

Anticoagulant used to treat VTE (venous thromboembolism) in pregnancy: a review

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ABSTRACT

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a medical condition that occurs when a blood clot forms in a deep vein that major cause of pregnancy-related maternal death. As pregnancy progresses, the risk of hypercoagulability increases, fibrinogen, factors VII, VIII, X and VWF (Von Willebrand Factor), plasminogen activator inhibitor-1, plasminogen activator inhibitor-2 are increases and 40-60% protein S decreases. Therefore, anticoagulant drugs are the mainstay of therapy for patients with VTE. The review aimed to select the best anticoagulant for pregnancy women with VTE. A scoping review was used. The type of articles reviewed were original articles obtained from four electronic journal databases published within 2012-2021. The main therapeutic agent recommended for use in the prevention and treatment of VTE in pregnancy is low molecular weight heparin (LMWH). LMWH has better bioavailability than other anticoagulants, has a lower risk of maternal bleeding, thromboembolic, thrombocytopenia and osteoporosis. The use of LMWH is actually better, more comfortable and safety for patients.

ABSTRAK

Tromboemboli vena (VTE), termasuk trombosis vena dalam (DVT) dan emboli paru (PE), adalah kondisi medis yang terjadi ketika pembekuan darah terjadi di vena dalam dan menjadi penyebab utama kematian ibu terkait kehamilan. Saat kehamilan, risiko hiperkoagulabilitas meningkat, fibrinogen, faktor VII, VIII, X dan VWF (Faktor Von Willebrand), penghambat aktivator plasminogen-1, penghambat aktivator plasminogen-2 meningkat dan 40-60% protein S menurun. Oleh karena itu, obat antikoagulan merupakan terapi utama bagi penderita VTE. Tinjauan pustaka ini bertujuan untuk memilih antikoagulan terbaik untuk wanita hamil dengan VTE. Tinjauan pelingkupan digunakan. Jenis artikel yang direview adalah artikel asli yang diperoleh dari empat database jurnal elektronik yang diterbitkan dalam kurun waktu 2012-2021. Agen terapeutik utama yang direkomendasikan untuk digunakan dalam pencegahan dan pengobatan VTE pada kehamilan adalah heparin dengan berat molekul rendah (LMWH). Antikoagulan ini memiliki bioavailabilitas yang lebih baik daripada antikoagulan lainnya, memiliki risiko perdarahan ibu, tromboemboli, trombotopenia, dan osteoporosis yang lebih rendah. Penggunaan LMWH sebenarnya lebih baik, nyaman dan aman bagi pasien.

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INTRODUCTION

Venous thromboembolism (VTE) is the major cause of pregnancy-related maternal death.¹ Pregnant women are one of the population who can suffer from VTE. The risk of pregnancy-associated VTE is up to 6 times compared to similarly aged non-pregnant women, with an incidence rate of 12 per 10,000 births in pregnant woman and 2 per 10,000 births in non-pregnant women.² Over a 10-year period of a population based study of 8 million births in Canada reported that the incidence of VTE increases annually with the overall incidence is 167.7 per 100,000 births.³ VTE is a rare but serious condition due to it is associated with the significant degree of morbidity and mortality of pregnant women. VTE is the third leading cause of pregnancy-related maternal deaths in the US, 9.2% during 2011-2013 and 9.6% during 2014-2017.^{1,4}

The risk factors of VTE can be classified based on severity such as weak, moderate and strong. For weak risk factors for VTE are obesity (BMI >30mg/m²), increasing age over 35 year, laparoscopic surgery, antepartum periode.⁵ For moderate risk factors are congestive heart or respiratory failure, oral contraceptives, thrombophilia, malignancy.⁶ For strong risk factors are major trauma, major general surgery, spinal cord injury, inflammatory disorders.⁷ Test for diagnosing VTE blood clots are: 1) presenting symptoms (fatigue, shortness of breath, pain in chest, fast heart beat, swelling, redness or warmth in one leg, dizziness or fainting and coughing up blood); 2) ultrasound; 3) blood test for D-dimer; 4) computerized tomography (CT) scan; 5) ventilation-perfusion (VQ) scan.⁸

Manifestations of VTE are deep vein thrombosis (DVT) and pulmonary embolism (PE). The disease process starts often in one of the large veins of the leg with the formation of a blood clot. This can be due to vessel wall injuries, a pathological increase in the coagulability of the blood or circulation deficits such

as venous stasis. The resulting blood clot consists mostly of red blood cells held to loosely together by strands of fibrin. A medical term for a blood clot is a thrombus. When the thrombus or blood clot breaks off and travels from one vein to another part of the body, it is called an embolus. Therefore, VTE stands for venous thromboembolism. Embolus that is travelling with the bloodstream through the heart and into the lungs, then the embolus or blood clot eventually blocks a pulmonary artery causes pulmonary embolism (PE). The affected area of the lung is no longer available for the oxygenation of blood. This life-threatening outcome can be traced back to an inappropriately triggered physiological process of blood coagulation.

