Time to redefine prolonged third stage of labor? A systematic review and meta-analysis of the length of the third stage of labor and adverse maternal outcome after vaginal birth

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OBJECTIVE: This study aimed (1) to assess the association between the length of the third stage of labor and adverse maternal outcome after vaginal birth and (2) to evaluate whether earlier manual placenta removal reduces the risk of adverse outcome.
DATA SOURCES: PubMed, MEDLINE, Embase, ClinicalTrials.gov, the Cochrane Library, Journals@Ovid, and the World Health Organization International Clinical Trials Registry were searched from January 1, 2000, to June 13, 2023.
STUDY ELIGIBILITY CRITERIA: All studies that assessed adverse maternal outcome, defined as any maternal complication after vaginal birth, concerning the length of the third stage of labor and the timing of manual placenta removal were included.
METHODS: The included studies were evaluated using the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology methodology. Pooled odds ratios with 95% confidence intervals were calculated. Heterogeneity (I^2 test) was assessed, subgroup analyses were performed, and 95% prediction intervals were calculated.
RESULTS: To meet the first objective, 18 cohort studies were included. The assessed cutoff values for the length of the third stage of labor were 15, 30, and 60 minutes. Women with a third stage of labor of ≥15 minutes had an increased risk of postpartum hemorrhage compared with those with a third stage of labor of <15 minutes (odds ratio, 5.55; 95% confidence interval, 1.74—17.72). For women without risk factors for postpartum hemorrhage, the odds ratio was 2.20 (95% confidence interval, 0.75—6.49). Among women with a third stage of labor of ≥60 minutes vs women with a third stage of labor of <60 minutes, the odds ratio was 3.72 (95% confidence interval, 2.36—5.89). The incidence of red blood cell transfusion was higher for a third stage of labor of ≥30 minutes than for a third stage of labor of <30 minutes (odds ratio, 3.23; 95% confidence interval, 2.26—4.61). Of note, 3 studies assessed the timing of placenta removal and the risk of adverse maternal outcome. However, the results could not be pooled because of the different outcome measures. Moreover, 1 randomized controlled trial (RCT) reported a significantly higher incidence of hemodynamic compromise in women with manual placenta removal at 15 minutes than in women with manual placenta removal at 10 minutes (30/156 [19.2%] vs 10/156 [6.4%], respectively), whereas 2 observational studies reported a lower risk of bleeding among women without manual placenta removal.
CONCLUSION: Although the risk of adverse maternal outcome after vaginal birth increases when the third stage of labor exceeds 15 minutes, there is no convincing supporting evidence that reducing the length of the third stage of labor by earlier manual removal of the placenta can reduce the incidence of adverse maternal outcome.

Key words: adverse maternal outcome, manual removal of the placenta, postpartum hemorrhage, third stage of labor, timing

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AJOG at a Glance

Why was this study conducted?

The length of the third stage of labor (TSL) and the timing of manual placenta removal may be the factors involved in reducing the increasing incidence of postpartum hemorrhage (PPH) in high-income countries. There is a lack of robust data on when is the best time to consider the TSL as "prolonged" and whether earlier manual removal of the placenta is beneficial in terms of overall maternal outcome.

Key findings

After vaginal birth, the risk of PPH increases once the TSL exceeds 15 minutes, particularly in women with PPH risk factors. Evidence regarding the benefits of reducing the length of the TSL by earlier manual placenta removal remains inconclusive.

What does this add to what is known?

Our study fills in gaps regarding the length of the TSL and the timing of manual placenta removal, providing opportunities for future research.

Introduction

Several high-income countries have reported an increase in the incidence of both mild and severe postpartum hemorrhage (PPH) in recent years. Although these observations may partly result from improved diagnosis or registration of PPH, they may also reflect a true increase in the incidence because of an increase in the prevalence of risk factors for PPH.[1−5] The increasing incidence of PPH emphasizes the need to reconsider established recommendations for PPH prevention, to turn this tide. Of note, 1 modifiable risk factor for PPH is the timing of manual removal of retained placenta (MROP) after vaginal birth in women with a prolonged third stage of labor (TSL).[6,7] Although the case fatality rate because of PPH caused by retained placenta in most high-income countries has become low, some countries have reported an increase in PPH-related deaths, some countries have reported an increase in PPH-related deaths, with retained placenta emerging as the leading cause of hemorrhage-related maternal deaths in countries, such as the Netherlands and Switzerland.[8,9]

The TSL is generally defined as the period from after the birth of the newborn to the complete expulsion of the placenta and membranes.[10,11] Several Cochrane reviews have been conducted to assess different aspects of the TSL.[12] These include reviews into the TSL regarding the use and mode of administration of prophylactic uterotonics and the timing of cord clamping.[13−16] However, none of these reviews evaluated the length of the TSL. The lack of robust data on when is the best time to consider the TSL as "prolonged" has resulted in considerable discrepancies between various clinical guidelines concerning the timing of MROP. Although professional societies in France and Canada recommend proceeding to MROP within 30 to 60 minutes after childbirth in the absence of bleeding, others, such as the American College of Obstetricians and Gynecologists, do not specify at which interval to proceed to MROP.[17,18]

Recently, several authors have challenged the current recommendations concerning the timing of MROP, proposing to reduce the interval before proceeding to MROP to <20 minutes minutes after the birth of the newborn to further reduce the risk of PPH.[19] However, it is unclear whether earlier MROP would be beneficial in terms of overall maternal outcome, as MROP itself has been associated with hemorrhage.[20] In addition, regardless of whether MROP is performed under epidural, spinal, or general anesthesia, it remains an inconvenient intervention for the woman.[11,21−23]

First, we aimed to assess the association between the length of the TSL and adverse maternal outcome after vaginal birth based on a systematic review and meta-analysis of the literature. Second, we aimed to evaluate whether the risk of adverse maternal outcome can be reduced by earlier intervention (MROP) compared with current clinical practice.

Materials and methods

Eligibility criteria, information sources, and search strategy

A literature search was performed on June 13, 2023. A search strategy was developed using free-text and Medical Subject Headings terms (Appendix 1). We restricted our search to publications in English, French, German, Italian, and Dutch, published between January 1, 2000, and June 13, 2023. The search was performed on PubMed, MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, Journals@Ovid, and the World Health Organization [WHO] International Clinical Trials Registry. To identify relevant publications not identified by our search in these search engines, we screened the websites of key organizations, such as the WHO and the International Federation of Gynaecology and Obstetrics, for relevant publications on risk factors for PPH, the length of the TSL, and practices around MROP. In addition, we screened the reference lists of national guidelines from different high-income countries on the prevention of PPH.[11,23−28]

The studies considered eligible for inclusion were randomized trials, comparative studies, and prospective and retrospective cohort studies. Articles excluded from our review were study protocols, reviews, letters to the editor, conference abstracts, and case reports.

Study outcomes

The primary study outcome was the risk of adverse maternal outcome according to the length of the TSL. Adverse maternal outcome was defined as any complication occurring to the woman during birth and/or after delivery, such

as PPH (blood loss of ≥500 or ≥1000 mL), blood transfusion (≥1 unit of packet cells), intensive care unit (ICU) admission, and peripartum hysterectomy. In addition, the decrease in hemoglobin level and the total amount of blood loss were assessed when available. The secondary study outcome was the risk of adverse maternal outcome according to the timing of MROP.

Study selection and data extraction

Studies were screened for eligibility by 2 authors (P.L.M.D.V. and E.V.). In case in which it was unclear from the title or abstract whether a study was eligible, the full-text article was obtained and read. Data extraction from the included studies was performed by 2 authors (P.L.M.D.V. and E.V.) and tabulated into a summary table. As not all articles could be included in the meta-analysis due to different outcome measures, we added a column indicating whether or not the article was included in the meta-analysis. Studies applying outcome measures of adverse maternal outcome other than the risk of PPH or red blood cell transfusion were not included in the meta-analysis because of the large heterogeneity in the definition of these outcomes and the limited number of studies. Alternatively, these studies were included in the narrative review.

Studies were categorized into 2 groups: (1) studies investigating the association between the length of the TSL and adverse maternal outcome and (2) studies investigating the timing of MROP and maternal outcome.

