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Review

A Comparison of Physiologic Third-Stage Care, Expectant Management, and Oxytocin Prophylaxis in the Prevention of Postpartum Hemorrhage Following Physiologic Labor and Birth: A Systematic Review

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Introduction: This systematic review compared the effects of physiologic care or expectant management during the third stage of labor with oxytocin prophylaxis in preventing postpartum hemorrhage following physiologic birth.

Methods: We searched MEDLINE, Embase, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials (to December 15, 2023), ClinicalTrials.gov (to July 8, 2024), and reference lists of eligible studies. We included randomized and nonrandomized studies of individuals who experienced physiologic birth or received minimal obstetric interventions. Two reviewers independently assessed eligibility and risk of bias. Random-effects meta-analyses were performed, and evidence certainty was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Results: Three randomized controlled trials and 4 nonrandomized studies (N = 7; 7091 participants) were included, with 3 studies contributing data to the quantitative analyses. For individuals with physiologic birth, low-certainty evidence from one nonrandomized study (3436 participants) suggests that physiologic third-stage care results in a large reduction in the risk of blood loss greater than 1000 mL compared with oxytocin (relative risk [RR], 0.29; 95% CI, 0.09-0.92; 18 fewer per 1000; 95% CI, 22 fewer to 2 fewer). In contrast, evidence from one randomized controlled trial (1686 participants) indicates that expectant management likely results in a large increase in the risk of excessive blood loss greater than 1000 mL (RR, 1.87; 95% CI, 1.36-2.57; 21 more per 1000; 95% CI, 9 more to 39 more; moderate certainty) compared with oxytocin but may not increase the risk of transfusion (low certainty) and results in little to no difference in well-being or breastfeeding (high certainty).

Discussion: Compared with oxytocin, physiologic third-stage care may result in a large reduction in the risk of excessive blood loss, whereas expectant management likely results in a large increase. Further research is needed to improve evidence certainty, focus on patient-important outcomes, and enhance generalizability.

Keywords: expectant management, midwifery model of care, oxytocin, physiologic management, postpartum hemorrhage, third stage of labor

INTRODUCTION

Postpartum hemorrhage (PPH) remains one of the leading causes of maternal deaths worldwide.[1] To prevent PPH, current national and international guidelines recommend routine active management of the third stage of labor, which includes prophylactic administration of oxytocin.[2] For individuals who experience a physiologic labor and birth without medical or pharmacologic intervention, other third-stage management options may be comparable in reducing the risk of PPH.[3,4] Systematic reviews of randomized controlled trials (RCTs) have typically used broad inclusion criteria and have not analyzed outcomes in physiologic and nonphysiologic births separately. Meanwhile, observational studies suggest that active management may increase the risk of PPH following physiologic birth.[3,5,6] This evidence gap has led to calls for further research into the effectiveness and safety of active management following physiologic birth.[7]

Physiologic Care and Expectant Management

Another limitation in the evidence base is the lack of clarity in defining the techniques used in third-stage management. Midwifery researchers have long observed that RCTs rarely compared active management with what is recognized in midwifery practice as physiologic third-stage care.[8,9] Instead, most trials have used the term expectant management to describe a hands-off wait-and-see approach as the comparator group to active management.[9] Although both expectant management and physiologic care avoid the routine use of interventions associated with active management, they reflect dis-

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Quick Points

- Physiologic care and expectant management reflect distinct models of care used during the third stage of labor.
- Conflation of these approaches in previous research has obscured potential differences in treatment effects and complicated interpretation.
- Findings from this review align with midwifery guidance that emphasizes the support of conditions which optimize physiologic third stage.

tinct models of care. Expectant management is characterized by inaction, whereas physiologic care involves intentional, supportive practices that facilitate the physiologic completion of the third stage.[10] This approach is generally considered appropriate only when the earlier stages of labor have progressed physiologically.[11–14] Conflating these approaches in RCTs and systematic reviews has obscured potentially different treatment effects and contributed to ongoing uncertainty. Definitions used in this review are summarized in Table 1.

Active Management of the Third Stage of Labor

Active management of the third stage of labor was introduced in the early twentieth century, based on the belief that shortening the third stage would reduce the risk of PPH.[15] Initially it consisted of a bundle of interventions: administration of a uterotonic agent, immediate umbilical cord clamping and cutting, controlled umbilical cord traction, and external uterine massage.[2] Over time, RCTs and systematic reviews have shown that uterotonic administration is the most effective component.[2] Current international guidelines now advise against routine early umbilical cord clamping and uterine massage, recommend controlled umbilical cord traction only when performed by a skilled health care provider, and identify oxytocin as the preferred uterotonic for PPH prevention in all births in which multiple uterotonic options are available.[16]

Objectives

This review aimed to compare the effects of physiologic care or expectant management in the third stage of labor with oxytocin prophylaxis on PPH outcomes following physiologic birth. Four primary comparisons were planned across 2 distinct populations. For individuals who experienced physiologic labor and birth, we compared physiologic care versus oxytocin prophylaxis (comparison group 1) and expectant management versus oxytocin prophylaxis (comparison group 2). For individuals who had labor and birth with minimal obstetric interventions, we compared physiologic care versus oxytocin prophylaxis (comparison group 3) and expectant management versus oxytocin prophylaxis (comparison group 4). We anticipated that some studies would contribute data to multiple comparisons, as studies meeting the criteria for physiologic birth would also fall into the broader category of minimal obstetric interventions.

METHODS

We registered our study protocol with PROSPERO (CRD42024543100) on May 14, 2024, and report our results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[17]

Search Strategy and Selection Process

We searched MEDLINE, Embase, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials databases from inception to December 15, 2023, with no language or publication date restrictions (see Supporting Information: Appendix S1). We also searched ClinicalTrials.gov (last search July 8, 2024) for ongoing, planned, or unpublished trials (Supporting Information: Appendix S2) and reference lists of eligible studies. Following calibration exercises to ensure agreement, pairs of reviewers independently screened titles and abstracts followed by full-text articles for inclusion using Covidence (Veritas Health Innovation, Melbourne, Australia). Where necessary, ChatGPT (OpenAI) and Google Translate were used for translation. Disagreements at any stage were resolved through discussion and third-party adjudication if necessary.

