Systematic Review

Efficacy of Postpartum Pharmacologic Thromboprophylaxis
A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate the effectiveness of pharmacologic venous thromboembolism (VTE) prophylaxis in postpartum patients.

DATA SOURCES: On February 21, 2022, a literature search was conducted on Embase.com, Ovid-Medline All, Cochrane Library, Scopus, and ClinicalTrials.gov using terms postpartum period AND thromboprophylaxis AND antithrombin medications including heparin and low molecular weight heparin.

METHODS OF STUDY SELECTION: Studies that evaluated the outcome of VTE among postpartum patients exposed to pharmacologic VTE prophylaxis with or without a comparator group were eligible for inclusion. Studies of patients who received antepartum VTE prophylaxis, studies in which this prophylaxis could not be definitively ruled out, and studies of patients who received therapeutic dosing of anticoagulation for specific medical problems or treatment of VTE were excluded. Titles and abstracts were independently screened by two authors. Relevant full-text articles were retrieved and independently reviewed for inclusion or exclusion by two authors.

TABULATION, INTEGRATION, AND RESULTS: A total of 944 studies were screened by title and abstract, and 54 full-text studies were retrieved for further evaluation after 890 studies were excluded. Fourteen studies including 11,944 patients were analyzed: eight randomized controlled trials (8,001 patients) and six observational studies (3,943 patients). Among the eight studies with a comparator group, there was no difference in the risk of VTE between patients who were exposed to postpartum pharmacologic VTE prophylaxis and those who were unexposed (pooled relative risk 1.02, 95% CI 0.29–3.51); however, six of eight studies had no events in either the exposed or unexposed group. Among the six studies without a comparator group, the pooled proportion of postpartum VTE events was 0.00, likely due to five of six studies having no events.

CONCLUSION: The current literature provided an insufficient sample size to conclude whether postpartum VTE rates differ between those exposed to postpartum pharmacologic prophylaxis and those unexposed, given the rarity of VTE events.

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Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is responsible for 9–30% of pregnancy-related mortality in high resource countries and remains a significant, increasing cause of severe maternal morbidity.[1–4] Although rising rates of comorbidities known to be risk factors for VTE (such as obesity and older age at the time of delivery) have contributed

to this problem, pregnancy itself is associated with both physiologic and anatomic changes that increase the risk for VTE approximately fivefold compared with the nonpregnant state due to hypercoagulability and venous stasis.[5–7] Approximately 50% of all VTE events occur in the early postpartum period and represents a window of time that patients remain at significant risk for adverse outcomes.[8–10] Specifically, the hypercoagulable state favoring thrombosis does not resolve to prepregnancy physiology until approximately 6–8 weeks postpartum.[11]

In light of the need for effective strategies for VTE prevention specific to postpartum patients, many professional obstetric societies and governing bodies have put forth recommendations addressing the role of postpartum pharmacologic VTE prophylaxis (ie, anticoagulation).[5,12–16] Yet, these guidelines lack consensus in regard to the specifics of thromboprophylaxis, due to the heterogeneity of both obstetric and nonobstetric literature used to develop them.[16] As a result the efficacy of thromboprophylaxis is unclear. The objective of this study was to conduct a systematic review and meta-analysis to estimate the magnitude to which pharmacologic prophylaxis affects the risk of VTE among postpartum patients.

SOURCES

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines and was registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42022323841) before beginning review and data abstraction.[17] The published literature was searched by a medical librarian (A.H.) for the terms postpartum period AND thromboprophylaxis AND antithrombin medications including heparin and low molecular weight heparin. These search terms were created using a combination of controlled vocabulary terms and keywords, executed in Embase.com, Ovid-Medline All, Cochrane Library, Scopus, and Clinicaltrials.gov from database inception (Appendix 1, available online at http://links.lww.com/AOG/D74). Results were limited to English-language through the use of database-supplied filters. All database searches were completed on February 21, 2022. Because all data were de-identified and available in the public domain, this study was exempt from Institutional Review Board approval. After duplicates were removed, two of the authors (M.C.O. and M.R.) independently screened the titles and abstracts of remaining publications for fulfillment of inclusion, and exclusion criteria and relevance to the present study.

Additional publications were identified by reviewing the bibliographies of selected studies.

STUDY SELECTION

The PICOT method (population, intervention, comparison, outcome, time) was used to develop the study question and inclusion criteria, which included studies of postpartum patients' status after vaginal or cesarean delivery who received pharmacologic VTE prophylaxis (either with or without an unexposed comparator group) with the outcome of VTE.[18] Study designs that compared postpartum patients exposed to heparin (unfractionated or low molecular weight) with an unexposed group (either placebo or no intervention) were eligible for inclusion. Studies were also eligible for inclusion if their design compared two or more groups that were exposed to pharmacologic thromboprophylaxis (for instance, two groups both exposed to a low molecular weight heparin but for different durations of prophylaxis) with or without the presence of an unexposed group. Exclusion criteria were studies that included patients who received antepartum pharmacologic prophylaxis or studies in which this exposure type could not be definitively ruled out, and patients who received therapeutic dosing of anticoagulation for specific medical problems or treatment of VTE. We excluded case reports, case series, review articles, abstracts without a corresponding full-text article, and full-text articles not published in a peer-reviewed journal.

The primary outcome of this study was postpartum VTE. Titles and abstracts were independently screened by two of the authors (M.C.O. and M.R.). Full-text articles were then retrieved if they were deemed relevant or relevance was queried. Full-text articles were again independently reviewed by two of the authors (M.C.O. and M.R.) against inclusion and exclusion criteria. Discrepancies regarding the decision to include or exclude a study were resolved by consultation with the senior author (A.I.F.) as needed. Data abstraction into a standardized form was performed by two of the authors (M.C.O. and M.R.). A single attempt was made to contact authors by email if there was insufficient information to complete the data abstraction.

In addition to information on the primary outcome, additional data points that were abstracted included: study inclusion and exclusion criteria; type and dose of anticoagulant studied; duration of anticoagulant exposure; presence or absence of an unexposed or other comparator group; duration of surveillance for postpartum VTE; descriptor of how VTE events were identified; and participant

characteristics. Missing or unclear information was clearly denoted as "not measured" or "unknown."