As pregnancy progresses, the risk of hypercoagulability increases, fibrinogen, factors VII, VIII, X and VWF (Von Willebrand Factor), plasminogen activator inhibitor-1, plasminogen activator inhibitor-2 are increase. Another changes in pregnancy are 40-60% protein S decreased where estrogen induced decrease in total of protein S and increase in C4b binding protein, which binds protein S, increase thrombomodulin factor (sign of vascular damage). A higher level of haemostatic activity during pregnancy is indicated by raised concentrations of coagulation markers such as prothrombin F1 & 2, D-dimer and thrombin-antithrombin (TAT) complexes, which remain elevated in the postpartum period and may take more than 8 wk to return to baseline. So, taking all of these things together, it has an uptick in the pro clotting system and decrease in the anti clotting system.⁹⁻¹¹ The review aimed to select the best anticoagulant for pregnancy women with VTE.

MATERIAL AND METHODS

Article criteria

The articles included in this review were selected based on the inclusion and

exclusion criteria follows. The inclusion criteria were 1) original article published between 2012-2021; 2) the article was written in English; 3) the subject of the research was pregnancy with VTE; 4) the drugs used in the research were anticoagulant; 5) the anticoagulants used were unfractionated heparin, warfarin, direct thrombin inhibitors, direct Xa inhibitors, vit K epoxide reductase inhibitors; and 6) the main outcome of this research was the safety of anticoagulant for VTE in pregnancy. The exclusion criteria were 1) patient who does not have VTE; 2) non-pregnant patient; 3) pregnant woman who does

not suffer VTE; 4) patient with diagnosed VTE but not pregnant; 5) using a method other than specified.

Information sources

The data for this research were accessed from PubMed, Science Direct, Wiley, Springer Link. Those databases were chosen because of eased to accessed and no cost needed to accessed using the search engine.

Article searching strategy

The articles were searched using keywords that were under the formulation of this research problem.

TABLE 1. The keywords were obtained using the PICO method

Question part	Question term
Population	Pregnant woman with VTE
Intervention	Anticoagulant
Comparison	-
Outcome	Safety of anticoagulants

Article selection process

The articles were selected based on the inclusion criteria. The process were conducted according to the preferred reporting items for systematic reviews, meta-analyses, randomized controlled trial (RCT), case report and article review.

Data extraction

The data extraction process extended from identifying the articles to study the content of the articles to gain information according to the aim of this research. The components that were included in the data extraction table were reference, pregnancy with VTE and the use of anticoagulants.

Data item

Data items used in this research were: (a) characteristics of obtained journals, including authors, publishing year, anticoagulants profile (b) main outcomes in this review, which was the safety of anticoagulants use to treat VTE in pregnancy.

RESULT

Selection result of source of evidence

The article searching process was conducted by inputting the keywords based on PICO analysis into five databases: PubMed, Science Direct, Wiley, Springer Link. There were 46 articles obtained from the mentioned databases (TABLE 2).

TABLE 2. Article searching result by using keywords based on PICO analysis.

Data base	Result
Pubmed	(anticoagulant) AND (pregnancy) AND (venous thromboembolism); 17 articles obtained
Science Direct	(anticoagulant) AND (pregnancy) AND (venous thromboembolism); 7 articles obtained
Springer Link	(anticoagulant) AND (pregnancy) AND (venous thromboembolism); 2 articles obtained
Wiley	(anticoagulant) AND (pregnancy) AND (venous thromboembolism); 1 articles obtained

Based on the preferred reporting items for all articles, the obtained articles were then screened for the years published, irrelevant title and incomplete article. Only 27 articles were processed into final reference. On the

title selection, 5 articles were excluded as those not relevant to the aim of this research. On screening for incomplete articles, 9 articles were excluded. On the screening for the year published, there were 5 articles published before 2012.

