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Research Article

The Relationship between Use of Low Molecular Weight Heparin during Pregnancy and Risk of Peripartum Adverse Events: A Meta-Analysis

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Abstract

Introduction: To summarize the trials investigated on relationship between low molecular weight heparin use during pregnancy and peripartum adverse events. Meta-analysis was performed to evaluate the effect of Low Molecular Weight Heparin (LMWH) on maternal and fetal complications.

Methods: Electronic research was performed in Cochrane Library, MEDLINE and EMBASE through October 2020. The primary outcome was the incidence of maternal and fetal complications during peripartum period. RevMan 5.3 was used for data analysis.

Results: 11 articles were finally included. Meta-analysis showed there was no significant difference in abortion, premature delivery, stillbirth, preeclampsia and postpartum hemorrhage events between pregnant women who used LMWH and those who not.

Conclusion: Using LMWH in pregnant women does not increase pregnancy related maternal and fetal complications.

Keywords: Low molecular weight heparin; Postpartum adverse events; Gestation

Introduction

The risk of thromboembolic diseases is significantly increased during pregnancy, particularly Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE). Venous Thromboembolism (VTE) is the main cause of maternal death during pregnancy, while pulmonary embolism is a common cause of maternal death in developed countries [1]. Although the overall risk of VTE events is low, pregnant women are five times more likely to develop VTE events than non-pregnant women of the same age [2]. Many scholars believe that this is caused by venous stasis due to the oppression of pregnant uterus and the imbalance of bleeding and coagulation status during pregnancy [3-5]. Common risk factors for venous thrombosis in pregnant women include age over 35, obesity, multiple pregnancies, genetic susceptibility, surgery or cesarean section, smoking and hormone therapy, pregnancy related diabetes, placental abruption and eclampsia [6]. Hospitalization before or after delivery may also increase the risk of VTE events. Besides, Women with a history of venous thrombosis before pregnancy also have an increased risk of recurrent venous thrombosis during pregnancy [7,8]. Low Molecular Weight Heparin (LMWH) is currently the preferred drug for the prevention or treatment of venous thrombosis in pregnant women. LMWH does not cross the placenta and has a more stable anticoagulant effect with a longer half-life and greater bioavailability [9]. LMWH allows daily subcutaneous administration and does not need laboratory monitoring. With the increased use of LMWH in pregnant women and relevant experience accumulation, the worrisome of the effectiveness and safety of LMWH during peripartum period is also increasing. Whether the use of LMWH in pregnant women increases peripartum adverse events in still debatable. Therefore, we did this work to analyze the relationship between use of LMWH during pregnancy and risk of peripartum adverse events, hoping to provide some guidance for the drug use.

Methods

Inclusion criteria

1) Pregnant women who received anticoagulant therapy with LMWH; 2) Anticoagulant therapy is maintained at least 6 weeks postpartum; 3) Study endpoints included pregnancy-related maternal and fetal complications.

Exclusion criteria

1) Combined use of other types of anticoagulants; 2) LMWH was used prior to pregnancy; 3) Studies not included pregnant women who use placebo or did not use anticoagulant drugs as control group; 4) Pregnant women had heparin induced thrombocytopenia; 5) Case reports.

Evaluation of efficiency

In our study, pregnancy related maternal and fetal complications were taken as the primary endpoints. Pregnancy related maternal and fetal complications included abortion, premature delivery, stillbirth, preeclampsia, fetal growth restriction, and postpartum hemorrhage. Postpartum hemorrhage was defined as the blood loss of 500mL or

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Table 1: Characteristics of included studies.