Although published quality scoring systems for both randomized and nonrandomized studies of health care interventions exist (eg, the Downs and Black[19] checklist), such checklists still involve subjectivity and there is a lack of consensus as to a cut-point that discriminates between high-quality and low-quality studies. On reviewing these checklists, it was felt that they did not adequately discriminate study quality for the purposes of our systematic review and meta-analysis. Thus, we assessed study quality and risk for pertinent forms of bias based on the presence or absence of five characteristics most likely to influence study validity: 1) documented anticoagulant type and dose, 2) documented duration of anticoagulation exposure, 3) presence of an unexposed comparator group, 4) documented VTE surveillance duration, and 5) the process of identifying and documenting postpartum VTE events.[20,21] The presence of criteria 1 and 2 were considered to reflect reduced risk for information bias. The presence of criterion 3 was considered to reflect a reduced risk for selection bias. The presence of criteria 4 and 5 were considered to reflect a reduced risk for misclassification bias and detection bias. The quality of each study was assessed independently by two study authors (M.C.O. and M.R.) with any discrepancies adjudicated by the senior author (A.I.F.). Overall study quality was determined to be high if all five criteria were met.

Data were abstracted from each study and, for studies with an unexposed comparator group, combined using the Der-Simonian-Laird random-effects model to account for both within- and between-study variances. Zero cells were adjusted for with a continuity correction of 0.5. The Peto odds ratio (OR) method also was performed given the rarity of events.[22,23] Pooled relative risk (RR) with 95% CIs were calculated for the primary outcome among studies with an unexposed comparator group. If a study included two or more different groups exposed to pharmacologic thromboprophylaxis (eg, two different anticoagulant types, and one unexposed comparator group), all exposed patients were combined and compared with the single unexposed comparator group. The proportion of VTE events and 95% CI was calculated among studies with no unexposed comparator group, for only those exposed to anticoagulation from studies with an unexposed or control group, and as a pooled proportion. Similarly, the pooled proportion of VTE events was calculated among all unexposed or control groups. Forest plots were used to graphically represent the data.

Heterogeneity was explored using Higgins' I^2.[24] Given the low statistical power of tests of heterogeneity, heterogeneity was further classified as small ($I^2 < 25\%$), moderate (I^2 25–50%), or large ($I^2 > 50\%$). The presence of moderate-to-large heterogeneity was further explored by stratification by study quality. Publication bias was assessed graphically using contrast-enhanced funnel plots, and small-study bias was assessed using the Harbord test.[25] Data were analyzed using STATA 16.0.

RESULTS

A flow diagram of study identification for the meta-analysis is shown in Figure 1. The initial literature search yielded 1,570 citations. Of those, 626 citations were duplicates and removed, leaving 944 studies to be screened by title and abstract.[26] After titles and abstracts were reviewed for relevance and screened against inclusion and exclusion criteria, 890 studies were excluded, and 54 full-text studies were retrieved for further evaluation. Review of bibliographies of selected papers against study criteria resulted in an additional six studies for consideration. Studies were subsequently excluded for the following reasons: abstract only (n=22); no full text available (n=4); did not include primary outcome of interest (n=6); data set was duplicated from another study (n=2); study included antenatal exposure to anticoagulation (n=3); inability to extract exposure data (n=8); and full-text not available in English (n=1).

Fourteen studies including 11,944 patients were analyzed: eight randomized controlled trials ([RCTs] 8,001 patients) and six observational studies (3,943 patients).[27–40] Study characteristics are shown in Table 1, including each study's year of publication, county of origin, inclusion and exclusion criteria, characteristics of prophylactic anticoagulant studied, definition of primary outcome (VTE), duration of surveillance, and whether an unexposed comparator group was included. The results of the methodologic quality assessment are shown in Table 2. Based on evaluation in five categories, three studies were deemed high-quality, and 11 studies were deemed low quality. Low-quality studies were at higher risk for misclassification bias with unspecified surveillance durations and ambiguous or unclear definitions of a VTE event; they were also more likely to have lower quality data with unclear details regarding anticoagulation dosing and duration of exposure.

There were eight studies (four RCTs, four observational studies) that compared the risk of VTE between those exposed to postpartum pharmacologic prophylaxis and an unexposed comparator group (either
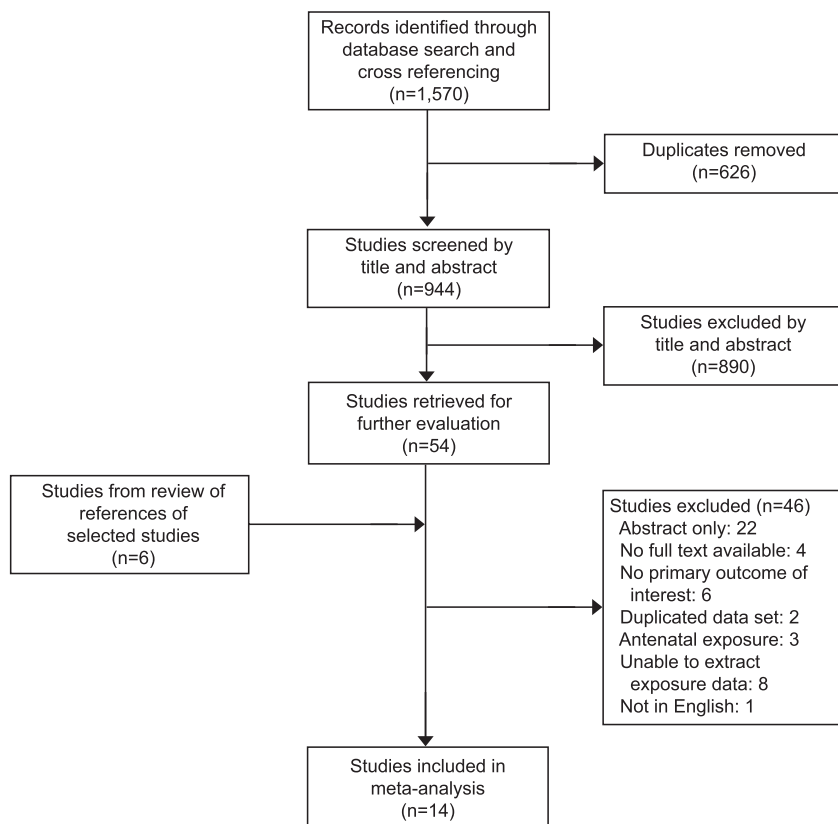
Fig. 1. Flowchart of study selection methodology.

Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.

placebo or no intervention).[27,28,31,33,35–38] Table 3 shows VTE rates in the exposed and unexposed groups, pooled RR and 95% CI, and heterogeneity of the primary outcome of VTE, as well as results of the stratified analysis. Overall, there was no difference in the risk of VTE between patients who were exposed to postpartum pharmacologic VTE prophylaxis and those who were unexposed (eight studies including six studies with imputed values for primary outcome due to no VTE events, pooled RR 1.02, 95% CI 0.29–3.51) (Fig. 2). There was also no difference in risk of VTE when using the Peto OR method to account for the rarity of VTE events (pooled RR 0.74, 95% CI 0.13–4.26) (Fig. 3). A moderate amount of heterogeneity was noted (I^2=39.63%), which was explored further with an analysis stratified by study quality (Fig. 4). Evaluation of high-quality studies (three studies, including two with imputed values for primary outcome due to no VTE events) revealed a significantly decreased RR of postpartum VTE for those exposed to pharmacologic VTE prophylaxis compared with those unexposed (RR 0.22, 95% CI 0.07–0.71) and no heterogeneity among studies (I^2=0.00%). Low-quality studies (five studies, including four with imputed values for primary outcome due to no VTE events) did not demonstrate a

significant difference in risk for postpartum VTE between exposed and unexposed groups (RR 2.13, 95% CI 0.51–8.87; I^2=19.37%). Findings were similar using the Peto OR method (Appendix 2, available online at http://links.lww.com/AOG/D74).

Visual inspection of a contrast-enhanced funnel plot of studies with an unexposed comparator group demonstrated evidence of publication bias. Specifically, there was a lack of studies with nonsignificant results favorable to the intervention (postpartum pharmacologic prophylaxis) (Fig. 5). The Harbord test was significant (*P*=.01), suggesting the presence of a small study effect.

The effect of postpartum pharmacologic VTE prophylaxis was assessed among studies that did not have an unexposed comparator group (n=6, four RCTs and two observational studies).[29,30,32,34,39,40] The pooled proportion of postpartum VTE events was 0.00 (5/6 studies with imputed values for primary outcome due to no VTE events) with no significant heterogeneity (I^2=0.00%), likely due to the extremely small number of events across studies. When including the exposed groups from studies with an unexposed comparator group (n=8; total 14 studies, including five with imputed values for primary

Table 1. Characteristics of Studies Included in Final Meta-Analysis

Study	Year	Country	Inclusion Criteria	Exclusion Criteria
Randomized controlled trials (n=8)				
Alalaf et al (N=7,020)	2015	Iraq	≥15 years old with risk factors for VTE based on RCOG 2009 Green-top Guideline,[13] absence of active bleeding and hemodynamic stability.	Already taking an anticoagulant, contraindication to LMWH
Burrows et al (N=76)	2001	Australia	Patient status post elective or emergency CD	History of bleeding disorder, need for therapeutic anticoagulation, history of thrombotic event, sensitivity to heparin, recent gastrointestinal hemorrhage or peptic ulcer, hepatic encephalopathy, renal dysfunction requiring dialysis, uncontrolled hypertension, non-English speaking
Cruz et al (N=646)	2011	Spain	Patient status post CD without exposure to thromboprophylaxis or treatment with LMWH during pregnancy	Allergy to heparin
Ellison et al (N=30)	2001	UK	Patient status post CD with one additional risk factor for thromboprophylaxis based on 1995 RCOG Report on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics[41]	Not specified
Gates et al (N=157)	2004	UK	Patient status post CD and clinical uncertainty that heparin thromboprophylaxis is indicated	Allergy to heparin
Gibson et al (N=17)	1998	UK	Patient status post unplanned CD or ≥1 risk factors for thromboembolic disease based on 1992 Thomboembolic Risk Factors Consensus Group[42]	Not specified
Rodger et al (N=25)	2015	Canada	Patients with low-risk thrombophilia or immobilization in antepartum period or ≥2 risk factors: postpartum infection, postpartum hemorrhage, prepregnancy BMI <25 kg/m², emergency CD, smoking >5 cigarettes/day prior to pregnancy, preeclampsia, or fetal growth restriction.	<6h or >36h since delivery at time of randomization, need for anticoagulation, contraindication to heparin, or received a dose of heparin or LMWH since delivery
Stephenson et al (N=84)	2015	US	Patient status post CD and BMI ≥35 kg/m²	Prior VTE, already taking an anticoagulant, allergy to enoxaparin, renal impairment, contraindication to treatment with enoxaparin
Observational studies (n=6)				
Anderson et al (N=500)	2014	US	Patient status post CD with 1 intermediate or high-risk factor or 2 low-risk factors based on RCOG 2009 Green-top Guideline[13]	Not specified
Ferres et al (N=1,677)	2011	US	Patient status post CD and >35 years old or BMI >30 kg/m²	Contraindication to heparin use

(*continued*)

Table 1. Characteristics of Studies Included in Final Meta-Analysis (*continued*)