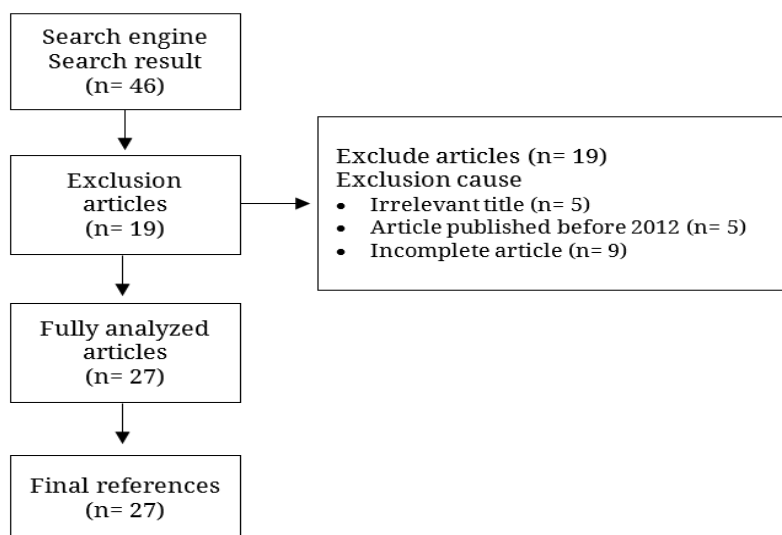


FIGURE 1. Flowchart diagram of article selection process

Source of evidence characteristics

Information obtained from the analyzed articles is relevant to the aim of this scoping review: pregnant woman, VTE, anticoagulant, unfractionated heparin, LMWH, fondaparinux, warfarin, direct thrombin inhibitors, direct Xa inhibitors, vit K epoxide reductase inhibitors.

Result of each data of evidence

Data extraction from the selected articles showed relevant and complete

of the content which consist of the discussion about definition, etiology, risk factors, diagnostic, clinical manifestation, pathophysiology and profile of the drugs.

DISCUSSION

Thromboembolism is a life-threatening condition in pregnancy. The risk increases in pregnant woman with heart disease and is ten times higher in caesarean delivery than in normal delivery. The incidence of VTE

during pregnancy is 5-12 cases per 10,000 pregnancies where the risk is 3 times compared to the nonpregnant population. Whereas the incidence of postpartum VTE (from delivery to 6 wk after delivery) is 3-7 cases per 10,000 pregnancies.¹² Anticoagulant drugs are the mainstay of therapy for patients with VTE. Specific treatment decisions are guided by balancing the risks and benefits of various anticoagulants. The ideal anticoagulant for VTE are predictable anticoagulation achieved, predictable and quick “on/off” time (short half life), ability to monitor, ability to reverse and zero fetal implication. The

main anticoagulant drugs are categorized into four classes i.e. heparins, vitamin K antagonists (VKAs), direct thrombin inhibitors (DTIs), and direct factor “xaban” (Xa) inhibitors.¹³ The side effect of the use of these anticoagulants is hemorrhage or bleeding. Anticoagulant drugs prevent or slow the formation of blood clots that occur. It is used in the prophylactic treatment of both arterial and venous thrombosis, and in patients with atrial fibrillation it may reduce the risk of embolism and stroke. Drugs in this class are divided into two groups based on the method of administration, there are injection and oral anticoagulants.^{14,1}

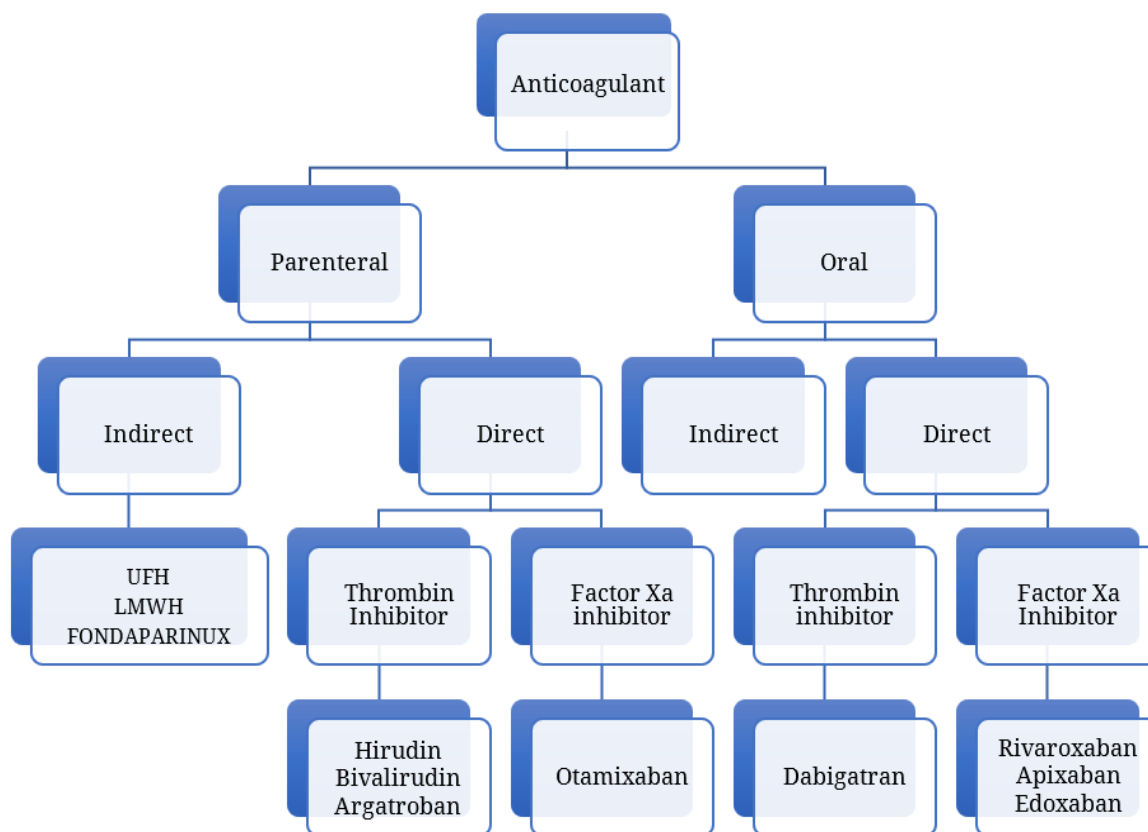


FIGURE 2. A rational classification of currently available anticoagulants, based on their route of administration (parenteral vs oral) and their mode of action.^{14,15}