Risk of bias assessment

We assessed the risk of bias using the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) methodology. The sources of selection bias considered were the definition of study period, hospital, regional or national cohort, the performance of an active TSL, and inclusion of women independent of the cause of hemorrhage. Active management of TSL was defined as the routine administration of a prophylactic uterotonic just before, at, or immediately after the birth of the newborn. Early cord clamping and controlled cord traction to expel the placenta were not considered as elementary components of active management based on the evidence that this does not further reduce the risk of PPH.[12,14] The potential causes of information bias were the method of blood loss quantification and the source of data extraction. Possible confounders included parity, body mass index, macrosomia, and multiple pregnancy because these are risk factors for PPH.[1,29,30]

Statistical analysis

For studies defining adverse maternal outcome as PPH or red blood cell transfusion, the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were pooled in a random-effects model. Where ORs were not given, they were calculated by P.L.M.D.V. and E.V. The risk of adverse maternal outcome was calculated for different lengths of the TSL: more or less than 15 minutes, more or less than 30 minutes, and more or less than 60 minutes. The risk of adverse maternal outcome was calculated for women giving birth vaginally with a low risk profile and a mixed risk profile for PPH. Risk factors for PPH were considered: previous PPH, primiparity, obesity, prolonged or augmented labor, multiple pregnancy, previous cesarean delivery, polyhydramnios, and macrosomia.[31] Women with a low risk profile for PPH did not present with these risk factors. Women with a mixed risk profile presented with one or more of these risk factors. Weighting of studies included in the meta-analyses was performed using the Mantel-Haenszel method. Heterogeneity was tested using the Cochran Q test, and the degree of heterogeneity was quantified using I^2 statistic. A P value of $<.05$ was considered statistically significant. In the presence of statistical heterogeneity ($I^2 \geq 30\%$), we performed subgroup analyses accordingly to 2 possible definitions of PPH (blood loss of ≥500 or ≥1000 mL). In addition, we addressed heterogeneity by calculating 95% prediction intervals (PIs), which show the range of true effect sizes in future studies similar to those in the meta-analysis. The likelihood of publication bias was assessed using the Egger test, with a P value of $<.10$ considered statistically significant publication bias. Analyses were performed using Stata software (version 16; StataCorp, College Station, TX).

Results

Study selection

The final search yielded 3903 records. After removing duplicates and records published before January 2000, 1655 articles were excluded based on the title of the article. Subsequently, the abstracts of the remaining 47 articles were read by P.L.M.D.V. and E.V. Moreover, 18 articles were selected: 16 addressing the length of the TSL and maternal outcome and 3 addressing MROP in the absence of bleeding and the association with maternal outcome. Overall, 18 studies were included: 16 studies investigating the association between the length of the TSL and adverse maternal outcome and 3 studies investigating the timing of MROP and maternal outcome. Moreover, 1 study was included in both groups (Figure 1).

Study characteristics

Most included studies (16/18) were conducted in high-income countries (the United States, Australia, Denmark, the Netherlands, Israel, Switzerland, Sweden, and Japan),[32–47] 1 study was conducted in a middle-income country (Egypt),[48] and 1 study was a multicountry study conducted in low-, middle-, and high-income countries.[49] Overall, 13 of 18 studies were single-center studies,[32–37,39,42,43,45,46,48] and 5 of 18 studies were multicenter studies (Table).[32–49]

The included studies were 2 RCTs,[36,45] 2 secondary analyses of an RCT,[35,49] and 14 observational studies (cross-sectional, longitudinal, and case-control studies).

Risk of bias of included studies

Overall risk of bias was low in 1 of 18 studies (6%), moderate in 7 of 18 studies (39%), and high in 10 of 18 studies (55%). The risks of selection bias were low or moderate in 1 of 18 studies (6%)

and 6 of 18 studies (33%), respectively, and high in 11 of 18 studies (61%). The risk of information bias was low in 6 of 18 studies (33%), moderate in 5 of 18 studies (28%), and high in 7 of 18 studies (39%) (Appendix 2).

Definition of outcome

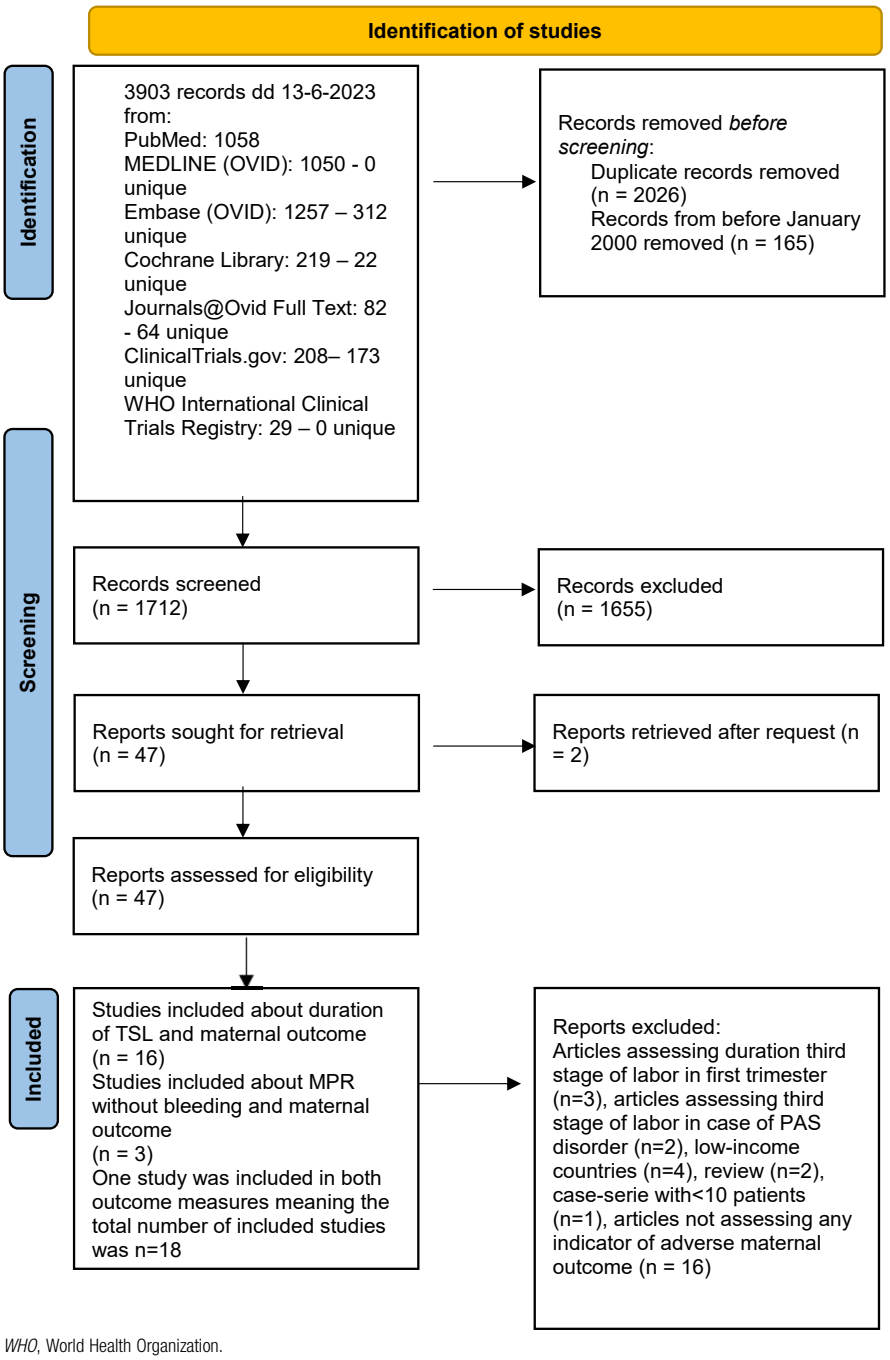
For the primary outcome, the definitions of adverse maternal outcome varied between studies. The risk of PPH was calculated in 12 studies.[32,33,35,37,38,41–45,47,48] Of these studies, 9 presented an OR for the risk of PPH and were included in the meta-analysis.

Of note, 4 studies assessed the risk of red blood cell transfusion regarding the length of the TSL,[42,43,45,46] 3 of which could be included in the meta-analysis.

Moreover, 2 studies assessed the total amount of blood loss concerning the length of the TSL as an adverse maternal outcome,[34,49] and 2 studies applied a composite primary outcome of a postpartum complication (defined as hemorrhage, endometritis, transfusion, maternal ICU admission, and/or hysterectomy)[39] and the need for manual or instrumented placenta extraction, chorioamnionitis, and endometritis.[40] In addition, 2 studies assessed the decrease in hemoglobin level as a primary outcome measure of the length of the TSL.[40,42,45]

Regarding the secondary outcomes, timing of MROP and risk of adverse maternal outcome, 2 studies defined adverse maternal outcome as the risk of PPH.[37,44] Moreover, 1 study addressed adverse maternal outcome as a hemodynamic compromise, defined as blood loss of ≥1000 mL and/or hemodynamic instability (inability to maintain blood pressure or pulse secondary to acute blood loss) and/or a decrease in hematocrit level ≥10 percentage points.[36] The TSL was "actively managed" in 16 of 18 studies.

FIGURE 1
Flowchart showing selection of studies included in the systematic review



WHO, World Health Organization.

