Meta-Analysis of Observational Studies in Epidemiology

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The risk of venous thromboembolism in women with inflammatory bowel disease during pregnancy and the postpartum period

A systematic review and meta-analysis

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Abstract

Pregnancy and inflammatory bowel disease (IBD) are independent risk factors for venous thromboembolism (VTE). Nevertheless, the optimal VTE prevention strategy for women with IBD in pregnancy and postpartum period has not been established yet. We assessed VTE risks during pregnancy and the postpartum period in women with IBD through systematic review and meta-analysis.

Systematic searches were conducted in MEDLINE (Ovid), Embase (Ovid), CENTRAL (Ovid), and Web of Science (Tomson Reuters) from the database inception till May 2017 to identify relevant studies reporting the risk of VTE during pregnancy and/or the postpartum period in women with IBD. Random effect meta-analyses were performed to compare VTE-related outcomes between women with IBD and without IBD. Our protocol was registered: CRD 42017060199 in the PROSPERO International prospective register of systematic reviews.

In the analysis of 5 studies reviewed, IBD population (n = 17,636) had a significantly increased risk of VTE during pregnancy (pooled risk ratio (RR) 2.13, 95% confidence interval (CI) 1.66–2.73) and postpartum (RR 2.61, 95% CI 1.84–3.69), comparing to the non-IBD population (n = 11,251,778). According to the location of VTE, the risk of deep vein thrombosis increased significantly by RR of 2.74 (95% CI 1.73–4.36) during pregnancy, whilst risk increase of pulmonary embolism was not statistically significant. In the subgroup analysis, the degree of VTE risk was higher in both periods in the UC group than in the CD group, as compared to that in the non-IBD population (UC group, during pregnancy: RR 2.24, 95% CI 1.6–3.11; postpartum period: RR 2.85, 95% CI 1.79–4.52).

Significantly increased risks of VTE during pregnancy were found in the women with IBD, according to the periods and type of IBD, which might support a detailed strategy regarding administration of prophylactic anticoagulants to women with IBD.

Abbreviations: CD = Crohn disease, CI = confidential intervals, DVT = deep venous thrombosis, GRADE = Grading of Recommendations Assessment, Development and Evaluation, IBD = inflammatory bowel disease, ICD = International Classification of Diseases, LMWH = low-molecular-weight heparin, PE = pulmonary embolism, RR = risk ratio, UC = ulcerative colitis, VTE = venous thromboembolism.

Keywords: Crohn disease, inflammatory bowel disease, pregnancy, ulcerative colitis, venous thromboembolism

1. Introduction

The incidence of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn disease (CD), is increasing worldwide, particularly in developed nations.[1] The peak ages of IBD disease onset overlap with the reproductive period of women, and therefore the proper management of pregnant patients is crucial.[2,3] Importantly, women with IBD may have higher

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incidences of adverse pregnancy outcomes including congenital abnormalities, miscarriages, stillbirth, prematurity, and abnormal growth patterns of the neonate.[4–9]

Venous thromboembolism (VTE) is one of the major life-threatening complications associated with pregnancy.[10–13] Despite its low incidence of 1 to 2 occurrences per 1000 pregnancies (and related puerperium periods), it remains a leading cause of pregnancy-related maternal mortality in developed countries[10] and a cause of long-term neurological morbidities like post-thrombotic syndrome.[11,14–17] Physiologic changes related to pregnancy and delivery, including hypercoagulability, hormonally induced changes in venous blood flow, mechanical obstruction by the gravid uterus, and vascular injury, contribute to the increased susceptibility to thrombosis-related morbidity.[18] The relative risk of VTE in pregnancy increases 4-fold to 6-fold comparing to non-pregnant women, and 5-fold increase in postpartum compared with that of the antepartum period.[11,15] The pregnancy-related changes in the physiological parameters return to pre-pregnancy levels at variable times during the postpartum period, but some changes do not resolve until 6 to 12 weeks postpartum.[16–18]

IBD is also an independent risk factor for VTE. The prevalence of VTE in non-pregnant IBD patients was reported at 1.2% to 6.7% with overall risk of 2- to 3-fold of that in non-IBD patients.[19–22] VTE occurrence has increased over the years in hospitalized IBD patients in the US, contributing to the elevated in-hospital mortality risk.[19,22] Many observational studies and case-control studies reported the VTE risk of IBD patients.[19–24] In meta-analyses, the overall risk of VTE (deep vein thrombosis and pulmonary embolism) was estimated to be 2- to 3-folds higher in IBD group than general population.[25,26] This relationship can be supported from crosstalk between coagulation and inflammation because pro-inflammatory stimuli activate the clotting cascade, and simultaneously, coagulation affects the inflammatory pathways.[27] Hospitalization, active disease, and surgery increase the relative risk of thrombosis in IBD patients.[28,29]

A combination of pregnancy and IBD poses a challenge in the patient management for the potential increase in VTE risk. The elevated VTE risks in women with IBD during pregnancy and postpartum period were suggested in observational studies.[30–34] However, the magnitude of risk-increase of VTE in pregnant patients with IBD, whether it is additive or synergistic, has not been clearly defined because it requires a large dataset to address the question. In addition, if UC and CD carry a different risk of VTE during pregnancy and post-partum has not been systematically examined. Furthermore, women with IBD are at increased risk of disease activation or the flares during pregnancy and postpartum, and it is unclear whether this exacerbation affects the onset of VTE.

