIa-recombinant activated factor VIIa

KQ5. Effectiveness of Systems-Level Interventions for Management of PPH

Key Points

- No clinical trials demonstrate effectiveness of a systems-level intervention for reducing severity of PPH or improving maternal outcomes.
- The sole cluster randomized trial in 106 French maternity units, with more than 146,000 births, used a multi-component intervention of academic detailing of protocols, local champions, protocol reminders, and peer review compared to passive dissemination. Prevalence of severe PPH did not differ between arms.
- In general, multi-component systems-level interventions do not reliably reduce severity of PPH.

- Two European pre-post studies used audit of PPH cases with feedback to teams and individual providers. Both reported significantly reduced incidence of severe PPH, in each case by more than 1 percent absolute risk among total births.
- No U.S. studies relied primarily on audit and feedback.
- One large urban teaching hospital in U.S., that dramatically revised clinical responsibilities of residents and attending physicians, had no maternal mortality from PPH in a 36-month intervention period that followed a 24-month window with two maternal deaths. Overall PPH severity did not change.
- Strength of the evidence is moderate for a lack of benefit for systems-level interventions in reducing PPH incidence or severity; preventing hysterectomy; and affecting ICU admissions. Strength of the evidence is moderate for no effect on the need for transfusion and insufficient for effects on mortality.

Overview of the Literature

We classified research as system-level interventions when an entire administrative unit within a health system was responsible for implementing policies or protocols that were intended to improve management of PPH. The level from which interventions were launched ranged from an entire region of a national health system, to multihospital collaborations, to individual department decisions about labor and delivery routines that encompassed all care providers. Interventions were varied and included broad multi-component interventions, implementation of emergency response teams, and audit and feedback of outcomes data about severe PPH to groups and individual providers.

We identified a total of eight studies that were designed to investigate the effectiveness of one or more system-level interventions for reducing severity of PPH or improving specific maternal outcomes.^{33-36, 109-112} Four were of fair quality,^{35, 36, 110, 111} and four were of poor quality.^{33, 34, 109, 113}

Because system-level randomized trials are rare, we decided during design of this review that we would include studies that were not randomized but examined the influence of multi-component systems-level interventions. Seven studies compared a baseline period with subsequent trends after implementation of the interventions intended to improve management of PPH and to reduce severity of adverse maternal consequences.^{33-35, 109-112} For brevity in tables and text we have called these pre-post assessments. One publication provided outcomes from a randomized trial.³⁶ The trial was conducted in 106 maternity units in defined maternity regions of France.³⁶ Of the pre-post studies, four were conducted in Europe,^{34, 35, 110, 112} and three in the United States.^{33, 109, 111}

When an entire system undertakes a change all the components are working in concert and are typically designed to do so. Given this intentional interaction between parts, the intervention that is being tested is the “bundle” of components that are being conducted together. For example the influence of audit and feedback in the context of an intervention that includes measuring blood loss, mock emergencies practice, and flow charts to track delivery of key treatments at specific intervals is being conducted in a different environment than audit and feedback in an intervention that does not measure blood loss, or use flow charts, but that did incorporate mock emergency practice.

At times in reviews of systems-level approaches the components are similar enough and the trials large enough that we can conduct meta-analyses of trials with well-operationalized

outcomes to attempt (while noting the strong influence of context) to partially isolate the influence of a single component on outcomes. In this literature, the lack of a group of strong trials, the variation in implementation of even similar types of components, and wide range of operational definitions of outcomes, made such analysis implausible. We thus considered all components of an intervention as one systems-level intervention in our analyses below.

Detailed Analysis

The outcomes of systems-levels interventions are summarized in Table 23 in reverse chronological order. We summarize outcomes by study design below.

Table 23. Systems-level interventions to improve management of PPH

Author, Year; Country	Study Type* & Time Period	Setting & Population Pre: PPH cases/births Post: PPH cases/births	Management Strategies Addressed by Intervention	Outcomes
Lappen et al. 2013 ¹⁰⁹ United States	Pre-Post	Urban tertiary care hospital Pre: 278/5812 (4.78%) Post: 341/6,690 (5.09%)	Multicomponent evidence-based patient safety program to assist in management of PPH: education of all nursing and physician staff, introduction of a management checklist, routine use of active management of third stage Goal: improvement in patient care and outcomes	Use of some interventions increased (uterotonic selection and dosing, B-lynch sutures at cesarean; all $p < 0.05$) but severity as assessed by patient outcomes such as EBL, lowest hemoglobin, transfusion, DIC, hysterectomy, or ICU admission did not change
Markova et al. 2012 ¹¹⁰ Denmark	Pre-Post 2003, 2005, 2007	Urban university hospital Pre: NR Post: NR (148 total transfusions for PPH among 10,461 births)	Multi-professional skills training for management of a range of obstetric emergencies including PPH Goal: reduce need for transfusion and shorten interval to PPH interventions	No effect of the intervention on transfusion for PPH and an unchanged delay in management of retained placenta with trend towards longer duration
Shields et al. 2011 ¹¹¹ United States	Pre-Post 2009, 2011	Rural hospital Pre: 62/2,939 (2.11%) Post: 148/5,813 (2.55%)	Labor and delivery nursing and physician education, with three progressive stages of intervention implementation Goal: promote early intervention, reduce stage of severity of hemorrhage, promote early use of blood products, and reduce DIC	Severity of PPH declined. After implementation 82% of women with PPH were treated successfully with Stage 1 intervention (supportive measures and uterine massage only or with a single dose of tocolytic) compared to 35% at baseline ($p = 0.02$)
Dupont et al. 2011 ¹¹² France	Pre-Post 2005, 2008	2 maternity units Pre: 77/4500 (1.71%) Post: 42/5112 (0.82)	Quarterly clinical audit meetings for review of all severe PPH Goal: reduce the incidence of severe PPH	Severe PPH declined from 1.52% to 0.96% of births at level III hospital ($p = 0.048$) and from 2.08% to 0.57% at level II hospital ($p < 0.001$)
Deneux-Tharaux et al. 2010 ³⁶ France	Cluster RCT 2004 - 2006	106 maternity units Control: 6.37% of 70,707 Intervention: 6.37% of 76,074	Passive vs. active dissemination of protocol with academic detailing, local nurse and physician champions, reminders, and peer review of severe PPH cases Goal: reduce severity of PPH through a multi-faceted early intervention	Proportion of women with severe PPH did not differ by intervention group (1.65% control sites and 1.64% intervention sites)

Table 23. Systems-level interventions to improve management of PPH (continued)

Author, Year; Country	Study Type* & Time Period	Setting & Population Pre: PPH cases/births Post: PPH cases/births	Management Strategies Addressed by Intervention	Outcomes
Audureau et al. 2009 ³⁵ France	Pre-Post 2002, 2005	19 maternity units Pre: 164/17,664 (0.93%) Post: 166/17,722 (0.94%)	Multifaceted intervention including dissemination of clinical guidelines, local opinion leaders, reminders, and blood collection bags Goal: Primary goals were use of intervention components, reducing prevalence of severe PPH analyzed as secondary outcome	Prevalence of severe PPH remained constant across time periods. Use of transfusion (p = 0.01) and hemostatic surgery increased significantly (p = 0.03)
Skupski et al. 2006 ³³ United States	Pre-Post 2000-2001, 2002-2005	Urban university hospital Major PPH Pre: 12/5811 (0.21%) Post: 49/12,912 (0.38%)	Multicomponent approach including rapid response team, clinical pathways, guidelines, and protocols, dedicated obstetric inpatient service, change in duties, didactic sessions Goal: reduce severity of PPH and improve maternal outcomes	Maternal deaths declined from two deaths in the baseline period to none in the follow-up period (p = 0.04). Severity of hemorrhage remained unchanged
Rizvi et al., 2004 ³⁴ Ireland	Pre-Post 1999 2002	Single hospital Pre: 54/3,176 (1.7%) Post: 15/3,300 (0.45%)	Audit of PPH > 1,000ml and near-miss maternal mortality for departures from guidelines; intervention included review of guidelines, staff training and practice drills Goal: reduce incidence of PPH > 1,000ml	PPH > 1,000ml declined from 1.7% to 0.45% (p < 0.001) with 100% adherence to guidelines in the follow-up period