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Synthesis of results

Primary outcome: adverse maternal outcome

Risk of postpartum hemorrhage. Overall, 9 studies evaluated the association between the length of the TSL and the risk of PPH.[32,33,35,37,38,42,43,47,48] In total, 3 of 9 studies evaluated different lengths of TSL.[37,43,48]

Of note, 4 studies evaluated the risk of PPH in women with a TSL of ≥15 minutes compared with those having a TSL of <15 minutes.[33,35,43,47,48] The results are summarized in Figure 2 for women with a mixed risk profile. Overall, a TSL of ≥15 minutes was associated with a 5-fold increase in the risk of PPH (OR, 5.55; 95% CI, 1.74–17.72; 95% PI,

TABLE
Characteristics and outcome measures of studies included in systematic review

Author, y	Study design	Study population	Healthcare setting	Outcome measure	Outcome according to high or low risk of PPH[a]	Included in the meta-analysis
Primary outcome						
Bais et al,[38] 2004	Population based cohort study	Nulliparous women who delivered vaginally at a GA of >20 wk (N=3464)[a]	Multicenter, high-resource setting	Incidence of PPH (blood loss of ≥500 mL[b]) Incidence of severe PPH (blood loss of ≥1000 mL)	Yes, analysis of findings both for women at low risk of PPH and for women at high risk of PPH High risk of PPH: labor induction/augmentation, macrosomia, prolonged second stage of labor, advanced maternal age, multiple pregnancy, instrumental vaginal delivery, episiotomy, or second-degree perineal tear or greater	Yes
Behrens et al,[39] 2019	Retrospective cohort study	Singleton second-trimester (13–26 wk) vaginal births (N=215)	Single-center, high-resource setting	Incidence of postpartum complication[c]	No	No, included for narrative review[d]
Chikkamath et al,[49] 2021	Retrospective cohort study. Secondary analysis of World Health Organization Carbetocin HAeMorrhage PreventION trial, RCT	Vaginal births with a TSL of ≤60 min of singleton pregnancies and without interventions.[e] Women with episiotomy or perineal tear requiring suturing were excluded (N=10,040)	Multicenter study, 10 countries in low-, middle-, and high-income settings	Quantity of blood loss (mL) per patient	No	No, included for narrative review[b]
Childress et al,[40] 2014	Retrospective chart review	Women who delivered between 16 and 27 wk of gestation (N=121)	Multicenter, high-resource setting	Drop in hemoglobin level Incidence of blood transfusion Incidence of composite endpoint (need for manual or instrumental placenta extraction, chorioamnionitis, and endometritis)	No	Yes
Edwards et al,[41] 2019	Retrospective cohort study	All vaginal births from 22 to 43 wk of gestation (N=43,357)	Multicenter study, high-resource setting	Incidence of PPH (EBL of ≥500, ≥1000, ≥1500, or ≥2000 mL)	No	No, included for narrative review[c]
Franke et al,[42] 2021	Retrospective cohort study	Women with retained placenta after vaginal birth ≥30 wk of gestation (N=296)	Single-center study, high-resource setting	Incidence of PPH (≥500 mL) Incidence of blood transfusion	No	Yes

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(continued)

TABLE
Characteristics and outcome measures of studies included in systematic review *(continued)*

Author, y	Study design	Study population	Healthcare setting	Outcome measure	Outcome according to high or low risk of PPH[a]	Included in the meta-analysis
Frolova et al,[43] 2016	Secondary analysis of a retrospective prospective study	Vaginal singleton births at ≥37 wk of gestation (N=7121)	Single-center study, high-resource setting	Incidence PPH (≥500 mL) Incidence blood transfusion	Yes, adjusted for induction of labor, prolonged first stage of labor, or prolonged second stage of labor	Yes
Abdo et al,[48] 2018	Cross-sectional study	Singleton vaginal births at >28 wk of gestation, spontaneous vaginal birth, no history of PPH and parity of <4 (N=600)	Single-center study, middle-income setting (Egypt)	Incidence PPH (≥500 mL)	Yes, women at high risk of PPH were excluded from analysis (multiparity, placenta previa, placental abruption, multiple pregnancy, polyhydramnios, fetal macrosomia, previous uterine scar, PPH history, PPH due to genital tract trauma, or coagulation disorders)	Yes
Jangsten et al,[45] 2011	RCT	Singleton pregnancies at 34−43 wk of gestation, vaginal births, without previous PPH (N=1631)	Single-center, high-resource setting	Incidence of PPH (blood loss of ≥1000 mL)	Yes, women at high risk of PPH were excluded from analysis (grand multiparity, preeclampsia, previous PPH, or intrauterine death)	No, included for narrative review[f]
Magann et al,[32] 2005	Prospective observational study	Vaginal births at >20 wk of gestation (N=6588)	Single-center study, high-resource setting	Incidence of PPH (blood loss of ≥1000 mL)	No	Yes
Magann et al,[35] 2008	Secondary analysis of a prospective randomized investigation	Singleton pregnancy, vaginal birth (N=1607)	Single-center study, high-resource setting	Incidence of PPH (blood loss of ≥1000 mL, decrease in hematocrit level by 10 points or the need for a red blood cell transfusion)	Partly, women at high risk of PPH were excluded from analysis (overdistended uterus or previous PPH)	Yes
Rabie et al,[33] 2018	Prospective observational study	Singleton vaginal birth at ≥24 wk of gestation (N=600)	Single-center study, high-resource setting	Incidence of PPH of ≥500 mL	No	Yes
Shinar et al,[46] 2016	Observational retrospective case-control study	Vaginal births with spontaneous and complete placenta separation shorter than 60 min (N=25,160)	Single-center study, high-resource setting	Incidence of blood transfusion	No	Yes

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

TABLE
Characteristics and outcome measures of studies included in systematic review *(continued)*

Author, y	Study design	Study population	Healthcare setting	Outcome measure	Outcome according to high or low risk of PPH[a]	Included in the meta-analysis
Ushida et al,[47] 2022	Retrospective cohort study	Singleton vaginal births at 27–41 wk of gestation (N=31,758)	Multicenter, high-resource setting	Incidence of PPH (≥1000 mL within 2 h after delivery)	Yes, women at high risk of PPH were excluded from analysis (multiple pregnancies, scarred uterus, low-lying placenta, or third- or fourth-degree perineal laceration placental abruption). The findings were adjusted for obesity, hypertensive disorder, labor induction or augmentation, instrumental delivery, macrosomia, and duration of second stage of labor	Yes
van Ast et al,[37] 2019	Retrospective cohort study	Singleton vaginal births at ≥32 wk of gestation, excluded women with immediate PPH within 1 h after delivery who needed MROP (N=7603)	Single-center, high-resource setting	Incidence of PPH (blood loss of ≥1000 mL)	Yes, women with high risk of PPH were excluded (history of PPH, GA under 32 wk, multiple births, history of MROP, women with immediate excessive blood loss after birth). The findings were adjusted for duration of second stage of labor, episiotomy, laceration, birthweight, ethnicity, GA, nulliparitys, and previous miscarriages	Yes
Whittington et al,[34] 2020	Retrospective case-control study	Twin pregnancy, vaginal births + normal singleton vaginal births. n=132 singleton pregnancies n=133 twin pregnancies	Single-center, high-resource setting	Estimated blood loss	No	No, included for narrative review[g]
Secondary outcome						
Fujita et al,[44] 2021	Retrospective cohort study	Singleton vaginal births at ≥22 wk of gestation MROP (n=112)[a] Non-MROP (n=36,342)	Multicenter, high-resource setting	Incidence of PPH (≥1000 mL within 2 h after delivery)	No	No, included for narrative review[e]

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

TABLE
Characteristics and outcome measures of studies included in systematic review *(continued)*

Author, y	Study design	Study population	Healthcare setting	Outcome measure	Outcome according to high or low risk of PPH[a]	Included in the meta-analysis
Magann et al,[36] 2012	RCT	Singleton pregnancies, vaginal birth. n=156 10-min group n=156 15-min group	Single-center, high-resource setting	Incidence of hemodynamic compromise: blood loss of >1000 mL and/or circulatory instability and/or decrease in the hematocrit level of ≥10 percentage points	No	No, included for narrative review[h]
van Ast et al,[37] 2019	Retrospective cohort study	Singleton vaginal births of ≥32 wk of gestation, excluded women with immediate PPH within 1 h after delivery who needed MROP (N=7603)	Single-center, high-resource setting	Incidence of PPH (blood loss of ≥1000 mL)	Yes, women with high risk of PPH were excluded (history of PPH, GA <32 wk, multiple births, history of MROP, and women with immediate excessive blood loss after birth). The findings were adjusted for length of the second stage of labor, episiotomy, laceration, birthweight, ethnicity, GA, nulliparous, and previous miscarriages	No, included for narrative review[i]

GA, gestational age; *MROP*, manual removal of the placenta; *OR*, odds ratio; *PPH*, postpartum hemorrhage; *RCT*, randomized controlled trial; *TSL*, third stage of labor.

[a] Risk factors for PPH: previous PPH, primiparity, obesity, prolonged or augmented labor, multiple pregnancy, previous cesarean delivery, polyhydramnios, and macrosomia; [b] Could not be included for meta-analysis because no absolute number of patients with PPH for different categories of the length of the TSL were given and could not be calculated; [c] Could not be included for meta-analysis because of the fact that no absolute number or was given or could be calculated for the different cutoff values of the TSL; [d] Could not be included for meta-analysis because of the outcome measure of this study, which was a composite of postpartum complication, applied only in 1 study; [e] Could not be included for meta-analysis because the outcome measure of this study, which was the incidence of PPH without applying a cutoff of the TSL, applied only in 1 study; [f] Could not be included for meta-analysis because of the fact that no absolute number or ORs were given or could be calculated for the different cutoff values of the TSL; [g] Could not be included for meta-analysis because only quantile regression estimates were given without absolute numbers or ORs for the incidence of PPH; [h] Could not be included for meta-analysis because the outcome measure of this study, which was a composite of the incidence of hemodynamic compromise, was applied only in this study; [i] Could not be included for meta-analysis because the outcome measure of this study, which was the incidence of PPH at a TSL cutoff of 60 minutes, was applied only in this study.