	Study Location	Type of study	Study features	Indication for LMWH use	Study duration	Funding agencies
[16]	Italy	A single center retrospective cohort study	• **Number of included women:** 88 • **LMWH type:** Unknown • **LMWH dose:** Preventive dose: LMWH 40mg/d, If body weight > 60kg, 60mg/d; Treatment dose: the dose was adjusted according to patient's weight and was given twice daily	Women with type I antithrombin deficiency	Between Jan 1, 1980 and Jan 1, 2018	No
[4]	Russia	A multi-center retrospective cohort study	• **Number of included women:** 68 • **Group:** Group I (n=50) received prophylaxis with LMWH±aspirin (50-100 mg/day) in preconception period or from the 1st trimester, during pregnancy and at least 6 weeks postpartum. Group II (n=18) received LMWH±aspirin from the II to III trimester. • **LMWH type:** Enoxaparin • **LMWH dose:** The dose was adjusted according to patient's weight (<50kg: 20mg LMWH, 50-70 kg: 40mg LMWH, 71-90kg: 60mg LMWH, 91-110 kg: 80mg LMWH, >110kg: 0.6mg/kg LMWH). The last dose of LMWH was used the day before of labor, at least 12h before the c/s or onset of labor and resumed in 6-8 h after delivery for a minimum of 6 weeks under the control of the hemostasis system.	Women with thrombophilia and a history of thrombosis	From 2009 to 2016	Unknown
[10]	Denmark	A cohort study	• **Number of included women:**166 • **Group:** 1. LMWH-treated:166; 2. LMWH-untreated:18020 • **LMWH type:** Tinzaparin (95.2%), dalteparin (4.8%) • **LMWH dose:** The majority (86.1%) was treated with tinzaparin 4,500 IU subcutaneously once daily or dalteparin 5,000 IU subcutaneously once daily. • **LMWH usage:** In half the cases (50.9%), treatment was commenced in the first trimester, but the time of initiation varied from 3rd to 39th gestational week. Treatment was discontinued at induction or onset of spontaneous labor, resumed 12 hours after delivery and generally continued until six weeks postnatally (75.3%; n=125).	• Prior or current VTE with or without thrombophilia; • Prior adverse obstetric event and thrombophilia; • Thrombophilic disorder; • Habitual abortion and thrombophilia; • Other reasons for treatment (prolonged immobilization, elevated D-dimer, impaired venous function and/or prior, adverse obstetric outcome).	From January 1, 2001 to December 31, 2005	Research grant from Hillerød Hospital
[14]	Turkey	A single-center retrospective cohort study	• **Number of included women:** 57; Number of pregnancies: 72; • **Groups:** 1) OAC warfarin (1-6w)-LMWH (6-12w)-OAC (12-36w)-LMWH (36-38w); 2) OAC warfarin + ASA (1-36w); 3) No anticoagulation; 4) LMWH treatment throughout pregnancy.	Pregnant women who underwent mechanical heart valve replacement	From January 1990 to December 2015	No
Carolina Arbuthnot. 2016	UK	A single-center retrospective cohort study	• **Number of pregnancies:** 16469. • **Group:** 1) Using LMWH (n=115): among them, 66 women received a prophylaxis dose of LMWH and 47 received a therapeutic dose of LMWH; 2) Control group (n=16415): no anticoagulant or antiplatelet therapy. • **LMWH usage:** LMWH was stopped 12h (for prophy-lactic LMWH) and 24h (for therapeutic LMWH) prior to delivery.	• VTE; • Thrombophilia; • Recurrent miscarriage • Recurrent VTE; • Multiple risk factors	From 2009 to 2013	No
[13]	Netherlands	A single-center retrospective cohort study	• **Group:** 1) LMWH treatment: 88; 2) No LMWH treatment: 352; • **LMWH type:** Fondaparinux, danaparoid or acenocoumerol; • **LMWH usage:** LMWH or another preparation was stopped at the start of spontaneous or induced labor and restarted 4-8 hours after delivery (when blood loss was normal) and stopped six weeks postpartum.	• History of VTE • Recurrent fetal loss • Asymptomatic Thrombophilic defects • VTE in current pregnancy	From 1999 to 2009	No
[17]	Netherlands	A single-center retrospective cohort study	• **Group:** 1) LMWH treatment: 95; 2) No LMWH treatment: 524 • **LMWH type:** Enoxaparin, Dalteparin, Nadroparin, Danaparoid, Tinzaparin; • **LMWH usage:** Discontinue LMWH as soon as either contractions started, membranes ruptured or to administer the last injection the morning before the day that induction of labour or a caesarean section was planned	• Current or history of VTE and thrombophilia; • Recurrent thrombophlebitis and thrombophilia; • Antiphospholipid syndrome; • Preeclampsia; • Prosthetic heart valve with or without heart thrombosis; • Current cerebrovascular accident.	From 1995 to 2008	No
[15]	UK	A case-control study	• **Group:** 1) LMWH treatment: 55; 2) No LMWH treatment: 110; • **LMWH type:** Enoxaparin; • **LMWH usage:** Twice daily	• Current or history of DVT and/or PE and a thrombophilia; • Prophylaxis for a thrombophilia; • Mitral valve replacement; • History of sagittal sinus thrombosis and a thrombophilia • Coronary aneurysm and nephrotic syndrome	From 2001 to 2005	No