DIC-disseminated intravascular coagulation; EBL-estimated blood loss; ICU-intensive care unit; PPH-postpartum hemorrhage

Randomized Controlled Trial

In 1998, the French government introduced perinatal networks organized within geographical regions. The networks encompass all public and private hospitals and include at least one tertiary care unit per network. The mandate for networks includes care coordination and quality improvement research. The single clinical trial of multi-component interventions was a large cluster randomized trial conducted in two large maternity care regions of France representing six networks; 106 of a potential 109 maternity units in these networks participated.³⁶ Sites were stratified within network and by size, then centrally randomized to implement the full intervention or to have the related protocol passively disseminated without programmatic support.

At intervention sites outreach visits were held to plan for implementation and anticipate challenges. A protocol intended to reduce the rate of severe PPH was introduced by usual channels and reinforced through academic detailing by local opinion leaders and by reminders in the maternity units. The intervention proceeded in two phases that allowed sites to consider how to best optimize the quality of implementation at their site, to prepare staff, and to make changes to facilities or resources on hand. All types of care providers were engaged and had roles in the protocol. The second phase included implementation tools such as emergency response kit to

hold key drugs, crisis response phone numbers, transfusion and lab order forms, and other items as desired by the units and provision of a “PPH chronological checklist” to track implementation of the protocol, estimate total estimated blood loss (EBL), and encourage minimal loss of time in crucial decisions. The intervention also included peer review of all births with severe PPH and critical analysis of the care provided in reference to the protocol guidance.

With a total of more 146,000 births in the two study arms, severe PPH did not differ across sites with an incidence of 1.64 percent at the intervention sites and 1.65 percent at the control comparison sites. Some components of the intervention suggested improvements in practice, such as involving senior staff sooner ($p = 0.005$), using second-line pharmaceutical options sooner ($p = 0.06$), and more prompt checks of hematocrit ($p = 0.09$). However, taken together these differences and the global intervention package did not significantly influence overall maternal outcomes. In a followup case series ($n = 9365$) from this RCT⁷⁰ that assessed transfusion practices, only half ($n = 423/858$, 49%) of women with PPH and a hemoglobin level below 7.0 g/dL received RBC transfusion. These results suggest poor compliance with transfusion recommendations in the national French guidelines.

Observational Studies

Seven non-randomized studies used prospective observational designs in which baseline data about processes of care and patient outcomes were collected for an extended period of time prior to implementation of a policy, protocol, or procedure change,^{33-35, 109-112} then followup data were collected over time after implementation. Across these studies numerous types of components were implemented and evaluated (Table 24).

Table 24. Components of interventions in systems-level studies

Problem solving/quality improvement stage
Specific protocols in place
Phased roll out
Educational components including training sessions or didactic materials
Clinical champions who assisted locally in engraving implementation
Multi-professional target group meaning nurses and physicians from obstetrics, anesthesia, and potentially pediatrics were included
Mock events or simulations to allow role play of response to PPH
Documented risk assessments such as risk scores recorded on admission to the labor and delivery unit
Use of tracking tools, checklists, or timelines to support protocol implementation and/or ensure timely response
Emergency response kits such as crash carts with key medications and drapes for measuring estimated blood loss
Tools like fluid collection drapes, approaches to weighing linens for fluid, and/or mandates for tracking estimated blood loss
New staffing response plans to provide additional or more senior staffing in the event of PPH
Audit and feedback in which individuals or groups regularly reviewed data from PPH events to examine trends and responsiveness to protocols

PPH-postpartum hemorrhage

All systems-level studies evaluated the influence of combinations of these approaches (see Table 25).^{33-36, 109-112} Two of the observational studies documented statistically meaningful changes in use of selected intervention components.^{35, 109} Increases in use of management strategies included use of uterotonics,¹⁰⁹ hemostatic sutures at cesarean,¹⁰⁹ hemostatic interventions including embolization and hysterectomy³⁵ and transfusion³⁵ in the period after new protocols were introduced. In neither of these studies were the primary maternal outcomes such as incidence of severe PPH, DIC, hysterectomy, or ICU admission decreased.

Three studies reported reduced severity of PPH after implementation of new multicomponent programs.^{111, 112, 114} In the most recent of these, conducted in the United States, the investigators established a staging system to define severity.¹¹¹ The staging was linked to the level of intervention ultimately required to control the hemorrhage with higher stages indicating greater morbidity. In the baseline data collection before implementation, 35 percent of women giving birth by cesarean or vaginally were successfully treated with only Stage 1 (basic) interventions such as a single dose of uterotonic and uterine massage. This improved to 82 percent after the systems-level intervention program was in place ($p = 0.02$). The program emphasized vigilant observation, tracking of time course, and formal measurement of EBL and also allowed for shifting of staff to better match acuity. A French study in two maternity units reported the incidence of severe PPH declined in both a level II and level III hospital with the greater reduction in the lower acuity hospital. Incidence in that hospital fell from 2.09 percent to 0.57 percent of all births ($p < 0.001$) with a significant but less than one percent drop in the level III unit.¹¹² Their program and that of the final study that reports reduced incidence was driven predominantly by a process of systematic audit of the charts of severe PPH cases with feedback to suggest improvements. The earliest group to examine audit and feedback reported similar scope of reductions in severe PPH (defined as $> 1,000\text{ml}$ EBL) from 1.7 percent to 0.45 percent ($p = < 0.001$) while noting that compliance with guidelines for intervention improved to 100 percent in the follow-up period. They attribute a portion of this success to training and use of practice drills.

Table 25. Summary of components of systems-level interventions

Components of interventions	Problem Solving/Quality Improvement Stage	Specific Protocols in Place	Phased Roll Out	Educational Component	Clinical Champions	Multi-Professional Target Group	Mock Events/Simulations	Documented Risk Assessments	Tracking Tools/Checklists to Support Protocols	Emergency Response Kits	Tools/Mandate for Tracking EBL	Staffing Response Plan for PPH	Audit and Feedback
Lappen et al., 2013 ¹⁰⁹	X	X		X					X				
Markova et al. 2012 ¹¹⁰				X		X	X						
Shields et al., 2011 ¹¹¹	X	X	X	X		X	X	X	X	X	X	X	
Dupont et al., 2011 ¹¹²		X											X
Deneux-Tharoux et al., 2010 ³⁶	X	X	X		X				X	X	X		X
Audureau et al., 2009 ³⁵	X	X		X	X	X			X		X		
Skupski et al., 2006 ³³	X	X		X		X		X		X		X	
Rizvi et al., 2004 ³⁴		X		X			X						X
Total Studies (n)	5	7	2	6	2	4	3	2	4	3	3	2	3

EBL-estimated blood loss; PPH-postpartum hemorrhage

A single study in one large urban teaching hospital in the United States examined maternal mortality over a 24-month baseline and a 36-month post-implementation phase.³³ They had two deaths in the period that prompted the systems-level intervention and none during the post-phase ($p = 0.036$). While this intervention included many similar components to others, the authors also report major adjustments to how operations were changed across the entire department to enhance the ability to have dedicated teams focused on laboring and postpartum women. These included separating coverage responsibilities for gynecologic and obstetric inpatients and redefining the oversight role of the covering obstetrician for both public and private patients. Such staffing and organizational changes exceed that in other studies.