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0.02−12.98), whereas the OR among women with a low risk profile for PPH was 2.20 (95% CI, 0.75−6.49) (Figure 3). Subgroup analyses showed the highest pooled OR for PPH defined as ≥1000 mL of blood loss (OR, 4.50; 95% CI, 3.46−5.86; I^2=0.0%) (Figure 4).

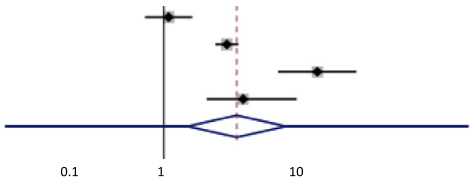
Of note, 6 studies evaluated the risk of PPH in women with a TSL of ≥30 minutes compared with those with a TSL of <30 minutes.[32,37,38,43,48] The results for women with a mixed risk profile are summarized in Figure 5, and the results for women with a low risk profile are summarized in Figure 6. Overall, a TSL of >30 minutes was associated with an almost 3 fold increase in the risk of PPH (OR, 3.12; 95% CI, 1.83−5.30; 95% PI, 0.50−19.46) among women with a mixed risk profile. Among women with a low risk profile of PPH, the OR was 3.28 (95% CI, 2.45−4.40) (Figure 6). Subgroup analysis showed the highest pooled OR for PPH defined as ≥1000 mL of blood loss (OR, 4.47; 95% CI, 2.72−57.35; I^2=80.1%; P=.007) (Figure 7).

The risk of PPH in case of a TSL of ≥60 minutes compared with a TSL of <60 minutes among women with a mixed risk profile for PPH are presented in Figure 8. Overall, a TSL of ≥60 minutes was associated with a nearly 4-fold increase in the risk of PPH compared with a TSL of <60 minutes (514/7297 vs 218/316; OR, 3.72; 95% CI, 2.36−5.89) (Figure 8). Only the study by van Ast et al[37] provided an additional OR for the risk of PPH in a low-risk population (OR, 4.3; 95% CI, 2.5−7.3).

Of note, 2 studies assessing the risk of PPH according to the length of the TSL could not be included in the meta-analysis.[41,45] Edwards et al[41] found that the length of the TSL was a statistically significant but weak predictor of the quantity of postpartum blood loss (β=0.004; P<.005), equivalent to a predicted increase in blood loss of 10.7% for every 10 minutes. Jangsten et al[45] found that the likelihood of PPH increased with each 5-minute increase in the TSL, with an OR of 1.18 (95% CI, 1.13−1.23; P<.001), without detailing the exact cutoff values of the length of the TSL,

FIGURE 2
PPH in mixed risk profile women for TSL 15 minutes

	< 15 min		≥ 15 min					
Study	**PPH**	**Total**	**PPH**	**Total**	**Log (odds ratio)**	**SE**	**Weight**	**Odds ratio IV, random, 95% CI**
Frolova et al. 2016	575	6816	14	150	0.11	0.28	26.2%	1.12 (0.64,1.95)
Ushida et al. 2021[1]	935	31232	63	526	1.48	0.14	27.4%	4.41 (3.36,5.78)
Rabie et al. 2018	21	576	14	24	3.61	0.47	23.7%	37.00 (14.7,92.9)
Magann et al. 2008[2]	Na	Na	Na	Na	-	-	22.6%	6.45 (2.73,22.84)
Total events	**1531**	**38624**	**91**	**700**				
Total (95% CI)							**100%**	**5.55 (1.74,17.72)**
95% prediction interval								**(0.02,1298)**



Heterogeneity: tau =0.4 Cochran's Q =43.65 df=3, I^2 = 93.1%, P < 0.001
Test for overall effect: Z=2.896; P=0.004
Egger test: β-1= -22.41, SE = 30.76, P= 0.49

[1] in the original manuscript, odds ratios were calculated according to parity. We calculated odds ratio's independently of parity, as in the other cited papers odds ratios are not calculated or available according to parity.
[2] Absolute number of events was not given and could not be calculated based on the available data.
PPH = postpartum hemorrhage, Na = not available, CI = confidence interval, SE = standard error

CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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which meant that these findings could not be included in the meta-analysis.

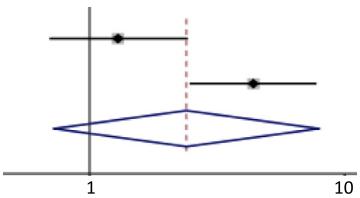
Quantity of blood loss. Two studies assessed the length of the TSL and total blood loss. Chikkamath et al[49] included in their study 10,040 women who gave birth vaginally and suggested that there is a positive correlation between the quantity of blood loss and the length of the TSL, describing a strong association curve until 20 minutes after birth of the newborn. However, they did not identify any "critical" length of the TSL, as the median blood loss did not exceed 350 mL in any of the women. Moreover, 1 study among women with twin pregnancies found that blood loss increased by 149.02 mL (95% CI, 100.2−197.8), 257.01 mL (95% CI, 117.9−396.0), and 381.53 mL (95% CI, 201.1−562.1) in the 50th, 90th, and 95th percentiles, which account for the TSL of 7, 14, and 23 minutes respectively.[34]

Risk of blood transfusion. Of note, 3 studies addressed the risk of blood transfusion (≥1 unit of packet cells) in the case of a TSL of ≥30 minutes, and their results are summarized in Figure 9.[40,43,46] The baseline risks of PPH were 4.11% in the group with a TSL of ≥30 minutes and 2.74% in the group with a TSL of <30 minutes. Overall, a TSL of >30 minutes was associated with an OR of 3.23 (95% CI, 2.26−4.92; 95% PI, 0.32−32.45) (Figure 9). No subanalysis could be performed for women at low risk of PPH because the risk of PPH was only calculated in women with a mixed risk profile. Contrastingly, Franke et al[42] found that, among women with retained placenta, the incidence of red blood cell transfusion was significantly lower in the group with a TSL of ≥60 minutes (4/203 [1.9%]) than in the group with a TSL of <60 minutes (9/93 [9.8%]) (P=.006).

Postpartum complication and drop in hemoglobin. Behrens et al[39] defined postpartum complication as a composite of endometritis, PPH (blood loss of ≥500 mL or a decline in hemoglobin level of ≥2 mg/dL), transfusion, ICU admission, and/or hysterectomy. They found that the risk of postpartum

FIGURE 3
PPH in low risk women for TSL 15 minutes

Study	**Log (odds ratio)**	**SE**	**Weight**	**Odds ratio IV, random, 95% CI**
Frolova et al. 2016	0.23	0.28	49.4%	1.26 (0.72,2.23)
Ushida et al. 2021[1]	1.60	0.19	50.6%	3.80 (2.26,6.36)
Total (95% CI)			**100%**	**2.20 (0.75,6.49)**



Heterogeneity: Cochran's Q =7.97; df=1, I^2 = 87.5%, P = 0.005
Test for overall effect: Z=4.272; P=<0.001

[1] in the original manuscript, odds ratios were calculated according to parity. We calculated odds ratio's independently of parity, as in the other cited papers odds ratios are not calculated or available according to parity.
PPH = postpartum hemorrhage, CI = confidence interval, SE = standard error

CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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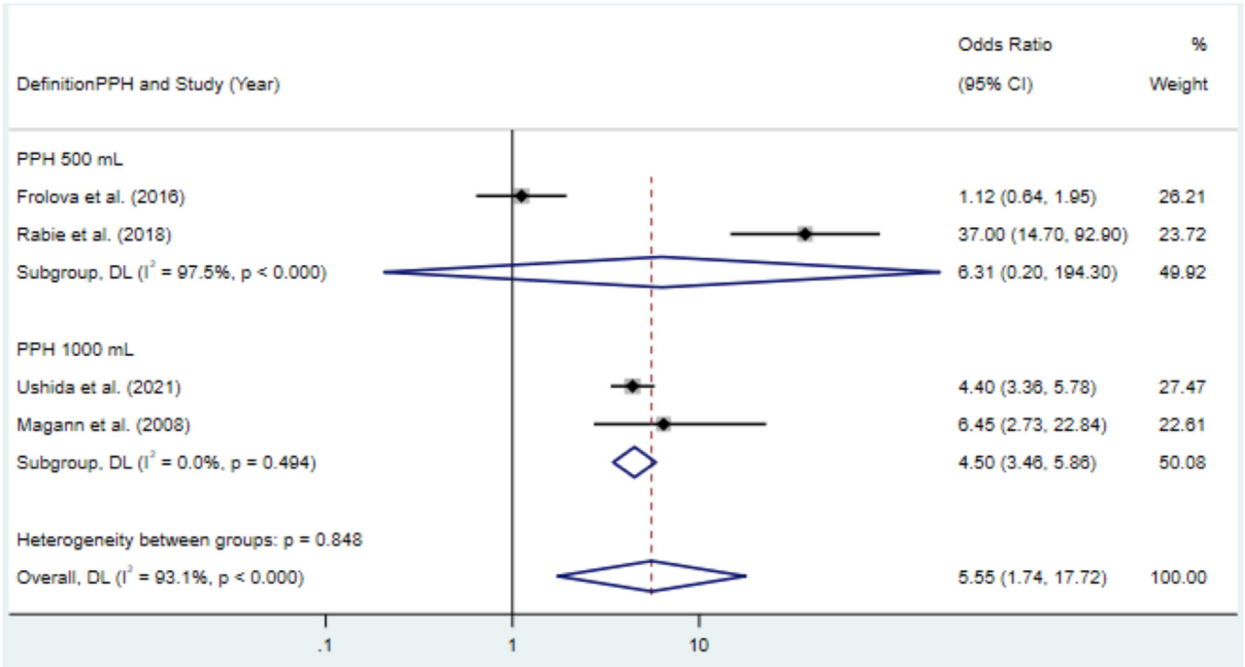
FIGURE 4
PPH in mixed risk profile women for TSL 15 minutes, by PPH definition



CI, confidence interval; *PPH*, postpartum hemorrhage; *TSL*, third stage of labor.

