

VTE, Thrombophilia, Antithrombotic Therapy and Pregnancy: A Norwegian adaptation of the 9th ed. of the ACCP Antithrombotic Therapy and Prevention of Thrombosis Evidence-based Clinical Practice Guidelines

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Disclaimer

This chapter is translated from the Norwegian guideline chapter on thrombosis in pregnancy

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Summary of recommendations

2 - General advice on the use of LMWH and warfarin during pregnancy

Not Set

For recommendations on thromboprophylaxis and treatment of VTE, we refer to specific sections on each topic.

2.1 - Low-molecular-weight heparin (LMWH)

Use of LMWH during pregnancy

Strong Recommendation

For pregnant women we recommend low molecular weight heparin (LMWH) both as treatment of and prophylaxis against venous thromboembolism rather than unfractionated heparin (UFH).

Use of LMWH during delivery

Strong Recommendation

For women using dose-adjusted LMWH we recommend that the delivery is scheduled and that LMWH is discontinued 22 to 24 hours before a caesarean or regional anesthesia. When induction is performed we recommend discontinuation 24 hours before the expected delivery or initiation of epidural. Individual judgments based on maturity of the cervix may qualify for discontinuation 12-24 hours before induction.

Remark: The risk of obstetric hemorrhage at birth and risk of bleeding associated with regional anesthesia should be minimized. If the patient is on a once daily regime, only half the dose should be given 24 hours prior to a scheduled caesarean. Before an induction the degree of cervical maturity must be evaluated to determine the time lapse between the last injection of LMWH and the start of the induction. Induction of labor is often appropriate to reduce the bleeding risk. At a very high risk of recurrence, or recent thrombosis (2 weeks) changing to iv unfractionated heparin (UH) should be considered with discontinuation 4-6 hours before expected delivery. If a caesarean is performed general anesthesia is preferable.

Fondaparinux (Arixtra)

Weak Recommendation

We suggest restricting use of fondaparinux to patients experiencing severe allergic reactions (including HIT) to LMWH.

2.2 - Long term anticoagulation during pregnancy, including pregnant women with mechanical heart valves

Warfarin

Weak Recommendation

For women who are on long-term treatment with warfarin and plan to become pregnant, we suggest to change to LMWH in the presence of a positive pregnancy test, rather than changing to LMWH during the period they're trying to become pregnant.

Weak Recommendation

For pregnant women on long-term anticoagulation (warfarin or new oral anticoagulants) we suggest changing to LMWH at therapeutic doses, alternatively 75% of the therapeutic dose, throughout pregnancy, rather than a prophylactic dose of LMWH. Postpartum we suggest to re-initiate warfarin rather than continuing LMWH. New oral anticoagulants should not be re-initiated until after breastfeeding is stopped.

Apixaban, rivaroxaban and dabigatran

Strong Recommendation

For pregnant women we recommend to avoid the new oral anticoagulants (direct thrombin and factor Xa inhibitors).

Pregnant women with mechanical heart valves

Strong Recommendation

We recommend one of the following treatment regimes:

1. Dose-adjusted LMWH twice daily throughout pregnancy with monitoring of anti-Xa levels 3-4 hours after injection (anti Xa reference range 0.5-1.2).
2. Dose-adjusted LMWH until week 13, then warfarin until 2-4 weeks prior to term at which point LMWH is resumed.

Remark: Women with thrombogenic old heart valves that carry a high risk of valve thrombosis or who experience treatment failure with LMWH should be referred for evaluation by the obstetric team at a regional hospital or centralized to Oslo University Hospital.

High risk for thromboembolism

Weak Recommendation

For pregnant women with heart valves where the efficacy and safety of LMWH is questionable (old valves or prior valve thrombosis) we suggest warfarin throughout pregnancy with the transition to LMWH or UH close to delivery, rather than the use of warfarin in the intermediate period.

Remark: These patients should be centralized for evaluation by the obstetric cardiac team at the regional hospitals or to Oslo University Hospital.

Weak Recommendation

In pregnant women with heart valves at increased risk of valve thrombosis we suggest the addition of low-dose ASA 75 mg / day.

4 - Acute DVT or pulmonary embolism (venous thromboembolism = VTE)

VTE prior to pregnancy

Strong Recommendation

For women with acute thrombosis who are already under treatment when they become pregnant we recommend LMWH rather than warfarin throughout pregnancy.

VTE during pregnancy

Strong Recommendation

For pregnant women with acute venous thromboembolism (VTE) we recommend weight-adjusted subcutaneous LMWH to be used throughout pregnancy and 6 weeks postpartum, rather than unfractionated heparin (UH).

Strong Recommendation

For pregnant women with acute venous thromboembolism (VTE) in pregnancy, we recommend LMWH rather than warfarin.

Duration of anticoagulation therapy

Weak Recommendation

We suggest anticoagulation with LMWH once or twice daily throughout pregnancy and for at least 6 weeks after birth (minimum total treatment 3 months) rather than shorter treatment.

5 - Assisted reproductive therapy and thromboprophylaxis

Ovarian hyperstimulation syndrome (OHSS) occurring after assisted reproductive therapy

Weak Recommendation

For women who develop ovarian hyperstimulation syndrome (OHSS) we suggest extended thromboprophylaxis (LMWH) for 3 months after clinical remission of symptoms.

Strong Recommendation

For women undergoing assisted reproduction we recommend against the use of routine thromboprophylaxis.

6 - Prior VTE and thromboprophylaxis

Duration of treatment postpartum

Weak Recommendation

For all pregnant women with previous venous thrombosis, we suggest postpartum prophylaxis for 6 weeks with LMWH or warfarin (INR 2.5 + / - 0.5).

Pregnant women at low risk of recurrent venous thrombosis (VTE): Prior VTE associated with transient risk factor not related to estrogen therapy or pregnancy.

Weak Recommendation

We suggest antepartum clinical vigilance rather than routine thromboprophylaxis.

Pregnant women with moderate to high risk of recurrent venous thrombosis (VTE): Prior unprovoked VTE, pregnancy or estrogen-related VTE, known thrombophilia or multiple previous VTE without long-term anticoagulation

Weak Recommendation

We suggest antepartum prophylaxis with prophylactic or intermediate dose LMWH.

7 - Thrombophilia and thromboprophylaxis

Homozygous factor V Leiden or homozygous Prothrombin 20210 A mutation

Weak Recommendation

We suggest thromboprophylaxis throughout pregnancy and 6 weeks postpartum with prophylactic or intermediate dose LMWH, alternatively postpartum warfarin (INR 2.5 + / -0.5).

Heterozygous factor V Leiden, heterozygous prothrombin 20210A mutation, combined Leiden and prothrombin mutation, protein C or protein S deficiency

Weak Recommendation

For pregnant women with no prior VTE, but a family history of VTE, we suggest antepartum clinical vigilance followed by postpartum prophylaxis for 6 weeks with either prophylactic- or intermediate dose LMWH or postpartum warfarin (INR 2.5 + / -0.5).

Weak Recommendation

For pregnant women with no prior VTE and no family history of VTE we suggest antepartum and postpartum clinical vigilance rather than prophylaxis.

Antithrombin deficiency

Weak Recommendation

We suggest thromboprophylaxis with high-or intermediate dose LMWH throughout pregnancy and 6 weeks postpartum. For women already on lifelong anticoagulation we recommend a treatment dose of LMWH.

Antiphospholipid syndrome (APLA)

Strong Recommendation

For women with recurrent early pregnancy loss (three or more miscarriages) that meet the laboratory criteria for APLA syndrome, we recommend prophylactic LMWH combined with low-dose ASA during the antepartum period.

8 - Caesarean section and thromboprophylaxis

No additional risk factors for venous thromboembolism (VTE)

Strong Recommendation

For women without additional risk we recommend against the use of any thromboprophylaxis other than early mobilization.

Moderate to high risk of VTE

Weak Recommendation

For women who are at increased risk of venous thrombosis after a cesarean section (one or more risk factors, see practical information) we suggest thromboprophylaxis with LMWH during the hospital stay. For women who have a contraindication to LMWH we suggest the use of compression stockings.

Very high risk of VTE

Weak Recommendation

For women who are at very high risk for venous thrombosis due to multiple major risk factors, we suggest thromboprophylaxis with LMWH in combination with compression stockings during the hospital stay, rather than LMWH alone.

Persistent high risk of VTE

Weak Recommendation

For women who are at very high risk of venous thrombosis and where the risk persists, we suggest prolonged thromboprophylaxis with LMWH until 6 weeks postpartum.

9 - Use of anticoagulation therapy during breastfeeding

Warfarin

Strong Recommendation

For women taking warfarin we recommend to continue doing so while breastfeeding.

Low molecular weight heparin (LMWH)

Strong Recommendation

For women using LMWH we recommend to continue doing so while breastfeeding.

Fondaparinux

Weak Recommendation

In breastfeeding women we suggest alternative anticoagulation rather than fondaparinux (Arixtra).

Dabigatran, apixaban, rivaroxaban

Strong Recommendation

For breastfeeding women we recommend alternative anticoagulation rather than oral thrombin inhibitor and factor Xa inhibitor.

Aspirin

Weak Recommendation

For women taking low-dose aspirin on vascular indication we suggest to continue doing so while breastfeeding.

10 - Reccurent early pregnancy loss and other complications

Screening for APLA

Strong Recommendation

For women with recurrent early pregnancy loss (three or more consecutive first trimester abortions) we recommend screening only for the APLA (antiphospholipid antibody) syndrome.

Screening for thrombophilia

Weak Recommendation

For women with pregnancy complications we suggest not to screen for hereditary thrombophilia.

Hereditary thrombophilias: Protein S and C deficiency, heterozygous factor V Leiden or heterozygous prothrombin- mutation.

Pregnancy complications: Habitual abortion, IUFD, growth retardation, preeclampsia or placental abruption

Women without thrombophilia or APLA

Strong Recommendation

For women with two or more spontaneous miscarriages without thrombophilia or APLA we recommend against thromboprophylaxis.

Treatment in women with recurrent early pregnancy loss who fulfill the criteria for APLA syndrome (see practical advice)

Strong Recommendation

For women with recurrent early pregnancy loss (three or more miscarriages) who meet the laboratory criteria for APLA syndrome, we recommend prophylactic LMWH combined with low-dose ASA (see section on prophylaxis in women with known thrombophilia).

Treatment in women with pregnancy complications and known hereditary thrombophilias

Weak Recommendation

For women with pregnancy complications and known hereditary thrombophilias, we suggest not to use thromboprophylaxis.

Pregnancy complications: IUFD, growth retardation, preeclampsia, placental abruption

Hereditary thrombophilias: Protein S and C deficiency, heterozygous Leiden and heterozygous prothrombin gene mutations.

Preeclampsia

Strong Recommendation

For women at risk of preeclampsia we recommend low-dose ASA 75 mg x 1 starting at week 13 and continued throughout the pregnancy.

1 - VTE, Thrombophilia, Antithrombotic Therapy and Pregnancy

Chapter editor: Anne Flem Jacobsen, Oslo University Hospital dept. of Obstetrics and Gynecology.

Panel members: Per Morten Sandset, Oslo University Hospital dept. of Cancer, Surgery and Transplants. Line Bjørge, Haukeland Hospital dept. of Obstetrics and Gynecology. Anette Løken Eilertsen, Oslo University Hospital dept. of Haematology. Tore Henriksen, Oslo University Hospital dept. of Obstetrics and Gynecology.

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Conflicts of Interest: COI are reported only for excluded, modified or new recommendations

Recommendation from AT9	Norwegian adaptation	Anne Flem Jacobsen	Line Bjørge	Anette Løken Eilertsen	Tore Henriksen
2.2.1. For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B).					
3.0.1. For women receiving anticoagulation for the treatment of VTE who become pregnant, we recommend LMWH over VKAs during the first trimester (Grade 1A), in the second and third trimesters (Grade 1B), and during late pregnancy when delivery is imminent (Grade 1A).					
3.0.2. For women requiring long-term VKAs who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and substituting LMWH for VKAs when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Grade 2C).					
3.0.3. For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) who cannot receive danaparoid (Grade 2C).	Danaparoid is excluded from the recommendation text.	-	-	-	-

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C).					
4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A).	Acenocoumarol and UFH are excluded from the recommendation text.	Primary financial COI: Educational speeches for Pfizer (dalteparin) and Nycomed (warfarin).	-	-	-
4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B).	Danaparoid and r-hirudin are excluded from the recommendation text.	As above	-	-	-
4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).					
4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C).					