[19]	Finland	A single-center retrospective cohort study	• **Group:** 1) LMWH treatment: 648; 2) No LMWH treatment: 626; • **LMWH dose:** 1) Normal prophylactic doses were enoxaparin 40mg/day or dalteparin 5000IU/day; 2) Intermediate (50% of treatment doses, i.e. enoxaparin 1mg/kg/day or dalteparin 100IU/kg/day); 3) Adjusted doses were defined as weight adjusted full treatment doses of LMWH (dalteparin 200IU/kg once daily or enoxaparin 1 mg/kg twice daily); • **LMWH usage:** Women with hereditary thrombophilias (Factor V Leiden mutation, prothrombin mutation, protein C/S deficiencies) and APLAs without a history of VTE received LMWH prophylaxis from the late third trimester (gestational weeks 34–36) until 6 weeks postpartum ; Women with combined thrombophilias or antithrombin (AT) deficiency, even without a history of VTE, received LMWH prophylaxis from gestational week 6 until 6 weeks postpartum; The median time of LMWH initiation was 17 gestational weeks and the mean duration was 22 weeks.	• Prior or current VTE; • Prior adverse obstetric outcome; • Mechanical heart valve; • Prior stroke; • Thrombophilia without any other indication; • Other reasons (immobilization, impaired venous function, cardiac disease etc.).	From February 1994 to January 2007	No
Joyce Lai. 2017	Canada	A single-center retrospective cohort study	• **Group:** 1) Anticoagulation with heparin: 137; 2) No anticoagulation: 1233	• Thrombosis history; • Hereditary thrombophilia; • Medical disorders associated with thrombosis	From March 2013 to March 2014	An educational grant from Sanofi.
HENRIK. 2000	Denmark	A population-based cohort study	• **Group: 1)** LMWH anticoagulation: 66; 2) No LMWH anticoagulation: 17259; • **LMWH type:** Enoxaparin, dalteparin, tinzaparin	Unknown	From 1991 to 1998	Danish Medical Research Council (grant no. 9700677) and EU BIOMED program (Contract No. BMH4-CT97–2430); Danish National Research Foundation

more during natural labour, and 1000mL or more during cesarean section.

Search strategy

We performed electronic research in Cochrane Library, MEDLINE, EMBASE, CQVIP, CNKI and Wanfang Database through October 2020 with the use of a combination of text words related to "heparin", "low molecular weight heparin", "LMWH", "Anticoagulant drug", "postpartum OR stegmonth OR puerperium" and "complication". No restrictions for language or geographic location were applied.

Methods of literature quality evaluation

All the studies included were non-randomized controlled trials. And the MINORS Scale was used to evaluate the study quality. The features of the included literatures and research objects are shown in Table 1 and 2.

Statistical Analysis

The RevMan5.3 software provided by the Cochrane Collaboration was used for statistical analysis. Heterogeneity test was performed using Chi-square test, and P >0.1 was considered as no statistical heterogeneity between studies. If there was no heterogeneity in studies, meta-analysis was described by fixed effect model. And if there was heterogeneity in studies, then random effect model was used.

Metrological data was described as weighted mean difference and its 95% CI, and the counting data were expressed as the odds ratio (OR) and its 95% CI.

Results

Study selection and study characteristics

A total of 1,631 literatures were retrieved, and 128 articles were included after preliminary screening. 117 articles were excluded according to the exclusion criteria: 1) The adverse outcome events of the study were not relevant to our meta-analysis; 2) No control group; 3) Concomitant use with other anticoagulation drugs except LMWH. Finally 11 literatures were included in our meta-analysis (Figure 1) [10-20].