Study	Year	Country	Inclusion Criteria	Exclusion Criteria
Gizzo et al (N=529)	2014	Italy	Patient status post elective CD and >35 years old, singleton gestation, term delivery	Not specified
Lok et al (n=859)	2018	China	Patient status post CD with ≥3 risk factors: ≥40 years old, BMI ≥25 kg/m², BMI ≥30 kg/m² (2 points), parity ≥3, preeclampsia, multiple pregnancy, preterm gestation, stillbirth, medical comorbidities, low-risk thrombophilia, current smoker, gross varicose veins, current systemic infection, immobility, 1st degree relative with VTE	Not specified
Roeters van Lennep et al (N=91)	2011	Netherlands	Asymptomatic patient with non-high-risk thrombophilia and first degree relative with VTE history, first-degree relative with VTE without thrombophilia, prior provoked VTE	Not specified
Snijder et al (N=1,527)	2012	Netherlands	Patient status post CD	History of coagulation disorder, antenatal anticoagulation

Study	Anticoagulant Studied	Duration of Anticoagulation Exposure (days)	Unexposed Comparator Group	Duration of Surveillance (days)	How Diagnosis of VTE (Primary Outcome) Was Defined
Randomized controlled trials (n=8)					
Alalaf et al (N=7,020)	Enoxaparin: 40 mg/d (n=2,340) Bemiparin: 3500 IU/d (n=2,340)	7 7	No intervention (n=2,340)	40	DVT confirmed by compression ultrasound or MRI; PE confirmed by CT pulmonary angiography
Burrows et al (N=76)	Dalteparin: 2500 IU/d (n=39)	5	Matching placebo (saline) (n=37)	42	Patients asked if they had any problems relating to thromboembolic disease; positive responses followed up through chart review or physician contact
Cruz et al (N=646)	Bemiparin 3500 IU/d (n=311) Bemiparin 3500 IU/d (n=335)	5 10	—	90	Not specified
Ellison et al (N=30)	Dalteparin: 5000 IU/d (n=10) Enoxaparin: 4000 IU/d (n=10) Tinzaparin: 50 IU/kg/d (n=10)	5 5 5	—	Not specified	Not specified
Gates et al (N=157)	Enoxaparin: 40 mg/d (n=141)	Not specified	Matching placebo (saline) (n=16)	180	Not specified

(*continued*)

Study	Anticoagulant Studied	Duration of Anticoagulation Exposure (days)	Unexposed Comparator Group	Duration of Surveillance (days)	How Diagnosis of VTE (Primary Outcome) Was Defined
Gibson et al (N=17)	Enoxaparin: 20 mg/d (n=6) Enoxaparin: 40 mg/d (n=5) UFH: 7500 IU BID (n=6)_	Not specified	—	Not specified	Not specified
Rodger et al (N=25)	Dalteparin: 5000 IU/d (n=14)	21	Matching placebo (saline) (n=11)	90	Adjudicated DVT or PE or asymptomatic proximal DVT detected by screening compression US of both legs performed within 24 hours of last dose of study drug
Stephenson et al (N=84)	Enoxaparin: 40 mg/d (n=42) Enoxaparin: 0.5 mg/kg BID (n=42)	Not specified	—	42	Not specified
Observational studies (n=6)					
Anderson et al (N=500)	UFH: 5000 IU/ d (n=500)	Not specified	No intervention	Not specified	Not specified
Ferres et al (N=1,677)	Enoxaparin, prophylactic dose (dose not standardized) (n=653)	Not specified ("daily until hospital discharge")	No intervention (n=1,024)	90	Based on hospital discharge or readmission diagnosis and summary, with detailed confirmation or review of radiographic evidence and treatment by at least 2 investigators
Gizzo et al (N=529)	Enoxaparin: 4000 IU/d Dalteparin: 5000 IU/d; total n=349 for both groups (no data on n participants per anticoagulant typ	7 7	No intervention (n=180)	42	Complete ultrasound examination of deep leg veins
Lok et al (n=859)	LMWH (unknown drug and dose) (n=28)	10	No intervention (n=831)	Not specified	Not specified
Roeters van Lennep et al (N=91)	Nandroparin: 2850 IU/d (n=91)	42	—	90	Adjudicated by 2 independent observers; defined as new or extended area of non-compressible deep venous segment seen on compression US or diagnosis of PE made by CT or VQ scan
Snijder et al (N=1,527)	Nandroparin: 2850 IU/d (n=1,527)	Not specified ("at least 3 days")	—	Not specified	Not specified

VTE, venous thromboembolism; RCT, randomized controlled trial; RCOG, Royal College of Obstetricians & Gynaecologists; LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; CT, computed tomography; CD, cesarean delivery; NS, not specified; UFH, unfractionated heparin; BMI, body mass index; FGR, fetal growth restriction; VQ, ventilation/perfusion scan.

* No data on no. of participants/anticoagulant type.

outcome due to no VTE events), there was no difference in the overall pooled proportion of VTE events (0.00%) (Fig. 6).[27,28,31,35–38] The pooled proportion of VTE events among those that did not receive anticoagulation from studies with an unexposed comparator group was 0.00% (eight studies, including four with imputed values for primary outcome due to no VTE events) (Fig. 7).

Table 2. Quality Assessment of Included Studies

Study	Documented Anticoagulant Type and Dose	Documented Duration of Anticoagulant Exposure	Unexposed Comparator Group	Documented VTE Surveillance Duration	VTE Event Well-Defined	Quality
RCTs						
Alalaf et al, 2015	X	X	X	X	X	High
Burrows et al, 2001	X	X	X	X		Low
Cruz et al, 2011	X	X		X		Low
Ellison et al, 2001	X	X				Low
Gates et al, 2004	X		X	X		Low
Gibson et al, 1998	X					Low
Rodger et al, 2015	X	X	X	X	X	High
Stephenson et al, 2015	X			X		Low
Observational studies						
Anderson et al, 2014	X		X			Low
Ferres et al, 2011			X	X	X	Low
Gizzo et al, 2014	X	X	X	X	X	High
Lok et al, 2018		X	X			Low
Roeters van Lennep et al, 2011	X	X		X	X	Low
Snijder et al, 2012	X					Low

VTE, venous thromboembolism; RCT, randomized controlled trial.