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breast-feed, we suggest continuing this medication (Grade 2C).					
5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B).	A new reference has been added, but the recommendation remains unchanged.				
5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C).					
6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B).					
6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).	The cut-off for thromboprophylactic treatment has been lowered from a baseline risk of 30/1000 to a risk of 15/1000. IPC has been excluded from the recommendation text.	See above		-	-
6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple	IPC has been excluded from the recommendation text.	-	-	-	-

additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone (Grade 2C).					
6.2.4. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital (Grade 2C).					
7.1.1. For pregnant women with acute VTE, we recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH (Grade 1B).					
7.1.2. For pregnant women with acute VTE, we recommend LMWH over VKA treatment antenatally (Grade 1A)					
7.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C).					
7.1.4. For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).	Some minor adjustments in the recommendation text has been made.	See above	-	-	-

8.2.1. For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).					
8.2.2. For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).					
8.2.3. For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).					
8.2.4. For pregnant women receiving long-term VKAs, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum, rather than prophylactic-dose LMWH (Grade 2C).					
9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and	The baseline risk of VTE is updated using data from one new study: Jacobsen et al: Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene	See above	-	-	-

postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).	G20210A polymorphism. J Thromb Haemost 2010;8:2443-9.				
9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).	Pregnant women with antithrombin deficiency have been excluded from the recommendation. Instead they are recommended both ante- and postpartum prophylaxis.	See above	-	-	-
9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).	The recommendation has been modified to suggest both ante- and postpartum prophylaxis.	Primary financial COI: See above Primary intellectual COI: Author on "Risk of venous...." that provided new data on baseline risk used in this recommendation.	-	-	-
9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).	Pregnant women with antithrombin deficiency have been excluded from the recommendation and are instead suggested both ante- and postpartum prophylaxis.	See above	-	-	-
	«New» recommendation for Antithrombin deficiency: We suggest high or intermediate dose prophylaxis throughout the pregnancy and 6 weeks postpartum. For women on prior lifelong treatment with anticoagulation	See above	-	-	-

	we recommend LMWH in therapeutic doses.				
10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for antiphospholipid antibodies (APLAs) (Grade 1B).					
10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C).					
10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B).	UFH is excluded from the recommendation text. The dose of aspirin is reduced to 75 mg daily.	See above	-	-	-
10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C).	A new reference has been added, but the recommendation remains unchanged.				
11.1.1. For women considered at risk for pre-eclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B).	A new reference has been added, but the recommendation remains unchanged.				
11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).	Three new references have been added, but the recommendation remains unchanged.				

12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A): (a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous-injection or (b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval activated partial thromboplastin time at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or (c) UFH or LMWH (as above) until the 13th week, with substitution by VKAs until close to delivery when UFH or LMWH is resumed.	UFH is excluded from the recommendation text.	See above	-	-	-
12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older generation prosthesis in the mitral position or history of thromboembolism), we suggest VKAs throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C).	UFH is excluded from the recommendation text.	See above	-	-	-
12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C).	The dose of aspirin is reduced to 75 mg daily. eim				

2 - General advice on the use of LMWH and warfarin during pregnancy

Not Set

For recommendations on thromboprophylaxis and treatment of VTE, we refer to specific sections on each topic.

Practical Advice

Key Info

	Benefits and harms
	Quality of evidence
	Preference and values
	Resources and other considerations

Rationale

References

2.1 - Low-molecular-weight heparin (LMWH)

Use of LMWH during pregnancy

Strong Recommendation

For pregnant women we recommend low molecular weight heparin (LMWH) both as treatment of and prophylaxis against venous thromboembolism rather than unfractionated heparin (UFH).

Practical Advice

Key Info

	Benefits and harms
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	LMWH is safe and effective in pregnancy as it does not pass the placental barrier, carries low maternal bleeding risk (ante and postpartum 2%) and lower risk of osteoporosis than UH. Single cases with osteoporosis have been reported with LMWH, but RCTs have shown no increased risk. For UH a 2-3% risk of vertebral fractures and up to 30% risk of osteopenia have been reported. Patients with a high baseline risk of osteoporosis will have an increased risk with the use of LMWH in pregnancy. Skin reactions occur in 2-30% with LMWH injections but they are for the most part benign in nature. In severe skin reactions fondaparinux (Arixtra) is an appropriate alternative. Heparin-induced thrombocytopenia (HIT) is very rare with the use of LMWH (<0.01%).
	Quality of evidence Moderate due to risk of bias. Risk estimates for maternal bleeds are based on a systematic review, while estimates for osteoporosis are more uncertain as they are based on small RCTs, case reports and observational studies.
	Preference and values As long as the treatment is safe for the child, reduces the risk of thrombosis and carries relatively small side effects for the mother, we assume that all or nearly all patients would prefer prophylaxis and treatment. Our threshold for providing a strong recommendation for prophylaxis is set at a 3% risk of recurrence of thrombosis. Preference studies have not been conducted.
	Resources and other considerations The price of prophylaxis for up to 46 weeks is about NOK 15,000. Treatment is refundable.

Rationale

LMWH is clearly superior with regard to both side effects and burden of treatment and should therefore be recommended to patients rather than UH. As with all strong recommendations we here make an assumption that all or nearly all pregnant women would elect to use LMWH if they were well informed about the benefits and harms.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Use of LMWH during delivery

Strong Recommendation

For women using dose-adjusted LMWH we recommend that the delivery is scheduled and that LMWH is discontinued 22 to 24 hours before a caesarean or regional anesthesia. When induction is performed we recommend discontinuation 24 hours before the expected delivery or initiation of epidural. Individual judgments based on maturity of the cervix may qualify for discontinuation 12-24 hours before induction.

Remark: The risk of obstetric hemorrhage at birth and risk of bleeding associated with regional anesthesia should be minimized. If the patient is on a once daily regime, only half the dose should be given 24 hours prior to a scheduled caesarean. Before an induction the degree of cervical maturity must be evaluated to determine the time lapse between the last injection of LMWH and the start of the induction. Induction of labor is often appropriate to reduce the bleeding risk. At a very high risk of recurrence, or recent thrombosis (2 weeks) changing to iv unfractionated heparin (UH) should be considered with discontinuation 4-6 hours before expected delivery. If a caesarean is performed general anesthesia is preferable.

Practical Advice

Consider moving information in the remark to this section.

Key Info

	Benefits and harms Please see the remark.
	Quality of evidence Overall moderate quality. Our confidence in the effect estimates is reduced as there are no studies on this population that have examined the risk of bleeding at different times of treatment termination. The evidence is provided by observational studies.
	Preference and values Women are believed to prefer the recommended treatment as they wish to minimize the risk of major bleeding at delivery and an epidural hematoma is expected to weigh heavily on their decision.
	Resources and other considerations -

Rationale

Our strong recommendation for scheduling delivery and timing for discontinuation of LMWH places a high value on avoiding risk of bleeds. We recognize the limited research evidence concerning the trade-off between risk of recurrent thrombosis and bleeds. The specifications on how to deal with induced labour was developed by the Norwegian panel as the AT9 guidelines did not provide guidance for this topic.

We do not recommend the use of vena cava filters. Although recommended some places internationally, it is seldom used in Norway.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Fondaparinux (Arixtra)

Weak Recommendation

We suggest restricting use of fondaparinux to patients experiencing severe allergic reactions (including HIT) to LMWH.

Practical Advice

Key Info

	Benefits and harms Fondaparinux may possibly pass the placenta barrier in small amounts (1/10 of maternal concentration has been detected in the umbilical cord) and could thus theoretically affect the fetus. Evidence to suggest a risk for fetal malformations has not been published.
	Quality of evidence Low. Our confidence in the existing research evidence for fondaparinux is reduced due to risk of bias and imprecision (few and small published studies) and indirectness (treatment mainly during the 2nd and 3rd trimester).
	Preference and values In the absence of relevant preference studies we assume that pregnant women would not initially elect to use fondaparinux. In the case of severe allergic reactions to LMWH and acute thrombosis we believe most pregnant women would choose fondaparinux as the best available treatment alternative.
	Resources and other considerations Fondaparinux is not pre-approved for general reimbursement, but an individual application to have the expenses refunded can be sent to office for health economics management (HELFO).

Rationale

Our weak recommendation for fondaparinux as the preferred treatment alternative in case of severe allergic reaction to LMWH is based on its anticipated beneficial effects on recurrence of thrombosis and low risk of serious side effects, taking into account the very low quality of evidence.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

2.2 - Long term anticoagulation during pregnancy, including pregnant women with mechanical heart valves

Warfarin

Weak Recommendation

For women who are on long-term treatment with warfarin and plan to become pregnant, we suggest to change to LMWH in the presence of a positive pregnancy test, rather than changing to LMWH during the period they're trying to become pregnant.

Practical Advice

Key Info

Benefits and harms

Women continuing to use warfarin until a pregnancy is confirmed will be spared the burden of self-injecting relatively high doses of LMWH (treatment doses) for longer than necessary. Women at risk for osteoporosis (use of steroids, very low BMI, heavy smokers) will further increase this risk through prolonged use of LMWH. The risk of birth defects from use of warfarin is assumed to be negligible for the fetus until 6 weeks gestation. There may be a small increased risk of spontaneous miscarriage with warfarin treatment until 6 weeks of gestation.

Quality of evidence

Low. We have low confidence in the effect estimates as they are based on small and few observational studies. This is unlikely to change in the near future as we are unaware of any major new studies in the pipeline for this field.

Preference and values

We assume that most women will choose to continue with well controlled warfarin treatment until a positive pregnancy test. Women who fear miscarriage will probably choose to change to LMWH before conception. Some women have irregular periods and might choose LMWH

over frequently repeated pregnancy tests. Preference studies have been published and underlie our recommendation.

Resources and other considerations

Warfarin therapy is reasonably cheap and will also be refunded. Use of LMWH during pregnancy and 1-2 weeks postpartum costs approximately NOK 12,000 and will be refunded also when changing to LMWH in the period before conception.

Rationale

The studies that underly our recommendation are considered applicable to Norwegian conditions with the exception of the cost issue where patients in Norway will get the anticoagulation treatment refunded. Our weak recommendation entails shared decision making with patients to tailor anticoagulation treatment to individual preferences.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Weak Recommendation

For pregnant women on long-term anticoagulation (warfarin or new oral anticoagulants) we suggest changing to LMWH at therapeutic doses, alternatively 75% of the therapeutic dose, throughout pregnancy, rather than a prophylactic dose of LMWH. Postpartum we suggest to re-initiate warfarin rather than continuing LMWH. New oral anticoagulants should not be re-initiated until after breastfeeding is stopped.

Practical Advice

Therapeutic dose LMWH: sc dalteparin 100 IU / kg x 2 or 200 IU / kg x 1, enoxaparin 1 mg / kg x 2 or 1.5 mg / kg x 1 or tinzaparin 175 mg / kg x 1

Key Info

Benefits and harms

LMWH is safe for the mother and does not affect the baby. There is a slightly increased risk of osteoporosis with LMWH and skin reactions around the injection site occur quite frequently. Warfarin however crosses the placental barrier, can cause malformations of the fetus in the first trimester, carries an increased risk of cerebral hemorrhage in the fetus and increases the maternal bleeding risk at delivery.

	Quality of evidence Low confidence in the risk estimates due to lack of research evidence; the studies are few and small.
	Preference and values Potential risk of harm to the child is believed to be essential in the maternal choice of which anticoagulation treatment to use throughout pregnancy.
	Resources and other considerations Price NOK 80-100 / day, refundable.

Rationale

Our weak recommendation for changing to long-term anticoagulation with adjusted dose LMWH is based on the very high risk of recurrent venous thrombosis without treatment and the potential harmful effects on the child through continued use of warfarin or NOAC, not present with the use of LMWH.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Apixaban, rivaroxaban and dabigatran

Strong Recommendation

For pregnant women we recommend to avoid the new oral anticoagulants (direct thrombin and factor Xa inhibitors).

Practical Advice

Key Info

	Benefits and harms No studies of the new oral anticoagulants (NOAC) have been conducted in pregnant women.
	Quality of evidence Low, in the absence of research evidence to inform about potential benefits and harms of NOAC in pregnant women.

Preference and values

We assume all or nearly all pregnant women would not want to take drugs that have not been tested in pregnancy, in particular given the potential harmful effects on the child.

Resources and other considerations

-

Rationale

Our strong recommendation against the use of NOAC is based on the lack of studies in pregnant women and the existing effective and safe treatment options for this population.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Pregnant women with mechanical heart valves

Strong Recommendation

We recommend one of the following treatment regimes:

1. Dose-adjusted LMWH twice daily throughout pregnancy with monitoring of anti-Xa levels 3-4 hours after injection (anti Xa reference range 0.5-1.2).
2. Dose-adjusted LMWH until week 13, then warfarin until 2-4 weeks prior to term at which point LMWH is resumed.

Remark: Women with thrombogenic old heart valves that carry a high risk of valve trombosis or who experience treatment failure with LMWH should be referred for evaluation by the obstetric team at a regional hospital or centralized to Oslo University Hospital.

Practical Advice

Anne: Could we provide contact information to obstetric care teams (eg. Oslo University hospital) here?

Key Info

Benefits and harms

All treatment options have limitations and risks for the mother and / or child. Warfarin increases the risk of birth defects in the child between weeks 6-12 (3-6%), and there is an increased risk of fetal hemorrhage at birth. On the other hand warfarin is relatively safe for the mother and seems to provide less risk of valve trombosis, but at the cost of an increased

	risk of bleeding at birth. LMWH is safe for the baby, but seems to give a higher risk of maternal valve thrombosis.
	Quality of evidence High. Risk estimates are based on consistent results from observational studies. Large randomized trials are unlikely to be conducted in this field.
	Preference and values The decision concerning the different treatment alternatives is considered to be so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that it warrants a thorough consultation between the patient and the expert clinician (hematologist, gynecologist and cardiologist), sensitive to the individual patient's preferences. Our experience suggests that most women put child safety before their own health, even at relatively high inherent risk for themselves.
	Resources and other considerations Treatment is refundable although not within currently approved summary product characteristics (SPC).