Synthesis of results

Abortion: Four studies were analyzed and heterogeneity test showed P <0.1, meaning these studies were not homogenous, so random effect model was used. The meta-analysis results showed using LMWH during pregnancy did not increase the risk of abortion as compared to women who did not use LMWH (OR=3.77, 95% CI: 0.77-18.35, Z=1.64, P>0.05) (Figure 2).

Preterm birth: Five studies were analyzed and heterogeneity

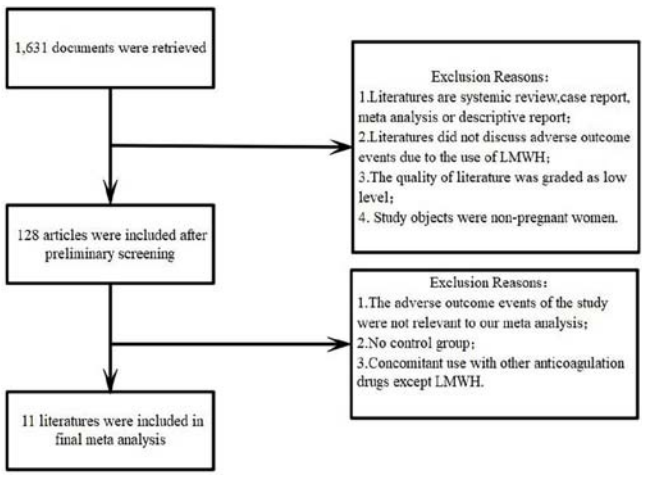

Figure 1: Literature inclusion and exclusion process.

Table 2: Characteristics of the study population.

	Pregnant age (year)	Gestational age (week)	BMI (kg/m^2)	Birth weight (g)	Mode of delivery	Maternal or fetal complications
[16]	26 (22-31)	Unknown	23 (20-26)	Unknown	**Natural labor:** 86 **Caesarean section:** 2	Miscarriages, late obstetrical complications (preterm delivery; small for gestational age newborns; preeclampsia, eclampsia, HELLP syndrome; placental abruption, stillbirth), and terminations (voluntary abortions).
[4]	28±7.7	Unknown	BMI >30; n=17	Unknown	**Group I:** Caesarean section: 21; Natural labor: 29; **Group II:** Caesarean section:8; Natural labor: 10;	Premature delivery, preeclampsia, severe preeclampsia, critical placental insufficiency, Placental abruption
[10]	**LMWH treatment group:** 20-43; **No LMWH treatment group:** 15-49	Unknown	**LMWH treatment group:** 16-46; **No LMWH treatment group**: 14-54	**LMWH treatment group:** 3280; **No LMWH treatment group:** 3540	**LMWH treatment group:** Caesarean section: 52; Natural labor: 114; **No LMWH treatment group:** Caesarean section: 3458; Natural labor: 14562	Miscarriage after 16th week, Stillbirth, Placental abruption, Preeclampsia, Preterm delivery, intrauterine growth restriction infant
[14]	Unknown	Unknown	Unknown	Unknown	Unknown	Postpartum valve thrombosis, Premature delivery, Low-birth-weight, Abortions, Stillbirth
Carolina Arbuthnot. 2016	25 (19-49)	Unknown	Unknown	Unknown	**LMWH treatment group:** Caesarean section: 32; Natural labor: 83; **No LMWH treatment group:** Caesarean section: 4559; Natural labor: 11856	Postpartum hemorrhage
[13]	30	39	Unknown	3360	**LMWH treatment group:** Caesarean section: 17; Natural labor: 71; **No LMWH treatment group:** Caesarean section: 68; Natural labor: 284	Postpartum hemorrhage
[17]	LMWH group: 32 (21-43); **No LMWH group:** 31 (18-44)	**LMWH group:** 39; **No LMWH group:** 39	Unknown	**LMWH group:** 3150 (365-4290); **No LMWH group:** 3235 (555-5035)	**LMWH treatment group:** Caesarean section: 22; Natural labor: 73; **No LMWH treatment group:** Caesarean section: 52; Natural labor: 472;	Postpartum hemorrhage
[15]	**LMWH group:** 27.4±6.3; **No LMWH group:** 26.7±6.9	**LMWH group:** 37.4 ± 2.5; **No LMWH group:** 8.3 ± 2.6	Unknown	Unknown	**LMWH treatment group:** Caesarean section: 20; Natural labor: 35; **No LMWH treatment group:** Caesarean section: 40; Natural labor: 70;	Postpartum hemorrhage
[19]	**LMWH group:** 31.6 (17-45); **No LMWH group:** 31.4 (17–44)	Unknown	**LMWH group:** 24.5 (17-76); **No LMWH group:** 23.4 (16-49)	**LMWH group:** 3439 (340-4970); **No LMWH group:** 3518 (365-4790)	**LMWH treatment group:** Caesarean section: 138; Natural labor: 530; **No LMWH treatment group:** Caesarean section: 119; Natural labor: 507	Bleeding, preeclampsia, foetal growth restriction, allergic skin reactions, thrombocytopenia, preterm delivery, stillbirth, osteoporotic fractures.
Joyce Lai. 2017	**LMWH group:** 34.0 (31.0-38.0); **No LMWH group:** 34.0 (31.0-37.0)	Unknown	**LMWH group:** 32.6 (28.3-42.2); **No LMWH group:** 29.2 (26.6-32.5)	Unknown	All women received Caesarean section	Spontaneous abortion, therapeutic abortion, ectopic pregnancy, intrauterine death, preeclampsia, heart disease, hemorrhage, and transfusion.
HENRIK. 2000	**LMWH group:** 29.1 (19-40); **No LMWH group:** 28.5 (13-47)	**LMWH group:** ≥37 weeks: 59; 34-36 weeks: 4; <34 weeks: 3; **No LMWH group:** ≥37 weeks: 16268; 34-36 weeks: 682; <34 weeks: 309	Unknown	**LMWH group:** 3.514 ± 712; **No LMWH group:** 3.483 ± 590	Unknown	Malformations, low birth weight, pre-term deliveries, stillborn