Four of the seven studies, along with the only systems-level RCT, did not document benefits of the tested intervention packages for reducing PPH severity or complications; this includes the study that reported reduced maternal mortality.^{33, 35, 109, 110} These studies shared common features among those without evidence of effectiveness as well as among those that reported reduced incidence and/or severity. No clear pattern emerges to suggest an “active ingredient” to these multicomponent interventions.

Audit and feedback was used in two of the three studies that reported reduced severity. In evaluating this evidence it is crucial to underscore that there was no masking of the definitions of severity, of those who assessed severity, or of the overall intent of the research. Because obstetric care providers may use charted EBL as a proxy for level of concern and desire for vigilance in follow-up assessments, it could be that a shift occurred from labelling someone as high risk by indicating high EBL at the time of the birth to a lower estimate of EBL with concerns captured elsewhere in the protocols.

Only the randomized trial conducted any multivariate analysis to take into account secular trends in factors such as proportions of birth by cesarean and vaginal route or scheduled versus emergent cesarean. They detected a statistical trend of falling overall risk of PPH at both control and intervention sites. The reduction was similar over time and did not confound the trial analysis. The authors also used multilevel models to account for clustering within site.

One team reported analyses stratified by potential confounders.³⁵ Others noted changes in trends that could modify risk, such as proportion of births by cesarean, but did not conduct adjusted analyses. Such factors alongside any changes in the risk profile of women receiving care can both obscure potential effects or introduce the appearance of an effect when there is none.

Grey Literature

In response to 10 requests for Scientific Information Packets, we received only one document, an unpublished systematic review conducted by a company that markets the Bakri Postpartum Balloon. The document yielded no studies of relevance for this review; all 23 identified studies were case series, typically with less than 20 participants, and a number were conducted in developing nations. Our search of ClinicalTrials.gov did not yield any results not identified in our other searches.

Discussion

State of the Literature

We included 52 unique studies (57 publications) in this review, including four randomized controlled trials (RCTs), two prospective and 13 retrospective cohort studies, eight pre-post studies, two case-control studies, and 23 case series. Most studies were conducted in Europe (n = 28), and 13 were conducted in the United States, eight in Asia, and two in Australia or New Zealand and one in Argentina. No studies were of good quality for effectiveness outcomes. We considered 20 studies as fair quality for effectiveness outcomes and 31 as poor (including case series, which we considered poor quality by default). One study provided only harms data. Among the 38 studies reporting harms, we considered seven as good quality for harms reporting and 31 as poor quality.

While a number of studies were classified as prospective or retrospective studies using our study classification algorithm (Appendix G), few cohort studies provided comparative analyses between the groups, and many were confounded by indication in that women who received interventions such as massive transfusion or hysterectomy likely had more severe cases of postpartum hemorrhage (PPH). Given the lack of data from randomized or controlled studies of PPH management, we present data from cohort studies and case series and note potential confounding as appropriate.

Overall, it appears that 78 deaths occurred in the included studies addressing non-systems level interventions out of roughly 149,000 participants (note that 139617 of these participants were included in a large database study reporting harms following methylergonovine maleate given in the peripartum hospitalization⁵⁸). Only one death was potentially linked to PPH management: a woman who was given methotrexate in conjunction with embolization died from methotrexate-related nephrotoxicity.⁸¹ The remaining deaths appear to be the result of PPH and its sequelae rather than interventions used for management.

Summary of Key Findings

KQ1. Effectiveness of Interventions for Management of PPH

Key Findings

Forty-one unique studies examined the effectiveness of interventions for management of PPH. Some studies addressed multiple interventions. We classified these studies broadly as medical interventions, procedures, and surgical interventions and more specifically by the type of intervention including pharmacologic interventions (10 studies), transfusion (three studies), intrauterine balloon tamponade (two studies), embolization (14 studies), uterine compression sutures (two studies), uterine and other pelvic artery ligation (four studies), embolization and hysterectomy (one study), hysterectomy (seven studies), and combined approaches (four studies).

Pharmacologic Interventions

Five of the pharmacologic intervention studies were small, single studies of fair and poor quality with mixed results. The other five pharmacologic intervention studies assessed the effectiveness of recombinant activated factor VIIa (rFVIIa). These small studies (largest n =

108) also had mixed results. Overall, additional research is needed for pharmacologic interventions, particularly in light of the fact that these are typically considered the first line in management of PPH.

Transfusion

Three studies of fair quality addressed transfusion for PPH management. Two of the studies found ICU admissions and death were higher with combined blood products versus single (whole blood or packed red blood cells [PRBC]) and massive transfusion versus non-massive transfusion. These differences may reflect that women in the groups with poorer outcomes had more severe PPH. A third study found cryoprecipitate and fibrinogen concentrate were equally efficacious.

Procedures

Both of the procedures (tamponade, embolization) we reviewed showed positive results for PPH management. The median success rate (defined as control of bleeding without additional procedures or surgeries) of intrauterine balloon tamponade as the initial second-line procedure (i.e., the first procedure used after first-line conservative management had failed to control bleeding) in one study was 86 percent. In this study of a protocol change to add tamponade as the initial procedure after medication failure, rates of some invasive interventions (beyond tamponade) decreased in women who had vaginal births. Tamponade is a relatively simple, fast, and inexpensive procedure that warrants further study. The median success rate for embolization as the initial second-line procedure among 14 studies was 89 percent (range = 58% to 98%). However, there was wide variation in the materials used for embolization, the arteries that were embolized, and the interventions that were used before and in conjunction with embolization. The availability of embolization, which is performed by an interventional radiologist, varies by hospital; therefore, this treatment modality is not available to all women with PPH.

Surgical Interventions

The effectiveness of surgical interventions varied. The success rate of uterine compression sutures was 70 percent in the one study from which this could be ascertained. Ligation appeared more successful with a median success rate of 92 percent in three studies (range = 36%-96%). The median success rate for hysterectomy in two studies was 57 percent (range = 20%-93%). One study compared embolization and hysterectomy and reported significantly more ICU admissions and a greater median length of stay in the hysterectomy group than the embolization group.

Combined Approaches

Three studies examined a combination of medical and surgical interventions for secondary PPH. In the two studies that compared medical and surgical approaches, hospital readmission and repeat surgical evacuation occurred more frequently in women who initially received medical management versus surgical.

KQ2. Evidence for Choosing Interventions and Proceeding to Subsequent Interventions

We did not identify any studies addressing this question.

KQ3. Harms of Interventions for PPH

Key Findings

Thirty-eight studies reported harms of interventions for management of PPH; seven of these were good quality for harms reporting and the remainder were poor. In three of the four studies that reported harms related to rFVIIa, 2 to 4 percent of women who received rFVIIa developed deep vein thrombosis or pulmonary embolism (PE). None of the women in the two of these studies that had comparator groups had thromboembolic events; however, this may be due to the small sample sizes rather than evidence of an adverse effect of the medication. The harms reported in embolization studies are diverse and few studies report the same harms. The most frequently reported adverse events were infertility (0-43%), PPH in subsequent pregnancy (5%-17%), spontaneous abortion in subsequent pregnancy (5%-15%), and hematoma at puncture site (1%-6%). The most frequently reported adverse events in seven hysterectomy studies were reoperation (6%-29%), infection (7%-21%), bladder lesion (6%-12%), and ureter lesion (0.4%-8%). Harms for other interventions were either incomparable across studies or were only reported in a single study per intervention.

KQ4. Effectiveness of Interventions for Acute Blood Loss Anemia After Stabilization of PPH

Key Findings

Two small, poor quality RCTs addressed interventions for acute blood loss after PPH is stabilized. In a study comparing women treated with intravenous versus oral iron supplementation after PPH, there was no significant difference in hemoglobin level at any time point between groups. In a study that assessed differences in fatigue and quality of life between women treated with blood transfusion versus no transfusion, the difference in these outcomes between groups was minimal and possibly clinically equivalent.