Eligibility Criteria

We included RCTs and nonrandomized studies of interventions involving low-risk individuals (as defined by study authors) at term (≥37 weeks' gestation), with a physiologic birth or a birth with minimal obstetric interventions. For this review, physiologic labor and birth was defined as the absence of intrapartum oxytocin, regional analgesia, or operative birth, whereas minimal obstetric intervention allowed for the use of epidural analgesia. This broader population was included because it aligned with a previous review,[18] increased the number of studies available for analysis, and allowed us to address the uncertainty regarding the impact of epidural analgesia use on outcomes.[19]

Included studies compared physiologic care or expectant management in the third stage of labor with the administration of intravenous (IV) or intramuscular (IM) oxytocin prophylaxis, with or without other components of active management such as early umbilical cord clamping or controlled traction. See Table 1 for definitions of key terms.

We included outcomes from the core outcome set for PPH prevention,[20] including blood loss (≥1000 mL), need for transfusion, use of additional uterotonics or hemostatic interventions, hypovolemic shock (as defined by study authors), death from all causes and death from PPH, adverse drug reactions (eg, nausea, vomiting, headache, abdominal pain), breastfeeding, well-being, and satisfaction.

Table 1. Key Terminology Used in This Review

Terminology	Definition
Physiologic labor and birth	Labor that is spontaneous in onset, progresses without pharmacologic or medical intervention, and culminates in a spontaneous vaginal birth.[4]
Minimal obstetric interventions	Labor and birth with no intrapartum oxytocin, no instrumental birth, and no or limited use of regional analgesia. Studies in this category either limited the population to physiologic birth or did not exclude regional analgesia use.
Expectant management of the third stage of labor	An approach characterized by passive observation and defined primarily by the absence of routine active management interventions. These include no administration of a prophylactic uterotonic, no cord clamping prior to cessation of pulsation, and no controlled cord traction.[10]
Physiologic care during the third stage of labor	An approach that avoids routine interventions associated with active management but differs in its use of proactive measures that support the physiologic completion of the third stage.[10] These may include creating a warm, safe environment, encouraging upright positioning, and promoting immediate skin-to-skin contact with the newborn.[11–13] Gentle lifting or easing out of the placenta is also compatible with physiologic care.[14]
Active management of the third stage of labor	Traditionally referred to a bundle of interventions, including immediate cord clamping, administration of a prophylactic uterotonic, controlled cord traction, and uterine massage.[2] Evidence now supports uterotonic administration as the most effective component.[2] The International Federation of Gynecology and Obstetrics, the International Confederation of Midwives, and the World Health Organization recommend oxytocin as the uterotonic of choice for postpartum hemorrhage prevention where multiple uterotonic options are available.[16] This review focuses on oxytocin prophylaxis.

Data Collection

One reviewer extracted data on study design, participant characteristics, setting, covariates in adjusted models, interventions, comparators, and outcomes of interest, which were independently verified by a second reviewer. Discrepancies were resolved by discussion.

Risk of Bias

Pairs of reviewers independently assessed the risk of bias for each outcome, resolving disagreements through discussion or third-party adjudication if needed. For RCTs, we used the Cochrane risk of bias tool, rating risk of bias as low, some concerns, or high across 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[21] For nonrandomized studies, we used the Risk Of Bias In Nonrandomized Studies of Interventions, rating risk of bias as low, moderate, serious, or critical across 7 domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results.[22]

Adjustment for confounding in nonrandomized studies was considered sufficient if studies conditioned on the variables identified in any one of the minimal sufficient adjustment sets derived from a directed acyclic graph developed from a synthesis of evidence (Supporting Information: Appendix S3).[23] To assess the risk of bias due to deviations from the intended intervention, we focused on the effect of assignment rather than adherence to the intervention, as this better reflects clinical practice. If deviations in the physiologic third-stage care or expectant management arms were or could have been therapeutic, they were not considered a risk of bias because these approaches include treatment of PPH as required. We used the robvis package in RStudio version 2024.02.2+764 to visualize risk of bias assessments.

Statistical Analysis

For each comparison and outcome, we conducted pairwise random-effects meta-analyses, using the DerSimonian-Laird estimator.[24] If meta-analysis was not appropriate, we synthesized the results using vote counting, considering both the direction and, when possible, the magnitude of the effect. All main analyses were based on the treatment as assigned (intention-to-treat). We reported relative risk (RR) with 95% CIs for all outcomes and calculated the absolute risk difference with corresponding 95% CI to facilitate interpretation. For blood loss greater than or equal to 1000 mL, we assumed a baseline risk of 2.47% in the prophylaxis arm.[25] For other outcomes, baseline risk was calculated as the weighted mean risk in this arm. When studies reported blood loss only as a continuous outcome (mean blood loss), we planned to use the Suissa method to estimate the risk of blood loss greater than or equal to 1000 mL,[26] assuming a normal distribution.[27]

Heterogeneity between pooled studies was assessed using visual inspection of the forest plots and the I^2 statistic. We were unable to statistically assess publication bias, as none of our analyses included 10 or more studies.[28] Investigation of important heterogeneity ($I^2 > 40\%$) and planned subgroup analyses based on birth setting (midwife-led unit or home vs hospital) and parity (nulliparous vs multiparous) could not be

conducted due to insufficient studies. All analyses were performed using the metan package in Stata, version 17.0.141.

