Received: 8 August 2023 | Revised: 16 October 2023 | Accepted: 17 October 2023

DOI: 10.1111/aogs.14712

AOGS Acta Obstetricia et Gynecologica Scandinavica

SYSTEMATIC REVIEW

Risk of venous thromboembolism in pregnant patients with active malignancy: A systematic review and meta-analysis

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Abstract

Introduction: Cancer currently occurs in about 1 in 1000 pregnancies. Both active malignancy and pregnancy are individual risk factors for venous thromboembolism (VTE). The purpose of this systematic review/meta-analysis was to evaluate the rate of VTE in pregnant patients with active malignancy compared with pregnant patients without malignancy.

Material and methods: Embase, Medline/PubMed, Cochrane Database, and clinicaltrial.gov were search by a trained librarian from inception until June 2021, and limited to English and French language human studies using keywords related to pregnancy, neoplasm, and thrombosis. This study was prospectively registered with PROSPERO (CRD42021245886). Title, abstract, and full-text review was performed using the Covidence data management system. Two authors reviewed the studies independently. Of the 3821 articles screened, seven cohort studies were included that reported VTE rate in patients with active malignancy in pregnancy.

Results: A total of 5928 individuals had active malignancy and pregnancy. Active malignancy in pregnancy significantly increased the odds of a VTE (odds ratio [OR] 6.8, 95% confidence interval [CI] 3.8–12.1). Specifically, patients with thyroid (OR 2.7, 95% CI 1.3–6.3), cervix (OR 6.6, 95% CI 2.4–18.0), or other gynecological (OR 10.6, 95% CI 4.4–25.8) cancers; Hodgkin's lymphoma (OR 8.7, 95% CI 3.3–23.4); or acute leukemia (OR 17.1, 95% CI 10.9–26.8) all had increased odds, whereas those with brain cancer (OR 6.1, 95% CI 0.4–98.2), breast cancer (OR 2.5, 95% CI 0.3–17.4), malignant melanoma (OR 5.5, 95% CI 0.3–88.1), or non-Hodgkin's lymphoma (OR 3.2, 95% CI 0.8–12.9) malignancies did not have statistically significant increased odds for VTE. No studies reported whether prophylactic anticoagulation was used during pregnancy in this population; nor did they report timing in pregnancy of the VTE. The absolute risk for VTE in those with active malignancy was 0.9% compared with 0.2% in those without active malignancy in pregnancy.

Abbreviations: CI, confidence interval; HCUP-NIS, Health Care Cost and Utilization Project—Nationwide Inpatient sample; LMWH, low-molecular-weight heparin; OR, odds ratio; VTE, venous thromboembolism.

Conclusions: Pregnancy with active malignancy confers a significant increased risk for VTE compared with pregnancy alone. Given this finding, prophylactic anticoagulation during pregnancy and postpartum could be considered in this patient population. Data are underpowered to make firm recommendations per cancer type.

KEYWORDS
cancer, malignancy, pregnancy, systematic review, thromboprophylaxis, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is one of the leading causes of maternal mortality. Most clinical guidelines recommend thromboprophylaxis during pregnancy if the patient is deemed high risk; with the Society of Obstetricians & Gynaecologists of Canada specifically recommending that prophylaxis is indicated if absolute risk for VTE is 1% or more.[1,2] Approximately 1 in every 1000 individuals have an active malignancy during pregnancy and the postpartum period.[3,4] Although still rare, the rates are increasing.[5] The management of pregnancy and active malignancy is often based on expert opinions rather than randomized controlled trial evidence.

Both active malignancy and pregnancy are independent risk factors for VTE. Management strategies for patients with both active malignancy and pregnancy have not been addressed in most guidelines for thrombosis in pregnancy.[1,2,6–8] A recent cohort study determined the rate of VTE during pregnancy in those with active malignancy at 75.2 per 10 000 pregnancies, compared with 10.7 per 10 000 pregnancies in those without an active malignancy.[9] Based on this evidence, some experts have advocated for thromboprophylaxis in this patient population given the high incidence of VTE.

The purpose of this systematic review/meta-analysis was to evaluate the rate of VTE in pregnant patients with active malignancy compared with pregnant patients without malignancy; and to evaluate the role of thromboprophylaxis within this population.

Key message

Active malignancy during pregnancy confers a high risk for venous thromboembolism and thromboprophylaxis can be considered in this population.