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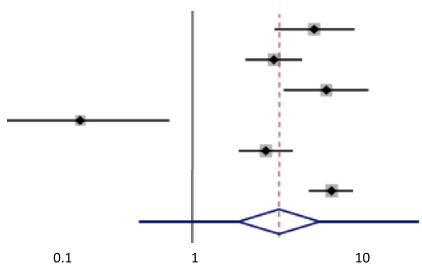
complication was almost twice as high (OR, 1.79; 95% CI, 1.16−2.77; *P*=.0091) per hour of having an unborn placenta. Childress et al[40] found a statistically significant increased risk of composite outcome in women with a TSL of >30 minutes compared with women with a TSL of <30 minutes (38/53 vs 16/67, respectively; OR, 8.07; 95% CI, 3.55−18.33). In addition, the authors reported a statistically significantly greater drop in hemoglobin levels among women with second-trimester births and a TSL of ≥30 minutes than among women with a TSL of <30 minutes (−1.6 vs −0.8 g/dL, respectively). However, Franke et al[42] did not report a correlation between a drop in

FIGURE 5
PPH in mixed risk profile women for TSL 30 minutes

	< 30 min		≥ 30 min					
Study	**PPH**	**Total**	**PPH**	**Total**	**Log (Odds ratio)**	**SE**	**Weight**	**Odds ratio IV, random, 95% CI**
Bais et al. 2004[1]	563	3247	100	217	1.59	0.27	17.0%	4.9 (2.92-8.32)
Van Ast et al. 2019	346	6735	100	582	1.06	0.19	18.5%	2.9 (2.00-4.20)
Frolova et al. 2016	606	7064	20	57	1.75	0.29	16.6%	5.8 (3.20,10.00)
Helmy et al. 2018	34	581	4	19	-1.47	0.60	10.2%	0.2 (0.07,0.74)
Bais et al. 2004[2]	91	3247	54	217	0.96	0.19	18.6%	2.6 (1.83,3.72)
Total events[3]	**1640**	**20874**	**278**	**1092**				
Magann et al. 2005[4]	1.82	Na	Na	Na	-	-	19.2%	6.2 (4.60-8.20)
Total (95% CI)							**100%**	**3.12 (1.83,5.30)**
95% prediction interval								**(0.50,19.46)**



Heterogeneity tau=0.4, Cochran's Q =42.01 df=5 (*P*<0.001), I² = 88.1%, *P*<0.001
Test for overall effect: Z=15.805 *P*= <0.001
Egger test: β-1=13.58, SE 90.7, Z=0.15, *P* =0.88
[1] Odds ratio calculated for PPH = 1000mL, [2] odds ratio calculated for PPH=500mL
[3] For the total number of women in each group, the study of Bais et al. was taken into account only once to prevent double inclusions
[4] Absolute number of events was not given and could not be calculated based on the available data.
PPH = postpartum hemorrhage, CI = confidence interval, SE = standard error

CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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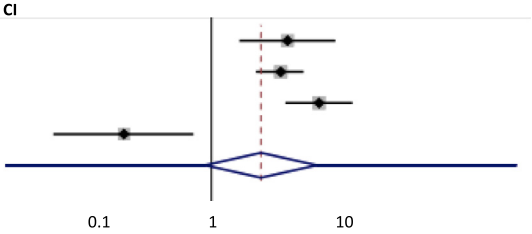
FIGURE 6
PPH in low risk women for TSL 30 minutes

Study	Log (Odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
Bais et al. 2004	1.07	0.37	24.5%	3.59 (1.60-8.03)
Van Ast et al. 2019	1.16	0.20	28.3%	3.2 (2.11-4.70)
Frolova et al. 2016	1.81	0.29	26.9%	6.1 (3.46-10.70)
Helmy et al. 2018	-1.47	0.60	20.3%	0.23 (0.07,0.74)
Total (95% CI)			**100%**	**3.28 (2.45,4.40)**
95% prediction interval				**(0.03 168.12)**

Heterogeneity tau=0.4, Cochran's Q =7.55 df=3(*P*<0.056), I^2 = 87.6%, *P<0.001*

Test of overall effect: z=15.517 p<0.001

PPH = postpartum hemorrhage, CI = confidence interval, SE = standard error



CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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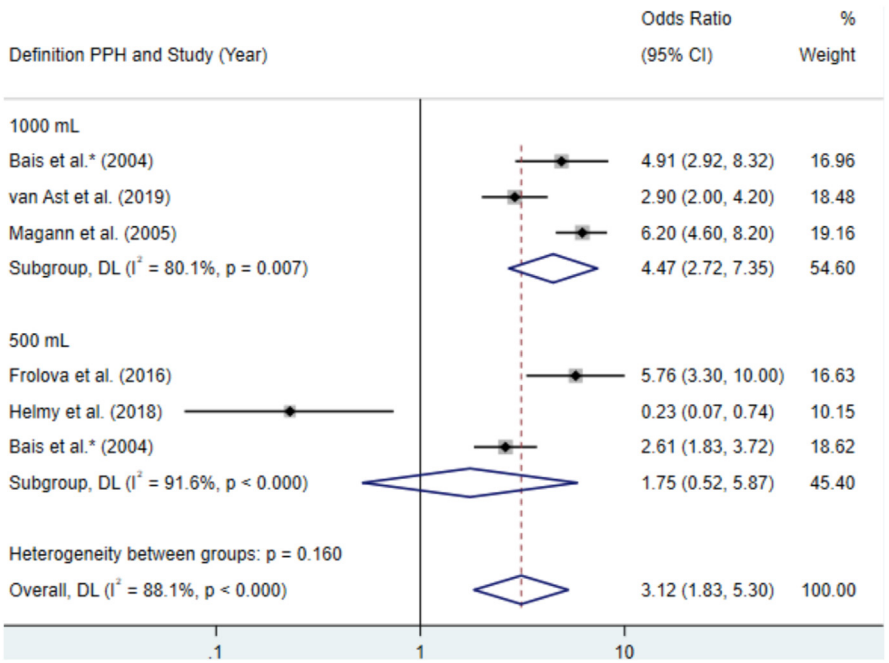
hemoglobin level and the length of the TSL (r=−0.04; P=.497).

Secondary outcome: timing of manual removal of retained placenta in the absence of bleeding and risk of adverse maternal outcome

Only 1 study was originally designed to assess the risk of maternal outcome concerning different timings of MROP, reporting a significantly higher incidence of hemodynamic compromise in women who underwent placental removal after 15 minutes (30/156 [19.2%]) than in women who underwent placental removal at 10 minutes (10/156 [6.4%]) (P<.001), accounting for a relative risk of 3.03 (95% CI, 1.52−5.47).[36] Fujita et al[44] assessed the risk of PPH among women who had MROP vs women who had spontaneous expulsion of the placenta and found an increased incidence of PPH among women with MROP (46/113 [41.1%]) vs women with spontaneous birth (1505/36,342 [4.1%]). Van Ast et al[37] assessed the risk of PPH in women with a TSL of >60 minutes having a spontaneous expulsion of placenta vs women with an MROP, both in the absence of bleeding. They found an increased OR of 9.5 (201/286 vs 24/113; 95% CI, 5.3−17.2) for the risk of PPH among women who had MROP compared with women with spontaneous expulsion of the placenta.

FIGURE 7
PPH in mixed risk profile women for TSL 30 minutes, by PPH definition



CI, confidence interval; *PPH*, postpartum hemorrhage; *TSL*, third stage of labor.

