Risk Factors for Venous Thromboembolism in Pregnancy and Postpartum: A Systematic Review and Meta-analysis

Chunxiang QIN[1], Siyuan Tang[1], Jiarui CHEN[1], Jing LU[2], Jiaying XIE[1], Mei SUN[1], and Chunxiang QIN[2]

[1]Central South University
[2]Central South University Third Xiangya Hospital

March 30, 2022

Abstract

Background: Venous thromboembolism (VTE) is a disease that could endanger maternal health, especially its serious complications. Although several previous studies have examined many risk factors of VTE in pregnancy and postpartum, we still lack studies that use quantitative methods to evaluate the strength, quality, and consistency of existing evidence. Objectives: to summarize risk factors for VTE in pregnancy and postpartum. Search Strategy: The search was conducted in PubMed、EMBASE, web of science、MEDLINE. Selection Criteria: Study reporting risk factors for VTE in pregnancy and postpartum. Data Collection and Analysis: Review Manager (RevMan, version 5.3) was used for meta-analysis, and the outcome of the analysis was presented as odds ratio (OR). Main Results: We included 24 studies (7 case-control studies, 2 nested case-control studies and 15 cohort studies) and 14 of them were used for the meta-analysis. There were 59 risk factors with positive evidence in all studies and we selected 13 risk factors for the meta-analysis. The three most significant risk factors in the meta-analysis were Factor V Leiden (FVL) (OR = 9.95, 95% CI: 5.93–16.70), Placenta previa (OR = 8.74, 95% CI: 3.40–22.50), and cardiac disease (OR = 7.77, 95% CI: 5.31–11.38). Conclusions: The number of risk factors for VTE during pregnancy and postpartum is very huge. Our study showed that the main risk factors are advanced age, overweight, cesarean section, multiple pregnancy, placenta previa, FVL, F2 20210A and cardiac disease.

Risk Factors for VenousThromboembolism in Pregnancy and Postpartum: A Systematic Review and Meta-analysis

HU Siqing[1]; TANG Siyuan[1]; LU Jing[2]; CHEN Jiarui[1]; XIE Jiaying[1]; SUN Mei[1]; QIN Chunxiang[1,2]

1 Xiangya Nursing School, Central South University, Changsha, China 410013.

2 The Third Xiangya Hospital, Central South University, Changsha China 410013.

Corresponding author: QIN Chunxiang, Health Management Centre, The Third Xiangya Hospital, Central South University, Changsha China 410013, Hunan, Peoples R China. Email: chunxiangqin@126.com

Abstract

Background: Venous thromboembolism (VTE) is a disease that could endanger maternal health, especially its serious complications. Although several previous studies have examined many risk factors of VTE in pregnancy and postpartum, we still lack studies that use quantitative methods to evaluate the strength, quality, and consistency of existing evidence.

Objectives: to summarize risk factors for VTE in pregnancy and postpartum.

Search Strategy: The search was conducted in PubMed、EMBASE, web of science、MEDLINE.

Selection Criteria: Study reporting risk factors for VTE in pregnancy and postpartum.

Data Collection and Analysis: Review Manager (RevMan, version 5.3) was used for meta-analysis, and the outcome of the analysis was presented as odds ratio (OR).

Main Results: We included 24 studies (7 case-control studies, 2 nested case-control studies and 15 cohort studies) and 14 of them were used for the meta-analysis. There were 59 risk factors with positive evidence in all studies and we selected 13 risk factors for the meta-analysis. The three most significant risk factors in the meta-analysis were Factor V Leiden (FVL) (OR = 9.95, 95% CI: 5.93–16.70), Placenta previa (OR = 8.74, 95% CI: 3.40–22.50), and cardiac disease (OR = 7.77, 95% CI: 5.31–11.38).

Conclusions: The number of risk factors for VTE during pregnancy and postpartum is very huge. Our study showed that the main risk factors are advanced age, overweight, cesarean section, multiple pregnancy, placenta previa, FVL, F2 20210A and cardiac disease.

Keywords: venous thromboembolism; VTE; risk factors; systematic review; meta-analysis

Tweetable abstract

Venous thromboembolism (VTE) is a disease that could endanger maternal health, especially its serious complications. Our systematic review summarized 59 risk factors for VTE in pregnant and postpartum women and conducted meta-analysis for 13 risk factors. The results suggested that the risk factors with the strongest associations with perinatal VTE were Factor V Leiden, placenta previa, cardiac disease, anemia, multiple pregnancy and F2 20210A. The evidence of different risk factors varies in quantity and quality, and more studies are needed to investigate the risk factors.

Introduction

Venous thromboembolism (VTE) refers to the abnormal coagulation of blood in the veins, resulting in complete or incomplete occlusion of a blood vessel[(1)]. It mainly includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PE). Pregnant women are considered a high-risk group for VTE[(2)]. It is reported that pregnant women are 6-8 times more likely to develop VTE than their non-pregnant peers[(3)], and the risk of postpartum VTE is even higher than that in pregnancy. VTE leads to limb pain, swelling, skin damage and other symptoms that affect the patient's quality of life[(4)]. Furthermore, it can be life-threatening if embolus detach. Pregnant women with VTE are at higher risk of complications which can be life threatening. Women with VTE during pregnancy are more likely to have adverse complications: such as preeclampsia, fetal growth restriction and repeated abortion[(5)]. VTE in pregnancy does not only endangers maternal health but also causes economic burden to society. The economic burden of VTE is considered to be costing the health care system in the United States more than $1.5 billion/year[(6)]. Thus, more attention needs to be paid to VTE in pregnancy and postpartum to enhance early identification and prevention.