test showed P<0.1, meaning these studies were not homogenous, so random effect model was used. The meta-analysis results showed using LMWH during pregnancy did not increase the risk of preterm birth as compared to women who did not use LMWH (OR=1.58, 95% CI: 0.90-2.77, Z=1.59, P>0.05) (Figure 3).

Still birth: Five studies were analyzed and heterogeneity test showed P <0.1, meaning these studies were not homogenous, so random effect model was used. The meta analysis results showed using LMWH during pregnancy did not increase the risk of still birth as compared to women who did not use LMWH (OR=1.45, 95% CI: 0.10-21.95, Z=0.27, P>0.05) (Figure 4).

Preeclampsia: Three studies were analyzed and heterogeneity test showed P <0.1, meaning these studies were not homogenous, so random effect model was used. The meta-analysis results showed using LMWH during pregnancy did not increase the risk of preeclampsia as compared to women who did not use LMWH (OR=1.23, 95% CI: 0.16-9.28, Z=0.20, P>0.05) (Figure 5).

Fetal growth restriction: Three studies were analyzed and heterogeneity test showed P=0.48, meaning these studies were homogenous, so fixed effect model was used. The meta-analysis results showed using LMWH during pregnancy could reduce the risk of fetal growth restriction as compared to women who did not use LMWH (OR=1.54, 95% CI: 1.01-2.35, Z=2.02, P=0.04) (Figure 6).

Postpartum hemorrhage: Seven studies were analyzed and heterogeneity test showed P=0.19, meaning these studies were homogenous, so fixed effect model was used. The meta-analysis results showed using LMWH during pregnancy did not increase the risk of postpartum hemorrhage as compared to women who did not use LMWH (OR=1.17, 95% CI: 0.95-1.43, Z=1.47, P>0.05) (Figure 7).