Assessment of the Certainty of Evidence and Reporting Results

We assessed the certainty of evidence using theGrading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[29,30] For each comparison and outcome, we rated the certainty as high, moderate, low, or very low based on considerations of imprecision, inconsistency, indirectness, risk of bias, and publication bias. For nonrandomized studies, we also considered large effect size, dose-response relationship, and the effect of plausible confounding.

To assess imprecision, we used a minimally contextualized approach, which considers whether CIs include a minimally important difference (MID) or the smallest clinically relevant change in an outcome.[31] To guide judgements on imprecision, we used MIDs sourced from studies of postpartum populations, where available, and validated through expert consultation (Supporting Information: Appendix S4). For blood loss greater than or equal to 1000 mL and blood transfusion, the MID of 0.5% was based on the prevalence of massive PPH (5.7 per 1000 births).[32] This MID also reflects concerns about high rates of inappropriate blood transfusions, which carry significant risks,[33,34] and accounts for the possibility that small changes may reflect variations in clinical practice rather than true clinical benefit. MIDs for patient-reported outcomes (headache, pain, nausea, vomiting, fatigue) were informed by a prospective study validating the Obstetric Quality of Recovery-10 (ObsQoR-10) in a French population.[35] The ObsQoR-10 measures various aspects of the postpartum recovery experience. We prioritized the 24-hour anchor-based estimates for these outcomes, as these better reflect clinically meaningful experiences in postpartum recovery. We derived the MID for the need for additional uterotonics based on the clinically meaningful difference in uterine tone identified in previous studies.[36,37] When CIs did not cross the MID but the relative effect was large, we used the optimal information size approach to assess imprecision.[31] This method evaluates whether the total number of participants or events in the meta-analysis exceeds the number needed in a conventional sample size calculation for an adequately powered study.

When an RCT was available for a specific comparison, we followed GRADE guidance to assess whether additional evidence from nonrandomized studies should be included.[38] If the certainty of evidence from RCTs was rated as high, we generally excluded such studies due to their expected risk of bias. If the RCT evidence was rated as moderate, low, or very low, we considered including nonrandomized studies if they did not lower the overall certainty of the evidence or if they provided valuable complementary information that addressed the limitations of the RCTs. We used GRADE simple language summaries to communicate our findings.[39]

RESULTS

We screened 3518 records and included 7 studies involving 7091 participants: 3 RCTs[40–42] and 4 nonrandomized studies (Figure 1).[3,43–45] We excluded 47 reports (Supporting Information: Appendix S5), including 3 non-English-language studies. One was translated and found to be ineligible,[46] and 2 could not be translated due to poor physical quality but contained sufficient information in their English-language abstracts to determine they did not meet the inclusion criteria.[47,48]

Characteristics of Included Studies

Study characteristics are summarized in Table 2. Two included studies required translation.[40,45] The studies were conducted in the Netherlands,[41–43] Australia,[3] Germany,[40] Pakistan,[44] and Iran,[45] primarily in the 1990s.

Three studies focused on individuals with physiologic birth,[3,42,43] whereas the remaining 4 did not exclude epidural analgesia use (see Supporting Information: Appendix S6 for additional participant characteristics). Episiotomy rates were reported in only 2 studies.[41,45] Two studies had ambiguity regarding population eligibility: Vasegh et al (included in the previous systematic review[18]) did not clearly exclude instrumental births,[45] and the study by Karim et al did not specify whether participants with labor augmentation were excluded.[44] However, both studies had extensive eligibility criteria, and participants were classified as having minimal obstetric interventions. Two studies focused exclusively on nulliparous individuals,[43,44] and one study stratified results by parity.[41]

Only one study met the definition of physiologic care during the third stage of labor[3]; all others involved expectant management, 2 of which included a placebo.[41,45] Prophylactic oxytocin doses ranged from 3 to 10 international units, with one study reporting an unspecified dose.[3] Routes of administration included IV bolus,[40,44] IV infusion,[45] and IM,[3,41,42] with one study unspecified.[43] Descriptions of timing of oxytocin administration included after the birth,[43,45] immediately after the birth,[40–42,44] or within one minute of the birth.[3] Three studies incorporated other components of active management with the prophylaxis.[3,44,45]

Blood loss was quantified in 4 studies,[40–42,44] visually estimated in 2 studies,[3,45] and measured by both methods in one study.[43] Two studies reported blood loss only as a continuous outcome,[40,44] and imputing blood loss greater than or equal to 1000 mL resulted in zero events in both arms, so the data could not be used. These studies also did not report any other outcomes included in the review. Only one study reported on well-being,[42] and none reported on satisfaction, hypovolemic shock, or death.

Risk of Bias

The risk of bias assessment for all outcomes is presented in Figure 2. Of the 3 RCTs, 2 had adequate allocation generation and concealment and were judged at overall low or moderate risk of bias for all outcomes.[41,42] The remaining trial raised some concerns related to randomization due to insufficient information and was judged at high risk of bias due to missing outcome data for reasons (excessive bleeding and retained placenta) associated with the outcome.[40] Although blood loss assessors were probably not blinded