Rationale

Our strong recommendation for continued long term anticoagulation includes two alternative treatment regimes that should be individualized through careful information and discussion with the patient, given the fine balance between potential serious side effects for the mother or child.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

High risk for thromboembolism

Weak Recommendation

For pregnant women with heart valves where the efficacy and safety of LMWH is questionable (old valves or prior valve thrombosis) we suggest warfarin throughout pregnancy with the transition to LMWH or UH close to delivery, rather than the use of warfarin in the intermediate period.

Remark: These patients should be centralized for evaluation by the obstetric cardiac team at the regional hospitals or to Oslo University Hospital.

Practical Advice

Anne: Could we provide contact information to obstetric care teams (eg. Oslo University hospital) here?

Key Info

	<p>Benefits and harms</p> <p>All treatment options have limitations and risks for the mother and / or child. Warfarin increases the risk of birth defects in the child between weeks 6-12 (3-6%), and there is an increased risk of fetal hemorrhage at birth. On the other hand warfarin is relatively safe for the mother and seems to provide less risk of valve thrombosis, but at the cost of an increased risk of bleeding at birth. LMWH is safe for the baby, but seems to give a higher risk of maternal valve thrombosis.</p>
	<p>Quality of evidence</p> <p>Low, with effect-estimates based on consistent results from small observational studies. Large randomized trials are unlikely to be conducted in this field.</p>
	<p>Preference and values</p> <p>The decision concerning the different treatment alternatives is considered to be so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that it warrants a thorough consultation between the patient and the expert clinician (hematologist, gynecologist and cardiologist), sensitive to the individual patient's preferences. Our experience suggests that most women put child safety before their own health, even at relatively high inherent risk for themselves.</p>
	<p>Resources and other considerations</p> <p>Treatment is refundable although not within currently approved SPC.</p>

Rationale

Our weak recommendation takes into consideration the increased risk of valve thrombosis for the mother weighed against the potential serious risk for fetal abnormalities. Decisions about treatment should be carefully individualized through information and discussion between the patient and expert clinicians.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Weak Recommendation

In pregnant women with heart valves at increased risk of valve thrombosis we suggest the addition of low-dose ASA 75 mg / day.

Practical Advice

Anne: Should we add when ASA should be discontinued? 1 week before delivery?

Key Info

Benefits and harms

ASA in combination with LMWH or warfarin may reduce the risk of valve thrombosis in high-risk patients, but will also provide greater bleeding risk if not discontinued before delivery.

Quality of evidence

Low, based on indirect evidence from non-pregnant patients with mechanical heart valves concerning anticipated effects of adding ASA to anticoagulation with warfarin or LMWH.

Preference and values

ASA has little or no side effects for the child and will thus probably be accepted by most pregnant women given the potential beneficial effects on valve thrombosis and limited increase in maternal bleeding risk.

Resources and other considerations

Treatment with ASA costs 1 NOK / day. Use of ASA for this indication is not within currently approved SPC.

Rationale

Our weak recommendation for adding ASA to anticoagulation therapy for pregnant women is based on the anticipated reduced risk of valve thrombosis and absence of harmful effects on the child.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

4 - Acute DVT or pulmonary embolism (venous thromboembolism = VTE)

VTE prior to pregnancy

Strong Recommendation

For women with acute thrombosis who are already under treatment when they become pregnant we recommend LMWH rather than warfarin throughout pregnancy.

Practical Advice

Key Info

Benefits and harms

LMWH does not cross the placental barrier and is thus safe for the child in addition to being an effective treatment for the mother. Warfarin will increase the bleeding risk of the mother at birth. Warfarin crosses the placental barrier and a 3,7 to 6,4% risk of malformations in the fetus have been reported in the first trimester. The most common birth defects are midfacial hypoplasia and dotted epiphyseal line. Warfarin also slightly increases the risk of miscarriage and CNS malformations (dorsal midline dysplasia and ventral-midline dysplasia) in each trimester. Fetal coagulopathy may also increase the risk of bleeding in the fetus especially at childbirth.

Quality of evidence

Overall high. We have high confidence in the effect estimates for the first trimester, based on several studies having shown increased risk of abnormalities, making it unethical to do further studies. We also have high confidence in the effect of discontinuing warfarin at term, in spite of the lack of studies in pregnancy. There is substantial indirect evidence of high bleeding risk with warfarin in other similar contexts. Moderate confidence in the effect estimates in the second and third trimesters regarding birth defects and fetal coagulopathy at the basis is few studies of low quality. The identified studies are applicable to Norwegian conditions.

Preference and values

Women are likely to be very reluctant to expose the fetus to increased risk. We therefore believe that the vast majority of pregnant women with acute thrombosis would select LMWH over warfarin, if they were well informed about the benefits.

Resources and other considerations

The price for LMWH is considerably higher than that of warfarin, but in this context we consider the increased costs to be of little relevance given the benefits of LMWH.

Rationale

Warfarin carries such a high risk for the fetus that we in the large majority of cases recommend the use of LMWH during pregnancy. Warfarin is only recommended in exceptional cases such as old mechanical heart valves where the risk of valve thrombosis is particularly large and LMWH has insufficient effect. These women should be treated by teams specialized on such cases.

References

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)

Rosfors S, Norén A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455. [11735184](#)

Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100:3484-3488. [12393647](#) 10.1182/blood-2002-01-0108

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (4.1)

Population: Pregnant women on long-term treatment for DVT and pulmonary embolism

Intervention: LMWH

Comparator: Warfarin

Outcomes: Recurrence of DVT or pulmonary embolism, major bleeding, post-thrombotic syndrome

Outcomes	Confidence in effect estimates	Relative effect	Warfarin	LMWH	Difference with	Participants (studies), Follow-up
Recurrence of VT (during pregnancy)	Moderate <i>Risk of bias</i>	RR: 0.62 (CI 0.46 - 0.84)	30 <i>per 1000</i>	19 <i>per 1000</i>	11 fewer (CI 16 fewer - 5 fewer)	2496 (7) 6 mnd
Major bleeding (during pregnancy)	Moderate <i>Imprecise estimates</i>	RR: 0.81 (CI 0.55 - 1.2)	20 <i>per 1000</i>	16 <i>per 1000</i>	4 fewer (CI 9 fewer - 4 more)	2727 (8) 6 mnd
Post-thrombotic syndrome -self reported (during pregnancy)	Low <i>Risk of bias and indirect data</i>	RR: 0.85 (CI 0.77 - 0.94)	480 <i>per 1000</i>	442 <i>per 1000</i>	38 fewer (CI 110 fewer - 29 fewer)	100 (1) 3 mnd

PICO References

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)

Rosfors S, Norén A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455. [11735184](#)

Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100:3484-3488. [12393647](#) 10.1182/blood-2002-01-0108

Kearon et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e691S-e736S [22315268](#)

PICO Summary

Bibliography: Kearon C, Akl EA, Comerato AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2)(supp 1):e418S-e494S.

Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100:3484-3488.

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99.

Rosfors S, Noren A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455.

Baseline risk estimates with vitamin K antagonists: For venous thromboembolism the baseline risk is based on a cohort study by Prandoni et al.

For major bleeding the risk is based on studies by both Prandoni et al and a cohort study of Beyth et al.

For post-thrombotic syndrome the risk is based on an observational study by Rosfors et al on pregnant women.

VTE during pregnancy

Strong Recommendation

For pregnant women with acute venous thromboembolism (VTE) we recommend weight-adjusted subcutaneous LMWH to be used throughout pregnancy and 6 weeks postpartum, rather than unfractionated heparin (UH).

Practical Advice

Duration of treatment: recommended throughout pregnancy and at least 6 weeks postpartum.
Minimum total treatment 3 months.

Dosage: tinzaparin (Innohep) can be dosed once daily. Enoxaparin (Klex) and dalteparin (Fragmin) can probably also be dosed daily, but studies have mostly used a twice daily dosing regimen. Monitoring of Anti Xa is not indicated but may be considered in very obese, patients with renal failure or severe pulmonary embolism.

At birth: Discontinue LMWH 22 to 24 hours before the scheduled delivery (sectio). By induction LMWH should be discontinued approximately 12-24 hours beforehand. Here one must consider cervix maturity, timing of VT, bleeding risk and patient's desire for an epidural. For acute VT with onset within 2 weeks before birth, one might consider transition to unfractionated heparin (UH) iv in connection with childbirth. UH should then be discontinued 4-6 hours before birth and re-initiated after 4-6 hours, depending on potential bleeding.
Epidural should be administered 24 hours or later after the last dose of LMWH

Key Info

Benefits and harms

LMWH constitutes a safe and effective treatment in pregnancy and it does not cross the placental barrier. Indirect evidence from a surgical population suggests a risk of recurrent VTE in 20 out of a 1000 pregnant women with LMWH. The risk of major maternal bleeding with LMWH is estimated to be 2% overall during the ante- and postpartum period.
Osteoporosis: Single cases with osteoporosis have been reported with LMWH, but RCTs have shown no increased risk. Patients with a high baseline risk for osteoporosis may be considered for a reduced dose of LMWH to 75% of full-dose after 4 weeks. Cutaneous reactions occur in 1,8 to 30% but are for the most part of tolerable. Heparin-induced thrombocytopenia (HIT) is very rare in treatment with LMWH (<0.01%).

Quality of evidence

Moderate, due to use of indirect evidence for effect estimates for VTE recurrence and major bleeds. Risk estimates for osteoporosis are uncertain as they are based on small RCTs, case reports and observational studies.

Preference and values

We assume that all or nearly all women would elect to use LMWH as primary treatment on the basis of efficacy, safety and side effects. We also assume that most women will prefer a once rather than twice daily regimen, but preference studies have not been conducted on this population.

Resources and other considerations

In Norway, dalteparin (Fragmin), enoxaparin (Klexane) and tinzaparin (Innohep) are available. The price for treatment is about NOK 100 / day, but is refundable.

Rationale

LMWH is clearly a better option with regard to side effects and is therefore preferred over UH and warfarin.

References

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)
Rosfors S, Norén A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455. [11735184](#)

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Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Strong Recommendation

For pregnant women with acute venous thromboembolism (VTE) in pregnancy, we recommend LMWH rather than warfarin.

Practical Advice

Key Info

Benefits and harms

LMWH does not cross the placental barrier and is thus safe for the child in addition to being an effective treatment for the mother. Warfarin will increase the bleeding risk of the mother at birth. Warfarin crosses the placental barrier and a 3,7 to 6,4% risk of malformations in the fetus have been reported in the first trimester. The most common birth defects are midfacial hypoplasia and dotted epiphyseal line. Warfarin also slightly increases the risk of miscarriage and CNS malformations (dorsal midline dysplasia and ventral-midline dysplasia) in each trimester. Fetal coagulopathy may also increase the risk of bleeding in the fetus especially at childbirth.

Quality of evidence

Overall high. We have high confidence in the effect estimates for the first trimester, based on several studies having shown increased risk of abnormalities, making it unethical to do further studies. We also have high confidence in the effect of discontinuing warfarin at term, in spite of the lack of studies in pregnancy. There is substantial indirect evidence of high bleeding risk with warfarin in other similar contexts.

Moderate confidence in the effect estimates in the second and third trimesters regarding birth defects and fetal coagulopathy at the basis is few studies of low quality. The identified studies are applicable to Norwegian conditions.

Preference and values

Women are likely to be very reluctant to expose the fetus to increased risk. We therefore believe that the vast majority of pregnant women with acute thrombosis would select LMWH over warfarin, if they were well informed about the benefits.

Resources and other considerations

The price for LMWH is considerably higher than that of warfarin, but in this context we consider the increased costs to be of little relevance given the benefits of LMWH.

Rationale

Warfarin carries such a high risk for the fetus that we in the large majority of cases recommend the use of LMWH during pregnancy. Warfarin is only recommended in exceptional cases such as old mechanical heart valves where the risk of valve thrombosis is particularly large and LMWH has insufficient effect. These women should be treated by teams specialized on such cases.

References

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)

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PICO (4.1)

Population: Pregnant women on long-term treatment for DVT and pulmonary embolism

Intervention: LMWH

Comparator: Warfarin

Outcomes: Recurrence of DVT or pulmonary embolism, major bleeding, post-thrombotic syndrome

Outcomes	Confidence in effect estimates	Relative effect	Warfarin	LMWH	Difference with	Participants (studies), Follow-up
Recurrence of VT (during pregnancy)	Moderate <i>Risk of bias</i>	RR: 0.62 (CI 0.46 - 0.84)	30 <i>per 1000</i>	19 <i>per 1000</i>	11 fewer (CI 16 fewer - 5 fewer)	2496 (7) 6 mnd
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Post-thrombotic syndrome -self reported (during pregnancy)	Low <i>Risk of bias and indirect data</i>	RR: 0.85 (CI 0.77 - 0.94)	480 <i>per 1000</i>	442 <i>per 1000</i>	38 fewer (CI 110 fewer - 29 fewer)	100 (1) 3 mnd

PICO References

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)

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Kearon et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e691S-e736S [22315268](#)

PICO Summary

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Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99.