DISCUSSION

Analysis of 16 studies published in the peer-reviewed literature that met inclusion criteria (N=11,944) for this meta-analysis found the risk of postpartum VTE did not differ between those exposed to thromboprophylaxis and unexposed groups. However, this study illustrates that, although universal postpartum VTE thromboprophylaxis is a recommended practice by

Table 3. Rates and Pooled Estimates for Primary Outcome and Analysis Stratified by Study Quality

Outcome	No. of Studies	Exposed Event Rate [n Outcome/n Eexposed (%)]	Unexposed Event Rate [n Outcome/n Uunexposed (%)]	Pooled Effect Size (RR)	95% CI	Heterogeneity (I^2) (%)
VTE	8	7/5,994(0.11)	14/5,358 (0.26)	1.02	0.29–3.51	39.63
Stratified by study quality						
High	3	3/5,043 (0.06)	9/2,534 (0.35)	0.22	0.07–0.71	0.00
Low	5	4/951 (0.42)	5/2,824 (0.18)	2.13	0.51–8.87	19.37

RR, relative risk; VTE, venous thromboembolism.

Fig. 2. Forest plot showing the risk of venous thromboembolism (VTE) for those exposed to postpartum pharmacologic VTE prophylaxis vs those unexposed. LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; REML, restricted maximum likelihood.

Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.

some professional societies, not only is the rate of postpartum VTE exceedingly low, but the limited high-quality evidence surrounding its efficacy limits the ability of this study to definitively make conclusions regarding its efficacy.

It is also important to note the high level of heterogeneity in the available studies included in our analysis. The two most important sources of heterogeneity were in patient selection and study population and definition or diagnosis of the primary outcome of
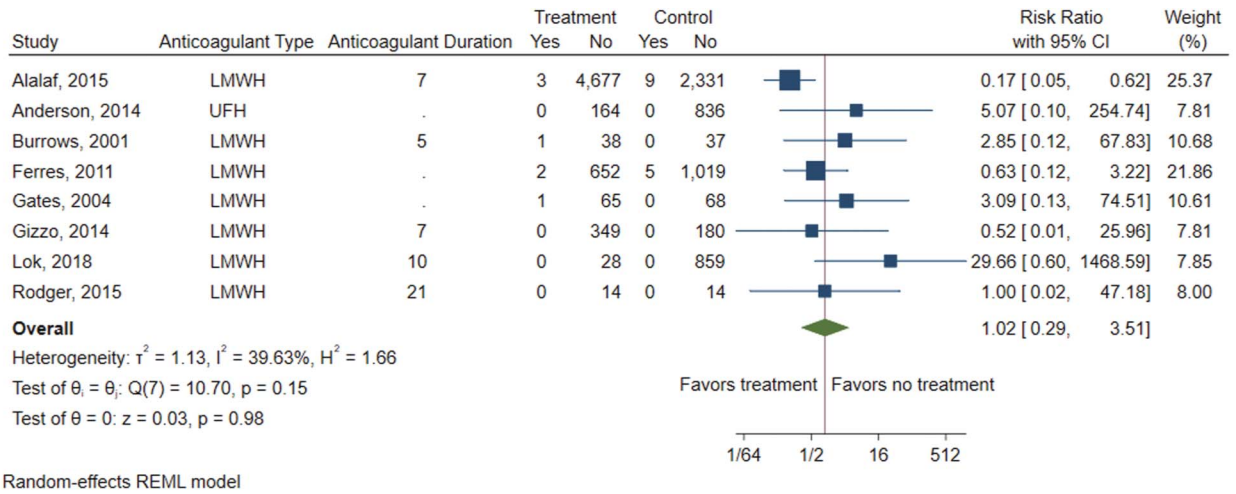

Fig. 3. Forest plot showing the risk of venous thromboembolism (VTE) for those exposed to postpartum pharmacologic VTE prophylaxis vs those unexposed, using Peto's odds ratio (OR) method. LMWH, low-molecular-weight heparin; REML, restricted maximum likelihood.