Assessing risk factors can effectively identify people at high risk and predict the occurrence of VTE[(7-9)]. Previous research has examined a number of risk factors for perinatal VTE and these include thrombophilia, obesity, advanced age, black race, route of delivery, parity, pregnancy complications, transfusion and many more[(10-15)]. Although results of these original studies are discrepant. Few studies[(16-19)] have provided narrative reviews of risk factors, while lacking quantitative methods to evaluate the strength, quality, and consistency of existing evidence. Therefore, the purpose of this study is to summarize the risk factors for VTE in pregnant and postpartum women through a systematic review of existing studies and conduct meta-analysis for some risk factors in order to provide more scientific evidence for the prediction and prevention of VTE.

Methods

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The search strategy was developed under the guidance of experts

in information retrieval. The following databases: PubMed, Excerpta Medica Database (EMBASE), web of science, the Medical Literature Analysis and Retrieval System Online (MEDLINE) were searched from September 1st 2019 to March 25th 2020 by two researchers respectively. VTE-related keywords ("venous thrombosis," "thromboembolism," "deep-vein thrombosis," and "pulmonary embolism"), pregnancy-related keywords ("pregnancy," "postpartum," "obstetric," "puerperium," and "antepartum"), and keywords related to risk factors ("risk factor," "determinant" and "correlates") were used in the search strategy. The complete search strategy is shown in appendix S1.

Study Criteria and Selection

Inclusion criteria include:(a) pregnant or postpartum women (to comprehensively collect risk factors, we did not limit the time of occurrence of postpartum VTE); (b) cross-sectional study, cohort study or case-control study; (c) reported risk factor or influencing factors for VTE in pregnancy or postpartum. The study was excluded if the response rate was lower than 50%.

All results retrieved from the searches were exported to EndNote software and removed duplicates. According to the established criteria, two researchers screened studies' titles and abstracts independently and excluded studies that apparently were irrelevant to our topic. They read the full text of the remaining studies and decided whether to include them in this study. When there were some disagreements between researchers, we reached a consensus through consultation with another researcher.

Quality Assessment

The Joanna Briggs Institute Critical Appraisal tools (checklists for analytical cross-sectional studies, case control studies, and cohort studies) were used to evaluate the quality of the studies. Each study was reviewed by two researchers. If there were a disagreement, a third researcher was asked to evaluate.

Data Extraction

The following data were extracted from all included studies: study country, research time, study setting, study design, sample size, time of VTE occurrence, measurement of risk factors, and their correlation with outcome variables (effect size). Studies used different approaches to adjustment, which would make them difficult to compare. Therefore, to obtain a consistent measure across studies, data were extracted from the least adjusted model. Risk factors are classified into the following four categories: (1) socio-demographic risk factors (including maternal age, BMI, race, lifestyles); (2) pregnancy-related risk factors (including pregnancy status and pregnancy complications); (3) genetic risk factors (including family history of VTE, thrombophilia, and other genetic variants); (4) comorbidity risk factors (including the circulatory system, respiratory system and any other diseases that independent of pregnancy). All extracted information was checked by another researcher who was not involve in the data extraction process to ensure its accuracy and credibility.

Statistical Analysis

We analyzed findings from the included studies through meta-analyses using the Cochrane Collaboration's software package, Review Manager (RevMan, version 5.3). Meta-analysis was conducted for each risk factor that was examined in two or more studies. The results are presented as odds ratios (ORs) with a 95% confidence interval (CI), and a P value <0.05 was considered statistically significant, unless otherwise specified. In addition, heterogeneity was quantified using the Q test and I^2 statistics. When the heterogeneity test indicated no significant difference ($P>0.1$ and $I^2<50\%$), a fixed-effect model was applied; otherwise, a random-effects model was used. Publication bias was assessed through the Egger's test in Stata SE (version 15) for those risk factors with less than 10 studies, funnel plots were used for those risk factors with more than 10 studies. All tests were two-sided, and the results were considered statistically significant at $P<0.05$.

Results

Characteristics of the included studies

A total of 1514 records were searched from the databases. After deduplication, a total of 780 references were identified in our initial search, 718 were excluded because their titles and abstracts clearly did not fit the theme of this study. After accessing the full text, of the remaining 62 studies, only 24 studies were eligible according to the established criteria for this study. Among these 24 eligible studies, 14 studies participated in the meta-analysis. Detailed exclusion process has been illustrated by a flow chart (Fig.1).