Discussion

Nowadays, the management of pregnancy-related thrombosis

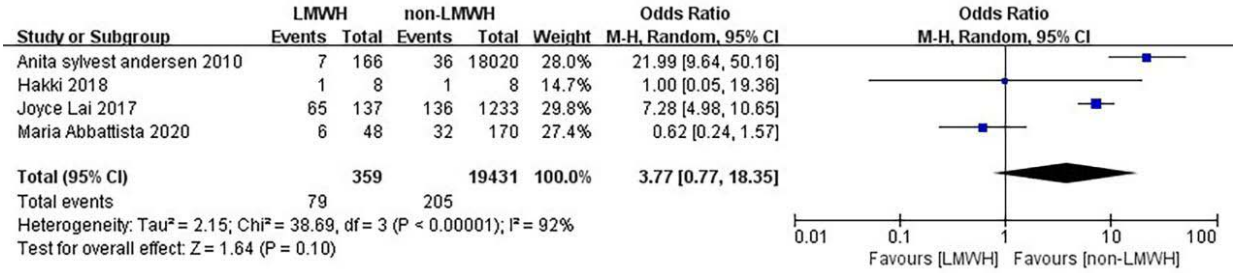

Figure 2: Abortion incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

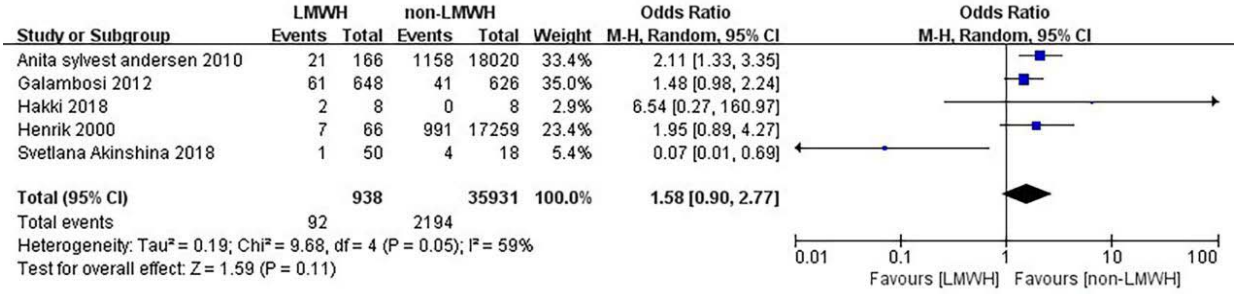

Figure 3: Preterm birth incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

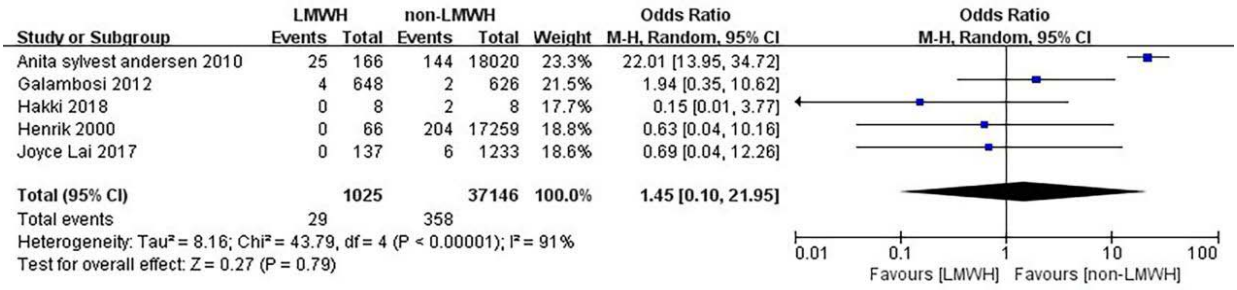

Figure 4: Still birth incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

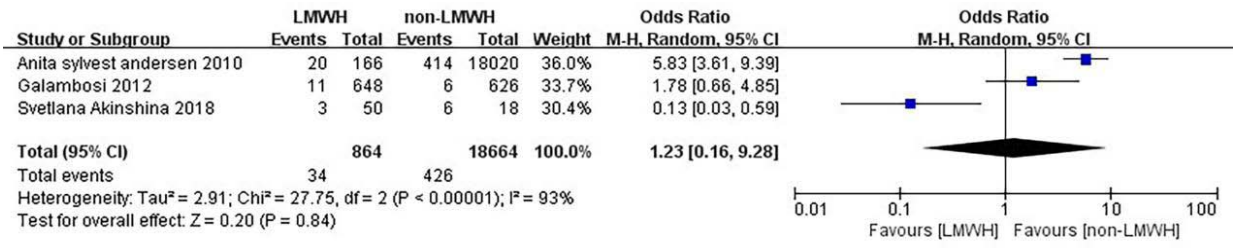

Figure 5: Preeclampsia incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

remains a challenge. Anticoagulants available to prevent and treat VTE include warfarin, Unfractioned Heparin (UFH), Low-Molecular Weight Heparin (LMWH), factor Xa inhibitors, and direct thrombin inhibitors. LMWH is widely used due to its more predictable pharmacokinetic and pharmacodynamic characteristics [21]. It is important to evaluate the benefit of LMWH for thromboprophylaxis in pregnant women. The results of this study showed that there were no statistically significant differences in the risk of abortion, preterm birth, stillbirth, preeclampsia, or postpartum hemorrhage between pregnant women who used LWMH as anticoagulant and those who did not use LWMH. Besides, LMWH use in pregnant women reduced the incidence of fetal growth restriction. This suggests that the use of LMWH does not increase the incidence of pregnancy-related maternal and fetal complications. Previous retrospective studies and meta-analysis also showed that prophylactic or therapeutic doses of LMWH could significantly reduce the risk of recurrent thrombosis