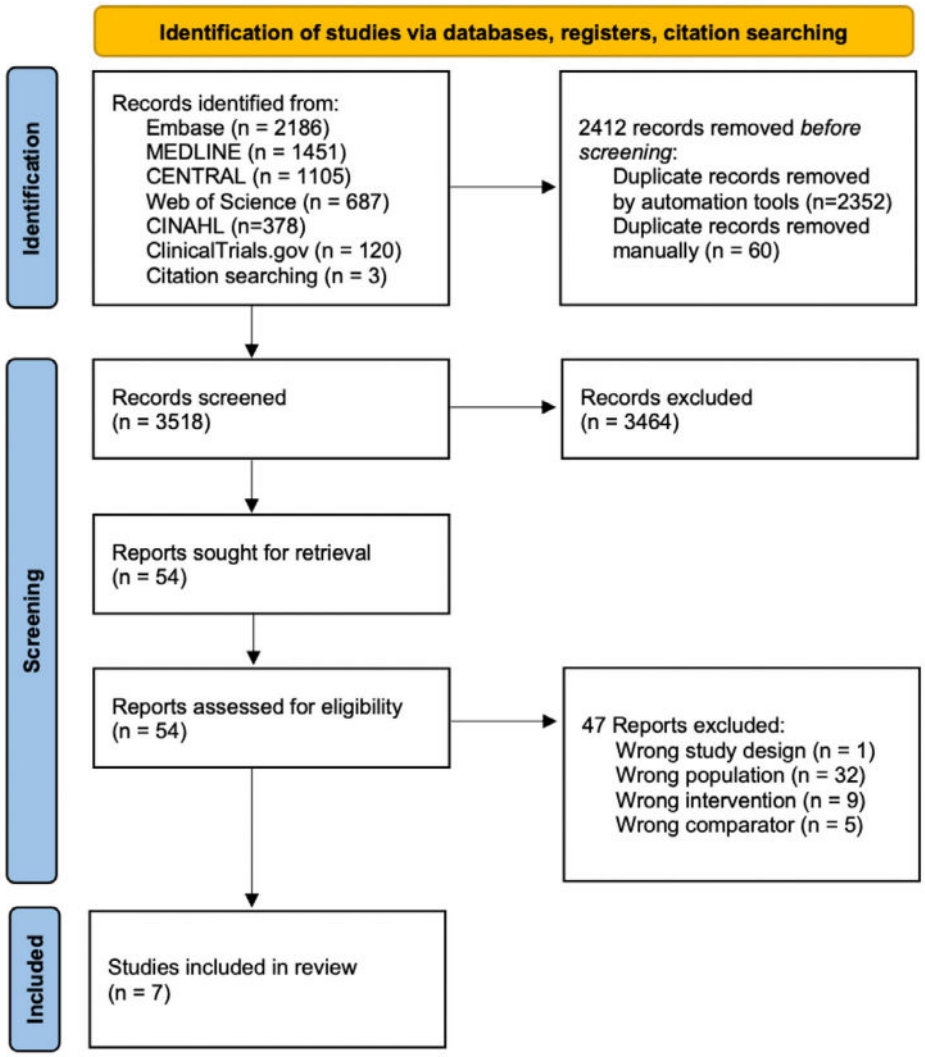

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram

in any of the trials, this was not a major concern because blood loss was objectively measured in all trials. All nonrandomized studies were rated at overall high risk of bias for all outcomes, primarily due to failure to control for key confounders.

Effects of the Interventions

Comparison Group 1: Physiologic Care Versus Oxytocin Prophylaxis Following Physiologic Labor and Birth

This comparison included one retrospective cohort study (n = 3436) by Fahy et al, conducted in Australia (2005-2008), which compared outcomes in 2 care settings: a tertiary maternity unit where oxytocin prophylaxis was the standard of care and a midwifery-led birthing unit where physiologic care was standard.[3]

Based on this evidence, physiologic care may result in a large reduction in the risk of blood loss greater than or equal to 1000 mL compared with oxytocin prophylaxis (RR, 0.29; 95% CI, 0.09-0.92). This corresponds to 18 fewer cases per 1000 (95% CI, 22 fewer to 2 fewer) (Table 3; Supporting Information: Appendix S7). The certainty of the evidence was low due to serious risk of bias from confounding and the imprecise CI that includes the possibility of a trivial effect. No other outcomes were reported.

Comparison Group 2: Expectant Management Versus Oxytocin Prophylaxis Following Physiologic Labor and Birth

One RCT (n = 1686) by Jans et al, conducted in the Netherlands (1996-1997) with participants receiving care from 20 community-based midwifery practices, contributed data for all outcomes for this comparison (Table 4; Supporting Information: Appendix S8).[42] The certainty of the evidence was high or moderate for most outcomes, with concern for some outcomes due to imprecise CIs, small sample sizes, or low event rates.

A nonrandomized study by Bais et al (n = 1416) was also identified for this comparison but excluded from the analysis due to insufficient comparative data.[43] The authors reported an overall 4% rate of blood loss greater than or equal to 1000

Table 2. Characteristics of Included Studies

Source	Design (Setting)	Obstetric Interventions in Study Population	Physiologic Third Stage Care/Expectant Management	Oxytocin Prophylaxis Management	Outcome Measures
de Groot 1996[41,a]	RCT (home or hospital, Netherlands, 1993-1994)	Epidural analgesia (unknown rate), episiotomy (33% in placebo group, 29% in prophylaxis group)	Expectant management N = 143: Oral placebo tablet immediately after birth, positioning "aiding gravity," encouragement of maternal effort for placental expulsion, flat hand placed on abdomen as a brace to aid pushing if needed, cord clamped after cessation of pulsation	N = 78: IM 5 IU immediately after birth, all other management as with expectant management	Blood loss ≥500 mL, blood loss ≥1000 mL, additional uterotonics, blood transfusion, manual removal of placenta, blood loss (mL)
Bader 2000[40,b]	RCT (hospital, Germany, 1998-1999)	Epidural analgesia, pudendal block (unknown rate, proportion comparable between groups)	Expectant management N = 60: No uterotonic prophylaxis, no uterine or cord manipulation, regular compression of the abdomen above the pubic symphysis to assess placental detachment (Küstner examination)	N = 60: IV 3 IU immediately after birth, all other care as per expectant management	Blood loss (mL), length of third stage, difference in hemoglobin
Bais 2004[43]	Cohort study (home or hospital, Netherlands, 1990-1994)	None: Physiologic birth	Expectant management N ≈ 708 (~ 50% of the low-risk group): No uterotonic prophylaxis, ECC only if nuchal cord or fetal distress, placental birth by maternal effort aided by suprapubic pressure after signs of separation, no CCT	N≈ 708: 5 or 10 IU after birth (route unspecified), otherwise, management as with expectant management	Blood loss (mL), blood loss ≥1000 mL, transfer to secondary care, retained placenta, blood transfusion
Vasegh 2005[45]	Quasi-experimental study (hospital, Iran, 1999)	Epidural analgesia (unknown rate), episiotomy (10.6% in expectant management, 14.9% in prophylaxis group), unclear whether instrumental births were excluded	Expectant management N = 47: IV 1 mL distilled water in 500 mL 5% glucose solution after birth, umbilical cord not clamped and cut until after cessation of pulsation, placenta expelled with gentle tension on the cord and maternal effort, supine position	N = 47: IV 10 IU in 500 mL 5% glucose solution after birth, ECC, placenta birthed by modified Brandt-Andrews method, supine position	PPH (undefined), duration of the third stage, retained placenta, hemoglobin/ hematocrit, nausea, vomiting, pain, breastfeeding