2 | MATERIAL AND METHODS

2.1 | Search strategy

This review followed MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines. EMBASE, Medline/PubMed, Cochrane Database and clinicaltrial.gov were searched, with the assistance of a trained librarian, from inception of the databases until June 2021 using a combination of keywords related to: pregnancy, neoplasm, and thrombosis/thromboprophylaxis. Before publication, August 2023, databases were researched to ensure that no new publications met the inclusion criteria. We limited the search to English and French language and human participants. Reference lists from review articles, systematic reviews, and manuscripts were hand searched to obtain additional articles.

2.2 | Study selection and eligibility criteria

Studies were included if the population had active malignancy in pregnancy. Exclusion criteria included VTE diagnosed before pregnancy, if the only malignancy reported was myeloproliferative disorder, and if pathology showed benign tumors. The primary outcome was the incidence of VTE during pregnancy or 6 weeks postpartum in women with active malignancy. The secondary outcomes included use of thromboprophylaxis during pregnancy with active malignancy and potential adverse pregnancy complications associated with its use.

Each study was screened by two reviewers in two stages, with abstract review followed by full-text review of selected articles. A third independent reviewer and discussion resolved discrepancies. The Covidence data-management system was used to organize article screening.

2.3 | Data extraction

The data extraction protocol was determined before beginning the literature search. Data extraction used a modified data form based on the Cochrane data collection form for non-randomized controlled trials and was performed by two independent reviewers.[10] Data extracted included type of malignancy, gestation age at malignancy, rate of deep vein thrombosis, pulmonary embolism, cavernous sinus thrombosis, other thrombosis, use of prophylactic anticoagulation in pregnancy and/or postpartum and complications of its use including

antepartum/postpartum hemorrhage, placental abruption, and heparin-induced thrombocytopenia.

2.4 | Assessment of risk of bias

Methodological quality and risk of bias of the included studies were assessed using the Newcastle-Ottawa scale.[11] Two authors assessed eligible studies independently with discrepancy resolved by a consensus meeting with a third author. The Newcastle-Ottawa scale contains eight categories relating to methodological quality and each study can receive a score up to 9. A score of 0–3 is low quality, 4–6 is moderate quality, and 7–9 is high quality. Articles scoring high were deemed low risk for bias.[11]

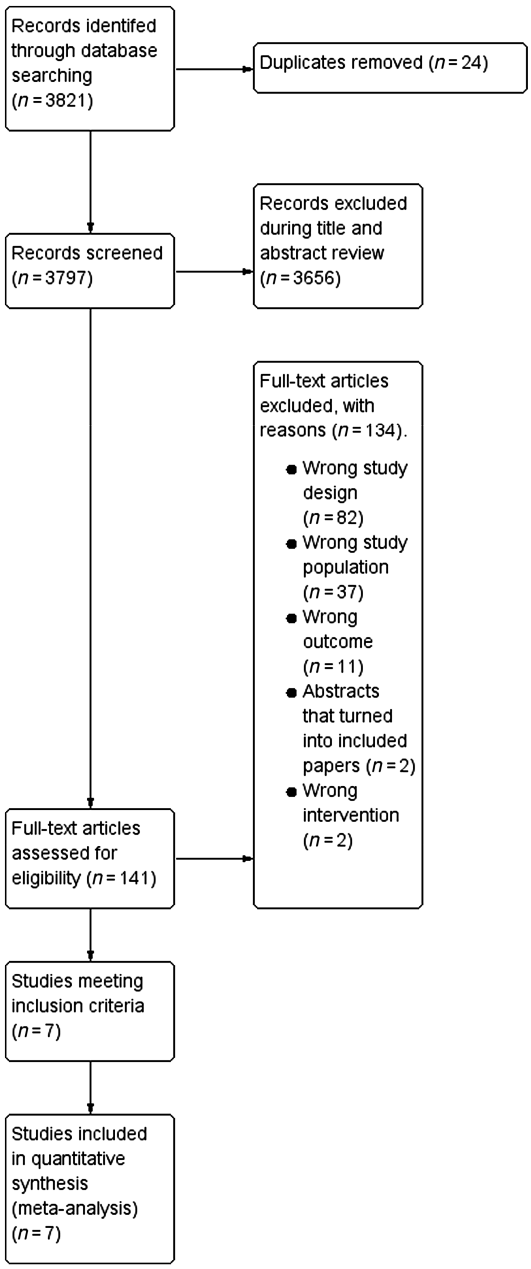

FIGURE 1 PRISMA diagram of the literature review.