Rosfors S, Noren A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455.

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For major bleeding the risk is based on studies by both Prandoni et al and a cohort study of Beyth et al.

For post-thrombotic syndrome the risk is based on an observational study by Rosfors et al on pregnant women.

Duration of anticoagulation therapy

Weak Recommendation

We suggest anticoagulation with LMWH once or twice daily throughout pregnancy and for at least 6 weeks after birth (minimum total treatment 3 months) rather than shorter treatment.

Practical Advice

Key Info

Benefits and harms

The burden of self-injecting with LMWH once or twice daily throughout pregnancy is outweighed by the high risk (5-10 fold) that these women carry for recurrence of VTE during pregnancy. Many of which will be proximal DVTs, the risk largely reduced by long term anticoagulation treatment.

Quality of evidence

Low, given absence of studies having examined the duration or dosage of anticoagulation and risk of recurrent VTE in this population.

Preference and values

Women will probably choose long term anticoagulation based on safety issues as long as the treatment is unlikely to harm the child. Preference studies have not been conducted.

Resources and other considerations

The price for LMWH is about NOK100 / day and is refundable.

Rationale

The low quality evidence underlying our weak recommendation for long-term anticoagulation entails shared decision making with the patient, especially with regard to dosing once or twice daily.

References

- Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91-99. [9727814](#)
- Rosfors S, Norén A, Hjertberg R, Persson L, Lillthors K, Törngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg.* 2001;22(5): 448-455. [11735184](#)
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5 - Assisted reproductive therapy and thromboprophylaxis

Strong Recommendation

For women undergoing assisted reproduction we recommend against the use of routine thromboprophylaxis.

Practical Advice

Key Info

Benefits and harms

The risk of venous thrombosis in assisted reproductive therapy is estimated to be in the range of 0.1% -0.3%. Use of LMWH will result in 1 fewer venous thrombosis per 1000 patients treated without a significant increased risk of maternal bleeding.

Quality of evidence

Moderate. Our confidence in the results is reduced due to the use of indirect evidence to generate relative effect-estimates, derived from a meta-analysis of thromboprophylaxis in surgery.

Preference and values

We believe most patients would elect not to use thromboprophylaxis given the marginal absolute effects on venous thrombosis and the burden of self-injecting with LMWH.

Resources and other considerations

Prophylactic treatment in this case is not refundable. The price is approximately 40 NOK/day.

Rationale

Our strong recommendation against the use of thromboprophylaxis in pregnant women undergoing assisted reproductive therapy is based on the marginal anticipated absolute benefit on venous thrombosis (1 fewer per 1000 women treated) and the burden of self-injecting with LMWH. We believe the vast majority of women would not elect to use LMWH in this situation.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Supl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Henriksson et al. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. BMJ. 2013 Jan 15;346:e8632. [23321489](#)

PICO (5.1)

Population: Women undergoing assisted reproduction, without OHSS

Intervention: LMWH

Comparator: No treatment

Outcomes: Recurrence thrombosis, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	30 <i>per 1000</i>	47 <i>per 1000</i>	17 more (CI 10 more - 26 more)	12.929 (44)
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	2 <i>per 1000</i>	1 <i>per 1000</i>	1 fewer (CI 1 fewer - 0 fewer)	12.698 (22)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. NEJM 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk is based on observational studies of women who underwent assisted reproduction. Several of the women were followed until they gave birth.

Ovarial hyperstimulation syndrome (OHSS) occurring after assisted reproductive therapy

Weak Recommendation

For women who develop ovarian hyperstimulation syndrome (OHSS) we suggest extended thromboprophylaxis (LMWH) for 3 months after clinical remission of symptoms.

Practical Advice

Key Info

	<p>Benefits and harms</p> <p>The risk of venous thrombosis in severe OHSS is estimated to be 4.1%. With treatment with LMWH the number of venous thrombotic events is reduced from 41 to 14 per 1000 patients treated. Major maternal bleeds is at the same time increased from 30 to 47 per 1000 patients treated.</p>
	<p>Quality of evidence</p> <p>Moderate. Our confidence in the effect-estimates is reduced due to the use of indirect evidence on the relative estimates of treatment effects (meta-analysis of thromboprophylaxis in surgery) and uncertainty in baseline risk (observational study with confidence interval ranging from 0.9 to 14.1% for the point estimate of 4.1%).</p>
	<p>Preference and values</p> <p>We believe the majority of women with OHSS would accept the burden of self-injecting with LMWH over three months if they were well informed about the substantial benefits in reducing venous thrombosis without a significantly increased bleeding risk.</p>
	<p>Resources and other considerations</p> <p>The use of LMWH costs approximately NOK 40 / day. Not refunded.</p>

Rationale

Our weak recommendation for extended prophylaxis in women with OHSS is based on the substantial benefits in reducing venous thrombosis without a significantly increased bleeding risk, implying that most well-informed women would accept the burden of self-injecting with LMWH over three months.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (5.2)

Population: Women undergoing assisted reproduction, with OHSS

Intervention: LMWH

Comparator: No treatment

Outcomes: Recurrence thrombosis, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	30 <i>per 1000</i>	47 <i>per 1000</i>	17 more (CI 10 more - 26 more)	12.929 (44)
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	40 <i>per 1000</i>	14 <i>per 1000</i>	26 fewer (CI 28 fewer - 15 fewer)	12.698 (22)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk is based on observational studies of women who underwent assisted reproduction. Several of the women were followed until they gave birth.

6 - Prior VTE and thromboprophylaxis

Duration of treatment postpartum

Weak Recommendation

For all pregnant women with previous venous thrombosis, we suggest postpartum prophylaxis for 6 weeks with LMWH or warfarin (INR 2.5 + / - 0.5).

Practical Advice

Key Info

Benefits and harms

The baseline risk of venous thrombosis postpartum is estimated to be 40 per 1000 women not on prophylaxis.
With 6 weeks treatment postpartum the rate of VTE is reduced from 40 to 18 per 1000 patients. At the same time the rate of major maternal bleeds is increased from 10 to 16 per 1000 patients.

Quality of evidence

Moderate. Our confidence in the effect-estimates is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH vs placebo in surgery. There are only two very small RCTs and several relatively small observational studies on the risk of recurrence in pregnant women with a history of VTE.

Preference and values

We believe most women would accept the burden of self-injecting with LMWH over six weeks postpartum if they were well informed about the benefits in reducing venous thrombosis which outweighs the increased bleeding risk.

Resources and other considerations

We consider this treatment to be cost-effective, with a cost about NOK 40 / day. The patient is reimbursed.

Rationale

Our weak recommendation for the use of LMWH 6 weeks postpartum is based on the anticipated reduction in thrombosis, weighed against the increased risk of maternal bleeds and burden of self-injecting with LMWH.

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](https://doi.org/10.1182/blood-2005-02-0626) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S-e736S [22315276](#) 10.1378/chest.11-2300

PICO (6.1)

Population: Thrombosis with previous thromboembolism: Low risk

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 <i>(CI 0.31 - 0.63)</i>	20 <i>per 1000</i>	9 <i>per 1000</i>	11 fewer <i>(CI 14 fewer - 7 fewer)</i>	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more <i>(CI 1 more - 3 more)</i>	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more <i>(CI 3 more - 9 more)</i>	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk for venous thromboembolism is based on several studies, primarily retrospective cohort studies (please see tabel S16 in the original CHEST publication), which provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

PICO (6.3)

Population: Thrombosis with previous thromboembolism: Moderate-high risk

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	40 <i>per 1000</i>	18 <i>per 1000</i>	22 fewer (CI 28 fewer - 15 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	3 more (CI 1 more - 3 more)	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk for venous thromboembolism is based on several studies, primarily retrospective cohort studies (please see tabel S16 in the original CHEST publication), which provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

Pregnant women at low risk of recurrent venous thrombosis (VTE): Prior VTE associated with transient risk factor not related to estrogen therapy or pregnancy.

Weak Recommendation

We suggest antepartum clinical vigilance rather than routine thromboprophylaxis.

Practical Advice

Key Info

Benefits and harms

The baseline risk of recurrent thrombosis in low-risk pregnant women is believed to be 20 per 1000 women not on prophylaxis.

With thromboprophylactic treatment during the antepartum period the rate of VTE is reduced from 20 to 9 per 1000 pregnant women.

At the same time the rate of major maternal bleeds is increased from 3 to 4 per 1000 women.

Quality of evidence

Low. Our confidence in the effect-estimates is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH vs. placebo during surgery. There are relatively few and small, mostly observational studies in pregnant women with a history of VTE.

Preference and values

We believe most pregnant women would choose not to take LMWH during pregnancy given the marginal absolute reduction in thrombosis combined with the increased risk of bleeds and burden of self-injections for such a long period of time. There are no published studies about preferences in this context, but a study is expected to be published within a few years.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered not to be cost-effective in women at low risk of recurrent VTE. Daily costs for self-injections amounts to NOK 40/ day and is not reimbursed.

Rationale

Our weak recommendation against thromboprophylaxis places a high value on the burden of long-term treatment and a lesser value on the marginal reduction of thrombosis. We infer that most pregnant women would elect not to use thromboprophylaxis.

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Supl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (6.1)

Population: Thrombosis with previous thromboembolism: Low risk

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 <i>(CI 0.31 - 0.63)</i>	20 <i>per 1000</i>	9 <i>per 1000</i>	11 fewer <i>(CI 14 fewer - 7 fewer)</i>	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more <i>(CI 1 more - 3 more)</i>	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more <i>(CI 3 more - 9 more)</i>	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of

randomized trials in general, orthopedic, and urologic surgery. NEJM 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk for venous thromboembolism is based on several studies, primarily retrospective cohort studies (please see tabel S16 in the original CHEST publication), which provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

Pregnant women with moderate to high risk of recurrent venous thrombosis (VTE): Prior unprovoked VTE, pregnancy or estrogen-related VTE, known thrombophilia or multiple previous VTE without long-term anticoagulation

Weak Recommendation

We suggest antepartum prophylaxis with prophylactic or intermediate dose LMWH.

Practical Advice

Key Info

Benefits and harms

The baseline risk of recurrent thrombosis in low-risk pregnant women is believed to be 40 per 1000 women not on prophylaxis.

With thromboprophylactic treatment during the antepartum period the rate of VTE is reduced from 40 to 18 per 1000 pregnant women.

At the same time the rate of major maternal bleeds is increased from 3 to 4 per 1000 women.

Quality of evidence

Low. Our confidence in the effect-estimates is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH vs. placebo during surgery. There are relatively few and small, mostly observational studies in pregnant women with a history of VTE.

Preference and values

Most pregnant women are likely to choose long term thromboprophylaxis given the absolute reduction in VTE weighed against the small increased risk of maternal major bleeds and

burden of self-injecting with LMWH during pregnancy. There are no published studies concerning preferences of pregnant women, but a study is expected to be published within a few years.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered to be cost-effective in women at moderate to high risk or recurrent VTE. Daily costs for self-injections amounts to NOK 40/ day and is reimbursed.

Rationale

Our weak recommendation for thromboprophylaxis places a high value on the substantial reduction in recurrent VTE and a lesser value on the burden of long-term self-injections with LMWH and the marginal increase in maternal bleeds. We assume that most pregnant women would elect to use thromboprophylaxis given these circumstances.

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (6.3)

Population: Thrombosis with previous thromboembolism: Moderate-high risk

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Recurrence thrombosis (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	40 <i>per 1000</i>	18 <i>per 1000</i>	22 fewer (CI 28 fewer - 15 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	3 more (CI 1 more - 3 more)	12.929 (44)

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: The baseline risk for venous thromboembolism is based on several studies, primarily retrospective cohort studies (please see tabel S16 in the original CHEST publication), which provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

7 - Thrombophilia and thromboprophylaxis

Homozygous factor V Leiden or homozygous Prothrombin 20210 A mutation

Weak Recommendation

We suggest thromboprophylaxis throughout pregnancy and 6 weeks postpartum with prophylactic or intermediate dose LMWH, alternatively postpartum warfarin (INR 2.5 + / -0.5).

Practical Advice

Prophylactic dose LMWH: sc dalteparin 5000 IU x 1, enoxaparin 40mg x 1, tinzaparin 4500 IU x 1 (with significant obesity dosages may be adjusted up: 7500, 60, 7000)

Intermediate dose LMWH: 5000 x 2 dalteparin, enoxaparin 40 x 2, tinzaparin 9000 x 1

Key Info

Benefits and harms

The baseline risk of thrombosis in pregnant women with a homozygous factor V Leiden mutation is estimated to be 2% with no family history and 7% with a family history.

With prophylaxis the rate of VTE is reduced from 20 to 9 per 1000 patients (no family history) and from 70 to 31 per 1000 women with a family history.

The number of antepartum haemorrhages increases from 3 without prophylaxis to 4 per 1000 pregnant women with prophylactic treatment, while postpartum haemorrhages increase from 10 to 16 per 1000.