(*Continued*)

Table 2. (Continued)

Source	Design (Setting)	Obstetric Interventions in Study Population	Physiologic Third Stage Care/Expectant Management	Oxytocin Prophylaxis Management	Outcome Measures
Fahy 2010[3]	Cohort study (hospital or midwifery-led birthing unit, Australia, 2005-2008)	None: Physiologic birth	Physiologic care N = 361 (midwifery-led unit): No uterotonic prophylaxis, immediate and sustained skin-to-skin contact to ensure warmth, midwife encourages focus on newborn while monitoring placental birth, self-attachment breastfeeding, placenta birthed by maternal effort and gravity	N = 3075 (tertiary hospital): IM (dose not specified) given within 1 min of birth, CCT, fundal massage after placenta birth	Blood loss: ≥500 mL <1000 mL, ≥1000 mL ≤1500 mL, >1500 mL
Karim 2015[44]	Quasi-experimental study (hospital, Pakistan, 2006)	Epidural analgesia (unknown rate)	Expectant management N = 50: No uterotonic prophylaxis, no cord clamping until cessation of pulsation, placental birth by maternal effort and gravity	N = 50: IV 10 IU immediately after birth, ECC, CCT after uterus contracts, fundal massage after placental birth	Blood loss (mL), duration of the third stage
Jans 2016[42,c]	RCT (community setting, Netherlands, 1996-1997)	None: Physiologic birth	Expectant management N = 845: No uterotonic prophylaxis, placental birth by maternal effort with abdominal support if needed, cord clamped and cut only after cessation of pulsation	N = 859: IM 5 IU immediately after birth, with or without light fundal pressure, no specific instructions for CCT or cord clamping	Blood loss >500 mL, blood loss >1000 mL, blood loss >1500 mL, additional uterotonics, blood transfusion, third stage duration, breastfeeding, nausea, vomiting, headache, abdominal pain, well-being, hypotension, hemoglobin/anemia

Abbreviations: CCT, controlled cord traction; ECC, early cord clamping; IM, intramuscular; IU, international units; IV, intravenous; PPH, postpartum hemorrhage; RCT, randomized controlled trial.
[a] Additional information on timing of cord clamping was obtained from study authors. Treatment arm not included: 0.4 mg ergonovine orally.
[b] Treatment arm not included: Acupuncture 2 needles (0.3 × 25 mm) applied 1.5 cm on either side of the navel (point Nil6).
[c] Additional information from study authors confirmed that all participants had a physiologic birth.

mL, with no significant difference in bleeding between the active and expectant management arms ($P = 0.8$) (serious risk of bias).

Based on the available evidence,[42] compared with oxytocin prophylaxis, expectant management likely results in a large increase in the risk of blood loss greater than or equal to 1000 mL (RR, 1.87; 95% CI, 1.36-2.57; 21 more cases per 1000; 95% CI, 9 more to 39 more; moderate certainty), but it may make little to no difference in the need for blood transfusion (RR, 1.22; 95% CI, 0.53-2.82; 3 more cases per 1000; 95% CI, 6 fewer to 21 more; low certainty). Expectant management also results in a large increase in the risk of

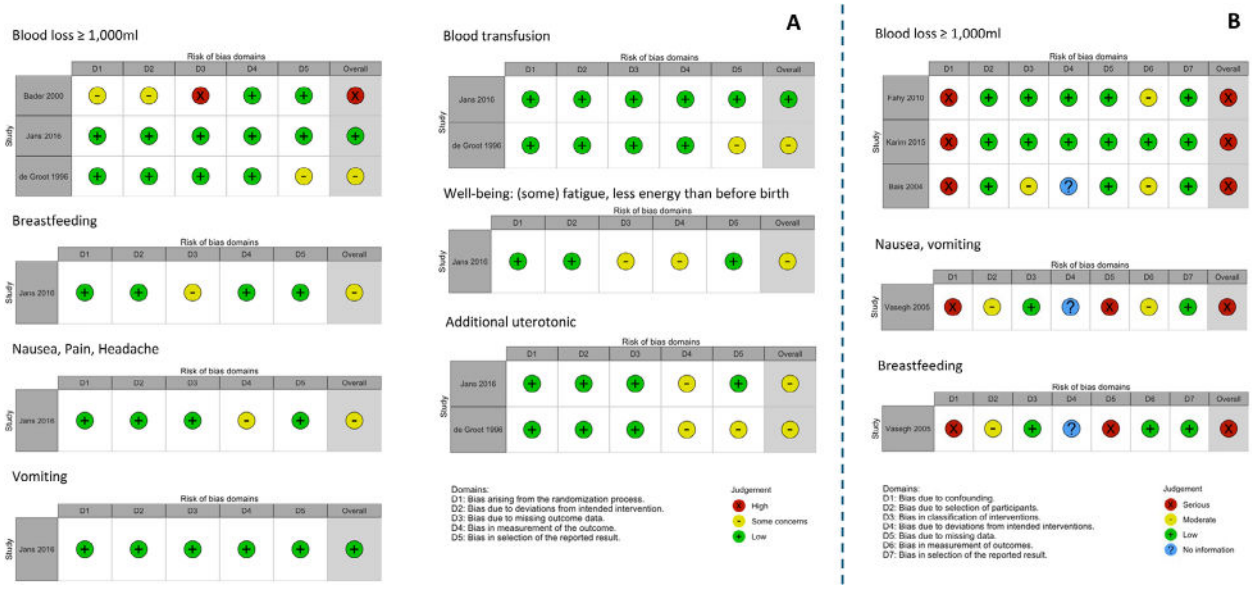

Figure 2. **Risk of Bias of Randomized Controlled Trials (Panel A) and Nonrandomized Studies of Interventions (Panel B)**