KQ5. Effectiveness of Systems-Level Interventions

Key Findings

Across a range of systems-level interventions that range from complex multiphase project with 11 distinctive components to simple three component models for audit and feedback, findings are inconsistent about benefit. All sites, including those participating in the active sites of the null cluster randomized trial were aware of a programmatic emphasis on improving response to and outcomes of PPH. Despite this built-in bias towards finding an effect – since EBL was rarely quantitatively measured and self-report of performance would be expected to be optimistic – results of a large trial and the higher quality studies do not demonstrate ability to reduce incidence or severity of PPH, or key maternal outcomes like transfusion, hysterectomy, and ICU admission.

Strength of the Evidence

Overall the evidence to answer questions about PPH management did not reach standards for high strength of evidence. The strength of evidence (SOE) tables summarize the total number of studies and the number of participants within those studies noting the study designs and quality

(Tables 26-32). The tables also provide the assessment of the study limitations, consistency of findings across studies, directness of the evidence, precision of the estimate, and presence of reporting bias. We included case series in our assessment of SOE for harms and success rates of interventions, and we rated SOE for outcomes we considered to be clinically significant, consistently defined, and plausibly linked to the intervention.

SOE is insufficient for all outcomes of misoprostol, tranexamic acid, carboprost tromethamine, thrombomodulin, and rFVIIa for PPH management due to the study sizes and lack of studies addressing each agent (Table 26). As noted, we identified few studies of medications meeting our review criteria; however, a number of studies of misoprostol and oxytocin have been conducted in developing countries. Four recent systematic reviews of interventions for PPH, including two Cochrane reviews, assessed uterotonics including misoprostol. We summarize these reviews fully in the Findings in Relation to What is Known section below and provide a brief summary here. In one Cochrane review, oxytocin infusion was more effective and caused fewer side effects when used as first-line therapy for the treatment of primary PPH compared with misoprostol.¹¹⁵ When used *after* prophylactic uterotonics, misoprostol and oxytocin infusion had similar effects. The review concluded that adding misoprostol for women receiving treatment with oxytocin did not appear beneficial. In another Cochrane review differences in maternal mortality and morbidity, except for fever, did not differ significantly between misoprostol and control groups.¹¹⁶ The investigators concluded that misoprostol did not increase or decrease morbidity or mortality, with the exception of fever, and the lowest effective dose should be used. In another review of misoprostol vs. placebo, misoprostol did not reduce PPH risk significantly compared with placebo.¹¹⁷ In the fourth review and meta-analysis, higher doses of misoprostol (600 vs. 400 micrograms) were no more effective at preventing blood loss.⁴⁸

Table 26. Strength of the evidence for studies addressing medications

Intervention / Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
TXA vs. No TXA							
<i>All outcomes (anemia, transfusion, ICU, blood loss)</i>	RCT-1 poor (144) ⁶⁰	High	Unknown	Direct	Imprecise	Undetected	Less blood loss, need for transfusion, progression to severe PPH in TXA group vs. control, p<.05, but insufficient SOE for all outcomes due to single small, short-term cohort study with high study limitations

Table 26. Strength of the evidence for studies addressing medications (continued)

Intervention / Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Misoprostol vs. Methylergonovine maleate							
<i>All outcomes (transfusion, uterine preservation)</i>	Retrospective cohort -1 fair (58) ⁶⁹	High	Unknown	Direct	Imprecise	NA	No group differences in need for transfusion, additional medical or surgical treatments. Insufficient SOE for superiority of one agent over another in affecting any outcome due to single small, short-term cohort study with high study limitations
Sulprostone							
<i>Intervention success</i>	Case series-1 poor (1370) ⁶¹	High	Unknown	Direct	Precise	NA	Bleeding controlled in 83% of 1370 women receiving sulprostone. Insufficient SOE for success in controlling bleeding due to single, short-term study with high study limitations

SOE-strength of the evidence; TXA-tranexamic acid

Table 26. Strength of the evidence for studies addressing medications (continued)

Intervention / Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Carboprost tromethamine							
<i>Intervention success</i>	Retrospective cohort-1 poor (237) ⁶²	High	Unknown	Direct	Imprecise	NA	Bleeding controlled by carboprost in 81% of 237 cases of PPH. Insufficient SOE for success in controlling bleeding due to single small, short-term cohort study with high study limitations
Thrombomodulin vs. no thrombomodulin							
<i>All outcomes (uterine preservation, bleeding, transfusion)</i>	Retrospective cohort-1 Fair quality (36) ⁶³	High	Unknown	Direct	Imprecise	NA	Greater D-dimer decrease from baseline in intervention arm vs. control, p<.05. Insufficient SOE for all outcomes due to single small, short-term cohort study with high study limitations

Table 26. Strength of the evidence for studies addressing medications (continued)

Intervention / Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
rFVIIa							
<i>Transfusion</i>	Case-control-1 fair (12) ⁶⁵ Retrospective cohort-1 fair (48) ⁶⁴	High	Inconsistent	Direct	Imprecise	NA	Greater need for transfusion in rFVIIA group in one study and no difference in the second. Insufficient SOE due to inconsistency in effects on transfusion, high study limitations
<i>Anemia</i>	Retrospective cohort-1 fair (48) ⁶⁴	High	Unknown	Direct	Imprecise	NA	Insufficient SOE due to one small study with high study limitations; ; need for transfusion greater in rFVIIa arm vs. control
<i>Uterine preservation</i>	Case-control-1 fair (12) ⁶⁵	High	Unknown	Direct	Imprecise	NA	Insufficient SOE. No difference in hysterectomy rates in one small, imprecise study with high study limitations
<i>LOS</i>	Retrospective cohort-1 fair (48) ⁶⁴	High	Unknown	Direct	Imprecise	NA	Insufficient SOE. Similar LOS for treated and untreated groups in one small, imprecise study with high study limitations

LOS-length of stay; NA-not applicable; RCT-randomized controlled trial; rFVIIa-recombinant activated factor VIIa; SOE-strength of the evidence

The SOE for outcomes related to transfusion and uterine tamponade is insufficient (Table 27). While there were three fair quality studies of transfusion, two of these were so confounded that we could not confidently ascertain their outcomes. There is low SOE for embolization controlling bleeding without additional procedures or surgeries.

Table 27. Strength of the evidence for studies addressing other medical interventions and procedures

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Transfusion							
<i>ICU admission and overall LOS</i>	Retrospective cohort-3 fair (1700) ⁷²⁻⁷⁴	High	Inconsistent	Direct	Precise	NA	Insufficient SOE due to inconsistency in direction of effect (greater LOS and ICU admission in transfusion or whole blood groups in 2 studies; no group differences in another study), high study limitations
Uterine tamponade							
<i>Intervention success*</i>	Pre-post-1 fair (43) ⁷⁵	High	Unknown	Direct	Imprecise	NA	Tamponade without further procedure/surgery controlled bleeding in 86% of women in one study, and tamponade plus additional intervention controlled bleeding in 98% in another. Insufficient SOE due to small sample size, high study limitations

Table 27. Strength of the evidence for studies addressing other medical interventions and procedures (continued)

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Embolization							
<i>Intervention success</i>	Prospective cohort-2 fair (22) ^{68, 92} Retrospective cohort-3 fair (109) ^{47, 81, 82} Pre-post-1 fair (20) ⁷⁵ Case-control-1 poor (53) ⁷⁷ Case series-8 poor (1115) ^{80, 83, 85, 86, 89-91, 93}	High	Consistent	Direct	Precise	NA	Low SOE for success of embolization in controlling bleeding without additional procedures or surgeries (median success rate of 89% as initial second-line intervention; conservative management and severity of PPH varied across studies). A higher SOE is not possible due to the lack of comparisons in this literature and small sample sizes

*Success defined as control of bleeding without additional procedures or surgeries when used as the initial second-line procedure (i.e., the first procedure used after first-line conservative management failed to control bleeding)
LOS-length of stay; NA-not applicable; SOE-strength of the evidence

There is insufficient SOE for the success of uterine compression sutures and hysterectomy (Table 28). There is low SOE for ligation controlling bleeding without further procedures or surgeries.