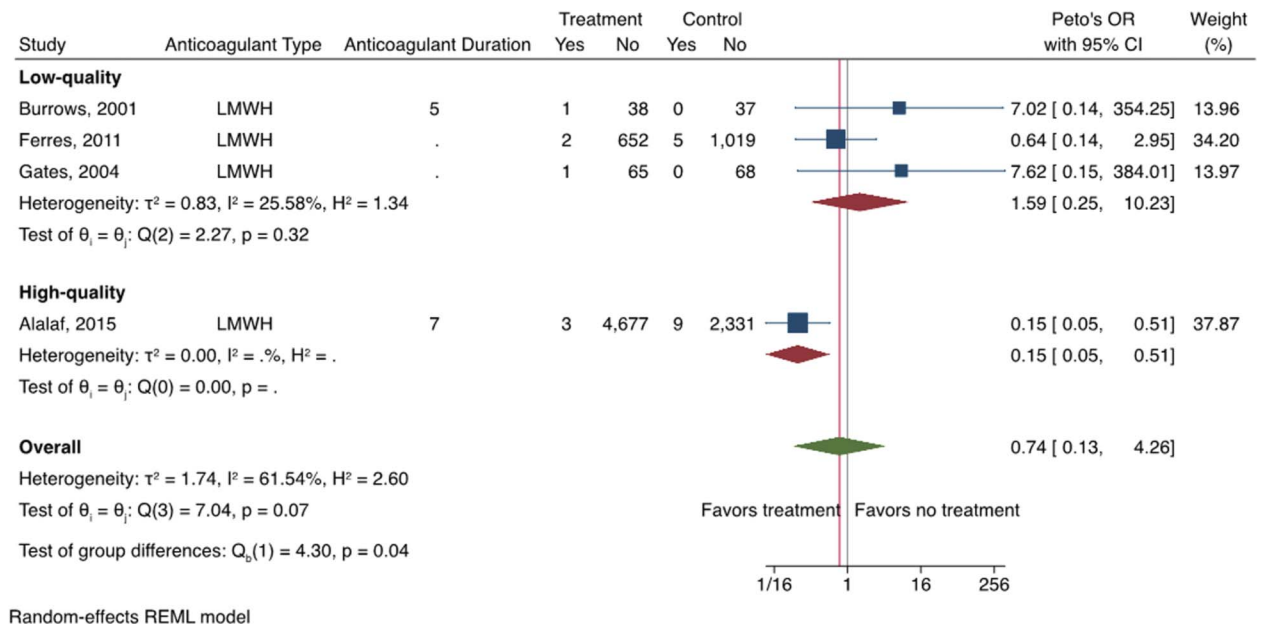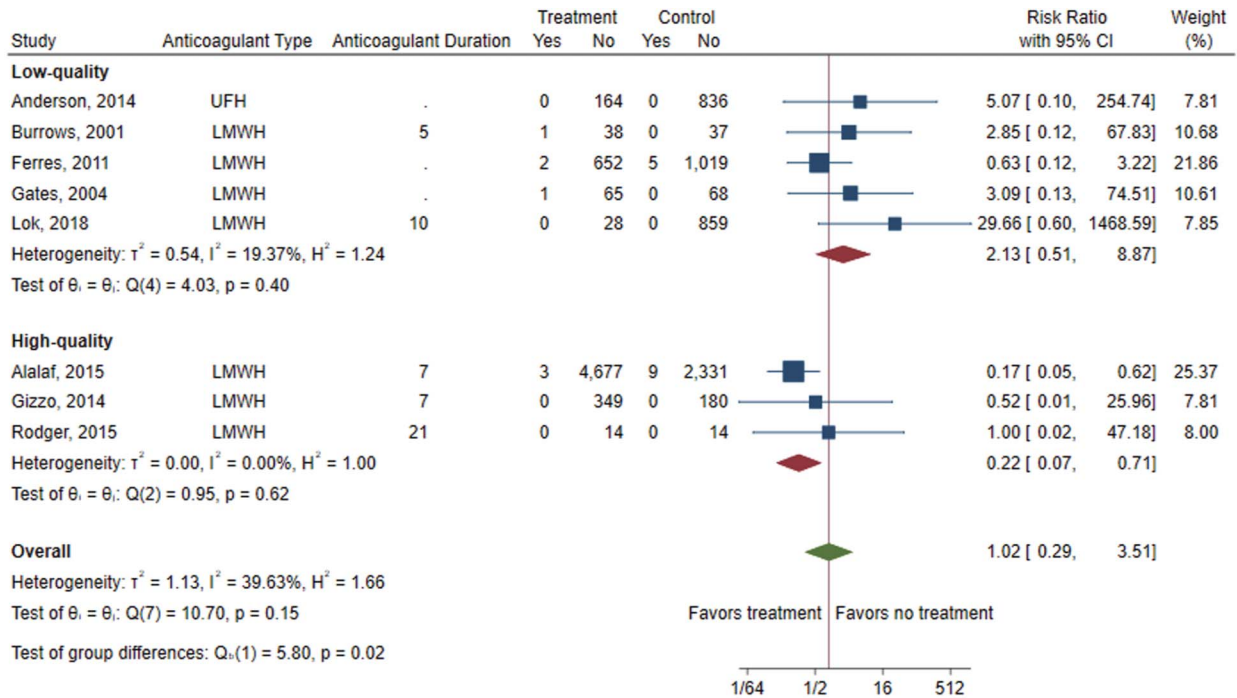*Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.*

Fig. 4. Forest plot showing the risk of venous thromboembolism (VTE) for those exposed to postpartum pharmacologic VTE prophylaxis vs those unexposed, stratified by study quality. UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; REML, restricted maximum likelihood.

Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.

VTE. The specific risk factors that defined populations as "at risk" for postpartum VTE and, therefore, those in need of pharmacologic prophylactic anticoagulation, varied greatly. A majority of studies in this analysis included only patients who underwent cesarean delivery (11/14, 78.6%), which is the most common surgery performed in the United States, with a rate that continues to rise.[28–32,34–38,40] In a review of published evidence-based guidelines on VTE prevention in pregnant and postpartum patients, almost half of the guidelines (4/9) recommended initiation of thromboprophylaxis for people who undergo
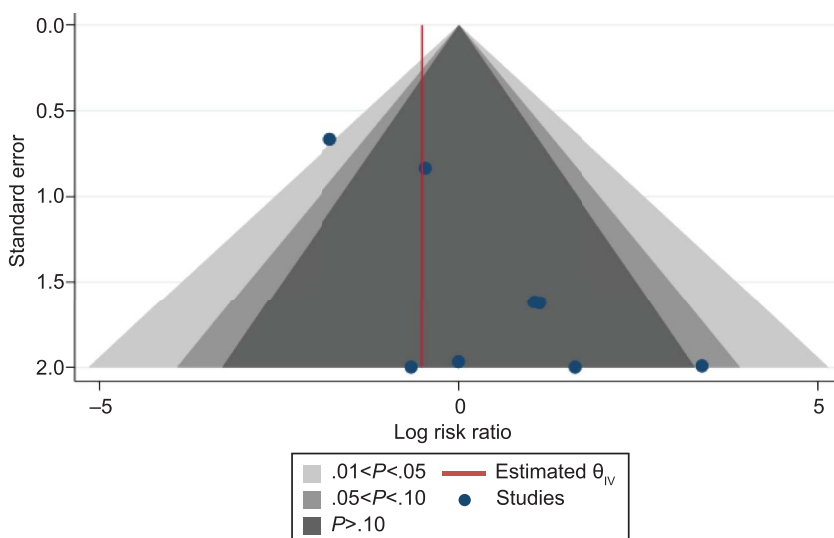

Fig. 5. Contour-enhanced funnel plot showing the risk of venous thromboembolism (VTE) for those exposed to postpartum pharmacologic VTE prophylaxis vs those unexposed.