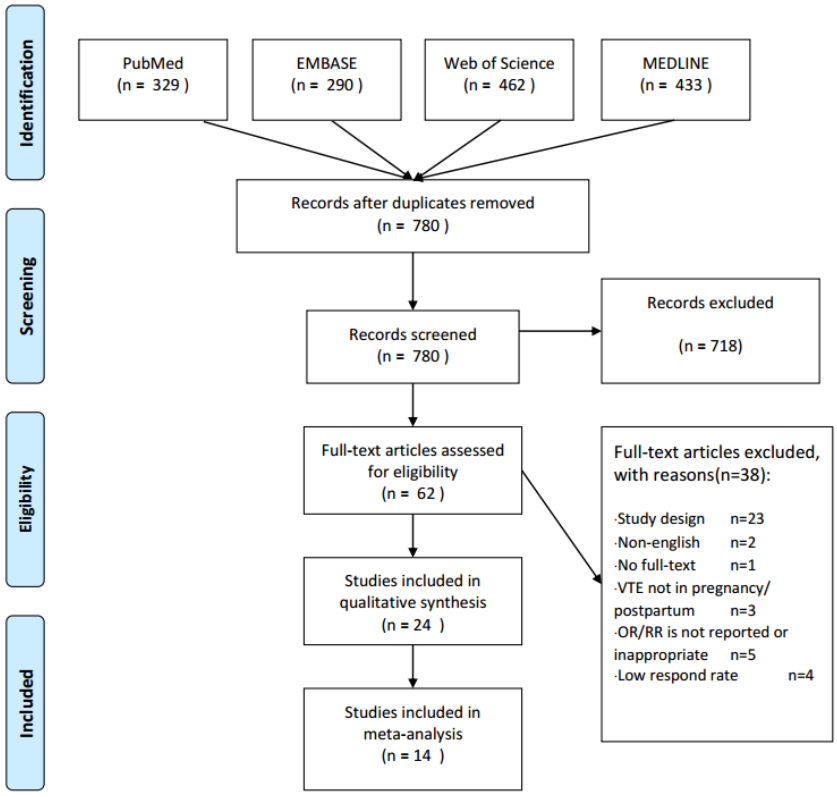

Fig. 1 Study selection

We included 24 studies, including case-control study(n=7), nested case-control study(n=2) and cohort study(n=15). Most of those studies were carried out in developed countries, especially in countries with established medical databases like The United States, Finland, Denmark, Norway. They published from 1999 to 2019. The median sample size was 45865, ranging from 75 to 8345262 deliveries. The characteristics of the 24 studies are summarized in Table 1. In a total of 24 studies, nearly 80 potential risk factors were discussed but 59 of them were statistically significant, which were divided into socio-demographic risk factors(n=6), genetic risk factors(n=26), pregnancy-related risk factors (n=9; including pregnancy status and pregnancy complications) and comorbidity risk factors (n=18; including diseases independent of pregnancy).

Author Year	Country	Study Design	Period	Period	Type of VTE
			Pregnancy	Postpartum	
Blondon 2016[20]	America	Case-control	[?]	3 months	DVT+PE
Cochery 2007[21]	France	Cohort	[?]	6 weeks	VTE
Galambosi 2017[22]	Finland	Cohort	\	180 days	VTE
Galanaud 2010[23]	France	Nested Case-Control	[?]	45 days	DVT+PE
Gerhardt 2000[24]	Germany	Case-control	[?]	6 weeks	DVT+PE

Author Year	Country	Study Design	Period	Period	Type of VTE
Grandone 2010[25]	Italy	Case-control	[?]	6 weeks	DVT+PE
Hansen 2017[26]	Denmark	Cohort	[?]	12 weeks	VTE
James 2006[27]	America	Cohort	[?]	[?]	DVT+PE
Kestenbaum 2003[28]	America	Cohort	[?]	[?]	DVT+PE
Klai 2012[29]	Tunisia	Case-control	[?]	[?]	VTE
Lindqvist 1999[30]	Sweden	Cohort	240 days before delivery	6 weeks	DVT+PE
Lindqvist 1999(heredity)[31]	Sweden	Cohort	[?]	3 months	DVT+PE
Martinelli 2002[32]	Italy	Case-control	[?]	6 weeks	DVT+PE
McColl 2000[33]	Britain	Case-control	[?]	6 weeks	DVT+PE
Mitić 2009[34]	Yugoslavia	Case-control	[?]	6 weeks	DVT+PE
Morris 2010[35]	Australia	Cohort	\	12 weeks	PE
Simpson 2001[36]	UK	Nested Case-Control	[?]	puerperium	VTE
Sugiura-Ogasawara 2019[37]	Japan	Cohort	[?]	1 month	VTE
Sultan 2013[38]	UK	Cohort	[?]	12 weeks	DVT+PE
Thurn 2018[15]	Sweden	Cohort	Delivery only	6 weeks	DVT+PE
Tormene 2001[39]	Italy	Cohort	[?]	3 months	DVT
Vora 2007[40]	India	Cohort	[?]	\	DVT
Wang 2017[41]	China	Cohort	\	40 days	PE(after CS)
Won 2011[42]	Korea	Cohort	[?]	4 weeks	proximal DVT

Table. 1 Study characteristics

[?]: Included corresponding period without specific time. DVT: deep vein thrombosis. PE: pulmonary embolism. Risk factors: 1.age; 2.weight; 3.smoke; 4.blood group; 5.race; 6.parity; 7.multiple pregnancy ; 8.GWG(gestational weight gain); 9.SGA/LGA; 10.hyperemesis; 11.caesarean; 12.preeclampsia; 13.retentio placentae; 14.threatened abortion; 15.regnancy loss; 16.stillbirth; 17.oligohydramnios; 18.conceptus weight; 19.IFV; 20.feeding at discharge; 21.chorioamnionitis; 22.antepartum hemorrhage; 23.postpartum hemorrhage; 24.transfusion; 25.postpartum anemia; 26.premature birth; 27.placenta previa; 28.abruptio placentae; 29.postpartum infection; 30.gestational hypertension; 31.gestational diabetes; 32.aPC resistance; 33.F5 G1691A(FVL); 34.F2 G20210A; 35.F12 C46T; 36.PROCR 6936G; 37.ANXA5 M2 haplotype; 38.PAI 4G/4G; 39.Protein S deficiency; 40.Protein C deficiency; 41.antithrombin deficiency; 42Endometriosis; 43.uterine fibroids; 44.Adenomyosis; 45.polycystic ovarian syndrome; 46.cancer; 47.history of VTE; 48. Thrombophilia; 49.antiphospholipid syndrome; 50.chronic hypertension; 51.varicose veins; 52.renal disease; 53.cardiac disease; 54.anemia; 55.urinary tract infection; 56. inflammatory bowel disease(IBD); 57.sickle cell disease; 58.lupus; 59.disorders of fluid, electrolyte, and acid-base balance

Socio-demographic Risk Factors

A total of 10 socio-demographic factors were involved in the included studies, but four of them (substance addiction, uninsured, breakfast, working hours) only appeared in a single study and showed no statistical significance. A total of six studies investigated the influence of age on VTE. Due to the high heterogeneity of these studies, we did not conduct a meta-analysis on them. Most studies showed that advanced age was related to an increased risk of VTE, but the definition of advanced age is slightly different. It is worth noting that Lindqvist's research shows that maternal age [?]19 is also a risk factor (OR=2.5 95%CI: 1.4-4.4). Blood group A has also been reported to increase the risk of both antenatal (OR=1.9 95%CI: 1.2-3.0) and postnatal VTE (OR=1.6 95%CI: 1.2-2.2). In addition, race is an uncertain risk factor. Compared with white people, black people have a higher risk of VTE (OR=1.4 95%CI: 1.2-1.6); but in another study, the difference between white and African American is not significant (Adjusted Hazard Ratio=1.5; 95%CI: 0.7-3.0, P=0.313). In addition, a study in Japan reported that moderate exercise is a protective factor(OR=0.52

95%CI: 0.28-0.99). The remaining two factors were supported by more studies and were included in the meta-analysis.