Table 28. Strength of the evidence for studies of surgical interventions

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Uterine compression sutures							
<i>Intervention success*</i>	Prospective cohort-1 fair (211) ^{68, 71}	Medium	Unknown	Direct	Imprecise	NA	Insufficient SOE due to single, small study; bleeding controlled by suture following conservative management in 70% of women in one study
Ligation							
<i>Intervention success*</i>	Prospective cohort-1 fair (20) ⁶⁸ Retrospective cohort-1 fair (48) ⁸² Case series-1 poor (265) ⁹⁵	Medium	Consistent	Direct	Precise	NA	Low SOE due to small sample size. 92% success rate for controlling bleeding without further procedure or surgery in 3 small studies
Hysterectomy							
<i>Intervention success*</i>	Retrospective cohort-2 fair (66) ^{47, 82}	Medium	Consistent	Direct	Imprecise	NA	Insufficient SOE due to small sample sizes in 2 studies provided data to calculate success rates; median success rate for controlling bleeding=57%

*Success defined as control of bleeding without additional procedures or surgeries when used as the initial second-line procedure (i.e., the first procedure used after first-line conservative management failed to control bleeding)
NA-not applicable; SOE-strength of the evidence

Table 29 outlines the SOE for studies of combination interventions. Two studies assessed length of stay; however, we considered the SOE for the effect of intervention to be insufficient given the small sample sizes and inconsistency in interventions.

Table 29. Strength of the evidence for studies of combination interventions

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
<i>LOS in women with primary PPH</i>	Retrospective cohort-1 fair (257) ¹⁰⁰	High	Unknown	Direct	Imprecise	NA	Greater LOS in women undergoing procedures/surgeries vs. medical management, p<.001. Insufficient SOE due to small, single study
<i>LOS in women with secondary PPH</i>	Retrospective cohort-2 fair (168) ¹⁰¹	High	Unknown	Direct	Imprecise	NA	No differences in LOS between surgical and medical management groups. Insufficient SOE due to small, single study

LOS-length of stay; NA-not applicable; SOE-strength of the evidence

The SOE for harms of interventions for management of PPH can be found in Table 30. Generally SOE was insufficient given diversity of harms reported in single studies. However, SOE rose above insufficient for selected harms related to embolization and hysterectomy due to the greater number of studies and more consistent reporting of adverse events. As noted, few studies of uterotonics met our inclusion criteria; however, harms reported in recent systematic reviews of uterotonics for PPH treatment included shivering and fever (see Findings in Relation to What’s Known section for full summary). In one review, oral misoprostol was associated with a significant increase in vomiting and shivering compared with either oxytocin or rectal misoprostol.¹¹⁵ In another review, differences in maternal mortality and morbidity, except for fever, did not differ significantly between misoprostol and control groups.¹¹⁶ Risk of fever was increased in misoprostol groups and was highest in studies with a misoprostol dose of 600 µg or more. In another review of misoprostol vs. placebo, shivering and fever were significantly more common in misoprostol arms.¹¹⁷ A fourth review noted more adverse effects related to misoprostol vs. placebo.⁴⁸

While evidence in the current review was insufficient to comment on the association between rFVIIa and thrombotic events, studies in other populations have suggested increased risk of arterial events. In one review of RCTs in non-hemophilia patients, the pooled relative risk of thrombotic events across studies of prophylactic and therapeutic uses of rFVIIa was 1.45 (95% CI: 1.02 to 2.05).¹¹⁸ Another review of fertility outcomes following embolization, ligation, and sutures concluded that the techniques reviewed did not appear to compromise fertility, but the number and quality of studies was limited.¹¹⁹

Table 30. SOE for harms of interventions for management of PPH

Intervention Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Pharmacologic							
Tranexamic acid <i>All harms</i>	RCT-1 good (114) ⁶⁰	Low	Unknown	Direct	Imprecise	Undetected	Insufficient SOE due to small sample size, but serious harms did not differ between groups and mild, transient harms occurred more often in TXA group
Sulprostone <i>All harms</i>	Case series-1 poor (1370) ⁶¹	High	Unknown	Direct	Precise	NA	Insufficient SOE as only one study considered poor quality for harms reporting

Table 30. SOE for harms of interventions for management of PPH (continued)

Intervention Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Pharmacologic							
Methylergonovine maleate <i>Acute coronary syndrome and myocardial infarction</i>	Retrospective cohort study- 1 good (139,617) ⁵⁸	Low	Unknown	Direct	Precise	NA	Low SOE for lack of association of methylergonovine maleate with acute coronary syndrome and myocardial infarction; no significant difference in the incidence of these conditions in the exposed and non-exposed groups
Carboprost tromethamine <i>All harms</i>	Retrospective cohort -1 poor (237) ⁶²	High	Unknown	Direct	Imprecise	Undetected	Insufficient SOE as only one study considered poor quality for harms reporting
rFVIIa <i>Thrombo-embolic events</i>	Case-control- 1 fair (12) ⁶⁵ Retrospective cohort-1 fair (48) ⁶⁴ Retrospective case series- 1 good, 1 poor (223) ^{66, 67}	High	Consistent	Direct	Imprecise	NA	Insufficient SOE; 3 of 4 studies reported thromboembolic events (pulmonary embolus, deep vein thrombosis, myocardial infarction) but sample sizes were small and study limitations are high

Table 30. SOE for harms of interventions for management of PPH (continued)

Intervention Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Other medical interventions							
Transfusion <i>All harms</i>	Retrospective cohort-2 poor (1574) ^{72, 73} Case series-2 poor fair (977) ^{59, 70}	High	Inconsistent	Direct	Precise	NA	Insufficient SOE due to inconsistency, study limitations
Procedures							
Uterine tamponade <i>All harms</i>	Pre-post-1 poor (43) ⁷⁵	High	Unknown	Direct	Imprecise	NA	Insufficient SOE due to single, small study with high limitations
Embolization <i>Infertility</i>	Retrospective cohort-2 poor (152) ⁷⁸⁻⁸¹ Case-control-1 poor (53) ⁷⁷ Case series-2 poor (169) ^{83, 84}	High	Inconsistent	Direct	Imprecise	NA	Low SOE for negative effect of embolization on future fertility. Infertility rate among women who had embolization in these studies was greater than that of the overall population rate (range 0-43%), but few women (n = 300) available for long-term followup; high study limitations and inconsistency among studies

Table 30. SOE for harms of interventions for management of PPH (continued)

Intervention Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Embolization							
<i>Spontaneous abortion in subsequent pregnancy</i>	Retrospective cohort-2 poor (152) ⁷⁸⁻⁸¹ Case-control-1 poor (53) ⁷⁷ Case series-1 good, 2 poor (345) ^{83, 84, 91}	High	Consistent	Direct	Imprecise	NA	Low SOE for lack of association between embolization and spontaneous abortion in subsequent pregnancy in the small number of women followed-up; rates ranged from 5-15%, which is comparable to estimates in the general population
<i>Menstrual changes</i>	Retrospective cohort-2 poor (152) ⁷⁸⁻⁸¹ Case-control-1 poor (53) ⁷⁷ Case series-1 good, 3 poor (596) ^{83, 84, 87, 91}	High	Consistent	Direct	Imprecise	NA	Low SOE for an association between embolization and menstrual changes. Rates of menstrual change (heavier, lighter, or irregular menses and amenorrhea) ranged from 2 to 22%
<i>Hematoma</i>	Retrospective cohort-2 poor (152) ⁷⁸⁻⁸¹ Case-control-1 poor (53) ⁷⁷ Case series-1 good, 1 poor (427) ^{87, 91}	High	Consistent	Direct	Precise	NA	Low SOE for association between embolization and hematoma; rates ranged from 5-15%