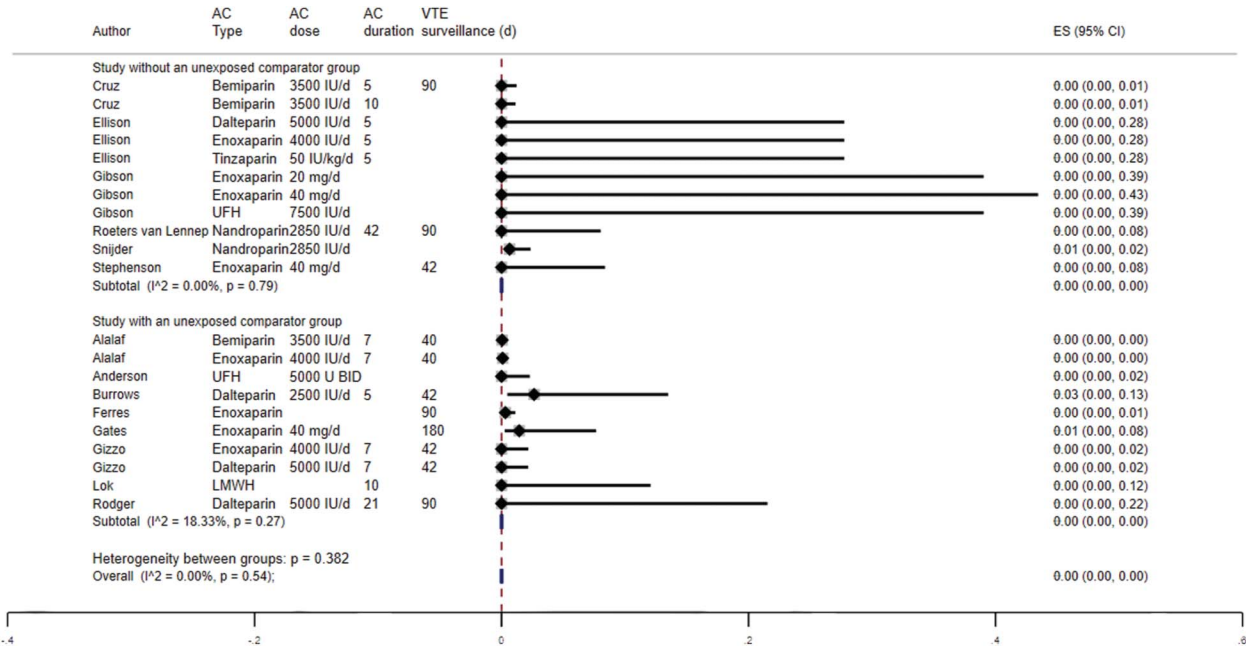*Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.*

Figure 6

Author	AC Type	AC dose	AC duration	VTE surveillance (d)	ES (95% CI)
Study without an unexposed comparator group					
Cruz	Bemiparin	3500 IU/d	5	90	0.00 (0.00, 0.01)
Cruz	Bemiparin	3500 IU/d	10		0.00 (0.00, 0.01)
Ellison	Dalteparin	5000 IU/d	5		0.00 (0.00, 0.28)
Ellison	Enoxaparin	4000 IU/d	5		0.00 (0.00, 0.28)
Ellison	Tinzaparin	50 IU/kg/d	5		0.00 (0.00, 0.28)
Gibson	Enoxaparin	20 mg/d			0.00 (0.00, 0.39)
Gibson	Enoxaparin	40 mg/d			0.00 (0.00, 0.43)
Gibson	UFH	7500 IU/d			0.00 (0.00, 0.39)
Roeters van Lennep	Nandroparin	2850 IU/d	42	90	0.00 (0.00, 0.08)
Snijder	Nandroparin	2850 IU/d			0.01 (0.00, 0.02)
Stephenson	Enoxaparin	40 mg/d		42	0.00 (0.00, 0.08)
Subtotal (I^2 = 0.00%, p = 0.79)					0.00 (0.00, 0.00)
Study with an unexposed comparator group					
Alalaf	Bemiparin	3500 IU/d	7	40	0.00 (0.00, 0.00)
Alalaf	Enoxaparin	4000 IU/d	7	40	0.00 (0.00, 0.00)
Anderson	UFH	5000 U BID			0.00 (0.00, 0.02)
Burrows	Dalteparin	2500 IU/d	5	42	0.03 (0.00, 0.13)
Ferres	Enoxaparin			90	0.00 (0.00, 0.01)
Gates	Enoxaparin	40 mg/d		180	0.01 (0.00, 0.08)
Gizzo	Enoxaparin	4000 IU/d	7	42	0.00 (0.00, 0.02)
Gizzo	Dalteparin	5000 IU/d	7	42	0.00 (0.00, 0.02)
Lok	LMWH		10		0.00 (0.00, 0.12)
Rodger	Dalteparin	5000 IU/d	21	90	0.00 (0.00, 0.22)
Subtotal (I^2 = 18.33%, p = 0.27)					0.00 (0.00, 0.00)
Heterogeneity between groups: p = 0.382					
Overall (I^2 = 0.00%, p = 0.54);					0.00 (0.00, 0.00)

Fig. 6. Forest plot showing the proportion of venous thromboembolism (VTE) for those exposed to postpartum pharmacologic VTE prophylaxis. AC, anticoagulation; ES, effect size; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