Table 3. **Summary of Findings of Physiologic Third-Stage Care Compared With Oxytocin Prophylaxis on Postpartum Hemorrhage Outcomes in Individuals With a Physiologic Birth**

What Was Measured	Number of Participants (Studies, Events)	Effect When Receiving Physiologic Care[a]	Certainty of the Evidence (GRADE)	What Happens When Receiving Physiologic Care
Blood loss ≥1000 mL	3436 (1 study, 90 events)	18 fewer per 1000 (22 fewer to 2 fewer)	Low[b,c]	May result in a large reduction in blood loss ≥1000 mL
Other outcomes		-		Not measured

[a]We assumed a baseline risk of 2.47% to calculate the absolute risk for blood loss ≥1000 mL.
[b]Downgraded 1 for risk of bias: Data comes from a single nonrandomized study with serious risk of bias due to confounding.
[c]Downgraded 1 for imprecision: The CI includes the possibility of a trivial effect.

requiring additional uterotonics (RR, 2.50; 95% CI, 1.96-3.19; high certainty).

Regarding side effects, the available evidence[42] suggests that, compared with oxytocin prophylaxis, expectant management likely results in little to no difference in the risk of nausea (RR, 1.12; 95% CI, 0.63-1.98; moderate certainty), vomiting (RR, 0.68; 95% CI, 0.19-2.41; moderate certainty), painful uterine contractions (RR, 1.12; 95% CI, 1.00-1.26; moderate certainty), or headache (RR, 0.80; 95% CI, 0.40-1.59; moderate certainty). Expectant management also results in little to no difference in the risk of having less energy (RR, 0.98; 95% CI, 0.89-1.08) or some fatigue (RR, 1.01; 95% CI, 0.96-1.05) at 3 months postpartum or in breastfeeding at one week (RR, 1.00; 95% CI 0.95-1.06) and 3 months (RR, 0.99; 95% CI, 0.89-1.11) postpartum (high certainty). Satisfaction, hypovolemic shock, and death were not measured.

Comparison Group 3: Physiologic Care Versus Oxytocin Prophylaxis Following Labor and Birth With Minimal Obstetric Interventions

This comparison was intended to include a broader population than comparison 1 by incorporating studies that did not exclude epidural analgesia use. However, no additional studies met inclusion criteria beyond those already included in comparison 1. Consequently, the evidence comes from the same nonrandomized study by Fahy et al (n = 3436),[3] which included only individuals who experienced a physiologic birth, and the results are unchanged: physiologic third-stage care may result in a large reduction in the risk of blood loss greater than or equal to 1000 mL (low certainty) (Supporting Information: Appendices S9-S10). No additional outcomes were reported.

Comparison Group 4: Expectant Management Versus Oxytocin Prophylaxis Following Labor and Birth with Minimal Obstetric Interventions

Two RCTs (n = 1907) contributed data for the following outcomes: blood loss greater than or equal to 1000 mL, blood transfusion, and need for additional uterotonics. These included the previously described study by Jans et al[42] and a trial by de Groot et al,[41] conducted in the Netherlands (1993-1994) across 2 university hospitals, a midwifery school, and independent midwifery practices.

Table 4. Summary of Findings of Expectant Management Compared to Oxytocin Prophylaxis on Postpartum Hemorrhage Outcomes in Individuals With a Physiologic Birth

What Was Measured	Number of Participants (Studies, Events)	Effect When Receiving Expectant Management[a]	Certainty of the Evidence (GRADE)	What Happens When Receiving Expectant Management
Blood loss ≥1000 mL	1686 (1 study, 153 events)	21 more per 1000 (9 more to 39 more)	Moderate[b]	Probably results in a large increase in blood loss ≥1000 mL
Blood transfusion	1686 (1 study, 22 events)	3 more per 1000 (6 fewer to 21 more)	Low[c]	May result in little to no difference in blood transfusion
Additional uterotonics	1672 (1 study, 274 events)	14 more per 100 (9 more to 21 more)	High	Results in a large increase in additional uterotonics
Nausea	1662 (1 study, 46 events)	3 more per 1000 (10 fewer to 26 more)	Moderate[d]	Likely results in little to no difference in nausea
Vomiting	1660 people (1 study, 10 events)	2 fewer per 1000 (6 fewer to 10 more)	Moderate[e]	Likely results in little to no difference in vomiting
Headache	1653 (1 study, 32 events)	4 fewer per 1000 (13 fewer to 13 more)	Moderate[f]	Likely results in little to no difference in headache
Pain	1665 (1 study, 686 events)	5 more per 100 (0 to 10 more)	Moderate[d]	Likely results in little to no difference in pain
Well-being at 3 mo				
(Some) fatigue	1571 (1study, 1309 events)	1 more per 100 (4 fewer to 4 more)	High	Results in little to no difference in (some) fatigue
Less energy	1543 (1study, 788 events)	1 fewer per 100 (6 fewer to 4 more)	High	Results in little to no difference in having less energy
Breastfeeding				
At 1 wk	1540 (1 study, 1224 events)	0 per 100 (4 fewer to 5 more)	High	Results in little to no difference in breastfeeding at 1 wk
At 3 mo	1222 (1 study, 613 events)	0.5 fewer per 100 (0.6 fewer to 0.6 more)	High	Results in little to no difference in breastfeeding at 3 mo