2.5 | Statistical analyses

Data analysis was performed using RevMan 5.4 software. Odds ratio (OR) and 95% confidence interval (CI) were calculated for the primary outcome. Statistical heterogeneity was determined using the Higgins I^2 statistics. Mantel-Haenszel random effects model was used to pool and analyze data from the studies.

This review was registered in PROSPERO (CRD42021245886); no published protocol. Patient consent and institutional review board approval was not required for this type of study.

3 | RESULTS

The initial literature search identified 3821 studies; 3656 articles were excluded after review of their titles and abstracts. In all, 141 full texts were assessed, and seven cohort studies met the inclusion criteria (Figure 1). No randomized control trials or unpublished abstracts were identified. All included studies were retrospective cohort studies of individuals with active malignancy in pregnancy.[9,12–17] Risk of bias using the Newcastle-Ottawa scale found all included studies were of high quality, and low risk of bias (Table 1).

A total of 5928 individuals with malignancy in pregnancy were included in this study. Characteristics of the included studies are described in Table 2. Studies included a wide range of malignancies in pregnancy, with breast, hematological, and thyroid being the most common.

Overall, the odds of a VTE in those with active malignancy were higher than in those without malignancy in pregnancy (OR 6.8, 95% CI 3.8–12.1) (Figure 2A). The absolute risk for VTE in those with active malignancy is 0.9%, compared to 0.2% without malignancy in pregnancy. A funnel plot demonstrated no evidence of publication bias for the primary outcome (Figure 3). A sensitivity analysis of our primary outcome was performed as six of the seven studies used the United States Health Care Cost and Utilization

TABLE 1 Risk of bias scores assessed using the Newcastle-Ottawa scale for all included trials.

Study	Selection	Comparability	Outcome	Study quality
Al-Halal et al.[12]	4	2	3	High
Bleau et al.[13]	4	2	3	High
El-Messidi et al.[14]	4	1	3	High
Greiber et al.[9]	4	1	3	High
Nazer et al.[15]	4	2	3	High
Nolan et al.[16]	4	1	3	High
Spiegel et al.[17]	4	1	3	High

Project—Nationwide Inpatient sample database (HCUP-NIS) with inclusion criteria that contained overlapping years.[12-17] We completed sequential analyses that included only cohorts that could be confirmed based on inclusion criteria to be exclusive of other included studies. The results of the sensitivity analyses did not differ from our main result; the OR for those with active malignancy in pregnancy was significantly increased compared with those without malignancy.

Only two studies provided data specifically for rate of deep vein thrombosis and pulmonary embolism. The odds of deep vein thrombosis were significantly higher in those with malignancy compared with those without (OR 4.9, 95% CI 2.4–9.8; Figure 2B), similarly, the odds of pulmonary embolism were significantly higher as well (OR 7.5, 95% CI 2.1–27.7; Figure 2C). No data were provided in any of the cohort studies regarding use of prophylactic anticoagulation during pregnancy or postpartum, timing of VTE, or for any other type of VTE.

The event rate of VTE was reported for specific malignancy types in some articles. Table 3 demonstrates the OR for VTE based on malignancy type. Odds of VTE were increased in pregnancy with active thyroid (OR 2.7, 95% CI 1.3–6.3), cervix (OR 6.6, 95% CI 2.4–18.0), or gynecological (non-cervical cancer) (OR 10.6, 95% CI 4.4–25.8) cancers; Hodgkin's lymphoma (OR 8.7, 95% CI 3.3–23.4); and acute leukemia (17.1, 95% CI 10.9–26.8) (Table 3).

TABLE 2 Characteristics of included studies.