BMI

In five of the 24 references, high BMI was associated with an increased risk of perinatal VTE. However, due to different classification of BMI, we only included three studies for meta-analysis with overweight (25[?]BMI<30 kg/m^2) as an indicator. Due to high heterogeneity (p for heterogeneity=0.01; I^2=78%), we chose to eliminate Galanaud,2010 after several attempts and got the final result. Using the fixed-effect model, the aggregated results suggest that overweight was highly associated with a significant increase in the VTE during pregnancy and postpartum(1.6; 95% CI: 1.25–2.04, p<0.01).

Smoking

We finally included three studies reporting relation between smoking and VTE. The test for heterogeneity is acceptable (p for heterogeneity=0.09; I^2=59%). The aggregated result suggests that smoking leads to a slight increase in the incidence of VTE (OR 1.34; 95% CI: 1.05–1.74, p=0.02).

Pregnancy-related Risk Factors

There were 30 potential pregnancy-related risk factors in the included studies, and 26 of them were supported by positive evidence. One of the most significant pregnancy complications is pregnancy-induced hypertension syndrome (PIH). Most studies reported that preeclampsia will increase the risk of VTE, but there is evidence which shows otherwise[38, 41]. Another complication is gestational diabetes: women with gestational diabetes were 1.24 to 2 times more likely to develop VTE than those without. The evidence of pregnancy complications associated with VTE was numerous, but the heterogeneity of the studies associated with these two diseases was too high to conduct a meta-analysis. Parity also affects the risk of VTE in pregnancy and postpartum, but it worthy of note that, regardless of the differences in the parity (e.g. parity=0, parity[?]2, parity[?]3), they were all reported to be statistically significant. Two papers included miscarriages, the OR of miscarriage in Galanaud's study[23] was extremely high (OR=134.1, 95%CI: 26.4-680.6), while that in Sugiura-Ogasawara's study[37] was 1.83 (95%CI: 1.14-2.92). Only a few studies separately reported that gestational weight gain, conceptus weight, postpartum infection, oligohydramnios, chorioamnionitis, assisted reproduction technology, and artificial feeding were the risk factors of VTE in pregnancy or postpartum.

Multiple pregnancy

A random-effects model was used due to the heterogeneity of the data (P=0.01, I^2=52%). A total of four papers were included in this analysis. Patients with multiple pregnancy exhibited a high propensity for VTE (OR=2.13, 95% CI=1.51–2.99, P<0.01) (Fig.2).

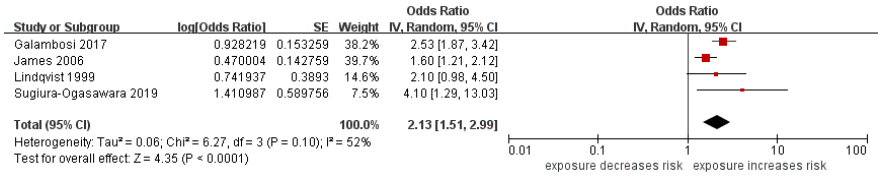

Fig. 2 Multiple pregnancy

Cesarean section

Through heterogeneity and sensitivity analysis, we selected the random effects model to analyze the five studies about the relationship between cesarean section and VTE during pregnancy and postpartum. The results showed that the risk of VTE was 1.91 times higher in women who had cesarean section than non-cesarean section women (Fig.3).

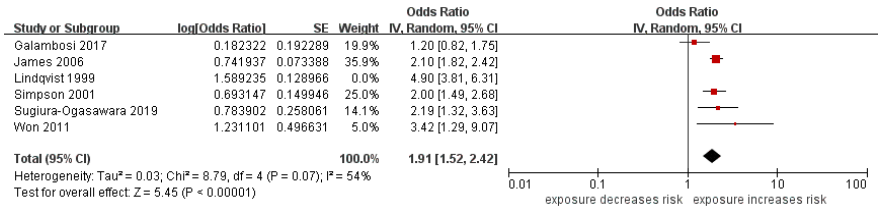

Fig. 3 Cesarean section

Premature birth

The data were analyzed by a random-effects model (P=0.11, I^2=50%). Women who experience premature birth had a higher risk of VTE in pregnancy and postpartum (OR=1.87, 95% CI: 1.29–2.72, P<0.001) (Fig.4).

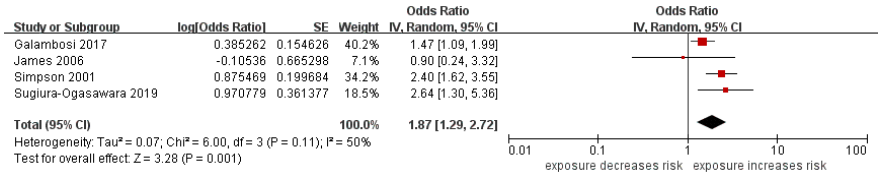

Fig. 4 Premature birth

Hyperemesis

We used a fixed-effects model for data analysis (P=0.36, I^2=0%). Two studies were included in the analysis. The result demonstrated that the effect of hyperemesis on VTE was not statistically significant (OR=1.09, 95% CI: 9.58–2.06, P=0.79).

Hemorrhage

Two studies reported the relationship between hemorrhage and perinatal VTE. The test for heterogeneity was significant. Using the random-effect model, the aggregated results suggest that both postpartum hemorrhage and antepartum hemorrhage was associated with incidence of VTE.