The treatment given is the administration of anticoagulant UFH and low molecular weight heparin (LMWH). The use of warfarin is avoided in pregnant patients because based on the Food Administration Category (FDA) warfarin is a category D drug because it can cross the placenta so that it can increase the miscarriage rate.

congenital anomalies, fetal bleeding and neurological disorders. The use of direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban is also avoided because in addition to these drugs also cross the placenta, research on the effectiveness and safety of using DOACs in pregnant patients has not been clearly established.⁸

Direct thrombin inhibitors

The DOACs consist of direct thrombin inhibitors named dabigatran. Dabigatran is a direct thrombin inhibitor with action that can cause negative effects in the formation of thrombus by decreasing the conversion of fibrinogen to fibrin, thrombin generation and platelet activation. Dabigatran is eliminated in the renal so in patients with renal failure there should be cautions and also contraindication for patients with creatinine clearance less than 30 mL/min.¹⁶ In the *ex vivo* study of placental transfer, dabigatran is present in milk and can cross the placenta as well as its prodrug (dabigatran etexilate mesylate).¹⁷

Direct Xa inhibitors

Direct acting oral anticoagulants consist of direct Xa inhibitors such as rivaroxaban, apixaban and edoxaban. Rivaroxaban is a direct factor Xa inhibitor that has an action on the free factor Xa and factor Xa within the prothrombinase complex. Rivaroxaban is eliminated in renal 66% (33% direct, 33% excreted after metabolic degradation), biliary excretion 28% and feces 7% unchanged. It is contraindicated in patients with creatinine clearance of less than 15mL/min. Rivaroxaban can cross the placenta membrane and present in breast milk.¹⁷

Apixaban is a direct factor Xa that binds to the free factor Xa and clot-bound factor Xa and indirectly induced platelet aggregation induced by thrombin, and decreases thrombin generation and the development of fibrin clot, thus prolonged the prothrombin time (PT), INR and aPTT.¹⁸ Apixaban is excreted by renal 25-30% and metabolised in the liver (biliary excretion : 30-35%). Therefore, it is contraindicated in patients with severe liver disease. Apixaban can increase the risk to the fetus through transmission of the placenta. It is estimated during *in vitro* studied that fetal blood concentration of apixaban is about 30%-50% of the parent blood concentration. Thus, serum in the fetus will have decreased ability to coagulate.¹⁹

Edoxaban is also a class of direct factor

Xa inhibitors. Edoxaban inhibits factor Xa without the need of antithrombin. Peak plasma concentration of the drug occurs 1-2 h following oral administration.²⁰ This drug is eliminated in renal. Edoxaban can cross the placenta so it can not be used in pregnant women.²¹

The safety and efficacy of DOACs make this agent an alternative to the vitamin K antagonist that has been established. Many women in DOACs therapy for VTE are at reproductive age, but the potential toxicity of DOACs in reproduction is not yet known. Animal model studies during pregnancy and lactation showed that DOAC has potential toxicity to reproduction. Dabigatran causes fetal growth restriction and anomalies, fetal mortality. Rivaroxaban causes postimplantation pregnancy loss and increased incidence of malformations. Edoxaban causes gallbladder anomalies and postimplantation pregnancy loss. Apixaban does not show toxicity to reproduction but the safety in pregnant women has not been ascertained. Data related to the use of DOAC in pregnancy is very limited. Therefore, in 2016, the International Society on Thrombotic and Haemostatic (ISTH) issued a guidance statement on the use of DOACs on women of reproductive ability. This guidance recommends that the use of DOAC should be stopped immediately if confirmed pregnant, but if still indicated it can be replaced with LMWH which does not cross the placenta and relatively safe for the fetus.^{22,23}

Studies of case series and pharmacovigilance reports on DOAC exposure and pregnancy outcomes have been conducted. There is a report of miscarriage with an average of 22%, the risk of embryopathy is lower than the 7% ever reported related to VKA exposure and the risk of malformation in the newborn is estimated at 3.5%. However, due to the study's limitations related to the lack and incomplete amount of data, the results do not indicate that DOAC exposure in pregnancy has a high risk of embryopathy or that the results can be used as counseling considerations for pregnancy termination.²³ Individual case

safety report with vigibase on the use of rivaroxaban and apixaban conducted in the global population, there are reports of cases of abortion namely 41 cases²⁴ congenital anomalies 14 cases. Therefore, DOACs are not recommended in pregnancy.⁸