Table 30. SOE for harms of interventions for management of PPH (continued)

Intervention Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Surgical Interventions							
Uterine compression sutures <i>All harms</i>	Case series-2 poor (804-not clear how many had sutures in one study) ^{94, 95}	High	Inconsistent	Direct	Imprecise	NA	Insufficient SOE due to inconsistency and limited harms reporting
Ligation <i>Surgical injury</i>	Retrospective cohort study-1 poor (48) ⁸² Case series-1 poor (539-not clear how many had ligation) ⁹⁴	High	Consistent	Direct	Imprecise	NA	Insufficient due to high study limitations and imprecision; injuries (inadvertent ligation of the ureters and secondary hysterectomy disunion with sepsis) related to ligation reported in both studies
Hysterectomy <i>Bladder and ureter lesions</i>	Prospective cohort-1 poor (108) ⁹² Case series-4 poor (2728) ^{93, 97-99}	High	Consistent	Direct	Precise	NA	Low SOE for association of hysterectomy and operative organ damage; rates of bladder and ureter lesions ranged from 6%-12% and 0.4%-8%, respectively Low SOE for association between hysterectomy and reoperation. Rates of reoperation ranged from 6-29%
<i>Reoperation</i>	Prospective cohort-1 poor (108) ⁹² Case series-3 poor (519) ^{93, 97, 98}	High	Consistent	Direct	Precise	NA	

LOS-length of stay; NA-not applicable; RCT-randomized controlled trial; SOE-strength of the evidence; TXA-tranexamic acid

SOE is insufficient for all outcomes and harms in studies of interventions for anemia after PPH given the few studies, small number of participants, and differences in intervention approaches (Table 31).

Table 31. Strength of the evidence for interventions for anemia after PPH

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Iron supplementation							
<i>Anemia</i>	RCT-1 poor (74) ¹⁰⁸	High	Unknown	Indirect	Imprecise	Undetected	No differences in groups receiving oral or IV iron. Insufficient SOE for effects on anemia due to small sample size, indirect measures.
Transfusion							
<i>Fatigue</i>	RCT-1 poor (519) ¹⁰⁷	High	Unknown	Direct	Imprecise	Undetected	No significant group differences. Insufficient SOE for effects on fatigue related to anemia due to single, small study with high study limitations
<i>Quality of life</i>	RCT-1 poor (519) ¹⁰⁷	High	Unknown	Direct	Imprecise	Undetected	No significant group differences. Insufficient SOE for effects on quality of life due to single study with high limitations

Table 31. Strength of the evidence for interventions for anemia after PPH (continued)

Outcome	Study Design Quality and Number of Studies (N Total with PPH)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Iron supplementation and transfusion							
<i>All harms (transfusion reactions, infections, endometritis, thromboembolic events)</i>	RCT-1 good, 1 poor (593) ^{107, 108}	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient SOE; harms were not pre-specified in one study. No serious adverse reactions were attributed to the study drugs in either RCT but reporting in one RCT is not clear

LOS-length of stay; RCT-randomized controlled trial; SOE-strength of the evidence

Overall the SOE for any systems-level intervention on any outcome is insufficient or moderate as the observational data is biased and a single, very large trial suggest that at least one clearly described and implemented program did not change risk of severe hemorrhage or meaningfully modify processes of care or overall maternal outcomes (Table 32). SOE is moderate that these multi-component interventions did not change specific outcomes such as severity of PPH, transfusion, hysterectomy, and ICU admission.

Table 32. Strength of the evidence for studies addressing multi-component, systems-level interventions

Outcome	Study Design Quality and Number of Studies (Participants with PPH/Total N)	Study Limit- ations	Consistency	Direct- ness	Precision	Reporting Bias	Findings and Strength of Evidence Grade
<i>Incidence of PPH</i>	Cluster RCT: 1 Fair (9350/146781) ³⁶	Medium	Unknown	Direct	Precise	Undetected	Moderate SOE for lack of benefit in reducing PPH incidence. Sites aware of objectives with regard to reducing PPH and assessors of a somewhat subjective outcome not masked
<i>Severity of PPH</i>	Cluster RCT: 1 Fair (9350/146781) ³⁶ Pre/Post: 2 fair, 3 poor (1305/67612) ^{34, 35, 109, 111, 112}	Medium High	Unknown Inconsistent	Direct Direct	Precise Precise	Undetected NA	Moderate SOE for lack of benefit in reducing severity of PPH. Sites aware of the objectives with regard to reducing severity of PPH and assessors of a somewhat subjective outcome not masked. Severity unchanged in RCT; reduced in 3 pre-post studies and no difference in 2

Table 32. Strength of the evidence for studies addressing multi-component, systems-level interventions (continued)

Outcome	Study Design Quality and Number of Studies (Participants with PPH/Total N)	Study Limit- ations	Consistency	Direct- ness	Precision	Reporting Bias	Findings and Strength of Evidence Grade
<i>Transfusion</i>	Cluster RCT: 1 Fair (9350/146781) ³⁶ Pre/Post: 3 Fair, 1 Poor (1307/56788) ^{35,} 109-111	Low Low	Unknown Inconsistent	Direct Direct	Precise Precise	Undetected NA	Moderate SOE for no effect on transfusion. Transfusion unchanged in RCT, increased in one pre-post study and unchanged in two; one with decreased use of total blood products related to decrease in risk of disseminated intravascular coagulation
<i>Hyster- ectomy</i>	Cluster RCT: 1 Fair (9350/146,781) ³ 6 Pre/Post: 1 Fair, 2 Poor, (1018/26652) ^{34,} 35, 109	Low Low	Unknown Inconsistent	Direct Direct	Precise Precise	Undetected NA	Moderate SOE for lack of benefit in preventing hysterectomy. Hysterectomy unchanged in RCT. No significant change in two pre-post studies but hysterectomies increased; risk significantly increased in one study and was similar between time periods in a third
<i>ICU admission</i>	Cluster RCT 1 Fair (9350/146781) ³⁶ Pre/Post: 2 poor (688/18978) ^{34,} 109	Low Low	Unknown Consistent	Direct Direct	Precise Precise	Undetected NA	Moderate SOE for lack of benefit. No change in RCT and no change in two pre-post studies
<i>Mortality</i>	Pre/Post:1 Poor; (61/18723) ³³	Medium	Unknown	Direct	Imprecise	NA	Insufficient SOE for benefit—one smaller study

LOS-length of stay; NA-not applicable; RCT-randomized controlled trial; SOE-strength of the evidence

Findings in Relation to What is Already Known

Findings in recent (2009-present) systematic reviews and meta-analyses of interventions to manage PPH are largely in line with findings reported here in that while reviews reported some positive effects, studies included in the reviews typically had significant limitations that precluded firm conclusions. Reviewers noted a lack of high quality literature, small sample sizes, limited followup, and a preponderance of observational studies of procedures or surgical approaches given the emergent nature of PPH. We summarize findings of reviews of pharmacologic studies conducted in developing nations as the current review contains few comparable studies of pharmacologic agents. We also summarize recent reviews of procedures and surgical approaches.

Few drug studies met our inclusion criteria, which specified studies must be conducted in the high-resource countries where care would be applicable to that in the United States. Four recent reviews, however, have addressed uterotonics, primarily in lower resource settings. Overall, these reviews had conflicting findings about the effectiveness of misoprostol; however, this medication was consistently associated with adverse effects, particularly fever and shivering.