In order to address these questions, we report here the first systematic review and meta-analysis for the risk of VTE related to pregnancy complicated with IBD. We consider the difference of VTE risk in the antepartum and postpartum period,[14,33,35,36] between the disease types of IBD[22–24,33] and disease severity.[19,28] Our aim is to provide summary estimates of the VTE risks in those women and uncertainties surrounding these estimates to inform the patient management and identify the immediate research needs for patients with IBD during pregnancy and post-partum periods.

2. Methods

The study protocol is registered with PROSPERO International prospective register of systematic reviews (protocol number: CRD 42017060199, http://www.crd.york.ac.uk/PROSPERO/display record.php?ID=CRD42017060199). We conducted the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[37]

As the present meta-analysis was performed based on previously published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy

The search was supervised by a librarian to ensure that all relevant studies were included. The following databases were searched from their inception till May 2017: MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Ovid), and Web of Science (Thomson Reuters) (Supplementary data 1, http://links.lww.com/MD/D250). Text words and, if applicable, database subject heading fields (e.g., Medical Subject Headings), were used to perform the searches: "Inflammatory bowel disease," "ulcerative colitis," "Crohn disease," "pregnancy," "pregnant," "antepartum," "antenatal," "postpartum," "puerperium," "thrombotic," "thromboembolism," "thrombo," "thrombic," "pulmonary embolism," "deep vein thrombosis," "thrombosis," "venous thromboembolism," "VTE," and "DVT." Subsequently, we examined the references of each of the identified studies and reviewed papers found during the search to identify further potential articles. Information available from relevant conferences was also reviewed. No language restrictions were applied.

2.2. Study selection

We established the following set of criteria to define the types of studies in peer-reviewed journals for our analyses:

1. studies of pregnant women with IBD, UC, or CD; and
2. studies assessing the risk of maternal thromboembolism diagnosed during the pregnancy period or postpartum, which included randomized controlled studies or non-randomized controlled studies, population-based studies, database analyses, cohort studies, and case-control studies.

We excluded animal studies, case reports, pilot studies containing a portion of patients evaluated in a later study of a larger sample size, and studies that did not contain original data. All available abstracts, titles, and keywords from the search were screened independently by 2 reviewers (YK and BP), who extracted the full text of all the studies that met the inclusion criteria. The same reviewers individually investigated these full text articles to ensure final agreement with the inclusion criteria, and then they selected adequate studies for inclusion in the review. Any discrepancy between the 2 reviewers was solved by discussion and eventual consensus between them. If it was deemed necessary, a third reviewer became involved (SI).

2.3. Data extraction

The data extractors reviewed each of the included studies independently and extracted the data according to pre-determined guidelines, using a pre-designed data extraction form. A

separate spreadsheet was created to document the details of the studies included in the review (author, publication year, study type, number of participants, and outcome measures). All studies excluded from this systematic review were documented in another spreadsheet with a description of the reason for exclusion. Every effort was made to retrieve any missing data from the study authors. In case of patient overlap between the studies, the study with the smaller population was excluded from the analysis.

The extracted information was divided into 3 categories: study variables, maternal variables, and outcomes. Included study variables were as follows: study type, publication date, study population, and number of women with IBD and comparison/control subjects. If reported, the data for each subgroup of IBD, specifically UC or CD, were separately extracted. The maternal variables were as follows: age, smoking, body mass index, cesarean section and chronic medical disease status, including diabetes, hypertension, and allergic or rheumatic diseases other than inflammatory bowel diseases. The outcome variables included the period during which the outcomes occurred (antepartum, during pregnancy, postpartum, or puerperium), confounders controlled for, numbers of occurrence of VTE, deep vein thrombosis and pulmonary embolism. Risk estimates of outcomes were extracted as odds ratios (ORs) or relative risk (RRs) and their 95% confidence intervals (CI), if reported. When data of IBD patients was not reported in the studies,[31,39] we combined data on UC and CD to derive the VTE risk estimates of IBD as a whole, because UC and CD are predominant IBD types.[40]

2.4. Data presentation

The selection process of the studies is documented using the PRISMA flow chart (Fig. 1), and includes an overall summary of the number and types of articles incorporated into the review.

2.5. Quality assessment of the studies

We used the Newcastle-Ottawa Scale to assess the quality of the included studies. The scale ranges from 0 to 9, with 0 being the