Indirect thrombin inhibitors

Low molecule weight heparin has the same effectiveness and safety when compared to UFH.²⁵ Another study stated that the use of LMWH has an effectiveness in reducing thromboembolic recurrence, reducing thrombotic complications better, severe bleeding and death due to the nature of LMWH that does not cross the placenta.²⁶ Heparins enhance the action of antithrombin, an endogenous anticoagulant. Unfractionated heparin (UFH) and LMWHs do not cross the placental barrier and are not secreted in the maternal milk. They are considered safe during pregnancy and the puerperium. The use of LMWH has a lower incidence of osteoporosis and heparin induced thrombocytopenia (HIT) but cannot be given to patients with renal impairment with a glomerular filtration rate (GFR) <30 mL/min, while the use of UFH can be used in patients with renal impairment with a GFR <30

mL/min. or patients requiring rapid anticoagulant therapy such as surgery or delivery. The LMWHs could be replaced with UFH, considering its shorter half-life, quick monitoring of its effect (aPTT) and easy reversibility.^{27,28}

The LMWH or UFH therapy can be given 6-12 h after normal delivery or 12-24 h after C-section (if there is no risk of bleeding). The incidence of VTE increases after 2 wk postpartum so anticoagulant therapy should be given at least 6 wk postpartum and ideally therapy is given for 3 mo (the length of therapy is patient centered and depends on the patient's VTE state).²⁶ The use of UFH as prophylactic VTE therapy for pregnancy can be given every 12 h subcutaneously at a dose of 5,000 U, but there are several studies that classify the UFH dose given according to the patient's trimester/gestational period (5,000-7,500 U in the first trimester, 7,500-10,000 U) in the second trimester and 10,000 in the third trimester). Dosage of LMWH such as enoxaparin 40 mg/kg SC once daily, heparin weight adjusted (0.5 mg/kg SC twice daily). Anti-Xa levels are checked every 4-6 weeks after dose adjustment.⁸ The doses of anticoagulants for prophylactic and therapy are presented in TABLE 3.

TABLE 3. Prophylactic and therapeutic anticoagulant dosing strategies^{29,30}

Drug	Prophylactic	Intermediate	Weight adjusted	Weight adjusted or full therapy
LMWH				
Enoxaparin	40 mg SC qd	40 mg SC BID	0.5 mg/kg BID	1 mg/kg BID
Dalteparin	5.000 U SC qd	5.000 U SC BID or 10.000 U daily		200 U/kg qd or 100 U/kg q12h
Tinzaparin	4.500 U SC qd	10.000 U daily	75 U/kg daily	175 U/kg daily
Nadroparin	2.850 U SC qd			86 U/kg BID or 171 U/kg qd
UFH	5.000-10.000 U SC BID	5.000-7500 U SC TID		17.500 U BID for goal anti-Xa 0.3-0.7 IU/mL
IV UFH				80 U/kg bolus then 18 U/kg/h; titrate for anti-Xa 0.3-0.7 IU/mL
Fondaparinux	2.5 mg SC qd			5 mg SC daily (weight <50 kg), 7.5mg (50-100 kg), 10mg (>100 kg)

BID= twice daily; TID= three time daily; qd= every day; q12h= every 12 h; SC=subcutaneous; UFH= unfractionated heparin

A meta-analysis study to evaluate the use of LMWH in patients with recurrent pregnancy loss was conducted.³¹ It was reported the use of LMWH monotherapy (enoxaparin, tinzaparin, dalteparin) could significantly increase the live birth rate (RR: 1.19; CI 95% CI 1.03-1.38; p-value 0.02) and reduced miscarriage rate (RR: 0.62; 95% CI 0.43-0.91; p-value 0.01) when compared to the group without LMWH (placebo, folic acid or no therapy). The use of enoxaparin sodium as thromboprophylaxis in caesarean section patients has good safety and efficacy in preventing pulmonary embolism (PE).³²

The mechanism of enoxaparin is to bind antithrombin and catalyzes its efficiency. Enoxaparin inhibits factor Xa and potentiates antithrombin III, metabolised by hepatic and excreted by renal clearance. However, unlike UFH, the combination LMWH-antithrombin is only capable of deactivating factor Xa and fewer in factor IIa, so the peak anti-Xa level must be monitoring every 4-6 h after dose (therapeutic dose: 1 mg/kg dose every 12 h). Enoxaparin can be either given SQ or IV depending on the indication. About 10 % of enoxaparin is renal eliminated as active fragments. Compared to UFH, LMWHs are more dependent upon renal clearance.^{13,33}