Quality of evidence

Low confidence in the results due to use of indirect evidence: Meta-analysis of randomized trials on LMWH / UFH vs. placebo during surgery. Additionally, there is some uncertainty regarding the true baseline risk of pregnant women with thrombophilia. Here the estimate is based on small studies with wide confidence intervals.

Preference and values

Most pregnant women are believed to choose long term thromboprophylaxis - regardless of family history of VTE - given the absolute reduction in VTE weighed against the small increased risk of maternal major bleeds and burden of self-injecting with LMWH during pregnancy. There are no published preference studies, but a study is expected to be published within a few years.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered to be cost-effective in women at moderate to high risk or recurrent VTE. Daily costs for self-injections amounts to NOK 40/ day and is reimbursed.

Rationale

The prevalence of factor V Leiden in Norway is high (7-8%). In a recently published, relatively large Norwegian case-control study, all pregnant women with homozygous Leiden developed a VTE. The incidence of first time VTE in pregnant women with homozygous Leiden was estimated at 4%. Family history of VTE was not reported.

We have in the adapted guideline chosen to deviate from the ACCP guidelines because we believe the incidence of thrombosis without family history to be higher than 2%, and probably closer to 4% based on Norwegian data. We therefore suggest prophylaxis to all with homozygous Leiden and homozygous prothrombin regardless of a family history of VTE. The ACCP provides a weak recommendation against prophylaxis in pregnant women without family history of VTE.

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Jacobsen et al: Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210A polymorphisms. *J Thromb Haemost*. 2010 Nov [20735725](#) 10.1111/j.1538-7836.2010.04038.x

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S-e736S [22315276](#) 10.1378/chest.11-2300

PICO (7.1)

Population: Thromboprophylaxis in homozygous Factor V Leiden and prothrombin 20210A mutation

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism (antepartum and postpartum)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	70 <i>per 1000</i>	31 <i>per 1000</i>	39 fewer (CI 48 fewer - 26 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more (CI 1 more - 3 more)	12.929 (44)

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Jacobsen et al: Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210A polymorphisms. *J Thromb Haemost*. 2010 Nov [20735725](#) 10.1111/j.1538-7836.2010.04038.x

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboembolism the baseline risk is based on several observational studies (please see table 7 in the original CHEST publication). The estimates in the original guideline have been updated with addition of a new Norwegian study by Jacobsen et al. These studies provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

Heterozygous factor V Leiden, heterozygous prothrombin 20210A mutation, combined Leiden and prothrombin mutation, protein C or protein S deficiency

Weak Recommendation

For pregnant women with no prior VTE, but a family history of VTE, we suggest antepartum clinical vigilance followed by postpartum prophylaxis for 6 weeks with either prophylactic- or intermediate dose LMWH or postpartum warfarin (INR 2.5 + / -0.5).

Practical Advice

Prophylactic dose LMWH: sc dalteparin 5000 IU x 1, enoxaparin 40 mg x 1, tinzaparin 4500 IU x 1 (with significant obesity dosages may be adjusted up)

Intermediate dose prophylaxis LMWH: 5000 x 2 dalteparin, enoxaparin 40 x 2, tinzaparin 9000 x 1

Key Info

Benefits and harms

With prophylaxis ante- and postpartum the rate of VTE is reduced as follows:

Heterozygous Leiden or prothrombin mutation: From 15 to 7 per 1000 patients.

Protein C or S deficiency: From 20 to 9 per 1000 patients.

For all women the number of antepartum haemorrhages increases from 3 without prophylaxis to 4 per 1000 pregnant women with prophylactic treatment, while postpartum haemorrhages increase from 10 to 16 per 1000.

Quality of evidence

Low. Our confidence in the results is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH vs. placebo during surgery. In addition, the baseline risk for pregnant women with thrombophilia is uncertain as it is derived from small studies with wide confidence intervals.

Preference and values

Given the small absolute reduction in thrombosis we believe most pregnant women would not want to self-inject with LMWH throughout pregnancy, but would want to do so for the shorter postpartum period. There are no published studies concerning patients preferences.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered not to be cost-effective in women at low risk or recurrent VTE. Daily costs for self-injections amounts to NOK 40/ day and is not refunded.

Rationale

For the postpartum period we believe most pregnant women would want to take thromboprophylaxis given the limited duration of 6 weeks with self-injecting LMWH. However, the fine balance between a reduction in VTE and increase in major maternal bleeds postpartum suggests that decisions about the use of thromboprophylaxis should be tailored to individual preferences.

Our weak recommendation against thromboprophylaxis antepartum thus places a high value on the burden of long term self-injections and marginal increase in bleeds weighed against the small absolute reduction in recurrent VTE

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Supl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (7.2)

Population: Thromboprophylaxis in heterozygous factor V Leiden and prothrombin 20210A mutation and family history, Leiden and prothrombin combination

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism (antepartum and postpartum)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 <i>(CI 0.31 - 0.63)</i>	15 <i>per 1000</i>	7 <i>per 1000</i>	8 fewer <i>(CI 10 fewer - 6 fewer)</i>	12,698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more <i>(CI 1 more - 3 more)</i>	12,929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more <i>(CI 3 more - 9 more)</i>	12,929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in

general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboembolism the baseline risk is based on several observational studies (please see table 7 in the original CHEST publication). These studies provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

PICO (7.3)

Population: Thromboprophylaxis in protein C and protein S deficiency with a family history

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism (antepartum and postpartum)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	20 <i>per 1000</i>	9 <i>per 1000</i>	11 fewer (CI 12 fewer - 26 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more (CI 1 more - 3 more)	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. NEJM 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboembolism the baseline risk is based on several observational studies (please see table 7 in the original CHEST publication). These studies provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

Weak Recommendation

For pregnant women with no prior VTE and no family history of VTE we suggest antepartum and postpartum clinical vigilance rather than prophylaxis.

Practical Advice

Key Info

Benefits and harms

The yearly incidence of VTE in pregnant women with thrombophilia without prior VTE or a positive family history is estimated to be 0.5-1.2%. Use of thromboprophylaxis would only marginally reduce this with 8 fewer per 1000 women treated, while at the same time increasing the risk of major maternal bleeds with 7 more per 1000.

Quality of evidence

Low. Our confidence in the results is reduced due to use of indirect evidence. In addition, the baseline risk estimates for pregnant women with thrombophilia are - with the exception of heterozygous Leiden - uncertain as they are based on relatively small studies with wide confidence intervals.

Preference and values

The absolute reduction in thrombosis is so small that we believe most pregnant women would elect not to use thromboprophylaxis. The low quality evidence and weak recommendation against prophylaxis implies the need for shared decision making with the patient as some patients particularly averse to having a thrombosis may want to use thromboprophylaxis. There are no published studies about patients' preferences.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered not to be cost-effective in women at low risk or recurrent VTE. Daily costs for self-injections amounts to NOK 40/ day and is not refunded.

Rationale

There is a high prevalence of heterozygous factor V Leiden in Norway, estimated to 7-8%. Our weak recommendation against thromboprophylaxis is based on the marginal reduction in VTE weighed against the increase in major bleeds and burden of self-injecting with LMWH during pregnancy.

References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (7.2)

Population: Thromboprophylaxis in heterozygous factor V Leiden and prothrombin 20210A mutation and family history, Leiden and prothrombin combination

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism (antepartum and postpartum)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	15 <i>per 1000</i>	7 <i>per 1000</i>	8 fewer (CI 10 fewer - 6 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more (CI 1 more - 3 more)	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of

randomized trials in general, orthopedic, and urologic surgery. NEJM 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboembolism the baseline risk is based on several observational studies (please see table 7 in the original CHEST publication). These studies provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al.

Antithrombin deficiency

Weak Recommendation

We suggest thromboprophylaxis with high-or intermediate dose LMWH throughout pregnancy and 6 weeks postpartum. For women already on lifelong anticoagulation we recommend a treatment dose of LMWH.

Practical Advice

Key Info

Benefits and harms

The incidence of VTE in women with antithrombin deficiency and a positive family history is estimated to 3% in the international literature. The incidence of VTE with antithrombin deficiency patients without family history is unknown, but estimated at 0.7% in the ACCP guidelines. Nordic studies of older date show significantly higher incidence rates of VTE (towards 50%), with a reduction to <10% with prophylaxis. We estimate an overall baseline risk of 3% of VTE, regardless of family history.

Treatment with thromboprophylaxis will reduce the number of VTE from 30 to 13 per 1000 patients treated.

The rate of major maternal bleeds antepartum will at the same time increase from 3 to 4 per 1000, and postpartum from 10 to 16 per 1000.

Quality of evidence

Low. Our confidence in the results is reduced due to use of indirect evidence and uncertainty regarding the baseline risk estimates for VTE in pregnant women with antithrombin deficiency, which is based on very small studies, preferably family studies, with wide confidence intervals. The Nordic studies included a mix of patients with both a prior history of VTE and a positive family history.

Preference and values

The absolute reduction in thrombosis is considered large enough that most pregnant women are believed to want to use long-term prophylaxis. The low quality evidence and weak recommendation for prophylaxis opens for shared decision making as some patients particularly averse to bleeds or self-injecting with LMWH may not want to use thromboprophylaxis.

Resources and other considerations

The costs associated with use of LMWH during the pregnancy period is considered to be cost-effective in women with antithrombin deficiency. Daily costs for self-injections amounts to NOK 40/ day and is refunded.

Rationale

In Norway we currently recommend that all pregnant women with antithrombin deficiency use thromboprophylaxis during pregnancy and in the post-partum period. Most of these women will have a family history of VTE or experienced a prior VTE. Due to the considerable uncertainty in the true baseline risk for those with and without a family history of VTE, we choose not to take the risk of recommending differing prophylaxis regimes.

References

- Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626
- Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531
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- Hellgren M et al. Pregnancy in women with Congenital AT III deficiency: experience of treatment with heparin and antitrombin. *Gynecol Obstet Invest*. 1982;14:127-41. [7117919](#)
- RCOG Green-top guidelines 37a, Reducing the risk of thrombosis and embolism during pregnancy and the puerperium, 2009. <http://www.rcog.org.uk/files/rcog-corp/GTG37aReducingRiskThrombosis.pdf>

PICO (7.4)

Population: Thromboprophylaxis in antithrombin deficiency with or without a family history

Intervention: LMWH**Comparator:** No treatment**Outcomes:** Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism (antepartum and postpartum)	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	20 <i>per 1000</i>	9 <i>per 1000</i>	11 fewer (CI 12 fewer - 7 fewer)	12.698 (22)
Major bleeding (during pregnancy)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	3 <i>per 1000</i>	4 <i>per 1000</i>	1 more (CI 1 more - 3 more)	12.929 (44)
Major bleeding (post-partum)	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	10 <i>per 1000</i>	16 <i>per 1000</i>	6 more (CI 3 more - 9 more)	12.929 (44)

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-1173.

Risk of bias: Several of the included studies in the meta-analysis were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboembolism the baseline risk is based on several observational studies (please see table 7 in the original CHEST publication). These studies provide evidence of an equal distribution of thromboembolic events in the ante and postpartum period.

For major bleeds the baseline risk estimates are derived from a systematic review by Greer IA et al. There is quite some uncertainty regarding the true baseline risk of VTE in pregnant women with antithrombin deficiency. Norwegian data imply a far greater risk than data used in AT9, where certain studies have shown a baseline risk of up to 50%.

Antiphospholipid syndrome (APLA)

Strong Recommendation

For women with recurrent early pregnancy loss (three or more miscarriages) that meet the laboratory criteria for APLA syndrome, we recommend prophylactic LMWH combined with low-dose ASA during the antepartum period.

Practical Advice

Key Info

Benefits and harms

With antepartum treatment the rate of miscarriage is reduced from 500 to 217 per 1000 women treated.

Studies so far have failed to show a significant effect on the rate of pre-eclampsia or intrauterine growth retardation.

Quality of evidence

Moderate. Our confidence in the results is reduced due to risk of bias in 3 small RCTs, summarized in an unpublished meta-analysis from AT9. The studies investigated the effects of unfractionated heparin, but we consider LMWH to have similar efficacy as UH and less side effects. Our recommendation is based on two small pilot studies comparing ASA + LMWH with ASA + UH.

Preference and values

We believe all or nearly all women who experience recurrent pregnancy loss and have known APLA would want to use thromboprophylaxis given the absolute benefits on the rate of miscarriages.

Resources and other considerations

Prophylactic treatment costs about NOK 40 / day. Refundable.

Rationale

Our strong recommendation for thromboprophylaxis in women with APLA and recurrent pregnancy loss is based on the large anticipated absolute effect on reducing miscarriages.