One 2014 Cochrane review assessed the effectiveness and safety of any intervention used for the treatment of primary PPH.¹¹⁵ The uterotonic interventions included in the search strategy were ergonovine, oxytocin, and prostaglandin medications. Seven RCTs evaluated misoprostol. Four RCTs (1,881 participants) compared misoprostol with placebo given in addition to other conventional uterotonics. Adjunctive use of misoprostol (600-1000 micrograms) with simultaneous administration of other uterotonics did not provide additional benefit for maternal mortality, serious maternal morbidity, admission to intensive care, or hysterectomy. Three RCTs (1,851 participants) compared oral misoprostol with oxytocin infusion (n=2 RCTs) or rectal misoprostol (n=1 RCT) as primary PPH treatment. Primary outcomes including maternal mortality, hysterectomy, ICU admission, and serious maternal morbidity did not differ between the groups. Oral misoprostol, however, was associated with a significant increase in vomiting and shivering compared with either oxytocin or rectal misoprostol. No RCTs of ergonovine or carboprost tromethamine met the inclusion criteria. The investigators concluded that, overall, the clinical trials included in the review were not adequately powered to assess impact on the primary outcome measures. Compared with misoprostol, oxytocin infusion was more effective and caused fewer side effects when used as first-line therapy for the treatment of primary PPH. When used *after* prophylactic uterotonics, misoprostol and oxytocin infusion had similar effects. Adding misoprostol for women receiving treatment with oxytocin does not appear beneficial.

A 2013 Cochrane review assessed maternal deaths in studies of misoprostol for prevention and treatment of PPH and included 78 RCTs reporting on 59,216 women; only seven of these studies focused on treatment vs. prevention, and most studies were conducted in low-resource countries.¹¹⁶ Overall, differences in maternal mortality and morbidity, except for fever, did not differ significantly between misoprostol and control groups. Risk of fever was increased in misoprostol groups and was highest in studies with a misoprostol dose of 600 µg or more. The investigators concluded that misoprostol does not increase or decrease morbidity or mortality, with the exception of fever, and the lowest effective dose should be used.

In another review including three RCTs (2,346 participants) of misoprostol vs. placebo, misoprostol did not reduce PPH risk significantly compared with placebo, and shivering and fever were significantly more common in misoprostol arms.¹¹⁷ A review of maternal deaths and dose-related effects of misoprostol included 46 trials with more than 40,000 participants. The investigators found more adverse effects related to misoprostol than placebo and no evidence, in

a meta-analysis, that higher doses of misoprostol (600 vs. 400 micrograms) were more effective at preventing blood loss. Fever was higher among women given misoprostol and occurred more frequently with higher doses (600 vs. 400-500 micrograms)⁴⁸

Applicability

We set inclusion criteria intended to identify studies with applicability to women being treated for primary or secondary PPH. Studies differed in terms of study population and outcome measures. Most studies did not make direct comparisons between treatments or characterize populations well in terms of severity of PPH and prior management strategies. This lack of direct comparison of treatment options hinders our ability to understand what treatments are most effective and in what order they should be used, both of which are paramount questions for clinicians. We summarize overall applicability below, and Appendix F contains applicability tables for individual interventions.

Overall, findings of studies in the review are generally applicable to the population of women who would be experiencing PPH in hospitals in high-resource nations. Most studies were conducted in Europe or the United States in tertiary care centers. Studies frequently included a number of women with PPH who were transferred from smaller or community hospitals, which can occur when women with PPH requiring additional treatment are stable enough to be moved to facilities with interventional radiology or other services. More women had PPH after cesarean birth than vaginal birth in the 38 studies reporting mode of birth (estimated 3,486 vaginal and 5,624 cesarean births among the 9,110 births for which mode was clearly reported). The most common cause of PPH was atony, which aligns with the most frequent cause of PPH in the larger community and literature. Studies of pharmacologic agents typically included women with mild to moderate to PPH while studies of procedures or surgical approaches generally included women with more severe PPH that had not been controlled with first-line therapies such as uterotonics.

Uterotonics and blood products studied are generally widely available; however, the accessibility to procedures such as embolization may be limited in smaller community hospitals. Similarly, community hospitals may lack personnel with experience with arterial ligation and compression sutures. Comparators across studies with more than one group were typically either no specific treatment (e.g., rFVIIa or no rFVIIa) or another treatment (e.g., embolization or ligation) and are likely confounded by patient and provider characteristics that may have affected the choice of intervention. For example, patients with more severe hemorrhage likely received more aggressive treatment, and providers could only offer the options available in their facilities. Outcomes addressed across studies were appropriate and clinically relevant; however, few studies reported on longer term outcomes such as future fertility or on patient-centered outcomes such as quality of life.

Among studies of interventions for anemia after PPH, findings may be limited by a more selective population in one study of iron supplementation, which included predominately women with lower levels of education and lower socioeconomic status. One study of transfusion vs. no transfusion was conducted at a tertiary care center.

The populations included in the systems-level interventions both in the United States and Europe reflect those typical of similar size and type (rural, academic, etc.) obstetric units in current labor and delivery environments in the United States. Likewise the interventions designed and implemented in these studies were informed by processes of identifying evidence and crafting guidance that conforms to typical quality improvement and outcomes based

research. The content of the interventions is feasible to implement across a full range of settings and the approaches to measuring outcomes are applicable to practice. Overall the systems-level interventions assessed have good applicability to current practice in the United States.

Implications for Clinical and Policy Decisionmaking

A limited body of evidence addresses interventions for managing PPH. Few studies addressed medications commonly used to treat PPH, precluding our ability to draw conclusions about their effectiveness. Success rates for uterine tamponade or surgeries are typically above 60 percent (e.g., success of uterine tamponade as the initial second-line therapy in one study was 86%; success rates for ligation as the first second-line intervention to control bleeding ranged from 36 to 96%). Studies of embolization suggested that it may be associated with a median rate of successful control of bleeding without need for additional procedures or surgeries of 89 percent, with a wide range of success (58% to 98%) across studies; however, few studies clearly provided data on the success of these interventions as the initial second-line approach, so rates are based on a small number of cases. Adverse events and longer term outcomes associated with procedures and surgical interventions are also not well-understood. Some studies reported menstrual changes and infertility rates higher than the general population rates after embolization. Studies of other procedures and surgical interventions did not consistently report fertility data. At this point, the evidence is insufficient to comment on the effectiveness and harms of most interventions for most outcomes.

Thus, given the mixed and insufficient evidence, clinicians will likely need to continue to make individual decisions about the care of women with PPH based on each woman's clinical situation and the management options available in the setting. Embolization, for example, requires an interventional radiologist and may not be widely available. Transportation to a radiology suite may also lead to treatment delays. Choice of some interventions may be guided by the availability of skilled clinicians or may naturally follow cesarean birth (when the abdomen is already open) vs. vaginal birth. This body of evidence does not provide clear answers to the key clinical questions of what interventions to use and in what order.

Limitations of the Comparative Effectiveness Review Process

We included studies published in English only. In our scan of the non-English language literature published since 1990 and located via our MEDLINE search, we determined that the majority would not meet our review criteria. Given the high percentage of non-eligible items in this scan (90%), we feel that excluding non-English studies did not introduce significant bias into the review. We also included only studies conducted very high human development countries as determined by the World Health Organization as these studies have systems of care most relevant to the United States. We recognize that this criterion eliminated many studies of first-line uterotonics such as misoprostol that have been conducted in developing or low resource nations. We provide a summary of recent systematic review of those studies to supplement our analysis (See Findings in Relation to What's Known section above).