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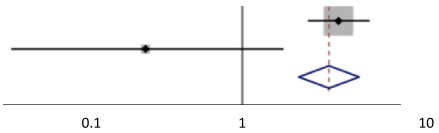
Comment

Principal findings

In this systematic review and meta-analysis, we aimed to investigate the association between the length of the TSL after vaginal birth and adverse maternal outcome. Furthermore, we assessed whether earlier MROP in the absence of bleeding reduces the risk of adverse maternal outcome. Our study revealed a low baseline risk of PPH in case of a TSL of <15 minutes, with an increased risk of PPH once the length of the TSL exceeds 15 minutes. The risk of PPH was higher in women with risk factors for PPH than in those with a low baseline risk of PPH. Other indicators of adverse maternal outcome, such as the risk of red blood cell transfusion, seemed to be more prevalent, particularly when the TSL exceeded 30 minutes. We did not find sufficient data to formulate any

FIGURE 8
PPH in mixed risk profile women for TSL 60 minutes

Study	< 60 min		≥ 60 min		Log(Odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
	PPH	Total	PPH	Total				
Van Ast et al. 2019	422	7204	24	113	1.46	0.24	95.1%	4.30 (2.70,6.90))
Franke et al. 2021	92	93	194	203	-1.46	1.06	4.9%	0.23 (0.03,1.87)
Total (95% CI)							**100%**	**3.72 (2.36,5.89)**
Total events	**514**	**7297**	**218**	**316**				



Heterogeneity: Cochran's Q =7.34 df=1; *P*<0.995; I2 = 86.4%, p=0.007
Test for overall effect: Z=5.63 p=<0.001
Egger test: β-1=-0.75, SE 1.033, Z=-0.73, *P* =0.467
PPH = postpartum hemorrhage, CI = confidence interval, SE = standard error

CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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conclusions regarding whether earlier MROP reduces the risk of adverse maternal outcome compared with current recommendations. Secondary considerations, such as the trade-off of earlier MROP, concerning patient satisfaction and financial costs were not assessed in the reviewed studies and were not included in the supplemental search strategy.

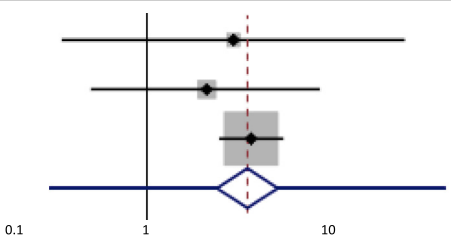
Comparison with existing literature

Currently, there is no consensus definition of "prolonged TSL" or "retained placenta." Most guidelines now use a cutoff of 30 minutes, based on previous findings showing an increased risk of PPH and blood transfusion after this threshold.[18,50,51] However, some countries have clinical guidelines permitting a waiting time of 60 minutes before proceeding to MROP in the absence of bleeding. Although these differences could be explained by different interpretations of the available data in terms of the risk of adverse maternal outcome, they may also relate to variations in obstetrical culture and organizational structures as suggested by Deneux-Tharaux et al.[17] Therefore, although the studies included in this meta-analysis may prompt clinicians to shorten the length of the TSL to 15 minutes, the applicability of these findings may depend on the healthcare setting. In addition, the reported associations in terms of the length of the TSL and risk of adverse outcome do not imply causality, and there is no evidence that reducing the length of the third stage by manually removing placentas that have not been spontaneously expelled lowers the risk of PPH.

In this systematic review, we did not find any study that compared MROP at 15 minutes with MROP at 30 minutes of TSL (in the absence of bleeding). However, 1 RCT reported that hemodynamic compromise decreased with MROP at 10 minutes compared with MROP at 15 minutes, which was mainly due to an increased rate of circulatory instability defined as the (inability to maintain blood pressure or pulse secondary to acute blood loss).[36] Although this finding could reflect increased blood loss in the 15-minute group, the incidence of PPH (defined as ≥1000 mL) was low and similar in both groups (1.3% in the 10-minute group vs 1.9% in the 15-minute group). Data on the median amount of blood loss between the 2 groups could have helped to better interpret these data. The results of this study are in contrast to the findings of van Ast et al,[37] which suggest that the incidence of PPH was eventually higher among women who had MROP than among those who had spontaneous placenta birth. Similar findings exist for women giving birth via cesarean delivery, as the risk of PPH among these

FIGURE 9
Red blood cell transfusion in mixed risk profile women for TSL 30 minutes

Study	< 30 min		≥ 30 min		Log (Odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
	Transfusion	Total	Transfusion	Total				
Frolova et al. 2016	60	7121	1	44	1.01	1.02	3.2	2.74 (0.37-20.24)
Childress et al. 2014	4	67	6	53	0.70	0.68	7.10	2.01 (0.52,7.52)
Shinar et al. 2016[1]	Na	Na	Na	Na	-	-	89.7	3.37 (2.32,4.92)
Total events	**64**	**7288**	**7**	**97**				
Total (95% CI)							**100%**	**3.23 (2.26,4.61)**
95% prediction interval								**(0.32,32.45)**



Heterogeneity: Cochran's Q =0.56 df=2; *P=0.756*; I2 = 0.0%
Test for overall effect: Z=6.450 p=<0.001
Egger test: β-1=-0.75, SE 1.033, Z=-0.73, *P* =0.467
[1] No absolute number of women was given according to the duration of the third stage. The baseline-risk for transfusion in the group of ≥ 30 minutes was 4.11% of women with third stage ≥ 30 min versus 2,74% in the group with a third stage < 30 minutes.
PPH = postpartum hemorrhage, Na = not available, CI = confidence interval, SE = standard error

CI, confidence interval; *PPH*, postpartum hemorrhage; *SE*, standard error; *TSL*, third stage of labor.

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women seems to be higher in cases of MROP than in cases of spontaneous expulsion of the placenta guided by controlled cord traction.

It has been suggested that the risk of PPH in the case of retained placenta is due to an underlying insufficient myometrial contractility, and a hereditary component has been described.[7,52] Resorting to MROP sooner may not influence this insufficient myometrial contractility, and therefore, it is not clear whether it would significantly reduce the risk of PPH or other indicators of adverse maternal outcome. In addition, secondary considerations of earlier MROP, which were not investigated in the reviewed studies, are the consequences of earlier intervention in terms of complications of the intervention itself, such as the risk of endometritis or the risk of uterine atony. In addition, complications may be related to the type of anesthesia necessary for the intervention.[53–55] Depending on the organization of the healthcare structure, women may need to be transferred to the operating theater for MROP. It is unclear what this means in terms of cost-effectiveness. Moreover, this also means that the mother will be separated from her child within the first hour after birth. In addition, earlier MROP may have consequences for continuity of care, resulting in reduced patient satisfaction and increased healthcare cost because of the transfer of patients from a birth center to a hospital.

Although some countries still apply a 60-minute cutoff for the TSL, only 2 studies assessed the risk of PPH at this stage. Some researchers have hypothesized that waiting 60 minutes may result in unnecessary delay and increased blood loss, whereas other researchers have suggested expectant management with close monitoring.[7,42] Several studies have shown that 80% to 95% of all placentas are expelled spontaneously within 15 minutes after birth. Studies assessing the need for MROP among women with retained placenta have consistently been reporting that delay in MROP (in the absence of bleeding) allowed for an additional 1% of placentas to be expelled spontaneously. These findings have to be balanced against the increased risk of bleeding but may justify a more expectant management in low-risk women in settings with easy access to operating rooms and blood products.[33,37,56,57]

Prospective studies have confirmed that there may be an increased risk of retained placenta in pregnant women with a gestational age of <26 weeks because of impaired placentation. However, it is not clear to what extent these women are at increased risk of PPH. Some researchers have stated that the risk of PPH may be higher in women who have a preterm birth, whereas other researchers did not find such an association.[22,58–60] These inconsistent findings may be related not only to geographic differences but also to confounding factors related to preterm birth, such as chorioamnionitis, preterm cesarean delivery, and increased use of uterotonics. In our meta-analysis, we were not able to stratify data according to term birth vs preterm birth, as most studies did not provide any detailed data on adverse maternal outcome according to gestational age. However, the studies in this systematic review that did investigate the risk of PPH according to preterm birth vs term birth did not reveal an increased risk of PPH.[33,40,48]

Strengths and limitations

This study has several strengths. (1) This systematic review and meta-analysis investigated the association between the length of the TSL and adverse maternal outcome after vaginal birth. An earlier narrative review included only 6 studies, 2 of which concerned data collected before the general introduction of the active TSL, which we did not include. (2) A rigorous methodology was used, and the risk of bias assessment was based on the COSMOS-E tool. (3) The study investigated the sources of heterogeneity through subanalyses and the calculation of 95% PIs. (4) The study separated the research question into 2 parts to avoid the assumption of causality between the length of the TSL and adverse outcome. (5) This study applied a narrative synthesis approach to the results of studies that could not be included in the meta-analysis. In addition, our study has some limitations. (1) A limited number of studies could be included in the meta-analysis because of the variable definitions of adverse maternal outcome. (2) There was substantial between-trial heterogeneity (I^2>80%), which was confirmed by the large 95% PIs showing a wide distribution of effects for future trials. This highlights the need to be very cautious when making our conclusions.[61] We explored the heterogeneity through 2 subgroup analyses. However, this did not explain the reported heterogeneity. Given the lack of data, we were unable to perform more subanalyses, such as gestational age, to explore the reported heterogeneity. (3) The heterogeneity reported in this study may reflect the variability in the study design, study population, methods to quantify blood loss, variations in the definitions of adverse maternal outcome, and differences in local obstetrical practices. (4) One may argue that MROP should have been included as an adverse outcome, given the described complications related to the intervention and the applied anesthetic technique. We hypothesized that MROP as an indicator of adverse maternal outcome in the primary objective of this study would have been difficult to interpret as MROP can also be performed because of bleeding and, in the absence of bleeding, depends on local practice, resources, and the obstetrician's preference. Therefore, we chose to assess it as an intervention in the secondary objective. (5) The risk of bias was high in 55% of the studies. However, we chose not to exclude these studies to allow us to calculate a more accurate estimate of the risk of adverse outcome. In addition, publication bias may have been introduced by the applied language filter in our search strategy, excluding publications not written in English, French, German, Italian, or Dutch. Although we tried to assess publication bias by performing the Egger test, the power of this type of tests and other tools, such as the use of funnel plots, was limited, given that our meta-analysis included <10 studies. Therefore, we should acknowledge that, despite the Egger test not showing any publication

bias in our analyses, publication bias cannot be excluded.[62,63]