References

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monit.* 2006(3):CR132-CR136. [16501426](#)
 Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ.* 1997;314:253-257. [9022487](#) 10.1136/bmj.314.7076.253

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol.* 1996;174:1584-1589. [9065133](#)

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (7.5)

Population: Thromboprophylaxis in Antiphospholipid Syndrome and habitual abortions

Intervention: UFH plus ASA

Comparator: ASA

Outcomes: Abortion, IUGR, preeclampsia

Outcomes	Confidence in effect estimates	Relative effect	ASA	UFH plus ASA	Difference with	Participants (studies), Follow-up
Abortion	Moderate <i>due to risk of bias</i>	RR: 0.44 (CI 0.33 - 0.66)	500 <i>per 1000</i>	217 <i>per 1000</i>	283 fewer (CI 353 fewer - 172 fewer)	212 (3), not reported
IUGR (during pregnancy)	Low <i>due to risk of bias and imprecise estimates</i>	RR: 1.71 (CI 0.48 - 6.17)	56 <i>per 1000</i>	95 <i>per 1000</i>	39 fewer (CI 29 fewer - 287 more)	134 (3), not reported
Preeclampsia	Low <i>due to risk of bias and imprecise estimates</i>	RR: 0.43 (CI 0.09 - 2.08)	74 <i>per 1000</i>	44 <i>per 1000</i>	30 fewer (CI 67 fewer - 89 more)	134 (3), not reported

PICO References

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monit.* 2006(3):CR132-CR136. [16501426](#)

Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ.* 1997;314:253-257. [9022487](#) 10.1136/bmj.314.7076.253

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol.* 1996;174:1584-1589. [9065133](#)

PICO Summary

Bibliography: The recommendation is based on data from an unpublished meta-analysis on three studies: Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol.* 1996;174:1584-1589.

Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or

antiphospholipid antibodies). BMJ. 1997;314:253-257.

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. Med Sci Monit. 2006(3):CR132-CR136.

Baseline risk with aspirin: The baseline risk is derived from the same meta-analysis.

8 - Caesarean section and thromboprophylaxis

These recommendations will require practice change as current guidelines in Norway recommend prophylaxis for all women after caesarean section.

Clinicians need to risk stratify women into low, moderate-high and very high risk (see practical advice for risk factors) and apply the weak recommendations appropriately.

Use of compression stockings in addition to LMWH is relevant to consider for women at increased risk, as detailed in the recommendations.

No additional risk factors for venous thromboembolism (VTE)

Strong Recommendation

For women without additional risk we recommend against the use of any thromboprophylaxis other than early mobilization.

Practical Advice

RISK FACTOR FOR VTE

If the patient has one risk factor we suggest giving thromboprophylaxis during the hospital stay. In the presence of more than one risk factor we suggest that extended prophylaxis be considered.

Compression stockings are only suggested if the patient has a high risk of bleeding.

Major risk factor	Immobility (strict bed rest > 1 week before section)
	Postpartum haemorrhage > 1000 ml in combination with surgery (reoperation)
	Former VTE
	Preeclampsia with child of low birth weight.
	Preeclampsia with vekstretardert children (not prot. C/S deficiency)
	SLE, cardiovascular disease, sickle cell anemia
	Postpartum infection
Minor risk factors	BMI > 30kg/m ²
	Twins / Triplets
	Postpartum haemorrhage > 1000 ml

	Smoking > 10 sig / d
	Growth retardation (<25 percentile)
	Thrombophilia: Protein S/C deficiency
	Preeclampsia

Key Info**Benefits and harms**

The rate of VTE is reduced from 5 to 3 per 1000 pregnant women treated with LMWH after a caesarean section.

The rate of major maternal bleeds is increased from 20 to 31 per 1000 patients.

Quality of evidence

Moderate. Our confidence in the results is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH vs. placebo during surgery. There are no large randomized trials of prophylaxis in patients undergoing caesarean section.

Preference and values

We believe all or nearly all women would elect not to use LMWH after a c-section if they were well informed about the marginal absolute reduction in thrombosis and the increased risk of bleeds combined with the burden of self-injecting post partum.

Resources and other considerations

-

Rationale

Norway has for many years recommended prophylaxis for all women undergoing a caesarean section. Our strong recommendation against the use of LMWH in women without risk factors reflects the close balance between benefits and harms of using LMWH which suggest that the vast majority of women would not elect to self-inject with LMWH if they were well informed about the consequences. Our recommendation will require a change in current practice in Norway.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (8.1)**Population:** Cesarean section in pregnant women at low risk of VTE**Intervention:** LMWH**Comparator:** No treatment**Outcomes:** Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
VTE	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	5 <i>per 1000</i>	2 <i>per 1000</i>	3 fewer (CI 3 fewer - 1 fewer)	12.698 (22)
Major bleeding	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	20 <i>per 1000</i>	31 <i>per 1000</i>	11 more (CI 6 more - 17 more)	12.929 (44)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. NEJM 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. Thromb Haemost. 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. Thromb Haemost. 2010;103(1):129-137.

Risk of bias: Several of the included studies in the meta-analysis by Collins et al. were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboemboli the baseline risk is derived from studies stating risk factors for VTE after a cesarean section (please see table S10 and S11 in the original CHEST publication). For major bleeds the baseline risk is derived from the meta-analysis by Blondon et al.

Moderate to high risk of VTE

Weak Recommendation

For women who are at increased risk of venous thrombosis after a cesarean section (one or more risk factors, see practical information) we suggest thromboprophylaxis with LMWH during the hospital stay. For women who have a contraindication to LMWH we suggest the use of compression stockings.

Practical Advice

RISK FACTOR FOR VTE

If the patient has one risk factor we suggest giving thromboprophylaxis during the hospital stay. In the presence of more than one risk factor we suggest that extended prophylaxis be considered. Compression stockings are only suggested if the patient has a high risk of bleeding.

Major risk factor	Immobility (strict bed rest > 1 week before section)
	Postpartum haemorrhage > 1000 ml in combination with surgery (reoperation)
	Former VTE
	Preeclampsia with child of low birth weight.
	Preeclampsia with vekstretardert children (not prot. C/S deficiency)
	SLE, cardiovascular disease, sickle cell anemia
	Postpartum infection
Minor risk factors	BMI > 30 kg/m ²
	Twins / Triplets
	Postpartum haemorrhage > 1000 ml
	Smoking > 10 sig / d
	Growth retardation (<25 percentile)
	Thrombophilia: Protein S/C deficiency
	Preeclampsia

Key Info

Benefits and harms

Treatment with LMWH in women at moderate to high risk decreases the rate of VTE from 30 to 13 per 1000 women in the postpartum period.

The rate of major bleeds is increased from 11 to 20 per 1000 patients on LMWH.

The use of compression stockings is not as effective as LMWH giving 11 more VTEs per 1000 women, but the rate of major bleeds is decreased by 7 per 1000 patients.

Quality of evidence

Moderate. Our confidence in the results is reduced due to use of indirect evidence from a meta-analysis of randomized trials on LMWH / UFH and placebo in surgery. The relative effect of compression stockings is also based on indirect estimates. There are no large randomized trials on prophylaxis in cesarean section.

Preference and values

The absolute reduction in thrombosis is relatively large for individual patients and most patients are expected to prefer treatment. Preference studies have not been performed.

Resources and other considerations

The hospital covers the cost of LMWH or compression stockings until discharge.

Rationale

Norway has for many years had guidelines recommending prophylaxis for all women undergoing a caesarean section. Changing practice with differentiating between high and low risk women can be somewhat challenging to implement. Compared to the original guideline from ACCP, we've opted to lower the baseline risk cut-off estimate to initiate prophylaxis: We suggest that treatment be given starting at a baseline risk of 15/1000 patients (1,5%), while the ACCP sets the cut off at 3%. We assume that implementing the recommendation will be facilitated by having just one risk factor qualify for prophylaxis. We believe that the benefits of prophylaxis exceeds the risk of bleeding and that most women thus will opt for following the recommendation.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (8.2)

Population: Cesarean section in pregnant women at moderate risk of VTE

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	15 <i>per 1000</i>	7 <i>per 1000</i>	8 fewer (CI 10 fewer - 6 fewer)	12.698 (22)
Major bleeding	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	20 <i>per 1000</i>	31 <i>per 1000</i>	11 fewer (CI 6 fewer - 17 fewer)	12.929 (44)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162-1173.

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137.

Risk of bias: Several of the included studies in the meta-analysis by Collins et al. were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboemboli the baseline risk is derived from studies stating risk factors for VTE after a cesarean section (please see table S10 and S11 in the original CHEST publication). For major bleeds the baseline risk is derived from the meta-analysis by Blondon et al.

PICO (8.3)

Population: Cesarean section in pregnant women at high risk of VTE

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 (CI 0.31 - 0.63)	30 <i>per 1000</i>	13 <i>per 1000</i>	17 fewer (CI 21 fewer - 11 fewer)	12.698 (22)

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Major bleeding	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 (CI 1.32 - 1.87)	20 <i>per 1000</i>	31 <i>per 1000</i>	11 fewer (CI 6 fewer - 17 fewer)	12.929 (44)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162-1173.

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137.

Risk of bias: Several of the included studies in the meta-analysis by Collins et al. were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboemboli the baseline risk is derived from studies stating risk factors for VTE after a cesarean section (please see table S10 and S11 in the original CHEST publication). For major bleeds the baseline risk is derived from the meta-analysis by Blondon et al.

Very high risk of VTE

Weak Recommendation

For women who are at very high risk for venous thrombosis due to multiple major risk factors, we suggest thromboprophylaxis with LMWH in combination with compression stockings during the hospital stay, rather than LMWH alone.

Practical Advice

RISK FACTOR FOR VTE

If the patient has one risk factor we suggest giving thromboprophylaxis during the hospital stay. In the presence of more than one risk factor we suggest that extended prophylaxis be considered. Compression stockings are only suggested if the patient has a high risk of bleeding.

Major risk factor	Immobility (strict bed rest > 1 week before sectio)
	Postpartum haemorrhage > 1000 ml in combination with surgery (reoperation)
	Former VTE
	Preeclampsia with child of low birth weight.
	Preeclampsia with vekstretardert children (not prot. C/S deficiency)
	SLE, cardiovascular disease, sickel cell anemia
	Postpartum infection
Minor risk factors	BMI > 30kg/m ²
	Twins / Triplets
	Postpartum haemorrhage > 1000 ml
	Smoking > 10 sig / d
	Growth retardation (<25 percentile)
	Thrombophilia: Protein S/C deficiency
	Preeclampsia

Key Info

Benefits and harms

Treatment with LMWH in women at very high risk decreases the rate of VTE from 40 to 18 per 1000 women in the postpartum period.

The rate of major bleeds is increased from 11 to 20 per 1000 patients on LMWH.

The addition of compression stockings further reduces the incidence of VTE to 7 per 1000 women.

Quality of evidence

Low. Our confidence in the results is reduced due to use of indirect evidence on both the relative effect of LMWH and compressions stockings and a lack of evidence for the combination treatment. Indirect evidence comes from meta-analysis of randomized trials on a mixed surgical population. There are no large randomized trials on cesarean patients.

Preference and values

The absolute reduction in thrombosis is relatively large for individual patients and we believe all or nearly all well informed patients would elect to use compression stockings in addition to LMWH. Preference studies have not been performed.

Resources and other considerations

The hospital covers the cost.

Rationale

Our strong recommendation for the use of LMWH and the addition of compression stockings is based on the substantial benefit in reducing venous thromboses in women at very high risk, weighed against the limited increase in absolute number of bleeds and the inconvenience of self-injecting with LMWH and using compression stockings.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S-e736S [22315276](#) 10.1378/chest.11-2300

PICO (8.3)

Population: Cesarean section in pregnant women at high risk of VTE

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 <i>(CI 0.31 - 0.63)</i>	30 <i>per 1000</i>	13 <i>per 1000</i>	17 fewer <i>(CI 21 fewer - 11 fewer)</i>	12.698 (22)
Major bleeding	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	20 <i>per 1000</i>	31 <i>per 1000</i>	11 fewer <i>(CI 6 fewer - 17 fewer)</i>	12.929 (44)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162-1173.

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137.

Risk of bias: Several of the included studies in the meta-analysis by Collins et al. were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboemboli the baseline risk is derived from studies stating risk factors for VTE after a cesarean section (please see table S10 and S11 in the original CHEST publication). For major bleeds the baseline risk is derived from the meta-analysis by Blondon et al.

Persistent high risk of VTE**Weak Recommendation**

For women who are at very high risk of venous thrombosis and where the risk persists, we suggest prolonged thromboprophylaxis with LMWH until 6 weeks postpartum.

Practical Advice**RISK FACTOR FOR VTE**

If the patient has one risk factor we suggest giving thromboprophylaxis during the hospital stay. In the presence of more than one risk factor we suggest that extended prophylaxis be considered. Compression stockings are only suggested if the patient has a high risk of bleeding.

Major risk factor	Immobility (strict bed rest > 1 week before sectio)
	Postpartum haemorrhage > 1000 ml in combination with surgery (reoperation)
	Former VTE
	Preeclampsia with child of low birth weight.

	Preeclampsia with vekstretardert children (not prot. C/S deficiency)
	SLE, cardiovascular disease, sickel cell anemia
	Postpartum infection
Minor risk factors	BMI > 30kg/m ²
	Twins / Triplets
	Postpartum haemorrhage > 1000 ml
	Smoking > 10 sig / d
	Growth retardation (<25 percentile)
	Thrombophilia: Protein S/C deficiency
	Preeclampsia

Key Info

Benefits and harms

Treatment with LMWH in women at very high risk decreases the rate of VTE from 40 to 18 per 1000 women in the postpartum period.