Limitations of the Evidence Base

There are a number of limitations in the studies that we reviewed. There is not a universally agreed management strategy for PPH. Medications were typically used as the initial treatment;

however, the specific drugs, dosages, and order varied. The selection of interventions, including which interventions were performed and in which order, was also inconsistent. Management was not well described in many studies, especially in for women who transferred from other hospitals. Overall, it was difficult to ascertain confidently the complete trajectory of care of women in many of the studies we reviewed.

Procedures and surgical interventions also differed across studies. For example, materials used for embolization varied as did the sites of embolization and ligation. There is no clear trigger for starting subsequent interventions, so success rates have limited reliability. It may be that women would have recovered after the first line treatment if time allowed. In addition, there is the potential for cumulative effects of multiple interventions that cannot be measured. Outcomes other than controlling bleeding can be difficult to assess. For example, transfusion could be an adverse outcome if treatment was not sufficient and timely to halt bleeding rapidly. Alternately early transfusion can be the appropriate intervention; therefore, it is sometimes hard to know whether to classify transfusion as an adverse outcome. There are also challenges for measuring harms. It can be difficult to assess in some cases if harms are due to PPH or management interventions and how much each contributed, especially to deaths. There is a significant lack of truly comparative studies and randomized studies, which would be ideal yet are complex to conduct with a life-threatening condition such as PPH. Studies were typically conducted or data collected over long time frames (median study duration = 5 years, range 6 months to 29 years), and it is likely that interventions and patient characteristics would have changed, but few studies account for secular changes such as the introduction of new interventions.

In the systems-level interventions, a natural tension exists between the desire to implement robust interventions and the challenges of understanding which components may have value. In the case of these interventions, it is particularly challenging since lower quality studies with looser measures of outcomes were more likely to see intervention effects. The literature about systems-level intervention is limited by lack of analyses that seek to adjust for secular trends and changes in confounders, such as proportion of births by cesarean and trends in rising BMI. Likewise lack of multivariable modelling may obscure the influence of elements of care, such as induction of labor, and comorbidities, such as chorioamnionitis, that could identify which predictors may be exerting substantial influence and inform new approaches to diminishing risk of PPH.

Research Gaps

Future research needs around management of PPH are both clinical and methodologic. Priorities for future research include:

- Reaching consensus on definitions and criteria for PPH and first-line management strategies to promote consistency within the literature.
- Conducting more rigorously controlled studies of all interventions for PPH management, especially medication studies in light of the fact that these are considered first-line management, and few studies in developed/high resource nations addressed agents commonly in use. While studies in this population are likely to be retrospective, studies should clearly describe first-line management to clarify the course of care. Studies must report *a priori* study size calculation to ensure that the number of subjects will be adequate to show a difference (if the study is designed for superiority). In addition, comparative studies must declare within the design and methods whether the study is a

- superiority trial or a non-inferiority trial.
- Conducting cluster randomized control trials of intervention bundles that address order of medications, manual interventions such as uterine massage and bimanual compression, number of times to repeat medications prior to moving on to second-line interventions, hemodynamic monitoring, and supportive care such as transfusion.
 - Clearly identifying the trajectory of care, including which interventions were used and in what order.
 - Conducting additional RCTs or controlled studies of treating anemia after PPH is stabilized.
 - Conducting additional prospectively designed and reported studies that report data from large national databases. These studies can describe effects in larger population samples and may be valuable for identifying longer-term harms, for example, effects on breastfeeding, psychological trauma, and future fertility.
 - Replicating the intrauterine balloon tamponade study that was found effective in reducing invasive interventions.
 - Using and clearly reporting objective methods to diagnose PPH, including accurate measurement of blood loss. Visual estimation of blood loss is too imprecise to be used in research.
 - Dedication to prospective objective measures like estimated blood loss, time course of intervention, and use of intervention components.
 - Greater capture and multivariable adjustment for known risk factors and confounders to allow better understanding of the attributable impact, if any, of the intervention.
 - Attention to the possibility that effect modifiers hide efficacy in some groups, which means studies will need to be powered and specify a priori stratified analyses by candidate effect modifiers, such as grand multiparity, route of birth, or infection in labor.
 - Prespecifying harms, differentiating harms of interventions from sequelae of PPH wherever possible, and studying longer term effects of procedures and surgical interventions.
 - The size of the study populations in systems-level interventions can clearly support multivariate modeling and could serve to drive better understanding of the general lack of effectiveness. In particular, such data are well-suited to use of risk-adjustment models that can allow comparison not only across time periods but across studies.
 - The possibility exists that systems-level interventions are working against a biologically determined risk of PPH, meaning that within a specific population with particular characteristics there is an irreducible level of risk and event rates cannot be driven below that “floor”. If this were demonstrated with risk adjustment methods, this finding would fundamentally change the focus of study design and care. A floor would suggest we need very large pragmatic trials aimed not at reducing the occurrence of PPH but at diminishing associated morbidity, mortality, personal harm and distress, and costs. The systems-level intervention studies available now cannot fully inform this goal but primary meta-analyses of the highest quality cohorts with risk adjustment could determine if the evidence seen in some of the included studies that suggest benefits are worth pursuing on a larger scale, including a scale large enough to separate the influence of candidate components to determine their individual contributions to improvements in care.

Conclusions

A limited body of evidence addresses interventions for managing PPH. The most effective treatments and the order in which to use treatments remain unclear. Diagnosis of PPH is subjective and management is emergent, which makes it difficult to compare the severity of PPH and how comparable participants are within and across studies. The trajectory of care, rationale for choice of intervention, and component of care ultimately responsible for controlling bleeding are also frequently unclear. Few studies addressed pharmacologic or medical management, and evidence is insufficient to comment on effects of such interventions. The success of uterine-sparing techniques, such as uterine tamponade, embolization, uterine compression sutures, and uterine and other pelvic artery ligation, in controlling bleeding without the need for additional procedures or surgeries ranged from 36 to 98 percent; however, these data come from a limited number of studies with a small number of participants. Harms of interventions are diverse and not well-understood. Some studies reported an association between rFVIIa and thromboembolic events, however; sample sizes were small. Some studies with longer term followup reported adverse effects on future fertility and menstrual changes in women undergoing embolization. Need for re-operation was also reported after hysterectomy. Evidence is insufficient to assess the effects of interventions for anemia after PPH is stabilized, and systems-level interventions showed little benefit in reducing the incidence or severity of PPH or the need for transfusion or hysterectomy. Further research is needed across all interventions for PPH management, especially pharmacologic interventions, which as first-line therapies are the most frequently used.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ANZHR	Australian and New Zealand Haemostasis Registry
ARDS	Acute respiratory distress syndrome
BMI	Body Mass Index
CER	Comparative Effectiveness Review
CI	Confidence Interval
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
EBL	Estimated blood loss
EPC	Evidence-Based Practice Center
FFP	Fresh Frozen Plasma
ICU	Intensive Care Unit
Hb	Hemoglobin
HELLP	Hemolysis, Elevated Liver enzymes, Low Platelet counts syndrome
KQ	Key Question
L	Liter
LOS	Length of Stay
mL	Milliliter
MRI	Magnetic Resonance Imaging
NHLBI	National Heart, Lung, and Blood Institute
NR	Not Reported
OR	Odds ratio
PE	Pulmonary Embolism
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, and Setting
PPH	Post-Partum Hemorrhage
PRBCs	Packed Red Blood Cells
PT	Prothrombin Time
RBC	Red Blood Cells
RCT	Randomly Controlled Trial
rFVIIa	Recombinant activated factor VII
RR	Relative risk
rTM	Recombinant Human Soluble Thrombomodulin
SD	Standard Deviation
SVT	Superficial Venous Thrombosis
TEP	Technical Expert Panel
TXA	Tranexamic Acid
UKOSS	U.K. Obstetric Surveillance System