Conclusions and implications

Our data include several important considerations. First, although most reviewed cohort studies suggest that a TSL of ≥15 minutes may be considered as prolonged, particularly among women with risk factors for PPH, strong evidence to recommend early MROP at this stage to reduce the risk of adverse maternal outcome is currently lacking. More prospective trials are needed to determine the association between the length of the TSL and adverse maternal outcome, preferably addressing the length of the TSL from 0 to 30 minutes after birth. Subsequently, RCTs are needed to assess the effect of earlier MROP on adverse maternal outcome. Ideally, patient satisfaction should be taken into account, and cost-effective analyses should be performed. Second, the benefits and risks of MROP should be carefully balanced, as it remains an inconvenient intervention for women, which has itself been associated with endometritis and lesions of the genital tract.[20,64] Third, very few studies have assessed the increased length of the TSL in terms of clinical sequelae, such as admission to the ICU, organ failure, and peripartum hysterectomy. It may be useful to address these elements in future research because they can be considered as indicators of the severity of hemorrhage-related maternity care.[65]

After vaginal birth, the baseline risk of PPH is the lowest among women who have a TSL of <15 minutes. Above this cutoff, we report a 5-fold increase in the risk of PPH, particularly among women at risk of PPH. Although these findings stress the need to increase vigilance for signs of bleeding among these women, there is currently no convincing evidence supporting an artificial reduction in the TSL through earlier manual removal of the placenta to reduce the incidence of adverse maternal outcome. This highlights the need for RCTs to resolve this issue. Ideally, these should consider the drawbacks and risks associated with earlier intervention, such as overtreatment, infection, risks of anesthesia, lesions in the genital tract, and maternal satisfaction. ■

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Appendix

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Cochrane

(("Time to Treatment" OR "Time" OR time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*") AND (remov* OR resect*) AND

("Labor Stage 3" OR "third labor stage*" OR "third labour stage*" OR "3rd labor stage*" OR "3rd labour stage*" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta" OR "Placenta" OR placenta*) AND ("Postpartum Hemorrhage" OR "Bleeding" OR hemorrhag* OR haemorrhag* OR "blood loss*" OR "bloodloss*" OR bleeding* OR "maternal outcome*" OR "Maternal Mortality" OR "Maternal Death" OR "Maternal Death" OR "Maternal Welfare" OR "Maternal Mortal*" OR "Maternal Death*" OR "Maternal Health" OR "Maternal Welfare" OR "Blood Transfusion" OR transfus* OR bloodtransfus* OR "hysterectomy" OR "hysterect*") AND ("risk" OR risk OR risks OR riskfactor* OR prevent*)):ti,ab,kw **OR** (("Time to Treatment" OR "Time" OR time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*"):ti,kw AND ("Labor Stage 3" OR "third labor stage*" OR "third labour stage*" OR "3rd labor stage*" OR "3rd labour stage*" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta" OR "Placenta" OR placenta*):ti AND ("Postpartum Hemorrhage" OR "Bleeding" OR hemorrhag* OR haemorrhag* OR "blood loss*" OR "bloodloss*" OR bleeding* OR "maternal outcome*" OR "Maternal Mortality" OR "Maternal Death" OR "Maternal Death" OR "Maternal Welfare" OR "Maternal Mortal*" OR "Maternal Death*" OR "Maternal Health" OR "Maternal Welfare" OR "Blood Transfusion" OR transfus* OR bloodtransfus* OR "hysterectomy" OR "hysterect*"):ti,kw) **OR** (("Time to Treatment" OR "Time" OR time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*"):ti AND ("Labor Stage 3" OR "third labor stage*" OR "third labour stage*" OR "3rd labor stage*" OR "3rd labour stage*" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta" OR "Placenta" OR placenta*):ti,ab,kw AND ("Postpartum Hemorrhage" OR "Bleeding" OR hemorrhag* OR haemorrhag* OR "blood loss*" OR "bloodloss*" OR bleeding* OR "maternal outcome*" OR "Maternal Mortality" OR "Maternal Death" OR "Maternal Death" OR "Maternal Welfare" OR "Maternal Mortal*" OR "Maternal Death*" OR "Maternal Health" OR "Maternal Welfare" OR "Blood Transfusion" OR transfus* OR bloodtransfus* OR "hysterectomy" OR "hysterect*"):ti AND ("risk" OR risk OR risks OR riskfactor* OR prevent*):ti,ab,kw)

WHO International Clinical Trials Registry Platform

(("Time to Treatment" OR "Time" OR time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*") AND ("Labor Stage 3" OR "third labor stage*" OR "third labour stage*" OR "3rd labor stage*" OR "3rd labour stage*" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta") AND ("Postpartum Hemorrhage" OR "Bleeding" OR hemorrhag* OR haemorrhag* OR "blood loss*" OR "bloodloss*" OR bleeding* OR "maternal outcome*" OR "Maternal Mortality" OR "Maternal Death" OR "Maternal Death" OR "Maternal Welfare" OR "Maternal Mortal*" OR "Maternal Death*" OR "Maternal Health" OR "Maternal Welfare" OR "Blood Transfusion" OR transfus* OR bloodtransfus* OR "hysterectomy" OR "hysterect*"))

ClinicalTrials.gov

Condition or disease

("Labor Stage 3" OR "third labor" OR "third labour" OR "3rd labor" OR "3rd labour" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta" OR "Placenta" OR placenta*)

Other terms

(time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*")

AND

Outcome measure

(Hemorrhage OR Bleeding OR hemorrhaging OR haemorrhage OR haemorrhaging OR "blood loss" OR bloodloss OR maternal OR Transfusion OR transfus* OR hysterectomy OR hysterect*)

Journals@Ovid Full Text

(("Labor Stage 3" OR "third labor" OR "third labour" OR "3rd labor" OR "3rd labour" OR "third stage of labor" OR "third stage of labour" OR "3rd stage of labor" OR "3rd stage of labour" OR "retained placenta" OR "Placenta" OR placenta*).ti AND (time OR timed OR timing OR early OR earlier OR late OR later OR delay* OR minute OR minutes OR hour OR hours OR hr OR hrs OR interval* OR "duration*").ti AND (Hemorrhage OR Bleeding OR hemorrhaging OR haemorrhage OR haemorrhaging OR "blood loss" OR bloodloss OR maternal OR Transfusion OR transfus* OR hysterectomy OR hysterect*).ti)

Appendix 2. Quality assessment included studies

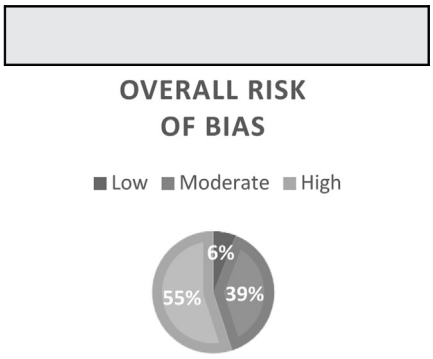
Risk of bias assessment:

- LOW: The study is judged to be at **low risk of bias for all domains**
- MODERATE: The study is judged to be at **low or moderate risk of bias for all domains**
- HIGH: The study is judged to be at **high risk of bias in at least one domain**

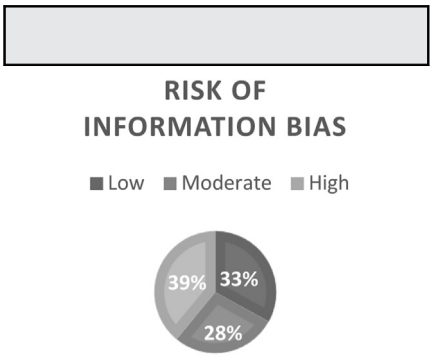
Domain of risk:

- o LOW: > 80% of questions is assessed as *Low*
- o HIGH: > 40% of questions is assessed as *High*

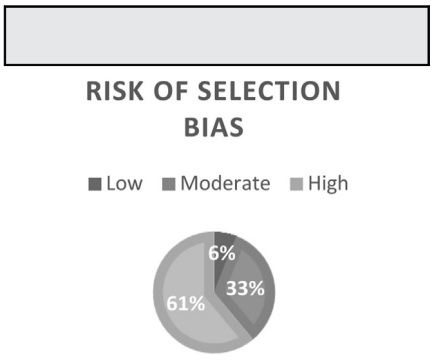
Conclusion



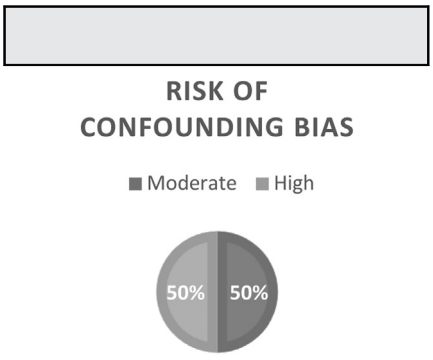
de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025.



de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025.



de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025.



de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025.

