South African National Essential Medicine List
Adult Hospital Level Medication Review
Component: Obstetrics

EVIDENCE SUMMARY

TITLE: The use of low molecular weight heparins (LMWH) for secondary venous thromboembolism (VTE) prophylaxis during pregnancy and the puerperium.

Date: November 2022

BACKGROUND

- Normal pregnancy is a hypercoagulable state due to physiological changes in haemostasis and this only returns to a pre-pregnancy state 6-8 weeks after delivery.
- There are three indications for anticoagulation during pregnancy:
    1. Mechanical heart valves
    2. Therapeutic, for acute venous thromboembolism (VTE; DVT and pulmonary embolus)
    3. **Prophylactic use to prevent VTE in women with:**
        a. **A previous VTE (requires prophylaxis during pregnancy and 6 weeks post-delivery)**
        b. Other risk factors (requires prophylaxis for 5 days following delivery)
        c. Thrombophilia's (tertiary care)

    NOTE: This evidence summary deals with point **3a** above (the bold/underlined indications); specifically for pregnant women without mechanical heart valves or any cardiac disease requiring prophylactic long-term anticoagulation. The use of warfarin in women with cardiac lesions was the basis of a medicine review (National Department of Health: Essential Drugs Programme. Adult Hospital medicine review: LMWH in pregnant women with mechanical heart valves, January 2020. Available at: https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list) and guidance is included in the Adult Hospital Level STGs and EML, 2019 edition: Obstetrics chapter.

Incidence and risks

The overall incidence of pregnancy-associated VTE is about 200 per 100,000 woman-years; compared to nonpregnant women of childbearing age, the relative risk is increased about fourfold. The risk during the postpartum period is about fivefold higher than the risk during pregnancy. (1) (2)

Risk stratification can help identify those pregnant women at higher risk for thrombosis, and appropriate prophylaxis can be recommended. The highest risk is in a pregnant woman who had a previous episode of VTE before the index pregnancy- the odds ratio for a repeat VTE in this scenario is 24.8 (17.1-36)](3).

These women requires thromboprophylaxis during pregnancy and for 6 weeks post-delivery, as they are at high risk serious complications and/or death(4). The challenge is the choice of agent:

- Vitamin K antagonists (e.g., warfarin) are known to act as teratogens. Warfarin is contra-indicated in the first trimester, as it is a known teratogenic drug (warfarin embryopathy in about 5% of cases). (EML)
- Warfarin should not be used in the last month of pregnancy/4 weeks prior to scheduled delivery due to the risk of excessive bleeding during labour. (EML)
- In addition, there is a warfarin risk to the fetus after the first trimester- (warfarin fetopathy in about 2-5% of cases), mainly due to cerebral and pulmonary haemorrhage leading to blindness, deafness, mental retardation or death.(5) The immature liver enzyme system and the low levels of vitamin K-dependent clotting factors in the fetus result in higher levels or overdosing of the fetus with oral anticoagulants, leading to haemorrhage. This damage is dose-dependent.(6)

REVIEW QUESTION

In pregnant women requiring prophylactic anticoagulation for VTE prophylaxis during the entire pregnancy (not for any cardiac/valve disease), is LMWH throughout pregnancy safer and/or more effective than switching to warfarin in second trimester and back to LMWH in the later third trimester?

P: pregnant patients requiring prophylactic anticoagulation

I: LMWH

C: LMWH 1st and 3rd trimester, warfarin from weeks 12 to 36

O: Fetal side effects, bleeding complications in the mother

No randomised trial was identified that answers this specific PICO.

SAFETY WARNINGS ON THE USE OF WARFARIN DURING PREGNANCY:

A. CIPLA-WARFARIN (SAPHRA) package insert:

CIPLA-WARFARIN is contra-indicated in the following settings:

- Where there are insufficient laboratory facilities.
- **Pregnancy and in breastfeeding mothers**
- Threatened abortion.
- **Children < 18 years, as safety has not been established.**

PREGNANCY AND LACTATION:

CIPLA-WARFARIN **should be avoided in pregnancy and lactation** as it is a recognised Teratogen. When CIPLA-WARFARIN is given in the first trimester of pregnancy it can cause the foetal warfarin syndrome. CNS or warfarin embryopathy abnormalities may develop following use in any trimester but **appear most likely after use in the second trimester**. Spontaneous abortion and stillbirth have been reported.

CIPLA-WARFARIN is distributed into milk only in its active form; studies in infants who are breast-fed while their mothers were taking CIPLA-WARFARIN did not find any effect on prothrombin time, however, breast-fed infants (especially neonates) are very sensitive to oral anticoagulants because of the low concentrations of vitamin K in breast milk."