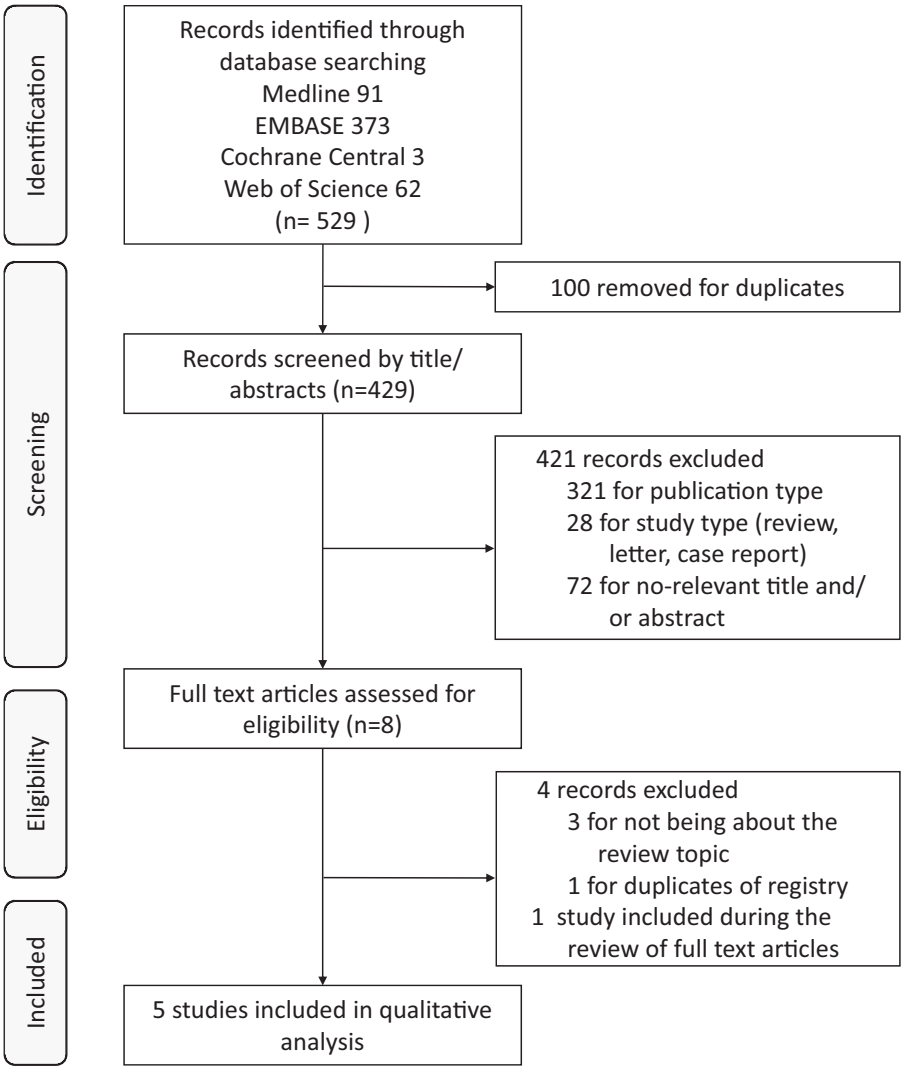

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the identification of studies on the venous thromboembolism risk during pregnancy, postpartum, or both.

lowest possible quality. The scale evaluates the following 3 main areas:

1. selection of case and control subjects (0–4 points),
2. comparability of the case and control subjects (0–2 points), and
3. analysis of outcomes (0–3 points).[41]

Regarding the comparability of the affected and control subjects, if maternal age was controlled for VTE outcomes in the studies, these studies received 1 point. If any other factor was controlled for, the studies received 2 points. Study quality was assessed independently by 2 reviewers.

2.6. Data analysis

All information was reported according to the PRISMA guidelines for reporting meta-analyses.[34] The Cochrane Collaboration's Review Manager Software (version 5.3) was used to perform the data analysis. After reviewing the extracted data from the studies, subgroup analyses were performed to determine the risk of VTE in pregnant women with UC and CD compared to pregnant women without IBD. During the data review, we noticed that some studies examined associations between disease flares during pregnancy and the subsequent or concomitant development of VTE. We therefore included them in the post-hoc subgroup analyses.

Dichotomous outcomes were pooled using the Mantel–Haenszel random-effects model, which was used to calculate the risk ratio (RRs) and corresponding 95% confidence intervals (CIs). The Chi-Squared test and I^2 statistics were used to measure heterogeneity, where an I^2 value $<40\%$ indicated as not important, 30% to 60% indicated moderate heterogeneity, values of 50% to 90% indicated substantial heterogeneity, and values $>75\%$ indicated considerable.[42] We also evaluated the presence of heterogeneity across the studies by utilizing a P value $<.10$ as evidence of statistically significant heterogeneity. To assess the potential for small study effects and publication bias, we constructed funnel plots to visualize possible asymmetry when 10 or more studies were available.[42]

When the reviewed article presented only OR or RR with 95% confidential intervals (CI) for dichotomous outcomes, the generic inverse variance method was used to combine the studies with different scales of outcome estimates for random-effect meta-analysis, calculating ln (RRs) and the SE (ln (RR)) from the event rates (available for a subset of studies). Then these studies were pooled separately for the subgroup analysis to examine the VTE risk during pregnancy and the postpartum period in women with UC and CD respectively, compared to women without IBD, because 1 study reported the number of events (VTE) and RR with 95% CI for VTE occurrence for the study population, not the number of women with CD and UC.

To make judgments regarding the quality (certainty) of evidence for each outcome, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[43] The certainty of our pooled estimates was assessed using the following criteria: risk of bias, consistency, directness, imprecision, and publication bias.

3. Results

3.1. Eligible studies

The search strategy identified 529 articles (Fig. 1), and 8 articles were selected for further analyses on the basis of the titles and abstracts. In the full text review, 3 articles were excluded owing to non-relevant outcomes and patients. Two studies used the same US registry with different study periods, and therefore, we excluded 1 with a shorter study period in favor of the 1 with a longer study period.[31,38] We found an additional article[38] during the review of full text articles, which was subsequently added to the meta-analysis.