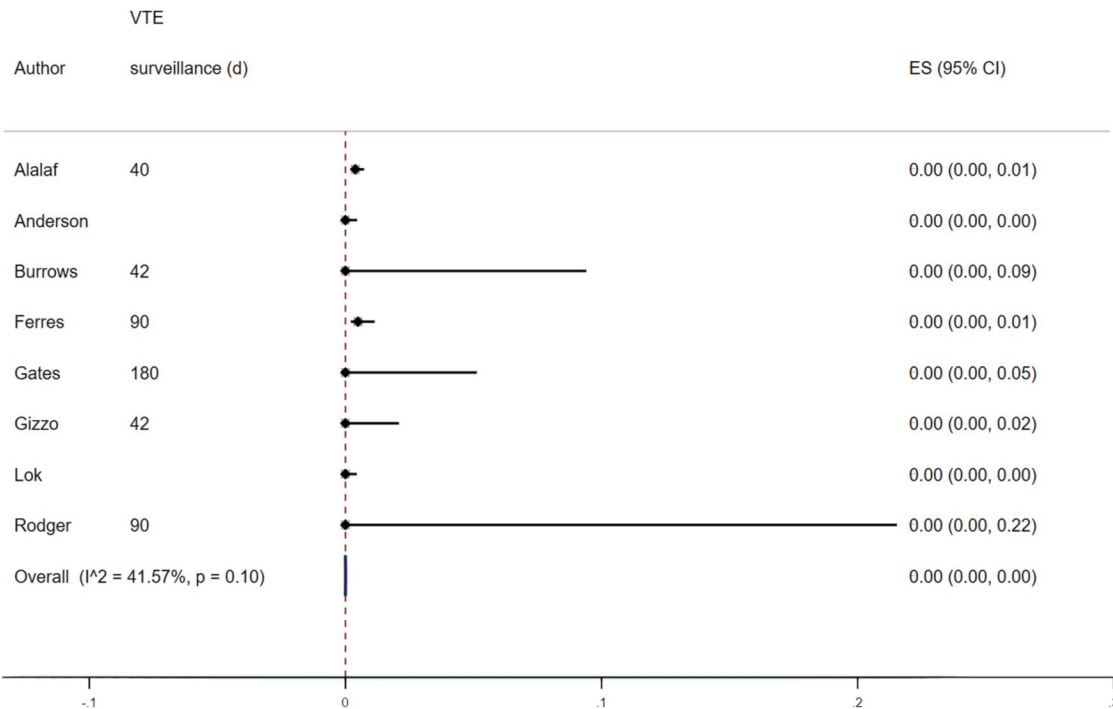*Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.*

Figure 7

Author	VTE surveillance (d)	ES (95% CI)
Alalaf	40	0.00 (0.00, 0.01)
Anderson		0.00 (0.00, 0.00)
Burrows	42	0.00 (0.00, 0.09)
Ferres	90	0.00 (0.00, 0.01)
Gates	180	0.00 (0.00, 0.05)
Gizzo	42	0.00 (0.00, 0.02)
Lok		0.00 (0.00, 0.00)
Rodger	90	0.00 (0.00, 0.22)
Overall (I^2 = 41.57%, p = 0.10)		0.00 (0.00, 0.00)

Fig. 7. Forest plot showing the proportion of venous thromboembolism (VTE) for those unexposed to postpartum pharmacologic VTE prophylaxis. ES, effect size.

Oakes. Review of Postpartum Thromboprophylaxis. Obstet Gynecol 2023.

cesarean delivery with the presence of an additional risk factor (eg, obesity).[16,31,35,37] Although it was not within the scope of this study to evaluate specific practice guidelines, our findings allude to a need for further studies to explore the effect of postpartum VTE prophylaxis, particularly in high-risk groups.

The diagnostic criteria for VTE in the studies included in this meta-analysis ranged from patient-reported symptoms to objective screening of all patients with compression ultrasonography. Further, 8 of 14 (57%) included studies did not provide details in regard to how VTE was diagnosed (including 5/8 [62.5%] of RCTs). The heterogeneity in method of VTE diagnosis and duration of screening introduces a great degree of selection bias, making the applicability of the findings challenging. The analysis presented here highlights that future studies should clearly state postpartum risk factors for VTE and identify the optimal drug, dose, and duration for VTE prevention. These studies must also include detailed VTE surveillance protocols and methods for identifying VTE events. Additionally, the duration of surveillance should span at least 6 weeks after delivery when the hypercoagulable state associated with pregnancy resolves.[11]

Among the strengths of this study are the rigorous, transparent data-collection methods and analysis, including an extensive literature search across five databases, performed by two reviewers with the assistance of a medical librarian with a Master of Library and Information Science. Three contemporary systematic review and meta-analyses concluded that either postpartum VTE prophylaxis did not reduce the risk of VTE events or there were insufficient data to make conclusions regarding the efficacy of postpartum VTE prophylaxis.[41–43] However, the present meta-analysis is unique in that it includes both patients who underwent vaginal and cesarean delivery and excludes studies that evaluated the effect of pharmacologic agents other than unfractionated and low-molecular-weight heparin used to prevent thrombosis (such as aspirin, warfarin, and hydroxyethyl starch). Further, the present meta-analysis includes both observational studies and RCTs.

Several limitations to this systematic review must be considered. Four of the eight comparative studies had zero events in both the exposed and unexposed groups, and an additional two of eight comparative studies had zero events in the unexposed group resulting in a need for imputation of the primary outcome to perform a meta-analysis. Despite the inclusion of both observational and randomized studies, our study was underpowered to detect a difference in the primary outcome between those exposed and unexposed to postpartum pharmacologic VTE prophylaxis, given the limited number of available patients and rarity of the primary outcome. Only two comparative studies included had VTE events in the unexposed group, and the rate of VTE events (0.96/1,000 births) was lower than estimated in the literature (1.72–1.86/1,000 births). However, the exclusion of studies that had patients with an elevated VTE risk independent of pregnancy (such as known thrombophilia) may account for some degree of this discrepancy. Studies that did not have an unexposed comparator group (such as those that compared two different durations of prophylactic anticoagulation without a control or untreated group) were included, given that these studies still contributed to estimating the proportion of VTE events among those exposed to prophylactic anticoagulation. However, comparing the pooled rate of VTE among all patients who received prophylaxis in the included studies (n=14) to patients who did not receive prophylaxis from studies that had an unexposed comparator group (n=8) arguably introduces a higher risk of selection bias. Finally, given the heterogeneity in reporting, we were unable to comment on important secondary and safety outcomes, such as postpartum bleeding and wound complications related to anticoagulation.

In conclusion, results of this systematic review and meta-analysis suggest that, although high-quality studies may signal a benefit of postpartum pharmacologic VTE prophylaxis, this evidence is extremely limited, and, currently, the existing literature is insufficient to conclude whether postpartum pharmacologic prophylaxis affects VTE risk. The effect of postpartum prophylactic anticoagulation needs to be further clarified by larger, well-conducted studies with particular attention to strict methods of identifying postpartum VTE events and appropriate surveillance duration to identify the appropriate postpartum population for whom this preventative strategy may be appropriate.

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