Genetic Risk Factors

Among the genetic risk factors, 12 related genes, 3 protein-related factors, and family history of VTE were discussed. Most studies focus on Factors V Leiden (FVL) and F2 20210A. Other studies have reported on F12 46T, PROCR 6936G, ANXA5 M2 haplotype separately, but the evidence is insufficient.

FVL

FVL is the most significant genetic risk factor, it was mentioned in all included studies that relate to heredity. We combined four studies concerning FVL and VTE in pregnancy and postpartum. The test for heterogeneity was significant (p for heterogeneity = 0.27; I^2 = 24%). Using the random-effect model, the aggregated result suggested that FVL was highly associated with a significant increase in the development of VTE (OR 9.95; 95% CI: 5.93–16.7, p<0.01) (Fig.5).

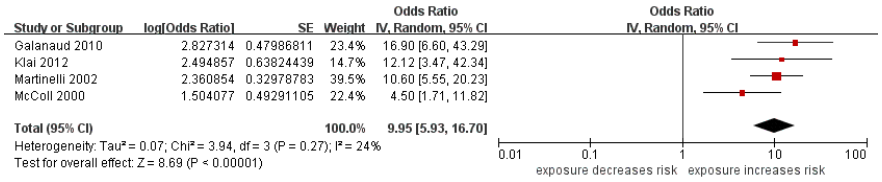

Fig.5 Factor V Leiden

F2 20210A

Through the random-effects model, the final results showed that F2 20210A would increase the risk of VTE during pregnancy and postpartum (OR 2,13; 95% CI: 1.84–2.47, p<0.01).

Comorbidity Risk Factors

Twenty-four possible comorbidity risk factors were investigated in 13 studies, 19 of them were reported to be statistically significant but only cardiac disease was reported in more than two studies. In all studies that included antithrombin deficiency, chronic hypertension, cardiac disease and anemia, the results showed that those factors increased the risk of VTE during pregnancy or postpartum. We performed a meta-analysis of cardiac disease and anemia.

Cardiac disease

Three studies reported the relationship between cardiac disease and VTE. The test for heterogeneity was acceptable (p for heterogeneity = 0.13; I^2 = 51%) and we used random-effect model. The result suggested that cardiac disease was associated with a significant increase in the incidence of VTE (OR 7.77; 95% CI: 5.31–11.38, p< 0.01) (Fig.6).

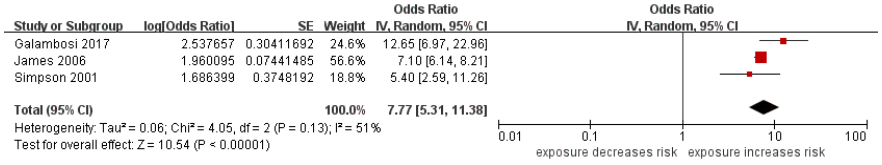

Fig. 6 Cardiac disease

Anemia

Only two studies dealt with anemia. However, their heterogeneity is large, we were reserved about the integrated result (OR 2.17; 95% CI: 1.43–3.29, p< 0.01).

Table 2 summarizes the results of all our meta-analyses. As there are less than 10 studies included in the meta-analysis of each risk factor, we only conducted Egger's test and the results showed no publication bias.

Risk Factor	No. Study	Effect Model	I^2, %	OR (95%CI)	Z score	P value
overweight(25[?]BMI<30)	2	F	0	1.60 (1.25,2.04)	3.74	0.0002*
Smoking	3	R	59	1.35 (1.05,1.74)	2.31	0.02*
multiple pregnancy	4	R	52	2.13 (1.51,2.99)	4.35	<0.0001*
cesarean section	6	R	54	1.91 (1.52,2.42)	5.45	<0.00001*
premature birth	4	R	50	1.87 (1.29,2.72)	3.28	0.001*
hyperemesis	2	F	0	1.09 (0.58,2.06)	0.27	0.79
placenta previa	2	F	0	8.74 (3.40,22.50)	4.49	<0.00001*
postpartum hemorrhage	3	R	60	1.43 (1.02,2.00)	2.07	0.04*

Risk Factor	No. Study	Effect Model	I^2, %	OR (95%CI)	Z score	P value
antepartum hemorrhage	2	R	65	1.95 (1.30,2.91)	3.23	0.001*
Factor V Leiden	4	F	24	9.95 (5.93,16.70)	8.69	<0.00001*
F2 20210A	3	R	0	2.13 (1.84,2.47)	10.19	0.00001*
cardiac disease	3	R	51	7.77 (5.31,11.38)	10.54	<0.00001*
Anemia	2	R	79	2.17 (1.43,3.29)	3.63	0.0003*

Table. 2 Study characteristics

F: fixed-effects model. R: random-effects model. I^2: the percentage of variability in estimates of effect size that is attributable to between-study variation (heterogeneity). OR: odds ratio. *P<0.05.

Discussion

We synthesized the potential risk factors of perinatal VTE in this systematic review. Our results presented that 59 of 79 potential risk factors had significant influence on perinatal VTE. We summarized them to four categories including socio-demographic risk factors, genetic risk factors, pregnancy-related risk factors and comorbidity risk factors. And we conducted a meta-analysis on 13 factors whose OR were reported in at least two studies. The results suggested that the risk factors with the strongest associations with perinatal VTE were FVL, placenta previa, cardiac disease, anemia, multiple pregnancy and F2 20210A.