[a] We assumed a baseline risk of 2.47% to calculate the absolute risk for blood loss ≥1000 mL. For other outcomes, baseline risk was calculated as the weighted mean risk in the oxytocin prophylaxis arms of the included studies.
[b] Downgraded 1 for imprecision: The relative effect of 87% increase represents a large, possibly implausible effect, and the sample size is less than the optimal information size (OIS). To detect a 25% relative risk reduction from a control event rate of 2.47%, with an αlevel of .05 and power of 80%, the OIS is approximately 9076 participants.
[c] Downgraded 2 for imprecision: The CI includes the possibility of important benefit and important harm.
[d] Downgraded 1 for imprecision: The CI includes the possibility of important harm.
[e] Downgraded 1 for imprecision: The relative effect is large (relative risk [RR] reduction >30%) with low number of events (the ratio of the upper CI boundary to the lower CI boundary for the RR is >3). Due to low baseline risk, we did not downgrade by 2.
[f] Downgraded 1 for imprecision: Few events reported.

Based on the available evidence,[41,42] compared with oxytocin prophylaxis, expectant management likely results in a large increase in the risk of blood loss greater than or equal to 1000 mL (RR, 1.78; 95% CI, 1.32-2.39; 19 more cases per 1000; 95% CI, 8 more to 34 more). The certainty of the evidence was moderate due to the small number of events. However, expectant management may make little to no difference in the risk of blood transfusion (RR, 1.14; 95% CI, 0.53-2.42; 2 more cases per 1000; 95% CI, 6 fewer to 18 more; low certainty) (Supporting Information: Appendices S11-S12). There was serious concern with the certainty of the evidence due to imprecise CIs and few events. The evidence for the need for additional uterotonics was very uncertain (RR, 1.66; 95% CI, 0.69-4.01; very low certainty) because of wide CIs that include important harm and significant unexplained heterogeneity (Supporting Information: Appendix S11-S12).

Regarding side effects, only the RCT by Jans et al already included in comparison 2 and involving individuals with physiologic birth (n = 1686)[42] contributed data. Consequently, the results are unchanged. Based on this evidence,

compared with oxytocin prophylaxis, expectant management likely results in little to no difference in the risk of nausea, vomiting, painful uterine contractions, or headache (moderate certainty) and results in little to no difference in the risk of having less energy or some fatigue at 3 months postpartum or in breastfeeding at one week and 3 months postpartum (high certainty).

A separate small nonrandomized study (n = 94) by Vasegh et al also reported on nausea, vomiting, pain, and breastfeeding[45] but was judged to be at serious risk of bias for these outcomes. Inclusion of this study in a sensitivity analysis did not improve the certainty of the evidence or contribute valuable complementary information (Supporting Information: Appendix S13). As a result, it was not included in the final synthesis.

DISCUSSION

Main Findings

This systematic review and meta-analysis compared physiologic care or expectant management in the third stage of labor with oxytocin prophylaxis. For individuals with a physiologic labor and birth, physiologic third-stage care may result in a large reduction in the risk of blood loss greater than or equal to 1000 mL compared with oxytocin, whereas expectant management likely results in a large increase in this risk, with little to no difference in the number of individuals requiring blood transfusion or reporting person-important outcomes such as well-being or breastfeeding. Expanding the population to include labor and birth with minimal obstetric interventions (ie, with epidural analgesia) yielded similar results. However, because studies meeting the criteria for physiologic birth also fell into the minimal intervention category, it was difficult to draw definitive conclusions for this broader group.

Strengths and Limitations

Strengths of this review include a comprehensive search strategy, duplicate screening, and use of rigorous tools to assess risk of bias and certainty of evidence. We also included nonrandomized studies, which are valuable in the context of physiologic birth in which RCTs may not be feasible.[49] Another strength is our differentiation between expectant management and physiologic third-stage care, which is a novel comparison that helps clarify differences in effects between these distinct management approaches.

Although not a limitation of the review itself, the body of evidence had important limitations. Only 7 studies met our inclusion criteria, most were conducted in the 1990s, and none were based in the United States. Recent reviews have included studies of low-risk individuals,[50,51] but we could not include them because participants who experienced a physiologic birth could not be separately identified, highlighting a challenge inherent in conventional aggregate data meta-analysis. An individual participant data meta-analysis could have addressed this issue[52] but was not feasible due to insufficient availability of original data. The limited number of eligible studies also prevented meaningful exploration of heterogeneity based on factors like parity or place of birth.

These limitations of the evidence base were reflected in the GRADE ratings of the certainty of evidence. For comparisons involving physiologic third-stage care, certainty was low due to reliance on a single nonrandomized study. Additional high-quality research is needed to strengthen the evidence base and inform clinical guidance on third-stage care following physiologic birth.

Interpretation of Findings

Although the included studies were conducted outside the United States several decades ago, we believe the findings remain applicable to healthy pregnant US individuals. The studies were carried out in well-resourced settings among low-risk populations, and third-stage care has remained relatively consistent. To enhance relevance, we calculated absolute risk differences using baseline risks that reasonably reflect contemporary US estimates for low-risk populations (eg, a 2.47% baseline risk for severe PPH).[53] Although the baseline risk for PPH requiring blood transfusion (1.2%) was slightly higher than current US rates,[54] sensitivity analyses using a lower rate estimate (eg, 0.4%) yielded similar effects with a narrower CI, increasing confidence in the findings. Contemporary MIDs were also selected, supporting the relevance of our interpretations to the US context.