Cohort study : Bais et al. (2004)	
Selection bias	***Moderate***
Was the study period well defined?	January 1990 - July 1994 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Regional *(moderate)*
Were women included if third stage of labor was managed actively?	Oxytocin left at practitioners' discretion *(moderate)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	***Moderate***
How was information collected ?	Prospectively registered in a database *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visual estimate or measurement by weighing used swaps *(moderate)*
Overall risk of bias	***Moderate***
Cohort study : Behrens et al. (2019)	
Selection bias	**High**
Was the study period well defined?	Jan 2011-june 2015 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Oxyotocin left at practitioners discretion *(moderate)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**Moderate**
How was information collected ?	Data extraction from electronic medical records *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visual estimate or measurement by weighing used swaps *(moderate)*
Overall risk of bias	**High**
Cohort study: Chikkamath et al. (2021)	
Selection bias	**Low**
Was the study period well defined?	July 7 — Jan 2018 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Multinational *(low)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	*No (low)*
Information bias	**Low**
How was information collected ?	Electronic case report forms *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Weighing of blood drapes *(low)*
Overall risk of bias	**Low**
Cohort study: Childress et al. (2014)	
Selection bias	**High**
Was the study period well defined?	2000-2002 *(moderate)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Not described *(high)*

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

(continued)

Cohort study: Childress et al. (2014)	
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**High**
How was information collected ?	Not described *(high)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Not described *(high)*
Overall risk of bias	***High***
Cohort study: Edwards et al. (2019)	
Selection bias	**Moderate**
Was the study period well defined?	01.01.2009-31.12.2013 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Regional *(moderate)*
Were women included if third stage of labor was managed actively?	Yes *(Low)*
Were women included independently of the cause of hemorrhage?	Partly, corrected for retained placenta *(Moderate)*
Information bias	**Low**
How was information collected ?	All data were retrieved from a database in which midwives and gynecologists registered baseline *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Weighing pads, collector bags and collection during surgery. Combined weighing + collector bags were used in all hospitals. *(low)*
Overall risk of bias	**Moderate**
Cohort study : Franke et al. (2021)	
Selection bias	**Moderate**
Was the study period well defined?	Jan 2009 - Dec 2016 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Women were included in case of retained placenta *(moderate)*
Information bias	**Moderate**
How was information collected ?	Electronic database. Two experienced clinical researchers extracted all the relevant data. *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Weighing pads, collector bags *(low)*
Overall risk of bias	**Moderate**
Cohort study: Frolova et al. (2016)	
Selection bias	**High**
Was the study period well defined?	April 2010-august 2014 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

(continued)

Cohort study: Frolova et al. (2016)	
Information bias	**High**
How was information collected ?	Trained research nurses prospectively abstracted all detailed information. Not described from where these data were abstracted. *(moderate)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visual estimation *(high)*
Overall risk of bias	**High**
Cross sectional study : Helmy et al. 2018	
Selection bias	**High**
Was the study period well defined?	March 2014-december 2015 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**High**
How was information collected ?	Not described (high)
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Measuring in graded collection containers (low)
Overall risk of bias	**High**
Randomized controlled trial: Jangsten et al. (2011)	
Selection bias	**Moderate**
Was the study period well defined?	November 2006-april 2008 (low)
Did the cohort represent the births on hospital-, regional or national scale?	Regional *(moderate)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Corrected for retained placenta and episiotomy *(moderate)*
Information bias	**Low**
How was information collected ?	Data collection protocols were piloted and included both methodological instructions and management procedures for the third stage of labor, these were filled out by the midwifes. Additional information was derived from the individual medical records. *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Weighing of all sanitary towels and pads before and after use *(low)*
Overall risk of bias	**Moderate**
Study : Magann et al. 2005, prospective observational study	
Selection bias	**High**
Was the study period well defined?	1 July 2000- 30th June 2002 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

(continued)

Study : Magann et al. 2005, prospective observational study	
Information bias	**High**
How was information collected ?	Not described *(high)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Collection devices and weighing sheets and drapes *(low)*
Overall risk of bias	**High**
Cohort Study : Magann et al 2008.	
Selection bias	**High**
Was the study period well defined?	3-2004/3-2005 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	No *(high)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**High**
How was information collected ?	Computerized medical reports *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Not mentioned *(high)*
Overall risk of bias	**High**
Study : Rabie et al. 2018, prospective observational study	
Selection bias	**High**
Was the study period well defined?	1 July 2000-june 30 2002 (low)
Did the cohort represent the births on hospital-, regional or national scale?	Hospital (high)
Were women included if third stage of labor was managed actively?	Not mentioned (high)
Were women included independently of the cause of hemorrhage?	Yes (high)
Information bias	**Low**
How was information collected ?	Medical files
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Blood loss was calculated by measuring blood collected in the plastic collecting drape, placental basin, weighing sponges and laparotomy pads. Amniotic fluid was captured in a separate basin.
Overall risk of bias	**High**
Case control study : Shinar et al.	
Confounding	**Low**
Where outcomes adjusted for parity?	Yes (low)
Where outcomes adjusted for BMI?	Yes (low)
Where outcomes adjusted for macrosomia?	Yes (low)
Where outcomes adjusted for multiple gestation?	Yes (low)
Selection bias	**High**
Was the study period well defined?	11/2010-5/2014 (low)
Did the cohort represent the births on hospital-, regional or national scale?	Hospital (high)

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

(continued)

Case control study : Shinar et al.	
Were women included if third stage of labor was managed actively?	Yes (low)
Were women included independently of the cause of hemorrhage?	Yes (high)
Information bias	**Moderate**
How was information collected ?	Computerized medical reports (low)
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visual estimation Need for blood transfusion during hospitalization (Moderate)
Overall risk of bias	**High**
Cohort study: Ushida et al. (2021)	
Selection bias	**Moderate**
Was the study period well defined?	2012-2018 *(moderate)*
Did the cohort represent the births on hospital-, regional or national scale?	Regional *(moderate)*
Were women included if third stage of labor was managed actively?	Most, but not all *(moderate)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**Low**
How was information collected ?	Weighing drapes and gauzes at three time points by trained midwives *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Not mentioned *(low)*
Overall risk of bias	**Moderate**
Cohort study: Van Ast et al. (2019)	
Selection bias	**High**
Was the study period well defined?	Sept 24- 2011 / Sept 27-2016 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**Moderate**
How was information collected ?	Patient reports preserved in a digital obstetrical data-management system *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visually estimated or measured by weighing gauzes in case of extensive blood loss *(moderate)*
Overall risk of bias	**Moderate**
Case control study: Whittington et al. (2020)	
Confounding	**High**
Where outcomes adjusted for parity?	No (*high)*
Where outcomes adjusted for BMI?	No *(high)*
Where outcomes adjusted for macrosomia?	No *(high)*
Where outcomes adjusted for multiple gestation?	Yes *(low)*

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025. *(continued)*

(continued)

Case control study: Whittington et al. (2020)	
Selection bias	**High**
Was the study period well defined?	Jan 2013 to June 2017 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Not described *(high)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**High**
How was information collected ?	Not described *(high)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Marked collection drapes, estimation was confirmed by pre- and post-delivery hematocrit *(low)*
Overall risk of bias	**High**

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Cohort study: Fujita et al. (2021)	
Selection bias	**High**
Was the study period well defined?	2010-2018 (moderate)
Did the cohort represent the births on hospital-, regional or national scale?	Regional (moderate)
Were women included if third stage of labor was managed actively?	No information (high)
Were women included independently of the cause of hemorrhage?	Yes (high)
Information bias	**Low**
How was information collected ?	Medical charts *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Gravimetric method at three different time point: delivery of placenta, 1h postpartum and 2h postpartum *(low)*
Overall risk of bias	**Moderate**
Randomised controlled trial: Magann et al (2012)	
Selection bias	**High**
Was the study period well defined?	July 2006-july 2010 (low)
Did the cohort represent the births on hospital-, regional or national scale?	Hospital (high)
Were women included if third stage of labor was managed actively?	No information (high)
Were women included independently of the cause of hemorrhage?	Yes (high)
Information bias	High
How was information collected ?	Not described (high)
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Not described (high)
Overall risk of bias	**High**
Cohort study: Van Ast et al. (2019)	
Selection bias	**High**
Was the study period well defined?	Sept 24- 2011 / Sept 27-2016 *(low)*
Did the cohort represent the births on hospital-, regional or national scale?	Hospital *(high)*
Were women included if third stage of labor was managed actively?	Yes *(low)*
Were women included independently of the cause of hemorrhage?	Yes *(high)*
Information bias	**Moderate**
How was information collected ?	Patient reports preserved in a digital obstetrical data-management system *(low)*
Was blood loss quantified by weighing or blood collector drapes? (Other than visual estimation)	Visually estimated or measured by weighing gauzes in case of extensive blood loss *(moderate)*
Overall risk of bias	**Moderate**

de Vries. Redefining the length of third stage of labor. Am J Obstet Gynecol 2025.