The rate of major bleeds is increased from 11 to 20 per 1000 patients on LMWH.

Studies on prolonged prophylaxis after a cesarean are lacking, but applying studies from general surgery indicate that prolonged prophylaxis is appropriate for this patient group.

Quality of evidence

Low. Our confidence in the results is reduced due to our use of indirect evidence for the effects of extended duration LMWH in pregnant women after a caesarian section.

Preference and values

The absolute reduction in thrombosis is relatively large for the individual patient and most patients are believed to prefer extended treatment. Preference studies have not been performed.

Resources and other considerations

-

Rationale

Our weak recommendation for extended duration of thromboprophylaxis with LMWH after a caesarian section in women with persistent high risk is based on the anticipated benefit in reducing thrombosis weighed against the inconvenience of self-injecting with LMWH long term and a smaller increase in major maternal bleeds. We do however believe that a limited treatment duration of up to 6 weeks will be acceptable to most women.

References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

PICO (8.3)

Population: Cesarean section in pregnant women at high risk of VTE

Intervention: LMWH

Comparator: No treatment

Outcomes: Thromboembolism, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	LMWH	Difference with	Participants (studies), Follow-up
Thromboembolism	Low <i>due to risk of bias and indirect data</i>	RR: 0.44 <i>(CI 0.31 - 0.63)</i>	30 <i>per 1000</i>	13 <i>per 1000</i>	17 fewer <i>(CI 21 fewer - 11 fewer)</i>	12.698 (22)
Major bleeding	Low <i>due to risk of bias and indirect data</i>	RR: 1.57 <i>(CI 1.32 - 1.87)</i>	20 <i>per 1000</i>	31 <i>per 1000</i>	11 fewer <i>(CI 6 fewer - 17 fewer)</i>	12.929 (44)

PICO References

Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *NEJM* 1988 [3283548](#) 10.1056/NEJM1988050531

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. *Thromb Haemost.* 2010;103(1):129-137. [20062923](#) 10.1160/TH09-06-0349

PICO Summary

Bibliography: Collins et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318(18):1162-1173.

Blondon MB, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. Thromb Haemost. 2010;103(1):129-137.

Risk of bias: Several of the included studies in the meta-analysis by Collins et al. were not blinded and the allocation procedures were not clear.

Indirect data: The systematic review by Collins et al. included several different surgical populations, including from urologic surgery, orthopedic surgery etc.

Baseline risk: For venous thromboemboli the baseline risk is derived from studies stating risk factors for VTE after a cesarean section (please see table S10 and S11 in the original CHEST publication).

For major bleeds the baseline risk is derived from the meta-analysis by Blondon et al.

9 - Use of anticoagulation therapy during breastfeeding

Warfarin

Strong Recommendation

For women taking warfarin we recommend to continue doing so while breastfeeding.

Practical Advice

Key Info

	Benefits and harms Warfarin is effective in reducing thromboembolic events and carries a low risk of major maternal bleeds in breastfeeding women. Warfarin is not detected in breast milk and does not induce an anticoagulant effect in the breastfed infant.
	Quality of evidence High. Our confidence in the anticipated effects of warfarin in breastfed infants is high because of the available evidence and absence of published serious side effects of warfarin taken during the breast-feeding period.
	Preference and values As long as the treatment is safe for the child and reduces the risk of thrombosis in the mother, we expect that patients will want to breastfeed while continuing warfarin therapy. This applies especially to women on long-term treatment. Most women who have shorter treatment (6-12 weeks postpartum) are believed to prefer LMWH as they will already have learned the injection technique and will not have to undergo frequent INR-controls. Preference studies are not published.
	Resources and other considerations Warfarin is cost-effective in the prevention of thromboembolic events and is reimbursed.

Rationale

Our strong recommendation for the use of warfarin during breastfeeding (in the presence of a clinical indication) is based on the benefit of anticoagulation, the high value Norwegian women place on being able to breastfeed and the safety of warfarin for the breastfed infant. We consider it important that women using anticoagulation are well informed so that they can maintain breastfeeding while taking warfarin.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Low molecular weight heparin (LMWH)

Strong Recommendation

For women using LMWH we recommend to continue doing so while breastfeeding.

Practical Advice

Key Info

Benefits and harms

LMWH is effective in reducing thromboembolic events and carries a low risk of major maternal bleeds in breastfeeding women.

The oral bioavailability of LMWH is very low and we expect no clinical effects of LMWH in the breastfed infant. There are no published reports of bleeding in breastfed infants with mothers using LMWH.

Quality of evidence

Moderate. Our confidence in the anticipated effects of LMWH during the breast-feeding period is reduced as it is based on few and small studies.

Preference and values

As long as the treatment seems safe for the baby and reduces the risk of thrombosis in the mother, we expect that women will want to breastfeed while on LMWH. Preference studies have not been published, but an international study is expected to be published within 2 years.

Resources and other considerations

LMWH is considered cost-effective both for treatment of VTE and in thromboprophylaxis. The treatment is reimbursed.

Rationale

Our strong recommendation for the use of LMWH during breastfeeding (in the presence of a clinical indication) is based on the benefit of anticoagulation, the high value Norwegian women place on being able to breastfeed and the safety of LMWH for the breastfed infant. We consider it important that women using anticoagulation are well informed so that they can maintain breastfeeding while on LMWH.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Fondaparinux

Weak Recommendation

In breastfeeding women we suggest alternative anticoagulation rather than fondaparinux (Arixtra).

Practical Advice**Key Info****Benefits and harms**

The effects of fondaparinux on breast-fed infants are unknown. Studies have been published showing transition of fondaparinux into the milk of lactating rats. Fondaparinux is a negatively charged oligosaccharide and is assumed to pass the intestinal barrier in very small quantities. The manufacturer recommends caution when using fondaparinux in breastfeeding women.

Quality of evidence

Low. Our confidence in the effect estimates is reduced due to the lack of studies in lactating women and existing evidence stemming from animal studies.

Preference and values

Breastfeeding women are likely to be very concerned about the safety of their children. Fondaparinux is typically considered in the case of allergic reactions to LMWH and for breastfeeding women the alternative option will then instead be warfarin. Women who place a high value on avoiding the added burden of warfarin treatment (INR monitoring and diet restrictions) may elect to use fondaparinux, but should then be well-informed about the potential risks.

Resources and other considerations

Fondaparinux is not covered by pre-approved reimbursement.

Rationale

Our weak recommendation for avoiding fondaparinux while breastfeeding is based on the lack of studies to demonstrate safety for the breast-fed infant and the presence of effective alternatives. If women can not tolerate LMWH or experience allergic reactions while taking LMWH we suggest warfarin to be the most appropriate alternative anticoagulation regime while breastfeeding.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Dabigatran, apixaban, rivaroxaban

Strong Recommendation

For breastfeeding women we recommend alternative anticoagulation rather than oral thrombin inhibitor and factor Xa inhibitor.

Practical Advice

Key Info

Benefits and harms

Breastfeeding women have been excluded from the studies that have been published on new oral anticoagulants. Product description for rivaroxaban indicates transition of the drug into breast milk. The manufacturers of rivaroxaban and dabigatran recommend against breastfeeding for patients taking these drugs.

Quality of evidence

Low. Our confidence in the effect estimates is reduced due to the absence of studies reporting safety of new oral anticoagulants in breastfeeding women.

Preference and values

Breastfeeding women are likely to be very concerned about the safety of their children. In the absence of safety data for the new oral anticoagulants we believe all or nearly all women would elect not to take these drugs while breastfeeding.

Resources and other considerations

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Rationale

Our strong recommendation against the use of new oral anticoagulants while breastfeeding is based on the absence of safety data. Given the high value Norwegian women place on breastfeeding we consider it important that women in the need of anticoagulation are well informed about alternative treatments (LMWH and warfarin) so that they can maintain breastfeeding while taking safe and effective anticoagulation.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Aspirin

Weak Recommendation

For women taking low-dose aspirin on vascular indication we suggest to continue doing so while breastfeeding.

Practical Advice

Key Info

	Benefits and harms <p>Low dose ASA (<100 mg daily) does not seem to have a negative effect on the child despite the fact that small amounts of salicylic acid can be detected in breast milk. Studies with low-dose ASA in late pregnancy have not shown reduced efficacy of the child's platelets and thus it is very unlikely that this will occur in the breastfeeding period.</p>
	Quality of evidence <p>Low. Our confidence in the anticipated effects is low due to few and small studies.</p>
	Preference and values <p>Lactating women are likely to be very concerned about the safety of their children. We believe most women would elect to use ASA if they were well informed about the low risk such treatment imposes on their children and the benefits for themselves.</p>
	Resources and other considerations <p>-</p>

Rationale

Our weak recommendation for continued use of ASA in the breastfeeding period (in the presence of a clinical indication) is based on existing evidence suggesting that such treatment is safe for the breast-fed infant.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

10 - Reccurent early pregnancy loss and other complications

Screening for APLA

Strong Recommendation

For women with recurrent early pregnancy loss (three or more consecutive first trimester abortions) we recommend screening only for the APLA (antiphospholipid antibody) syndrome.

Practical Advice

Here we need information about APLA criteria:

Key Info

Benefits and harms

With the APLA syndrome there is an increased risk of recurrent early pregnancy loss (estimated 5-times increase) and also late abortions. The association is strongest with positive lupus anticoagulant, but is also seen in moderate to high titers of IgG and IgM anticardiolipin antibodies (two positive tests, 12 weeks apart are required). The association is somewhat less clear for anti-beta2-glycoprotein I antibodies.

Quality of evidence

Moderate. Our confidence in the results is reduced due to relatively few and small studies that on the other hand do provide consistent findings.

Preference and values

Women who experience habitual abortions are likely to place a high value on identifying APLA as a possible cause as effective treatment is currently available.

Resources and other considerations

-

Rationale

Our strong recommendation in favor of screening for APLA is based on the associated high risk for recurrent pregnancy loss with the presence of effective therapy, as detailed in the recommendations below.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Screening for thrombophilia

Weak Recommendation

For women with pregnancy complications we suggest not to screen for hereditary thrombophilia.

Hereditary thrombophilias: Protein S and C deficiency, heterozygous factor V Leiden or heterozygous prothrombin- mutation.

Pregnancy complications: Habitual abortion, IUFD, growth retardation, preeclampsia or placental abruption

Practical Advice

Key Info

Benefits and harms

IUFD and preeclampsia appears to be associated with hereditary thrombophilia, while the association is weaker for growth retardation and placental abruption. The uncertainty in the observed associations and the lack of evidence for treatment effects does not suggest a benefit of screening for hereditary thrombophilias.

Quality of evidence

Low. Our confidence in the results is reduced due to few and small studies with risk of bias.

Preference and values

Women who experience serious pregnancy complications are likely to want to identify potential causes and get effective treatment. We do however believe most women would not want to be screened for thrombophilias if they were well informed about the lack of evidence of a benefit for screening for thrombophilias or the potential subsequent treatment.

Resources and other considerations

We consider screening for thrombophilias not to be cost-effective given the absence of evidence of a treatment effect.

Rationale

Our weak recommendation against screening for thrombophilia is based on the uncertain association between presence of thrombophilias and pregnancy complications and the absence of evidence for effective treatment. High prevalence of factor V Leiden in Norway will provide many positive test results and lead to substantial, probably unnecessary, uncertainty surrounding questions on prophylactic treatment.

References

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Women without thrombophilia or APLA

Strong Recommendation

For women with two or more spontaneous miscarriages without thrombophilia or APLA we recommend against thromboprophylaxis.

Practical Advice

Key Info

	<p>Benefits and harms</p> <p>With antepartum treatment the rate of miscarriage is reduced from 500 to 217 per 1000 women treated.</p> <p>Studies so far have failed to show a significant effect on the rate of pre-eclampsia or intrauterine growth retardation.</p>
	<p>Quality of evidence</p> <p>Moderate. The recommendation is based on two randomized trials and our confidence in the results is reduced due to imprecise effect-estimates.</p>
	<p>Preference and values</p> <p>We believe women would not want to self-inject with LMWH during pregnancy if they were well informed about the lack of effect.</p>
	<p>Resources and other considerations</p> <p>-</p>

Rationale

Our strong recommendation against treatment is based on a lack of evidence to support a beneficial effect of anticoagulant treatment in reducing spontaneous miscarriages, combined with the burden of self-injecting with LMWH long term and an increased risk of major maternal bleeds.