3.2. General characteristics

The general characteristics of the 5 articles are described in Table 1. They were all retrospective, population-based, cohort studies and published after 2010. One study matched a pregnant IBD patient with 5 non-IBD pregnancy controls in age, parity, and year and month of birth. All studies used domestic registry databases in each of the 5 countries: the United States, UK, Denmark, Sweden, and Australia.[32,33,36,38,44] In total, the analysis of 17,636 pregnant women with IBD and 11,251,778 pregnant women without IBD as a control was conducted (Table 2). Four studies were included in the subgroup analysis of the risk of VTE in pregnant women with UC and CD, compared to pregnant women without IBD. The incidence of pregnancy complicated by IBD was reportedly 0.1% to 0. 6% of all deliveries,[32,36,38,44] and in the subgroups of IBD, the relative proportions of UC and CD were different among the studies. In the women with singleton birth in Sweden,[33] the number of women with UC (about 60.3%) was higher than that with CD (39.6%), whilst the study from the US found that the prevalence of disease was 4.19 for UC vs 6.76 for CD of 10,000 deliveries.[38] In Australia,[44] of total pregnant women with IBD, those with UC and CD accounted for 42.5% and 46.3%, respectively.

All the studies adjusted the VTE risks with various confounders (Table 1), including the general risk factors like age, smoking, parity and BMI, and maternal various co-morbidities. Postpartum VTE risk was adjusted by obstetric morbidities of multiple pregnancy, acute, or planned cesarean section and postpartum hemorrhage.[32,44]

3.3. Risk of bias within studies

In the quality assessment of individual studies (supplementary data 2, http://links.lww.com/MD/D250) using the Newcastle–Ottawa scales, 3 studies[32,33,36] were 9-star, and 2 studies[38,44] were 8-stars. One study was rated 1 out of 2 stars assigned to comparability section due to inadequate adjustment,[38] and 1 study was rated at 2 out of 3 stars assigned to outcome section due to incomplete follow-up of outcome in the participants.[44]

3.4. Findings of the meta-analysis

Five studies reported on the VTE risk during pregnancy and the postpartum period in women with IBD compared to those without IBD (Table 2). An IBD-associated increase of VTE risk in pregnancy was noted in 4 studies, and a postpartum risk increase was reported in 3 studies. In the meta-analysis, a significant increase in the VTE risk during pregnancy was found in women with IBD compared to no-IBD controls: the pooled RR of 2.13 (95% CI 1.78–2.66, $P<.001$) with not-important heterogeneity (Chi-Squared = 3.48, $I^2=14\%$). For the postpartum risk increase, the pooled RR of VTE was 2.61 (95% CI 1.83–3.67, $P<.001$) with no discernible heterogeneity (Fig. 2). In the subgroup analysis according to the location of VTE, the pooled RR of deep

Table 1

Study characteristics.

Study (year), country and design	Study periods	Source and characteristics of study population	IBD assessment	No. of patients with IBD	outcomes studied and assessment method			Time period of outcomes studied	IBD, outcomes and Time periods meta-analyzed	Quality of study No. of star (0–9)
					Outcomes studied and definition	Methods of VTE assessment	Confounders for adjustment			
Bleau et al (2014)[38]; USA; retrospective cohort study	2003–2011	The nationwide inpatient samples databases (HCUP-NIS); all delivery related admission cases	UC and CD identified using ICD-9 codes - clinical modification (ICD-9 CM) in medical records	Antepartum IBD (8671; CD, 5352; UC,3319)	Primary end-point defined as VTE, a diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE)	Identified in recorded medical codes at the admission for delivery using ICD-9 codes	Maternal age	Identified disease codes obtained at the delivery related admission time	1, 3, 4, 5, 6	8
Sultan et al (2013)[36]; UK; Cohort study	1995–2009	Electronic database of THIN; all ending in live birth or stillbirth for women aged 15-44	IBD status identified in medical records inpatient and outpatients	Antepartum IBD (1472), postpartum IBD (1472)	All first VTEs including DVT and PE (excluding superficial VTE)	Based on recorded medical codes and by evidence of anticoagulation prescription or a medical diagnosis indicating anticoagulant therapy within 90 days of the event or death within 30 days of the event date.	Maternal age, smoking, parity, varicose veins and acute systemic infections	Antepartum (from the date of conception to the pregnancy outcome) and postpartum (up to 12 weeks after the pregnancy outcome)	1, 2	9
Hansen et al (2017)[32]; Denmark; Cohort study	1980–2013	Population from the DNPR and the MBR; all deliveries in Denmark	Inpatient and outpatient diagnosis codes identified by the ICD-8 from 1977 until the end of 1993, and ICD-10 thereafter	Antepartum and postpartum IBD (11,978), postpartum IBD (11,978)	Both first and recurrent VTEs, and superficial thrombosis as an outcome	Recorded medical codes inpatient and outpatients, identified by the ICD-8 and 10	Antepartum: maternal age, smoking and BMI; postpartum: acute/ planned cesarean section and PPH	Diagnosed during pregnancy or the first 12 weeks postpartum	1, 2, 3, 4, 5, 6	9
Bröms et al (2012)[33]; Sweden; Population based study	2006–2009	Population from the Medical Birth Register, the Patient Register and the Prescribed Drug Register in Sweden; women with singleton births	Recorded diagnosis of UC or CD in the registry Identified by the ICD 8–10 codes*	Antepartum, IBD (2161; CD, 857; UC, 1304)	VTE diagnosed antepartum and around delivery time	From the Medical Birth and the Patient Registers, we obtained information concerning diagnoses recorded during pregnancy and at delivery for VTE	Maternal age, smoking, parity and co-morbidities†	Obtained the disease codes during pregnancy and at delivery	1, 5, 6	9
Shand AW et al (2016) [44]; Australia; Cohort study	2001–2011	Linkage of NSW perinatal data and inpatient data collection, women who gave birth at >20 weeks of gestation	Identified from the hospital data, according to the (ICD10AM)	Postpartum IBD (2781; CD, (1287; UC, 1183)	Thromboembolic events (puerperal deep vein thrombosis, pulmonary embolism or cerebral VTE)	Based on the longitudinal linkage registry of pregnancy and non-pregnancy hospital admission as well as birth history	Maternal age, smoking, parity, country of birth, SES, residence, co-morbidities‡ and multiple gestations	Up to 42days postpartum	2,5,6	7