Our results align with findings from observational studies of similar populations, showing that physiologic care in the third stage, compared with active management using undefined prophylactic uterotonic agents, may reduce the risk of blood loss greater than or equal to 1000 mL.[5,6] One biologically plausible explanation is that, in the context of physiologic birth, exogenous oxytocin may interfere with the endogenous hormonal and physiologic cascade necessary for effective uterine contractions and placental separation.[55] Dixon et al have also hypothesized that pre-exposure to synthetic oxytocin with prophylaxis may desensitize myometrial oxytocin receptors, reducing the effectiveness of uterotonic treatment when needed.[6]

For expectant management, our findings are also consistent with those of Erickson et al, who conducted a secondary meta-analysis of 2 previous Cochrane reviews comparing prophylaxis with oxytocin alone or oxytocin and ergometrine to no uterotonic prophylaxis in individuals who did not receive synthetic oxytocin during labor. Both of our studies found an increased risk of blood loss greater than or equal to 1000 mL with expectant management, although the results from Erickson et al were characterized by greater uncertainty. These findings suggest that a hands-off approach (expectant management) may not alone be sufficient to prevent excessive blood loss. This aligns with midwifery guidance, which emphasizes that the physiologic completion of the third stage requires expertly intentional support for the release of endogenous oxytocin, including providing a birth environment that is warm, safe, and allows for uninterrupted interaction between the birthing person and their newborn.[11–13]

Implications for Research and Practice

This review highlights several important considerations for future research. First, it underscores the importance of

distinguishing between expectant management and physiologic third-stage care, as these are recognized as distinct approaches with potentially different treatment effects.[10] Second, it emphasizes the need to focus on synthetic oxytocin as prophylaxis in active management to limit variability in treatment effects and ensure consistency with current guidelines.

Another key consideration for future PPH-prevention research is prioritizing person-important outcomes. Variations in blood loss findings between comparisons in this review may reflect differences in measurement methods. For example, the study by Jans al,[42] a key driver of our findings on expectant management, used objective blood loss measurement, potentially explaining the higher volumes observed compared with the Fahy et al study on physiologic third-stage care,[3] in which blood loss was visually estimated. However, focusing on blood loss measurement, an approach with uncertain prognostic[57] or practical[58] value, and one that may interfere with a physiologic third stage, limits understanding of how third-stage management affects outcomes that matter to the birthing person. A recent qualitative systematic review identified preventing mortality, avoiding profound fatigue, and minimizing psychological distress as the most important factors for women in PPH prevention.[59] Patient-representatives have also strongly advocated for the inclusion of well-being, satisfaction, and breastfeeding into the core outcome set for PPH prevention.[60] Notably, only one study in our review contributed data on fatigue and breastfeeding,[42] finding no difference between expectant management and synthetic oxytocin prophylaxis.

Physiologic care during the third stage of labor remains a core component of midwifery practice in some areas,[61–63] particularly for individuals who have had a physiologic birth. Given that these individuals represent an important proportion of births with lower baseline risk and potential variations in pathophysiology that could impact treatment effects, evidence specific to this subgroup is essential. More broadly, the limited number of studies identified in this review underscores the significant gap in knowledge about physiologic birth, which remains an understudied area of inquiry in perinatal epidemiology.[64] As Bovbjerg et al have argued, without baseline data on what are considered the normal processes of birth, it is difficult to distinguish between biologically expected variation and pathology, leading to unnecessary intervention and potentially harm.[64]

CONCLUSION

Compared with oxytocin prophylaxis, physiologic third-stage care and expectant management may have opposing effects on the risk of excessive blood loss following physiologic birth. Physiologic third-stage care may result in a large reduction of the risk, whereas expectant management likely results in a large increase in the risk, although it may not increase the need for blood transfusion and results in little to no difference in well-being or breastfeeding. Additional high-quality research is needed to inform clinical practice.

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To include all relevant studies, titles, abstracts, and full texts from non-English reports were translated using ChatGPT (OpenAI) and Google Translate. After translation, one of the authors (V.H.) reviewed both versions to ensure accuracy and consistency before including them in the systematic review process. The authors take full responsibility for the content of the publication.

All relevant data are within the article and Supplementary file.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Database Search Strategy and Results

Appendix S2. ClinicalTrials.gov Search Strategy and Results

Appendix S3. Minimal Sufficient Adjustment Sets for Estimating the Total Effect Of Third Stage Management on PPH

Appendix S4. Minimally Important Differences (MID) Used to Guide Judgements on Imprecision

Appendix S5. Characteristics of Excluded Studies

Appendix S6. Additional Participant Characteristics of Included Studies

Appendix S7. Forest Plot for Analysis of Physiologic Care in the Third Stage vs Oxytocin Prophylaxis Following Physiologic Labour and Birth (Comparison 1)

Appendix S8. Forest Plots for Analyses of Expectant Management vs Oxytocin Prophylaxis Following Physiologic Labour and Birth (Comparison 2)

Appendix S9. Summary of Findings of Physiologic Third Stage Care Compared to Oxytocin Prophylaxis on Postpartum Hemorrhage Following Labour and Birth With Minimal Obstetric Interventions (Comparison 3)

Appendix S10. Forest Plot for Analysis of Physiologic Third Stage Care vs Oxytocin Prophylaxis Following Labour and Birth With Minimal Obstetric Interventions (Comparison 3)

Appendix S11. Summary of Findings of Expectant Management Compared to Oxytocin Prophylaxis on Postpartum Hemorrhage Outcomes Following Labour and Birth With Minimal Obstetric Interventions (Comparison 4)

Appendix S12. Forest Plots for Analyses of Expectant Management vs Oxytocin Prophylaxis Following Labour and Birth With Minimal Obstetric Interventions (Comparison 4).

Appendix S13. Forest Plots for Analyses of Expectant Management vs Oxytocin Prophylaxis Following Labour and Birth With Minimal Obstetric Interventions – With Inclusion Of Non-Randomized Studies of Interventions

Supporting Information

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