Fondaparinux is one of drugs that can be used to treat VTE in pregnancy. Fondaparinux can be given in intolerant patient to UFH and LMWH. Fondaparinux has anticoagulant effects due to its ability to interact selectively to factor Xa and antithrombin. The study of fondaparinux use in pregnancy reported that fondaparinux was not associated with increased bleeding, thromboembolic complications, and fetal abnormalities.³⁴ In pregnancy, the use of direct thrombin (e.g. dabigatran) should be avoided. Recent study reported that dabigatran and its prodrug can cross the placenta so it might be able to have adverse effects on fetal coagulation. There is no available data that evaluates use of direct thrombin to treat VTE in

pregnancy.³⁵

When heparin and LMWH intolerance or HIT occurs in pregnant women who need thromboprophylaxis, there are limited alternative anticoagulant choices, fondaparinux could be suggested as an option. Fondaparinux 2.5 mg O.D. should be considered as a prophylaxis dose. The standard dose for the treatment of VTE, especially DVT or PE is 7.5 mg daily. This should be increased to 10 mg daily for body weight >100 kg and decreased to 5 mg daily for body weight <50 kg.³⁶

Vit K epoxide reductase inhibitor

Warfarin affects the synthesis of vitamin K which plays a role in blood clotting, resulting in the depletion of factors II, VII, IX and X. Warfarin acts in the liver by inhibiting the carboxylation of vitamin K from its precursor protein. The factor VII depletion occurs cause the half-life of each blood clotting factors affect prothrombin time prolonged. However, the antithrombotic effect only reached its peak after depletion of these four factors. Thus, the anticoagulant effect of warfarin may take several days because of its effect on newly formed clotting factors rather than factors already present in the circulation. Warfarin does not has direct effect with thrombus, but it can prevent the expansion of the thrombus. With warfarin, prothrombin time should be monitored regularly. The onset of action is usually detected in plasma within one hour of administration, with a half-life of 20-60 h.^{37,16}

Warfarin is not used to treat VTE in pregnancy. Warfarin is at risk of teratogenicity because it is able to cross the placental barrier in the first trimester and 6% risk of embryopathy if taken between 6 and 12 wk gestation, especially during early gestation (pregnancy level D) and metabolism by hepatic (> 90% inactive metabolites). Complications of warfarin in the first half of pregnancy include: spontaneous abortion, prematurity, fetal deformity,

stillbirth, retro-placental hemorrhage and intracranial hemorrhage. Warfarin embryopathy consists of bone and cartilage abnormalities, nasal hyperplasia, optic atrophy, blindness, mental retardation and seizures. Warfarin is rarely recommended in

pregnancy except in women with prosthetic (mechanical) heart valves who are at the highest risk of thrombotic complications, but even then should only be continued under specialist maternal medicine care jointly with a cardiologist.^{38,9}

TABLE 4. Pharmacology and dosage of anticoagulant agents for prophylaxis and treatment VTE in pregnancy.^{30,39,40}

Drug	Mechanism	Therapeutic dose	Monitoring	Metabolism/clearance	Pregnancy category	Present in milk	Crosses the placenta
Unfractionated heparin	Potentiates antithrombin III	Variable (TABLE 3)	aPTT	Hepatic metabolism and renal clearance	B	No	No
Low molecular weight heparin	Inhibits factor X	Variable (TABLE 3)	Anti-Xa level	Hepatic metabolism and renal clearance	B	Unknown	No
Fondaparinux	Inhibits factor Xa and potentiates antithrombin III	2.5 mg once daily	Anti-Xa level	Renal	B	Unknown	No

CONCLUSION

In conclusion, fetal safety is an important and crucial issue when considering an anticoagulant therapy in pregnancy. Therefore, an accurate evaluation of risks and benefits of the anticoagulants should always be performed and the results discussed with the patient. The use of anticoagulants in pregnancy woman with VTE has limitations compared to nonpregnant women. This is due to the presence of as pregnancy progresses, the risk of hypercoagulability increases, fibrinogen, factors VII, VIII, X and VWF (Von Willebrand Factor), plasminogen activator inhibitor-1, plasminogen activator inhibitor-2 are increases and 40-60% protein S decreases. So, it has an uptick in the pro clotting system and decrease in the anti clotting system. Low molecular weight heparin has better

bioavailability than other anticoagulants, has a lower risk of maternal bleeding, thromboembolic, thrombocytopenia and osteoporosis. The use of LMWH is actually better, more comfortable and safety for patients. However, due to the limited availability of the drugs in the majority of hospitals and limited facilities that can not carry out anti-Xa level checks for monitoring the dosage of LMWH, it was decided to use heparin (UFH) which can be controlled using the dose by checking aPTT regularly.