1. IBD vs non-IBD for VTE antepartum, 2. IBD vs non-IBD for VTE postpartum, 3. IBD vs non-IBD for DVT, 4. IBD vs non-IBD for PE, 5. UC vs non-IBD for VTE, 6. CD vs non-IBD for VTE.

BMI = body mass index, BMR = Medical Birth Registry, DNPR = the Danish National Patient Registry, ICD = international classification of disease, ICD10 AM = International Classification of Disease Version 10 Australian Modification, NSW = New south Wales of Australia, PPH = postpartum hemorrhage, SES = socioeconomic status, THIN = the health improvement network of UK.

* including the patients at least 2 visits with a recorded diagnosis of UC or CD or 1 visit in combination with a record of medical or surgical treatment for IBD.

† Co-morbidities including diabetes, hypertension, primary sclerosing cholangitis, primary biliary cirrhosis, psoriasis or asthma, rheumatoid arthritis, vasculitis, or systematic lupus erythematosus were used for adjustment of risk of VTE.

‡ postpartum risk, chronic hypertension and pre-gestational diabetes were adjusted.

Table 2

Venous thromboembolism in patients with inflammatory bowel disease vs controls.

Outcome of interest	No. of studies	Patients with IBD (n)	Controls (n)	Risk ratio, random mode (95% CI)	HG $\chi 2$	HG *P* value	Grade of evidence
IBD vs Control							
VTE							
Antepartum	4	24,282	10,261,002	2.13 (1.66, 2.734)	3.01	.39	Low[†]
Postpartum	3	16,231	3,332,191	2.61 (1.84, 3.69)	1.96	.38	Moderate[‡]
DVT							
Antepartum	2	20,649	9,875,505	2.74 (1.73, 4.36)	1.77	.18	Low[†]
PE							
Antepartum	2	20,649	9,875,505	1.82 (0.81, 4.05)	0.12	.73	Very low[§]
UC vs Control[*]							
VTE							
Antepartum	3	12,056	14,087,117	2.24 (1.61, 3.11)	1.11	.57	Low[†]
Postpartum	2	8528	2,957,509	2.85 (1.79, 4.52)	0.1	.76	Low[†]
CD vs Control[*]							
VTE							
Antepartum	3	10,849	9,879,800	1.87 (1.09, 3.19)	3.21	.20	Low[†]
Postpartum	2	5933	2,957,509	1.69 (0.85, 3.38)	0	.97	Very Low[§]
Disease flares							
VTE							
Antepartum	2	5033	1,973,243	7.81 (0.90, 67.78)	26.95	<.001	Low[†]

CD = Crohn's disease, DVT = deep venous thrombosis, HG = heterogeneity, PE = pulmonary embolism, UC = ulcerative colitis, VTE = venous thromboembolism.

[*] The number of patients with IBD was estimated through the generic inverse variance method.

[†] Considering all the studies were observational studies, other outcomes were graded as low.

[‡] There was no reason to reduce the rating across the studies in the assessment, and the magnitude of the estimated effect of the pooled risk was large enough to raise the grade to moderate.

[§] Given very few studies, we graded the evidence regarding the antepartum PE risk in IBD group and postpartum VTE risk in CD group as very low.

vein thrombosis significantly increased in pregnant women with IBD, compared to non-IBD pregnant women, by 2.73 (95% CI, 1.78–2.66, $P < .001$), with moderate heterogeneity (Chi-Squared = 1.77; $I^2 = 44\%$). For pulmonary embolism, the pooled RR increased in pregnant women with IBD but the increase was not significant (1.82, 95% CI 0.81–4.05, $P = .15$).

Fig. 3 shows the forest plots of the subgroup analysis of UC and CD in the 4 studies for the risk of VTE, comparing to women without IBD, as the control for both. The pooled RR of VTE in patients with UC significantly increased during pregnancy (RR 2.24, 95% CI 1.61–3.11, $P < .001$) and postpartum (RR 2.85, 95% CI 1.79–4.52, $P < .001$). In the CD group, the risk in pregnancy significantly increased, with a pooled RR of 1.87 (95% CI 1.09–3.19, $P = .001$) with moderate heterogeneity (Chi-Squared = 3.21, $I^2 = 38\%$), but not in the postpartum period (RR 1.69, 95% CI 0.84–3.38, $P = .14$).

Two studies reported the incidence of VTE (2 during antepartum and 1 during postpartum) in the context of the disease flares during pregnancy. The pooled RRs of pregnancy-associated VTE during disease flares increased to 7.81 (95% CI 0.90–67.78).[32,33]

We evaluated the synthesized evidence applying the GRADE system (Table 2). The quality of the evidence of the postpartum VTE risk in the overall IBD group was graded as moderate. There was no reason to reduce the rating across the studies in the assessment, and the magnitude of the estimated effect of the pooled risk was large enough to raise the grade to moderate. Given very few studies, we graded the evidence regarding the antepartum PE risk in IBD group and postpartum VTE risk in CD group as very low. Considering all the studies were observational studies, other outcomes were graded as low.