References

Kaandorp SP, Mariette Goddijn M, van der Post JAM, et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. *N Engl J Med*. 2010;29:1586-1596 [20335572](#) 10.1056/NEJMoa1000641

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Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood*. 2010;115:4162-4167 [20237316](#) 10.1182/blood-2010-01-267252

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Visser G et al. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. Habenox: a randomised multicenter trial. Thromb Haemost 2011 Feb;105(2):295-301. [21103659](#) 10.1160/TH10-05-0334

PICO (10.2)

Population: Prophylaxis of habitual abortion without known thrombophilia

Intervention: ASA

Comparator: No treatment

Outcomes: Abortion, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	ASA	Difference with	Participants (studies), Follow-up
Abortion	Moderate <i>due to imprecise estimates</i>	RR: 1.16 (CI 0.8 - 1.69)	300 <i>per 1000</i>	348 <i>per 1000</i>	48 more (CI 60 fewer - 207 more)	202 (1) 9 mnd
Major bleeding (during pregnancy)	Moderate <i>due to indirect data</i>	RR: 1.54 (CI 1.3 - 1.82)	15 <i>per 1000</i>	23 <i>per 1000</i>	8 more (CI 5 more - 12 more)	95.000 (6) 3.8-10 år

PICO References

Kaandorp SP, Mariette Goddijn M, van der Post JAM, et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. N Engl J Med. 2010;29:1586-1596 [20335572](#) 10.1056/NEJMoa1000641

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005 [15811953](#) 10.1182/blood-2005-02-0626

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PICO Summary

Bibliography: Kaandorp SP, Mariette Goddijn M, van der Post JAM et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. New Engl J Med. 2010;29;362:1586-1596.

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Greer IA, Nelson-Piercy C. Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401-407.

Baseline risk: The baseline risk for abortion is derived from the two studies på Kaandorp et al. For major bleeds antepartum the baseline risk is derived from Greer et al.

Use of indirect data giving reduced confidence in the effect estimate: Data on major bleeds is derived from studies on primary prevention of cardiovascular disease.

PICO (10.4)

Population: Prevention of preeclampsia in pregnant women without known thrombophilia

Intervention: ASA

Comparator: No treatment

Outcomes: Preeclampsia, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	ASA	Difference with	Participants (studies), Follow-up
Low risk for preeclampsia	Moderate <i>due to heterogeneity</i>	RR: 0.83 (CI 0.77 - 0.89)	60 <i>per 1000</i>	50 <i>per 1000</i>	10 fewer (CI 14 fewer - 7 fewer)	32.590 (43), not reported
High risk for preeclampsia	Moderate <i>due to heterogeneity</i>	RR: 0.83 (CI 0.77 - 0.89)	210 <i>per 1000</i>	174 <i>per 1000</i>	36 fewer (CI 26 fewer - 23 fewer)	32.590 (43), not reported
Major bleeding (during pregnancy)	Moderate <i>due to indirect data</i>	RR: 1.54 (CI 1.3 - 1.82)	15 <i>per 1000</i>	23 <i>per 1000</i>	8 more (CI 5 more - 12 more)	95.000 (6) 3.8-10 yrs

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005 [15811953](#) 10.1182/blood-2005-02-0626

Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007;(2):CD004659. [17443552](#) 10.1002/14651858.CD004659

PICO Summary

Bibliography: Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007;(2):CD004659.

Greer IA, Nelson-Piercy C. Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401-407.

We had reduced confidence in effect estimates due to:

Heterogeneous estimates: May be due to differences in the type and dose of antiplatelet agent as well as variation in patient population regarding the risk factors for preeclampsia.

Indirect data: Studies on primary prevention of cardiovascular disease have been included.

Baseline risk: The baseline risk for preeclampsia is derived from the control arm in the meta-

analysis. High risk was in the systematic review defined as women who were either normotensive or had chronic hypertension without preeclampsia at baseline and had one or more of the following: History of severe pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease. The baseline risk for major bleeds is derived from Greer et al. Major bleeds is defined as a major antenatal maternal bleed.

Treatment in women with recurrent early pregnancy loss who fulfill the criteria for APLA syndrome (see practical advice)

Strong Recommendation

For women with recurrent early pregnancy loss (three or more miscarriages) who meet the laboratory criteria for APLA syndrome, we recommend prophylactic LMWH combined with low-dose ASA (see section on prophylaxis in women with known thrombophilia).

Practical Advice

With the APLA syndrome there is an increased risk of recurrent early pregnancy loss (estimated 5-times increase) and also late abortions. The association is strongest with positive lupus anticoagulant, but is also seen in moderate to high titers of IgG and IgM anticardiolipin antibodies. Two positive tests at 12 weeks apart are required to fulfill criteria for a positive APLA test. The association is somewhat less clear for anti-beta2-glycoprotein I antibodies.

This uncertainty contributes to making the diagnosis of APLA not always that straight forward. We therefore strongly advice that further details be sought elsewhere, as diagnosis is not covered by the scope of this guideline.

Most commonly used are the revised Sapporo criteria/Sydney criteria: Definite APLA is considered if at least one of the following clinical criteria and at least one of the following laboratory criteria are satisfied:

Clinical criteria	Vascular thrombosis
	or pregnancy morbidity: Unexplained fetal death at ≥ 10 weeks gestation, ≥ 1 premature births < 34 weeks gestation due to eclampsia, preeclampsia, or placental insufficiency, ≥ 3 early (< 10 week gestation) unexplained pregnancy losses.
Laboratory criteria	IgG and/or IgM aCL in moderate or high titer
	Antibodies to $\beta 2$ -glycoprotein I (anti- $\beta 2$ GPI) of IgG or IgM isotype
	Lupus anticoagulant (LA)

Key Info**Benefits and harms**

For 1000 women treated with LMWH combined with low-dose ASA during pregnancy:

Abortions: 283 fewer (500 without treatment)

Intrauterine growth reduction and pre-eclampsia: No significant differences, compared to no treatment.

Major maternal bleeds: to be inserted (not present in AT9 evidence profile)

Quality of evidence

Low. Our confidence in the effect-estimates is reduced due to risk of bias and imprecision in the meta-analysis of 3 trials.

Preference and values

We believe all or nearly all women experiencing habitual abortions would elect to use LMWH and low-dose ASA given the substantial absolute benefit in reducing abortions in the current pregnancy.

Resources and other considerations

Prophylaxis costs about NOK 40 / day and is refunded.

Rationale

Our strong recommendation for thromboprophylaxis in women with APLA and recurrent pregnancy loss is based on the large anticipated absolute effect on reducing miscarriages.

References

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monit.* 2006(3):CR132-CR136. [16501426](#)

Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ.* 1997;314:253-257. [9022487](#) 10.1136/bmj.314.7076.253

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol.* 1996;174:1584-1589. [9065133](#)

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PICO (10.3)

Population: Prophylaxis of antiphospholipid syndrome and habitual abortions

Intervention: UFH plus ASA

Comparator: ASA

Outcomes: Abortion, IUGR, preeclampsia

Outcomes	Confidence in effect estimates	Relative effect	ASA	UFH plus ASA	Difference with	Participants (studies), Follow-up
Abortion	Moderate <i>due to risk of bias</i>	RR: 0.44 (CI 0.33 - 0.66)	500 <i>per 1000</i>	217 <i>per 1000</i>	283 fewer (CI 353 fewer - 172 fewer)	212 (3), not reported
IUGR (during pregnancy)	Low <i>due to risk of bias and imprecise estimates</i>	RR: 1.71 (CI 0.48 - 6.17)	56 <i>per 1000</i>	95 <i>per 1000</i>	39 more (CI 29 fewer - 287 more)	134 (3), not reported
Preeclampsia	Low <i>due to risk of bias and imprecise estimates</i>	RR: 0.43 (CI 0.09 - 2.08)	74 <i>per 1000</i>	32 <i>per 1000</i>	30 fewer (CI 67 fewer - 89 fewer)	134 (3), not reported

PICO References

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. Med Sci Monit. 2006(3):CR132-CR136. [16501426](#)

Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ. 1997;314:253-257. [9022487](#) 10.1136/bmj.314.7076.253

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996;174:1584-1589. [9065133](#)

PICO Summary

Bibliography: The recommendation is based on data from an unpublished meta-analysis based on three studies: Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996;174:1584-1589.

Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ. 1997;314:253-257.

Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. Med Sci Monit. 2006(3):CR132-CR136.

The baseline risk with aspirin: Data derived from the same meta-analysis.

Treatment in women with pregnancy complications and known hereditary thrombophilias

Weak Recommendation

For women with pregnancy complications and known hereditary thrombophilias, we suggest not to use thromboprophylaxis.

Pregnancy complications: IUFD, growth retardation, preeclampsia, placental abruption
Hereditary thrombophilias: Protein S and C deficiency, heterozygous Leiden and heterozygous prothrombin gene mutations.

Practical Advice

Key Info

Benefits and harms

The association between pregnancy complications and thrombophilias is weak and prophylaxis with LMWH has shown no effect.

Quality of evidence

Low. Our confidence in the results is reduced due to small RCT studies and observational studies with risk of bias.

Preference and values

Women who are well informed about the lack of evidence to support the use of thromboprophylaxis to prevent pregnancy complications and the risk of major maternal bleeds are likely not to elect self-injecting with LMWH during pregnancy.

Resources and other considerations

Thromboprophylaxis is not considered cost-effective given the absence of evidence to demonstrate beneficial effects on pregnancy complications.

Rationale

Our weak recommendation against the use of LMWH to prevent pregnancy complications in women with known thrombophilias is based on evidence showing no benefit of treatment, but an increased risk of major maternal bleeds and the known inconvenience of self-injecting with LMWH during pregnancy. Given these factors we believe that few women would opt for treatment.

References

Martinelli I et al. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood*, 2013 Apr 5;119(14):3269-75 [22289887](#) 10.1182/blood-2011-11-391383

Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST* 2012; 141(2)(Supl):e691S–e736S [22315276](#) 10.1378/chest.11-2300

Preeclampsia

Strong Recommendation

For women at risk of preeclampsia we recommend low-dose ASA 75 mg x 1 starting at week 13 and continued throughout the pregnancy.

Practical Advice

Key Info

Benefits and harms

Treatment with ASA from week 13 of the pregnancy and continued until delivery reduces the risk of preeclampsia in:

Low risk women from 60 to 50 per 1000 women treated.

High risk women from 210 to 174 per 1000 women treated.

Major maternal bleeds increases from 15 to 23 per 1000 patients.

Quality of evidence

Moderate. Our confidence in the effect-estimates (meta-analysis of 43 RCTs) is reduced due to inconsistent results across studies. This heterogeneity is primarily due to different doses of ASA being tested and different populations of pregnant women with regard to risk of preeclampsia. The bleeding risk is not documented in the studies on preeclampsia studies and our estimate here is based on indirect evidence from studies on cardiovascular disease.

Preference and values

We believe all or nearly all pregnant women at risk of preeclampsia well informed about the beneficial effects of using ASA and the limited increase in bleeds would elect to take such treatment during pregnancy.

Resources and other considerations

We consider this treatment to be highly cost-effective.

Rationale

Our strong recommendation for the use of ASA from week 13 and onwards during the pregnancy is based on a substantial effect in reducing the incidence of preeclampsia combined with a limited increase in major maternal bleeds. Given this balance we believe that nearly all women will concur with the recommendation.

References

- Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005 [15811953](#) 10.1182/blood-2005-02-0626
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- Villa PM et al. Aspirin in the prevention of preeclampsia in high risk women, a randomised placebo-controlled PREDO Trial and a metaanalysis of randomised trials, *BJOG* 2013;1:64-74 [23126307](#) 10.1111/j.1471-0528.2012.03493

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PICO (10.4)

Population: Prevention of preeclampsia in pregnant women without known thrombophilia

Intervention: ASA

Comparator: No treatment

Outcomes: Preeclampsia, major bleeding

Outcomes	Confidence in effect estimates	Relative effect	No treatment	ASA	Difference with	Participants (studies), Follow-up
Low risk for preeclampsia	Moderate <i>due to heterogeneity</i>	RR: 0.83 (CI 0.77 - 0.89)	60 <i>per 1000</i>	50 <i>per 1000</i>	10 fewer (CI 14 fewer - 7 fewer)	32.590 (43), not reported
High risk for preeclampsia	Moderate <i>due to heterogeneity</i>	RR: 0.83 (CI 0.77 - 0.89)	210 <i>per 1000</i>	174 <i>per 1000</i>	36 fewer (CI 26 fewer - 23 fewer)	32.590 (43), not reported
Major bleeding (during pregnancy)	Moderate <i>due to indirect data</i>	RR: 1.54 (CI 1.3 - 1.82)	15 <i>per 1000</i>	23 <i>per 1000</i>	8 more (CI 5 more - 12 more)	95.000 (6) 3.8-10 yrs

PICO References

Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005 [15811953](#) 10.1182/blood-2005-02-0626

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Greer IA, Nelson-Piercy C. Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401-407.

We had reduced confidence in effect estimates due to:

Heterogeneous estimates: May be due to differences in the type and dose of antiplatelet agent as well as variation in patient population regarding the risk factors for preeclampsia.

Indirect data: Studies on primary prevention of cardiovascular disease have been included.

Baseline risk: The baseline risk for preeclampsia is derived from the control arm in the meta-analysis. High risk was in the systematic review defined as women who were either normotensive or

had chronic hypertension without preeclampsia at baseline and had one or more of the following:
History of severe pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease.
The baseline risk for major bleeds is derived from Greer et al. Major bleeds is defined as a major antenatal maternal bleed.

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- 2 Kaandorp SP, Mariette Goddijn M, van der Post JAM, et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. *N Engl J Med*. 2010;29:1586-1596 [20335572](#) 10.1056/NEJMoa1000641
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