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REFERENCES

1. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011-2013. *Obstet Gynecol* 2017; 130(2):366-73.
<https://doi.org/10.1097/AOG.0000000000002114>
2. Center for Disease Control and Prevention. Pregnancy mortality surveillance system. Available at: <http://www.cdc.org/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm>
3. Abbasi N, Balayla J, Laporta DP, Kezouh A, Abenhaim HA. Trends, risk factor, and mortality among women with venous thromboembolism during labour and delivery: a population-based study of 8 million births. *Arch Gynecol Obstet* 2014; 289(2):275-84.
<https://doi.org/10.1007/s00404-013-2923-8>
4. Parunov LA, Soshitova NP, Ovanesov MV, Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (VTE) associated with pregnancy. *Birth Defects Res C Embryo Today* 2015; 105(3):167-84.
<https://doi.org/10.1002/bdrc.21105>
5. Katherine M, Stanislav H, Mark A. Venous thromboembolism associated with pregnancy: JACC Focus Seminar. *J Am Coll Cardiol* 2020; 76(18):2128-41.
<https://doi.org/10.1016/j.jacc.2020.06.090>
6. Carlos J, David R, Farjat AE, Gloria K, MacCallum P, Lopez RD, *et al.* Pregnancy-associated venous thromboembolism: insights from GARFIELD-VTE. *TH Open* 2021; 5(1):e24-34.
<https://doi.org/10.1055/s-0040-1722611>
7. Karl E, Ainle FN. VTE risk assessment in pregnancy. *Res Pract Thromb Haemost* 2019; 4(2):183-92.
<https://doi.org/10.1002/rth2.12290>
8. Nichols KM, Henkin S, Creager MA. Venous thromboembolism associated with pregnancy: JACC Focus Seminar. *J Am Coll Cardiol* 2020; 76(18):2128-41.
<https://doi.org/10.1016/j.jacc.2020.06.090>
9. Lim A, Samarage A, Lim BH. Venous thromboembolism in pregnancy. *Obstet Gynecol Reprod Med* 2016; 26(5): 133-9.
10. ACOG. ACOG practice bulletin No. 196: thromboembolism in pregnancy. *Obstet Gynecol* 2018; 132(1):e1-17.
<https://doi.org/10.1097/AOG.0000000000002706>
11. Ro A, Kageyama N, Mukai T. Pathophysiology of venous thromboembolism with respect to the anatomical features of the deep veins of lower limbs : a review. *Ann Vasc Dis* 2017; 10(2):99-106.
<https://doi.org/10.3400/avd.ra.17-00035>
12. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. *The Lancet* 2013; 375(9713):500-12.
[https://doi.org/10.1016/S0140-6736\(09\)60996-X](https://doi.org/10.1016/S0140-6736(09)60996-X)
13. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. *J Thromb Thrombolysis* 2016; 41(1):15-31.
<https://doi.org/10.1007/s11239-015-1314-3>
14. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, *et al.* General mechanisms of coagulation and targets of anticoagulants (Section I). *Thromb Haemost* 2013; 109(04):569-79.
<https://doi.org/10.1160/TH12-10-0772>
15. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. *West J Emerg Med* 2015; 16(1):11-7.
<https://doi.org/10.5811/westjem.2014.12.22933>
16. Ferreira JL, Wipf JE. Pharmacologic therapies in anticoagulants. *Med Clin N Am* 2016; 100(4):695-718.
<https://doi.org/10.1016/j.mcna.2016.03.007>
17. Yarrington CD, Valente AM, Economy