4. Discussion

The risk of VTE during pregnancy was found to be 2-fold higher in the IBD group compared to the non-IBD control group. The risk increase was even higher in the postpartum period, with a pooled RR of 2.6. When deep vein thrombosis and pulmonary embolism were analyzed separately, we found the IBD-associated risk increase was pronounced in deep vein thrombosis compared to pulmonary embolism. In the subgroup analysis of IBD types, patients with UC exhibited significantly higher RRs of VTE in both pregnancy and postpartum period, while the risk increase in those with CD was statistically significant only during pregnancy. However, it should be interpreted with caution because weaker association might be related to relatively small numbers of pulmonary embolism and women with CD.

In general, pregnant women develop VTE 4 to 5 times more frequently than non-pregnant women.[11,15] Furthermore, IBD is also reported as an independent risk factor of VTE.[18,19,22] Because pregnancy itself is a hypercoagulable state, a combination of IBD and pregnancy is likely to intensify the risk of VTE, showing a synergistic interaction between the 2 factors. Indeed, our analysis proposed that the VTE risk increase in pregnant IBD women is 10-fold compared to non-pregnant women without IBD.

Concerning the risk of VTE in patients with UC and CD, the pooled RRs in patients with UC were significantly higher in both during pregnancy and postpartum period than non-IBD pregnant women. The increased VTE risk in patients with CD was significant only during pregnancy. This result is comparable with the findings of 2- to 3-fold increased odds of VTE in pregnant women with UC vs a 1- to 2-fold increase in those with CD.[32,33,44] Some studies of non-pregnant population reported higher VTE rates in UC patients than CD patients.[23,25,26,45] The reports that have identified a discrepancy of VTE risk between UC and CD, including the findings of the pooled data herein, might raise an issue of IBD type-specific approach.

IBD flares reportedly increase the risk of VTE, although few studies have quantified this finding in pregnant women.[28,46–48] The point estimate of the pooled RR of VTE in pregnancy increased about 8 times in women with IBD flares, but this was