Study	Study type	Type of cancer	Individuals with malignancy	Primary outcome
Al-Halal et al.[12]	Retrospective cohort	Cervical	294	Rate of VTE in pregnancy
Bleau et al.[13]	Retrospective cohort	Breast (567) Ovarian (119) Cervical (257) Hematological (1421) CNS (113) Thyroid (223) Other (126)	2826	Rate of VTE in pregnancy
El-Messidi et al.[14]	Retrospective cohort	Hematological non-Hodgkin's lymphoma	427	Rate of VTE in pregnancy
Greiber et al.[9]	Retrospective cohort	Breast (229) Cervical (196) CNS (41) Gastrointestinal (52) Hodgkin's lymphoma (32) Leukemia (38) Melanoma (362) Non-Hodgkin's lymphoma (14) Ovarian (53) Thyroid (45) Other (268)	1330	Rate of VTE in pregnancy
Nazer et al.[15]	Retrospective cohort	Ovarian Malignant ovarian mass (88) Fallopian tube (1) Uterine adnexa (2) Ovarian tumor of low malignant potential (88)	179	Rate of VTE in pregnancy
Nolan et al.[16]	Retrospective cohort	Hematological AML (178) ALL (99) Acute leukemia NYD (14)	291	Rate of VTE in pregnancy
Spiegel et al.[17]	Retrospective cohort	Thyroid	581	Rate of VTE in pregnancy

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; NYD, not yet diagnosed; VTE, venous thromboembolism.

4 | DISCUSSION

The results of this meta-analysis demonstrate a significant increased risk for VTE during pregnancy with active malignancy. Unfortunately, none of the included cohort studies reported whether prophylactic anticoagulation was used during pregnancy within this patient population. In addition, given the rarity of this patient population, no randomized controlled trials have been or are likely be conducted to address this topic.

Both pregnancy and active malignancy are conditions where all three components of Virchow's triad for the development of VTE—venous stasis, hypercoagulable state, and endothelial vessel-wall damage—are present.[18] Pregnancy physiology significantly increases hypercoagulation and venous stasis and cancer physiology significantly alters expression of hemostatic proteins, production of inflammatory cytokines, and adhesion of tumor cells to the endothelium; providing the perfect milieu for the development of VTE.[19,20]

Most clinical practice guidelines, including the Society of Obstetricians and Gynaecologists of Canada, American College of Obstetricians and Gynecologists, and Royal College of Obstetricians and Gynaecologists identify cancer as a risk factor for VTE in pregnancy.[1,7,8] At present, none of the clinical practice guidelines recommend thromboprophylaxis if the only risk factor is active malignancy. The Society of Obstetricians and Gynaecologists of Canada guideline reports absolute risk for VTE in this population at less than 0.4%, whereas other guidelines simply state that active malignancy is a risk factor.[1,21] This meta-analysis of recent cohort studies demonstrates that the risk for VTE is much higher than previously reported in patients with active malignancy in pregnancy. Similarly, cancer literature has now shown