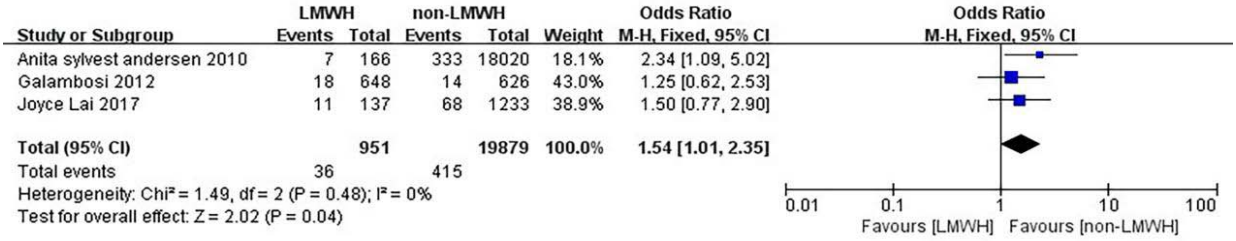

Figure 6: Fetal growth restriction incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

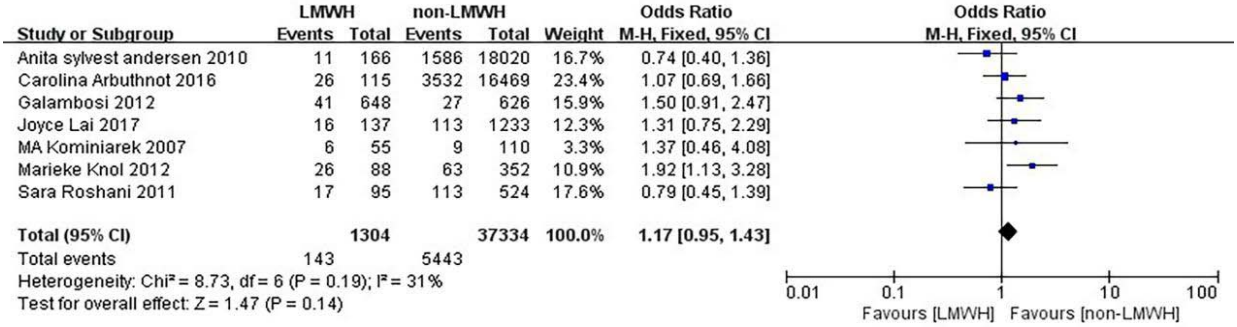

Figure 7: Postpartum hemorrhage incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

during pregnancy and postpartum [22-24].

Conclusions

Our analysis demonstrates that the use of LMWH in pregnant women reduces the risk of thromboembolism without increasing the incidence of relevant adverse outcomes. For pregnant women who meet the anticoagulant treatment criteria, the use of LMWH may bring more benefits to them.

Limitation of this Study

Heterogeneity existed in the selected studies may result in our analysis conclusion more influenced by large sample studies. Moreover, considering the ethical requirements, all the included studies were non-randomized controlled studies which may affected the accuracy of the results to some extent.

Declaration

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Author Contributions: Yang Xiaorong, Lin Shan and Sun Shengjia wrote the manuscript together. Lin Shan, Li Junping and Sun Tao performed the statistical analysis. Li Junping, Zhu Moli, Sun Tao and Li Dongping performed the literature search and review.

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