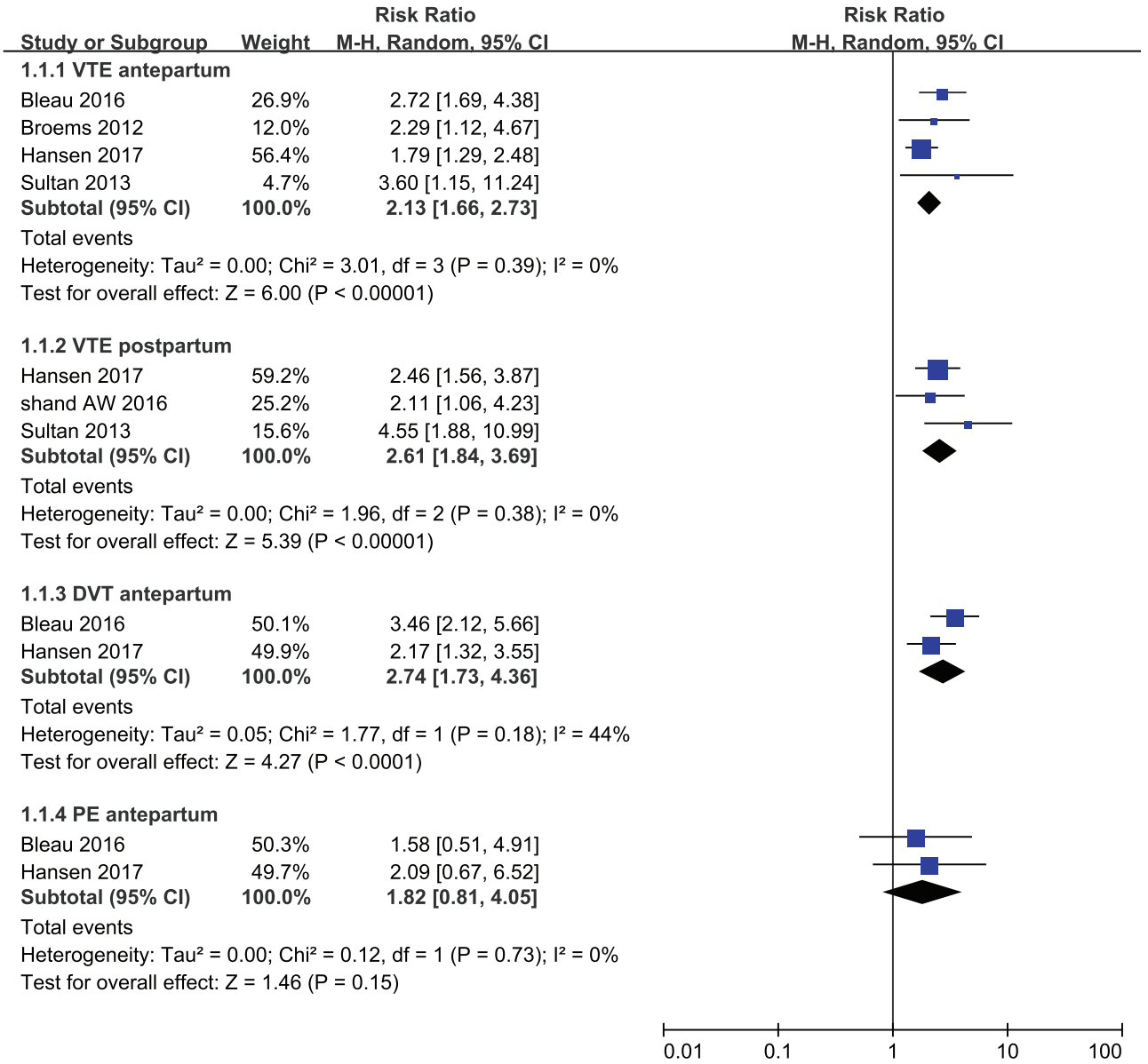

Figure 2. Comparison of outcomes of pregnant women with inflammatory bowel disease (IBD) and those without IBD. The outcomes were venous thromboembolism (VTE) during pregnancy (1.1.1), VTE postpartum (1.1.2), deep vein thrombosis (DVT) during pregnancy (1.1.3), and pulmonary embolism (PE) during pregnancy (1.1.4). Test for heterogeneity: χ^2 statistics with degrees of freedom (df) and *P* values, inconsistency among the results: I^2, test for overall effect: Z statistic with *P* value. CI = confidence interval.

not statistically significant with a high degree of heterogeneity (Chi-Squared = 26.95, $I^2 = 96$). This analysis included only 2 studies to assess the association between VTE and flares, which was differently defined in both. Consequently, this result is limited to clinical application. The flares during pregnancy occurred to over one-third of women with IBD,[32] and more prevalently in UC patients (36.7%) than CD (25.6%).[33] A prospective study for the clinical course of IBD related to pregnancy also noted women with UC were more likely to relapse in both periods during pregnancy and postpartum than non-pregnant UC women, whereas the CD women showed no difference in disease course.[2] Further studies are required to determine whether the observed increased risk of VTE in patients with UC is due to the increased risk of flare and active disease in pregnancy among patients with UC, rather than due to the diagnosis of UC itself.

In the present study, we divided the timing of onset of VTE occurrence into 2 periods: during pregnancy and postpartum. Several studies examined VTE risk in the different stages of pregnancy and the postpartum period.[49,50] The highest prevalence was found during the third trimester of the pregnancy at a 6-fold higher rate than anytime outside of pregnancy. For the postpartum period, the peak occurrence of VTE was in the first 3 weeks after delivery.[16,49] We speculate that use of an in-patient delivery registry is prone to overestimation of VTE occurrence during pregnancy because of the inclusion of VTE cases that occurred just after delivery, but during the same admission period.[15,16,38] On the contrary, estimation of the risk of VTE in