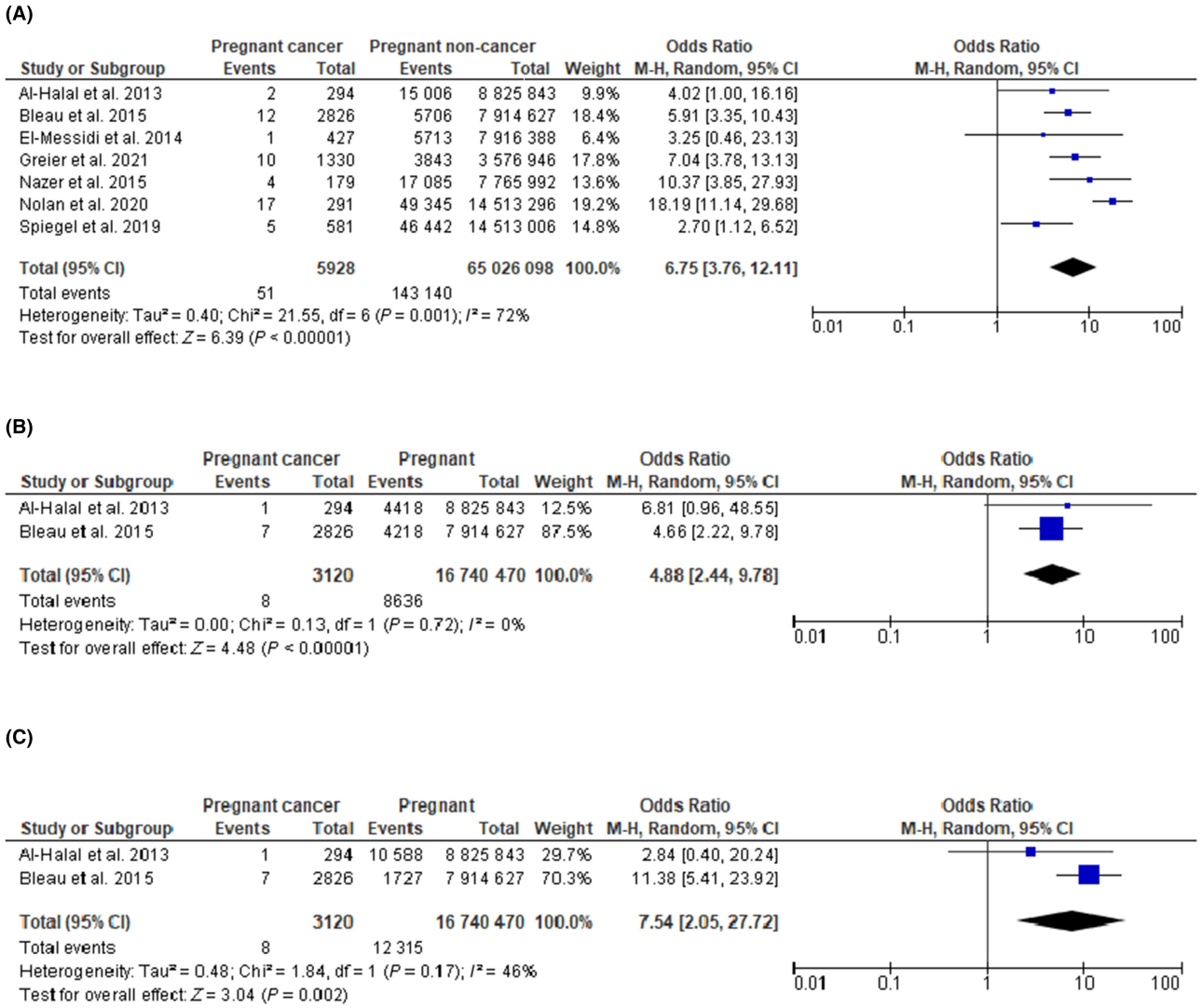

FIGURE 2 (A) Forrest plot of venous thromboembolism rate in pregnant individuals with malignancy compared with non-malignancy pregnant individuals. (B) Forrest plot of deep vein thrombosis rate in pregnant individuals with malignancy compared with non-malignancy pregnant individuals. (C) Forrest plot of pulmonary embolism rate in pregnant individuals with malignancy compared with non-malignancy pregnant individuals.

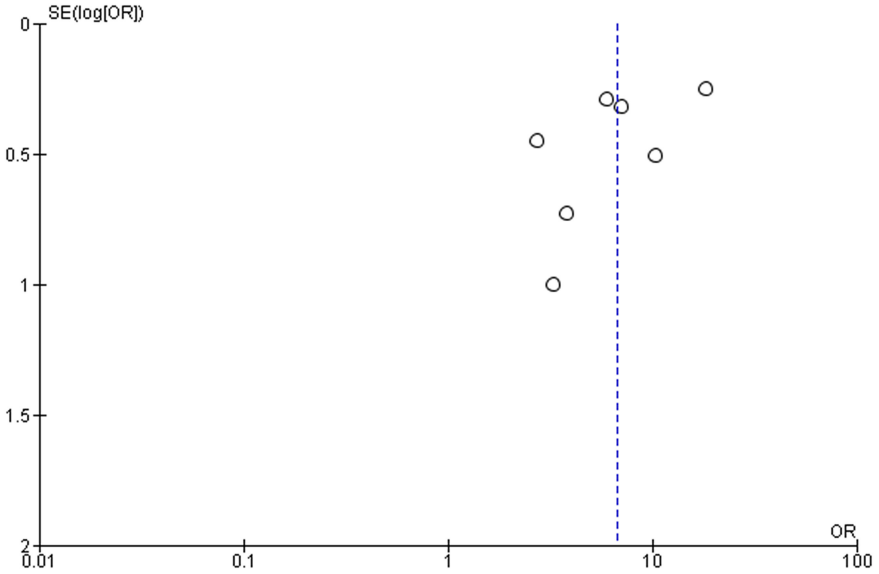

FIGURE 3 Funnel plot for venous thromboembolism rates in all studies comparing patients with malignancy in pregnancy to non-malignancy pregnant individuals.

TABLE 3 Odds ratio for venous thromboembolism in pregnancy by malignancy type.