The risk factors for perinatal VTE were different from other populations. We found 26 reported risk factors of perinatal VTE which were closely related to pregnancy. The most frequently reported factors were cesarean section[15, 22, 27, 30, 35-38, 42] and multiple pregnancy[15, 22, 27, 30, 35, 37, 42]. Cesarean section increases the incidence of perinatal VTE because women after cesarean section have active coagulation, and their serum D-dimer is higher than the women after vaginal delivery[43]. In addition, women have less physical activity after cesarean section and it will take quite a longer time to return to daily activities than women after vaginal delivery[44]. Studies have also shown that women with multiple pregnancy have higher incidence of perinatal VTE. Multiple pregnancy always accompanied with cesarean section, preterm labor, gestational hypertension, gestational diabetes, and postpartum hemorrhage, all of which were reported to increase the risk of VTE[45]. This also shows a strong interrelation between perinatal VTE risk factors, which is not obvious in the general population. The risk factors of VTE during pregnancy and postpartum are varied, but each risk factors' evidence is limited.

Some risk factors of VTE which have been reported in the studies of non-pregnant women have also been high frequently presented in our systematic review, and these include advanced age, overweight, smoking, FVL, F2 20210A, and heart disease. Their mechanism of action has been widely discussed[46-49]. However, many factors that increase the risk of VTE in other populations were not addressed in our study, such as immobility[50], hypercholesteremia[51, 52]. We cannot determine that these factors are irrelevant with perinatal VTE, hence more evidence is needed to explore their relationship with perinatal VTE.

We conducted meta-analysis of all risk factors that have clearly OR values in two or more studies, but only a few risk factors were included in our meta-analysis (13/59). The possible reasons could be: 1) Some risk factors (27/59) were excluded from meta-analysis because they only appeared statistically significant in one study; 2) The included studies used different statistical analysis methods and their effect sizes varied, which cannot be synthesized; and 3) the report of risk factors is incomplete, the method, time or classification was not reported.

Among the 13 factors, FVL had the highest synthesized OR (OR=9.95; 95% CI: 5.93–16.7) , which is nearly twice as high as that of another meta-analyses in general population[49]. We consider that, this may be related to the region of studies. Three of the four included studies were conducted in Europe. The small number of included studies is also a possible reason for the difference. In the meta-analysis, placenta previa (OR=8.74, 95% CI: 3.40-22.50) also had a strong influence on perinatal VTE. Women with placenta previa

are required to stay in bed for long periods of time and they are recommended for cesarean section[53], which increases the risk of VTE. Cardiac disease also showed a great impact on perinatal VTE (OR=7.77, 95% CI: 5.31–11.38). Accumulated evidence show that endothelial cells play a pivotal role in modulating thrombosis, by separating blood clotting factors from exposure to subendothelial prothrombotic extracellular matrix components[54]. Cardiac diseases are associated with dysfunction of the endothelial cells, which leads to impaired thrombotic modulation. The other risk factors, including smoking, overweight and F2 20210A, had a relatively low OR, which were similar to the meta-analysis in other populations[46, 48, 49, 55].

We have studied it in a scientific, systematic way and have a quantitative synthesis, but there still are some limitations. Firstly, we did not conduct meta-analysis on some risk factors, because there were only few relative studies or there was no appropriate outcome indicator in relevant studies. Secondly, we found that studies used different approaches to adjustment, which may affect the accuracy of our results. Thirdly, due to the limited evidence, we were unable to discuss the risk factors of prenatal and postnatal VTE separately in the meta-analysis.

Implications for Clinicians

Our study indicates advanced age, overweight, cesarean section, multiple pregnancy, placenta previa, FVL, F2 20210A and cardiac disease as the main risk factors of VTE. The findings from this study provides clinicians the opportunity for early identification of pregnant and postpartum women at risk of VTE, in order to initiate thrombosis prevention programs, such as strengthening exercise, wearing stretch socks, etc. Furthermore, clinicians can counsel women to avoid unnecessary cesarean section since it is indicated as an important risk factor for VTE. However, if cesarean section is an inevitable option for some complications like placental previa, early thromboprophylaxis should be administered postoperatively. Although FVL and F2 20210A had a high correlation with VTE in the meta-analysis, but they have received less attention in the clinical practice and this has contributed to the unknown prevalence of FVL and F2 20210A[56, 57]. Also, the cost-effectiveness of genetic testing during pregnancy is not clear, so it should be temporarily ignored in clinical work.

Implications for Future Research

During the review process, we find the following limitations in the included studies and make a prospect to the future research: 1) The amount of evidence for each risk factor varies widely, and factors that increase the risk of VTE in other populations were not addressed in our study. Risk factors for VTE during pregnancy and postpartum are unclear, therefore, we call for more evidence to explore both existing and potential risk factors. 2) Different study design and statistical method lead to various effect sizes. For this reason, it is difficult to synthesize studies from different regions through meta-analysis. In future studies, appropriate and consistent effect size should be selected as far as possible. 3) The actual cases of VTE may not be recorded in some retrospective studies. We recommend screening all pregnant women in a prospective study to obtain the cases, because it can maximally reflect the reality of perinatal VTE risk factors. 4) most of the programs report unclearly about the details of the risk factors, such as definitions, classification, measurement method and time. We suggest researchers to refer the guidelines or quality assessment tools for the corresponding research types when reporting their study.

Conclusion

There are numerous risk factors for VTE during pregnancy and postpartum but our study showed that the main risk factors are advanced age, overweight, cesarean section, multiple pregnancy, placenta previa, FVL, F2 20210A and cardiac disease. The evidence of different risk factors varies in quantity and quality, and more studies are needed to investigate the risk factors.

Funding

This research was funded by National Natural Science Foundation of China (72074225), Philosophy and Social Science Foundation of Hunan Province (19YBA351) and Key R&D plan of Hunan Province (2020SK2089).

Acknowledgements

We thank Lisa Lommel and CHEN Qirong for their contribution advice.

Reference:

1. Lippi G, Franchini M. Pathogenesis of Venous Thromboembolism: When the Cup Runneth Over. Seminars in Thrombosis and Hemostasis. 2008;34(8):747-61.

2. Kesik JJ, Zubilewicz T, Terlecki P, Paluszkiewicz A, Ilecki M. Prevention and treatment of venous thromboembolism in pregnancy. Przeglad Menopauzalny. 2010;9(4):275-9.