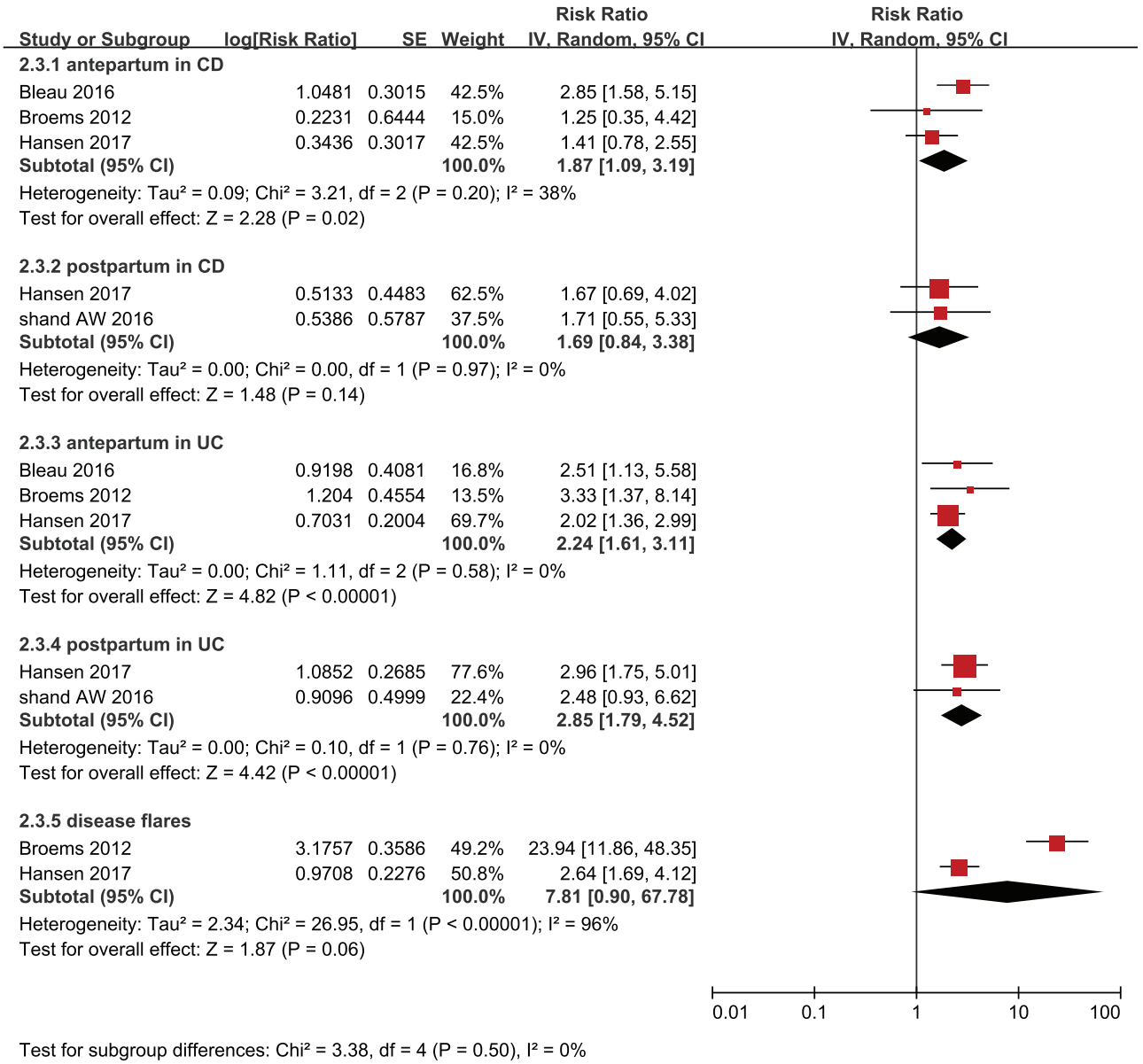

Figure 3. The subgroup analysis. Comparison of outcomes of pregnant women with Crohn disease (CD) and ulcerative colitis (UC) to those without inflammatory bowel disease, respectively. Outcomes are as follows: venous thromboembolism (VTE) during pregnancy with CD (2.3.1), VTE postpartum with CD (2.3.2), VTE during pregnancy with UC (2.3.3), VTE postpartum with UC (2.3.4), and VTE during pregnancy in women with flares during pregnancy (2.3.5). Test for heterogeneity: χ^2 statistics with degrees of freedom (df) and *P* values, inconsistency among results: I^2, test for overall effect: Z statistic with *P* value. CI = confidence interval, SE = standard error.

the postpartum period may be affected by missing mild cases that were confirmed and treated in an outpatient setting.[44]

Current guidelines for management of VTE during pregnancy commonly state previous history of VTE and/or thrombophilia as an independent risk factor and recommend prophylactic anticoagulants.[52–59] However, inclusion of IBD as a VTE risk factor is not consistent. For example, the clinical practice guidelines from the American College of Chest Physicians (ACCP)[53,54] and the American College of Obstetricians and Gynecologists do not include IBD as a VTE risk factor for pregnant patients.[55–57] In contrast, the UK guideline by the Royal college of Obstetricians and gynecologists, IBD is an intermediate risk factor to consider antenatal prophylaxis with low-molecular-weight heparin (LMWH), and for postpartum period, to administer at least 10 days' postnatal prophylactic LMWH.[51,58] In the Society of Obstetricians and Gynaecologists of Canada guideline, thromboprophylaxis during pregnancy is determined by the presence of multiple clinical or pregnancy related VTE risk factors where the overall absolute risk of VTE is greater than 1%. Specifically, IBD is assigned 0.3% to 0.5% absolute VTE risk as one of the multiple risk factors to consider antepartum thromboprophylaxis in women admitted for bedrest. If there is another concomitant risk factor in women with IBD in postnatal assessment, postpartum thromboprophylaxis is recommended as well.[52] In the Canadian expert meeting for the management of pregnant women with IBD, it was strongly recommended that LMWH therapy be indicated from the time of admission during hospitalization in women with IBD having planned cesarean sections.[34]

Our study has some limitations. First, all the studies were observational studies of registry data including the medical records of a large-sized population. In pooling the data of these registry studies, there might be inconsistencies among the studies based on characteristics that were unique to each registry: for example, the definition or identification of the disease/event, and inclusion or exclusion criteria of the population. Sultan et al investigated the VTE incidence using the registry of medical records in primary and secondary care, and found that the differences in incidences of IBD cases were related to a time lapse in the recording of the diagnosis.[16] Various versions of the International Classification of Diseases (ICD) might have led to a different rate of detection of disease in pregnancy because of the differences in coding across the versions. For example, ICD-9 was often reported to have limitations in the inclusion of VTE cases and IBD diseases.[59,60] For the inclusion criteria, multiple-gestation pregnancies were reported to be associated with an increased risk of VTE, but studies that only included singleton pregnancies could have underestimated the absolute incidence of VTE.[33] Second, variations in observation periods in pregnancy and postpartum period exist among the studies. For example, Shand et al followed a study population to observe for the occurrences of postpartum VTE 6 weeks after delivery,[44] which is discordant with other studies that observed patients for 12 weeks postpartum. Third, the reviewed studies were all published after 2010, but the populations in the previous periods were included. Over the course of these years the detection rate of the adverse events or the disease may have changed due to differences in the disease code classifications, strategies of management, and newly published guidelines. Fourth, we cannot assess the funnel plot asymmetry for publication bias due to the small number of studies reviewed. But considering large size of data examined across the studies, the publication bias could be neglected.

In conclusion, the results of this meta-analysis suggest that IBD pregnant women are at 2 to 3 times higher risk for occurrence of VTE during pregnancy and the postpartum period than non-IBD pregnant women. The subgroup analysis further showed that the VTE risk increase during pregnancy and the postpartum period was more apparent in patients with UC than those with CD. Further studies are needed to establish recommendation for thromboprophylaxis for this specific population.

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