Malignancy type	OR (95% CI)
Brain	6.1 (0.4–98.2)[13]
Thyroid	2.7 (1.2–6.3)[13,17]
Breast	2.5 (0.3–17.4)[13]
Cervix	6.6 (2.4–18.0)[12,13]
Gynecological, non-cervical	10.6 (4.4–25.8)[13,15]
Malignant melanoma	5.5 (0.3–88.1)[13]
Hodgkin's lymphoma	8.7 (3.3–23.4)[13]
Non-Hodgkin's lymphoma	3.2 (0.8–12.9)[13,14]
Leukemia	17.1 (10.9–26.8)[13,16]

that during the first year after a cancer diagnosis the risk for VTE is elevated over eightfold.[22]

Prophylactic anticoagulation with low-molecular-weight heparins (LMWH) has been demonstrated to be safe in pregnancy and postpartum. Downfalls of prophylactic anticoagulation in pregnancy include patient discomfort with injections, the cost of medication, and a potential delay in neuraxial anesthesia.[1] Risk for antepartum hemorrhage is minimally elevated at 0.4%, skin reaction at 0.9%, and osteoporosis at 0.3%, but there were no cases of heparin-induced thrombocytopenia.[1,23] A recent systematic review found, in the context of pregnancy, that using LMWH is preferred by pregnant individuals given its net benefit if they meet the criteria for thromboprophylaxis.[24] Only one prospective hospital-based database trial has been published; using a scoring system when patients were admitted to hospital and assessing the role of LMWH in pregnant individuals with malignancy. Principal findings from this study included that most women scored as high risk for VTE, and prophylaxis use may reduce maternal morbidity and mortality in pregnant individuals with malignancy.[25] Given this increased risk for VTE in this population and the relative safety of prophylactic treatment, thromboprophylaxis during pregnancy and postpartum should be considered.

When assessing risk for VTE based on cancer type, we found that not all malignancies were associated with increased odds for VTE. Not all studies reported data by cancer type and therefore these results are based on small numbers. The principal investigators of these papers were contacted, but unfortunately, due to limitations of the data sets used in their original papers, they were not able to provide us with individual cancer types to aid with this subgroup analysis. In addition, several trials reporting type of cancer used overlapping years of the HCUP-NIS, and therefore the same patients may have been included twice in the analysis. Given the limited numbers, we feel we are unable to make recommendations based on specific cancer types.

This is the first systematic review/meta-analysis addressing VTE rate in patients with active malignancy during pregnancy. Included cohort studies were all of high quality and had low risk for bias. The funnel plot demonstrated no evidence of publication bias. Studies included used large population-based databases helping to increase the generalizability of the findings. Limitations include inherent challenges to a meta-analysis including how the data were reported in the original trials. We attempted to contact the original authors to obtain breakdown of cancer types with VTE; however, this information was not available due to limitation of their original data collection. Six of the included trials used the HCUP-NIS with overlapping years; we did attempt to adjust for this by performing a sensitivity analysis; however, we may be over-reporting the true risk for VTE in this population. The heterogeneity between studies was high, limiting the generalizability of the findings. Similarly, no included cohort study reported if patients were offered

prophylactic anticoagulation during pregnancy. It is likely that some patients in these studies were treated with prophylactic anticoagulation given that previous papers advocate this approach, and therefore we may be underreporting the true risk for VTE in this population. Similarly, we are unable to comment on the role of prophylactic anticoagulation to reduce the risk for VTE in this population based on the available published included studies. Lastly, whether patients' received surgery and/or chemotherapy in pregnancy was not reported and therefore we are unable to assess whether these interventions further raised the risk for VTE.

Further directions for research in this area should include the development of a prospective database of individuals with active malignancy in pregnancy to collect data regarding VTE rate and the use of prophylactic anticoagulation during pregnancy by difference cancer types.

5 | CONCLUSION

Pregnancy in individuals with active malignancy confers a significant increased risk for VTE; the use of prophylactic anticoagulation during pregnancy and postpartum can be considered within this population.

AUTHOR CONTRIBUTIONS

CMN and AM: study design; CMN and SF execution/analysis; CMN, AM, and SF manuscript drafting.

ACKNOWLEDGMENTS

The authors thank Darlene Chapman, IWK Health Centre-funded librarian for designing and performing the literature search for this study.

FUNDING INFORMATION

This project did not receive any funding.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to report.