- KE. Cardiovascular management in pregnancy : antithrombotic agents and antiplatelet agents. *Circulation* 2015; 132(14):1354-64.
<https://doi.org/10.1161/CIRCULATIONAHA.114.003902>
18. Mandernach MW, Beyth RJ, Rajasekhar A. Apixaban for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism: an evidence-based review. *Ther Clin Risk Manag* 2015; 11:1273-82.
<https://doi.org/10.2147/TCRM.S68010>
 19. Komori M, Hayata E, Nakata M, Yuzawa H, Oji A, Morita M. Apixaban therapy in a pregnant woman with heparin-induced thrombocytopenia and venous thromboembolic events caused by congenital antithrombin deficiency: a case report. *Case Rep Womens Health* 2020; 27:e00200.
<https://doi.org/10.1016/j.crwh.2020.e00200>
 20. Stacy ZA, Call WB, Hartmann AP, Peters GL, Richter SK. Edoxaban : a comprehensive review of the pharmacology and clinical data for the management of atrial fibrillation and venous thromboembolism. *Cardiol Ther* 2016; 5(1):1-18.
<https://doi.org/10.1007/s40119-016-0058-2>
 21. James AH. Pregnancy, contraception and venous thromboembolism (deep vein thrombosis and pulmonary embolism). *Vasc Med* 2017; 22(2):166-9.
<https://doi.org/10.1177/1358863X17690601>
 22. Cohen H, Arachchillage DR, Middeldorp S, Beyer-Westendorf J, Abdul-Kadir R. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC and ISTH: reply. *J Thromb Haemost* 2017; 15(1):195-7.
<https://doi.org/10.1111/jth.13535>
 23. Beyer-Westendorf J, Michalski F, Tittl L, Middeldorp S, Cohen H, Abdul-Kadir R, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants and the challenge of event reporting. *coagulation and fibrinolysis*. *J Thromb Haemost* 2016; 116(4):651-8.
<https://doi.org/10.1160/TH16-04-0305>
 24. Sessa M, Mascolo A, Callerus T, Capuano A, Rossi F, Andersen M. Direct-acting oral anticoagulants (DOACs) in pregnancy: new insight from vigibase. *Sci Rep* 2019; 9(1):7236.
<https://doi.org/10.1038/s41598-019-43715-4>
 25. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Annals Intern Med* 2014; 140(3):175-83.
<https://doi.org/10.7326/0003-4819-140-3-200402030-00008>
 26. McIntock C, Brighton T, Chunilal S, Dekker G, McDonnell N, McRae S, et al. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. *Aust N Z J Obstet Gynecol* 2012; 52(1):14-22.
<https://doi.org/10.1111/j.1479-828X.2011.01361.x>
 27. Sanches SMV, Cerqueira MMBF, Junqueira PL, Gomez MT. Thromboprophylaxis during the pregnancy-puerperal cycle-literature review. *Rev Bras Ginecol Obstet* 2020; 42(4):218-27.
<https://doi.org/10.1055/s-0040-1708096>
 28. Galambosi P, Hiilesmaa V, Ulander VM, Laitinen L, Tiitinen A, Kaaja R. Prolonged low-molecular-weight heparin use during pregnancy and subsequent bone mineral density. *Thromb Res* 2016; 143:122-6.
<https://doi.org/10.1016/j.thromres.2016.05.016>
 29. Fogerty AE. Challenges of anticoagulation therapy in pregnancy. *Curr Treat Options Cardio Med* 2017; 19(10):76.
<https://doi.org/10.1007/s11936-017-0575-x>
 30. Sucker C, Zotz RB. Prophylaxis and treatment of venous thrombosis and

- pulmonary embolism in pregnancy. *Rev Vasc Med* 2015; 3(2):24-30.
<https://doi.org/10.1016/j.rvm.2015.05.003>
31. Jiang F, Hu X, Jiang K, Pi H, He Q, Chen X. The role of low molecular weight heparin on recurrent pregnancy loss: a systematic review and meta-analysis. *Taiwan J Obstet Gynecol* 2021; 60(1):1-8.
<https://doi.org/10.1016/j.tjog.2020.11.001>
 32. Goto M, Yoshizato T, Tatsumura M, Takashima T, Ogawa M, Nakahara H, *et al.* Safety and efficacy of thromboprophylaxis using enoxaparin sodium after cesarean section: A multi-center study in Japan. *Taiwan J Obstet Gynecol* 2015; 54(3):248-52.
<https://doi.org/10.1016/j.tjog.2014.09.008>
 33. Tang AW, Greer I. A systematic review on the use of new anticoagulants in pregnancy. *Obstet Med* 2013; 6(2):64-71.
<https://doi.org/10.1177/1753495X12472642>
 34. Dempfle CE, Koscielny J, Lindhoff-Last E, Linnemann B, Bux-Gewehr I, Kappert G, *et al.* Fondaparinux pre-, peri-, and/or postpartum for the prophylaxis/treatment of venous thromboembolism (Fonda PPP). *Clin Appl Thromb Hemost* 2021; 27: 10760296211014575.
<https://doi.org/10.1177/10760296211014575>
 35. Bapat P, Kedar R, Lubetsky A, Matlow JN, Aleksa K, Berger H, *et al.* Transfer of dabigatran and dabigatran etexilate mesylate across the dually perfused human placenta. *Obstet Gynecol* 2014; 123(6):1256-61.
<https://doi.org/10.1097/AOG.0000000000000277>
 36. Carolis SD, Pasquo ED, Rossi E, Sordo GD, Buonomo A, Schiavino A, *et al.* Fondaparinux in pregnancy: could it be a safe option? *Thromb Res* 2015; 135(6):1049-51.
<https://doi.org/10.1016/j.thromres.2015.04.001>
 37. Witt DM, Clark MP, Katz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis* 2016; 41(1):187-205.
<https://doi.org/10.1007/s11239-015-1319-y>
 38. Gibson PS, Powrie R. Anticoagulants and pregnancy: when are they safe? *Clev Clin J Med* 2009; 76(2):113-27.
<https://doi.org/10.3949/ccjm.75a.072272>
 39. DeWald TA, Washam JB, Becker RC. Anticoagulants: pharmacokinetics, mechanisms of action, and indications. *Neurosurg Clin N Am* 2018; 29(4):503-15.
<https://doi.org/10.1016/j.nec.2018.06.003>
 40. Alshawabkeh L, Economy KE, Valente AM. Anticoagulation during pregnancy: evolving strategies with a focus on mechanical valves. *J Am Coll Cardiol* 2016; 68(16):1804-11.
<https://doi.org/10.1016/j.jacc.2016.06.076>