3. Fogerty AE. Management of Venous Thromboembolism in Pregnancy. Current treatment options in cardiovascular medicine. 2018;20(8):69.

4. Labropoulos N, Waggoner T, Sammis W, Samali S, Pappas PJ. The effect of venous thrombus location and extent on the development of post-thrombotic signs and symptoms. J Vasc Surg. 2008;48(2):407-12.

5. Revelj M, Hagman A, Hellgren M. Recurrence of VTE, obstetric and neonatal outcomes in 78 women with venous thromboembolism during pregnancy and puerperium. Thrombosis Research. 2015;135:S79.

6. Dobesh PP. Economic Burden of Venous Thromboembolism in Hospitalized Patients. Pharmacotherapy. 2009;29(8):943-53.

7. Chauleur C, Quenet S, Varlet M-N, Seffert P, Laporte S, Decousus H, et al. Feasibility of an easy-to-use risk score in the prevention of venous thromboembolism and placental vascular complications in pregnant women: a prospective cohort of 2736 women. Thrombosis research. 2008;122(4):478-84.

8. Hase EA, de Barros V, Igai AMK, Francisco RPV, Zugaib M. Risk assessment of venous thromboembolism and thromboprophylaxis in pregnant women hospitalized with cancer: Preliminary results from a risk score. Clinics. 2018;73.

9. Weiss N, Bernstein PS. Risk factor scoring for predicting venous thromboembolism in obstetric patients. Am J Obstet Gynecol. 2000;182(5):1073-5.

10. Blondon M, Harrington L, Boehlen F, Robert-Ebadi H, Righini M, Smith N. Pre-pregnancy BMI and delivery BMI as risk factors for postpartum VTE: A population-based, case-control study. Journal of Thrombosis and Haemostasis. 2015;13:106.

11. Burch DJ, O'Neill AM. Obesity and pregnancy. Obesity is a risk factor for thromboembolism. Bmj. 2009;338:b388.

12. Evangelista MS, Slompo K, Timi JRR. Venous Thromboembolism and Route of Delivery - Review of the Literature. Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia. 2018;40(3):156-62.

13. Jaya-Bodestyne S, Tan TC, Tan LK, Tan KH, Yeo G, Ostbye T, et al. Incidence, risk factors, and outcomes of pregnancy-associated venous thromboembolism in Singapore. BJOG: An International Journal of Obstetrics and Gynaecology. 2018;125:86.

14. Kolettis D, Craigo S. Thromboprophylaxis in Pregnancy. Obstet Gynecol Clin North Am. 2018;45(2):389-402.

15. Thurn L, Wikman A, Lindqvist PG. Postpartum blood transfusion and hemorrhage as independent risk factors for venous thromboembolism. Thromb Res. 2018;165:54-60.

16. Armstrong EM, Bellone JM, Hornsby LB, Treadway S, Phillippe HM. Pregnancy-Related Venous Thromboembolism. J Pharm Pract. 2014;27(3):243-52.

17. Dresang LT, Fontaine P, Leeman L, King VJ. Venous thromboembolism during pregnancy. Am Fam Physician. 2008;77(12):1709-16.

18. Hague WM, Dekker GA. Risk factors for thrombosis in pregnancy. Best practice & research Clinical haematology. 2003;16(2):197-210.

19. Tsikouras P, von Tempelhoff GF, Rath W. [Epidemiology, Risk Factors and Risk Stratification of Venous Thromboembolism in Pregnancy and the Puerperium]. Z Geburtshilfe Neonatol. 2017;221(4):161-74.

20. Blondon M, Harrington LB, Boehlen F, Robert-Ebadi H, Righini M, Smith NL. Pre-pregnancy BMI, delivery BMI, gestational weight gain and the risk of postpartum venous thrombosis. Thromb Res. 2016;145:151-6.

21. Cochery-Nouvellon E, Mercier E, Lissalde-Lavigne G, Daures JP, Quere I, Dauzat M, et al. Homozygosity for the C46T polymorphism of the F12 gene is a risk factor for venous thrombosis during the first pregnancy. Journal of thrombosis and haemostasis : JTH. 2007;5(4):700-7.

22. Galambosi PJ, Gissler M, Kaaja RJ, Ulander V-M. Incidence and risk factors of venous thromboembolism during postpartum period: a population-based cohort-study. Acta obstetricia et gynecologica Scandinavica. 2017;96(7):852-61.

23. Galanaud JP, Cochery-Nouvellon E, Alonso S, Chauleur C, Mercier E, Lissalde-Lavigne G, et al. Paternal endothelial protein C receptor 219Gly variant as a mild and limited risk factor for deep vein thrombosis during pregnancy. Journal of thrombosis and haemostasis : JTH. 2010;8(4):707-13.

24. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. New England Journal of Medicine. 2000;342(6):374-80.

25. Grandone E, Tiscia G, Colaizzo D, Chinni E, Pisanelli D, Bafunno V, et al. Role of the M2 haplotype within the annexin A5 gene in the occurrence of pregnancy-related venous thromboembolism. Am J Obstet Gynecol. 2010;203(5):461.e1-5.

26. Hansen AT, Erichsen R, Horváth-Puhó E, Sørensen HT. Inflammatory bowel disease and venous thromboembolism during pregnancy and the postpartum period. Journal of Thrombosis and Haemostasis. 2017;15(4):702-8.

27. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006;194(5):1311-5.

28. Kestenbaum B, Seliger SL, Easterling TR, Gillen DL, Critchlow CW, Stehman-Breen CO, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(5):982-9.

29. Klai S, Fekih-Mrissa N, Sassi RB, Mrissa R, Rachdi R, Gritli N. Effects of prothrombotic markers and non-O blood group in maternal venous thromboembolism during pregnancy and postpartum. Blood Coagul Fibrinolysis. 2012;23(7):649-52.

30. Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: A population study. Obstetrics and Gynecology. 1999;94(4):595-9.

31. Lindqvist PG, Svensson PJ, Maršál K, Grennert L, Luterkort M, Dahlbäck B. Activated protein C resistance (FV:Q506) and pregnancy. Thrombosis and Haemostasis. 1999;81(4):532-7.

32. Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost. 2002;87(5):791-5.

33. McColl MD, Ellison J, Reid F, Tait RC, Walker ID, Greer IA. Prothrombin 20210 G -> A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. British Journal of Obstetrics and Gynaecology. 2000;107(4):565-9.

34. Mitić G, Povazan L, Lazić R, Spasić D, Maticki-Sekulić M. Deficiency of the natural anticoagulant proteins in women with pregnancy related venous thromboembolism. Medicinski pregled. 2009;62(1-2):53-62.

35. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. Journal of thrombosis and haemostasis : JTH. 2010;8(5):998-1003.

36. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RDT. Venous thromboembolism in pregnancy and the puerperium: Incidence and additional risk factors from a London perinatal database. British Journal of Obstetrics and Gynaecology. 2001;108(1):56-60.

37. Sugiura-Ogasawara M, Ebara T, Matsuki T, Yamada Y, Omori T, Matsumoto Y, et al. Endometriosis and Recurrent Pregnancy Loss as New Risk Factors for Venous Thromboembolism during Pregnancy and Post-Partum: The JECS Birth Cohort. Thrombosis and Haemostasis. 2019;119(4):606-17.

38. Sultan AA, Tata LJ, West J, Fiaschi L, Fleming KM, Nelson-Piercy C, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood. 2013;121(19):3953-61.

39. Tormene D, Simioni P, Prandoni P, Luni S, Zerbinati P, Sartor D, et al. Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women. Haematologica. 2001;86(12):1305-9.

40. Vora S, Ghosh K, Shetty S, Salvi V, Satoskar P. Deep venous thrombosis in the antenatal period in a large cohort of pregnancies from western India. Thromb J. 2007;5:9.

41. Wang H-C, Tsai P-S, Li K-Y, Fan Y-C, Huang C-J. Perioperative risk factors for postpartum pulmonary embolism in Taiwanese Cesarean section women. Asian journal of anesthesiology. 2017;55(2):35-40.

42. Won HS, Kim DY, Yang MS, Lee SJ, Shin H-H, Park JB. Pregnancy-Induced Hypertension, But Not Gestational Diabetes Mellitus, Is a Risk Factor for Venous Thromboembolism in Pregnanc. Korean circulation journal. 2011;41(1):23-7.

43. Epiney M, Boehlen F, Boulvain M, Reber G, Antonelli E, Morales M, et al. D-dimer levels during delivery and the postpartum. Journal of Thrombosis and Haemostasis. 2005;3(2):268-71.

44. Ma J, Martin R, Chan B, Gofeld M, Geary MP, Laffey JG, et al. Using Activity Trackers to Quantify Postpartum Ambulation A Prospective Observational Study of Ambulation after Regional Anesthesia and Analgesia Interventions. Anesthesiology. 2018;128(3):598-608.

45. Wen SW, Demissie K, Yang QY, Watker MC. Maternal morbidity and obstetric complications in triplet pregnancies and quadruplet and higher-order multiple pregnancies. American Journal of Obstetrics and Gynecology. 2004;191(1):254-8.

46. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism - A meta-analysis. Circulation. 2008;117(1):93-102.

47. Li M, Guo Q, Hu W. Incidence, risk factors, and outcomes of venous thromboembolism after oncologic surgery: A systematic review and meta-analysis. Thrombosis Research. 2019;173:48-56.

48. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis A PRISMA-compliant systemic review and meta-analysis. Medicine. 2016;95(32).

49. Simone B, De Stefano V, Leoncini E, Zacho J, Martinelli I, Emmerich J, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. European Journal of Epidemiology. 2013;28(8):621-47.

50. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, Vlieg AvH. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. Journal of Thrombosis and Haemostasis. 2014;12(3):290-6.

51. Liu Y, Wang J, Guo L, Ping L. Risk factors of embolism for the cardiac myxoma patients: a systematic review and metanalysis. Bmc Cardiovascular Disorders. 2020;20(1).

52. Mahmoodi BK, Cushman M, Naess IA, Allison MA, Bos WJ, Braekkan SK, et al. Association of Traditional Cardiovascular Risk Factors With Venous Thromboembolism An Individual Participant Data Meta-Analysis of Prospective Studies. Circulation. 2017;135(1):7-+.

53. Rao KP, Belogolovkin V, Yankowitz J, Spinnato JA, II. Abnormal Placentation: Evidence-Based Diagnosis and Management of Placenta Previa, Placenta Accreta, and Vasa Previa. Obstetrical & Gynecological Survey. 2012;67(8):503-19.

54. Wang M, Hao H, Leeper NJ, Zhu L, Early Career C. Thrombotic Regulation From the Endothelial Cell Perspectives. Arteriosclerosis Thrombosis and Vascular Biology. 2018;38(6):E90-E5.

55. Zhang M-X, Chen C-Y, Fang Q-Q, Xu J-H, Wang X-F, Shi B-H, et al. Risk Factors for Complications after Reduction Mammoplasty: A Meta-Analysis. Plos One. 2016;11(12).

56. Dassoler FJ, Matiollo C, Bratti LdOS, de Moraes ACR. Prevalence of Factor V Leiden in a healthy population in Santa Catarina, Southern Brazil. International Journal of Laboratory Hematology. 2020.

57. Mahmutbegovic E, Marjanovic D, Medjedovic E, Mahmutbegovic N, Dogan S, Valjevac A, et al. Prevalence of F5 1691G>A, F2 20210G>A, and MTHFR 677C>T polymorphisms in Bosnian women with pregnancy loss. Bosnian Journal of Basic Medical Sciences. 2017;17(4):309-14.