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REFERENCES

1. Chan WS, Rey E, Kent NE, et al. SOGC clinical practice guideline 308: venous thromboembolism and antithrombotic therapy in pregnancy. *J Obstet Gynaecol Can*. 2014;36:527-553.
2. Thrombosis Canada. *Clinical guide pregnancy: thromboprophylaxis 2020*. Accessed February 2023. https://thrombosiscanada.ca/clinicalguides/
3. Hepner A, Negrini D, Hase EA, et al. Cancer during pregnancy: the oncologist overview. *World J Oncol*. 2019;10:28-34.
4. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol*. 2003;189:1128-1135.
5. Lee Y, Roberts C, Dobbins T, et al. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994–2008: a population-based linkage study. *BJOG*. 2012;119:1572-1582.
6. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2:3317-3359.
7. Nelson-Piercy C, MacCallum P, Mackillop L. *Green Top Guideline No 37a: Reducing the Risk of Venous Thromboembolism during Pregnancy and Puerperium*. Royal College Obstetricians & Gynaecologists UK; 2015. https://www.rcog.org.uk/media/qejfhcaj/gtg-37a.pdf
8. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins. ACOG practice bulletin No 196: thromboembolism in pregnancy. *Obstet Gynecol*. 2018;132:e1-e17. doi:10.1097/AOG.0000000000002706
9. Greiber I, Mikkelsen A, Karlsen M, et al. Cancer in pregnancy increases the risk of venous thromboembolism: a nationwide cohort study. *BJOG*. 2021;128:1151-1159.
10. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated march 2011]. 2011. *The Cochrane Collaboration*. Accessed February 20, 2023. www.cochrane-handbook.org
11. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomiazed studies in meta-analysis*. Accessed February 20, 2023. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
12. Al-Halal H, Kezouh A, Abenhaim HA. Incidence and obstetrical outcomes of cervical intraepithelial neoplasia and cervical cancer in pregnancy: a population-based study on 8.8 million births. *Arch Gynecol Obstet*. 2013;287:245-250.
13. Bleau N, Patenaude V, Abenhain HA. Risk of venous thromboembolic events in pregnant patients with cancer. *J Matern Fetal Neonatal Med*. 2016;29:380-384.
14. El-Messidi A, Patenaude V, Abenhaim HA. Incidence and outcomes of women with non-Hodgkin's lymphoma in pregnancy: a population-based study on 7.9 million births. *J Obstet Gynaecol Res*. 2015;41:582-589.
15. Nazer A, Czuzoj-Shulman N, Oddy L, Abenhaim HA. Incidence of maternal and neonatal outcomes in pregnancies complicated by ovarian masses. *Arch Gynecol Obstet*. 2015;292:1069-1074.
16. Nolan S, Czuzoj-Shulman N, Abenhaim HA. Obstetrical and newborn outcomes among women with acute leukemias in pregnancy: a population-based study. *J Matern Fetal Neonatal Med*. 2020;33:3514-3520.
17. Spiegel E, Spence AR, Czuzoj-Shulman N, Abenhaim HA. Pregnancy outcomes after thyroid cancer. *J Perinat Med*. 2019;47:710-716.
18. Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol*. 2008;143:180-190.
19. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol*. 2003;16:153-168.
20. Brenner B, Avivi I, Lishner M. Haematological cancers in pregnancy. *Lancet*. 2012;379:580-587.
21. Sultan AA, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. *Blood*. 2013;121:3953-3961.
22. Cronin-Fenton DP, Sondergaard F, Pederson LA, et al. Hospitalization for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006. *Br J Cancer*. 2010;103:947-953.
23. Greer IA, Nelson-Piercy C. Low-molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005;106:401-407.

24. Leon-Garcia M, Humphries B, Maraboto A, et al. Women's values and preferences on low-molecular-weight heparin and pregnancy: a mixed-methods systematic review. *BMC Pregnancy Childbirth*. 2022;22:747.
25. Hase EA, de Barros VIP, Igai AMK, et al. Risk assessment of venous thromboembolism and thromboprophylaxis in pregnant women hospitalized with cancer: preliminary results from a risk score. *Clinics*. 2018;73:e363-e368.

How to cite this article: Folkins S, Miller A, Nash CM. Risk of venous thromboembolism in pregnant patients with active malignancy: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2023;00:1-8. doi:10.1111/aogs.14712