B. FDA website (package insert for Coumadin)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

"COUMADIN is contraindicated in women who are pregnant (except in pregnant women with mechanical heart valves, who are at high risk of thromboembolism, and for whom the benefits of COUMADIN may outweigh the risks). COUMADIN can cause fetal harm when administered to a pregnant woman. COUMADIN exposure during pregnancy causes a recognized pattern of major congenital malformations (warfarin embryopathy), fetal haemorrhage, and an increased risk of spontaneous abortion and fetal mortality. Mental retardation, blindness, schizencephaly, microcephaly, hydrocephalus, and other adverse pregnancy outcomes have been reported following warfarin exposure during the second and third trimesters of pregnancy."

C: Society recommendations based on systematic reviews:

i. The Royal College of Obstetricians and gynaecologists (RCOG) guideline (7)

- Warfarin use in pregnancy is restricted to the few situations where heparin is considered unsuitable, e.g., some women with mechanical heart valves.
- LMWHs are the agents of choice for antenatal and postnatal VTE thromboprophylaxis.
- AGREE 2 score assessment of 92%, good quality

The RCOG summarises the odds ratios (ORs) for VTE associated with each risk factor derived from various studies (Table 2). Women with multiple risk factors for VTE, even those with no history of thrombophilia or VTE, were reported to have an increased risk of VTE in pregnancy, especially in the third trimester and postpartum (12). Factors contributing substantially to rates of VTE includes age greater than 35 years, obesity and caesarean section (13).

Table 2: Adjusted odds ratios for risk factors for VTE reported in the RCOG (2015) include (7):

Risk factor	Adjusted odds ratio (95% CI)	Reference
Previous VTE	24.8 (17.1, 36)	13, 14
Emergency caesarean section	2.7 (1.8, 4.1)	15
Age > 35	1.3 (1.0, 1.7)	15
Current smoker	2.7 (1.5, 4.9)	16
Pre-eclampsia	2.9 (2.1, 3.9)	15
Parity ≥3	2.4 (1.8, 3.1)	15
PPH > 1 litre	4.1 (2.3, 7.3)	17

ii. The American College of Obstetricians and gynaecologists (ACOG) guideline (8)

- Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta and both are considered to be safe in pregnancy.
- Low-molecular-weight heparin is recommended in place of warfarin.
- AGREE 2 score assessment of 75%, moderate quality (this is a practice bulletin).

Why is there a different recommended regimen of anti-coagulation for pregnant women with mechanical cardiac valves?

Pregnant women with a mechanical prosthetic heart valves are at high risk complications due to the hypercoagulable state of pregnancy combined with the inherently thrombogenic mechanical valve. The EML recommends warfarin for prophylaxis in women with mechanical heart valves over LMWH- a medicine review was presented to NEMLC in 2020. The reason stated in this review is warfarin throughout pregnancy (in this specific group of women) was associated with the lowest rate of maternal death, followed by warfarin/LMWH used sequentially. The highest rate of maternal death was in the LMWH group.

There is concern in the literature about the use of LMWH in mechanical heart valves if monitoring with FactorXa is not available or if patients are not fully compliant(9). A 2022 systematic review and meta-analysis on the risk of bleeding complications in women with mechanical heart valves during pregnancy found that a combination of unfractionated heparin (UFH) and vitamin K antagonist (VKA); and single VKA therapy showed the lowest risk of bleeding (8 and 12%). The highest risk of bleeding was found in women receiving a combination of low-molecular-weight-heparin (LMWH) and VKA (33%) or mono-therapy with LMWH (22%).

RECOMMENDATIONS ON DOSE AND SAFETY OF LMWH FOR VTE PROPHYLAXIS IN PREGNANCY:

A. Systematic review and meta-analysis: safety

Jacobson et al 2020 (10) did a systematic review and meta-analysis on the safety and efficacy of enoxaparin use in pregnancy. In the 24 clinical trials selected, not enough information was available to assess efficacy of VTE prophylaxis with a pooled meta-analysis, but they could make a conclusion on safety in pregnancy. Enoxaparin was associated with significantly lower complications than aspirin and reports of thromboembolic events, thrombocytopenia, and congenital malformations were rare.

B: Randomised controlled trials: dose

Bistervels et al 2022 (11) conducted an open-label, randomised, controlled trial in women with a history of objectively confirmed venous thromboembolism and a current pregnancy with gestational age <14 weeks. The aim was to determine the optimal dose of LMWH to prevent recurrent VTE. Randomisation was to either a weight-adjusted dose (as extrapolated form non-pregnant populations) or a fixed low-dose (for enoxaparin 40mg if <100kg or 60mg if >100kg; see alternatives in table below) of LMWH during the remainder of the pregnancy and for 6 weeks post-delivery. Venous thromboembolism occurred in 11 (2%) of 555 women in the weight-adjusted dose group and in 16 (3%) of 555 in the fixed low-dose group (relative risk [RR] 0·69 [95% CI 0·32–1·47]; p=0·33. They conclude that low-dose LMWH for thromboprophylaxis during pregnancy is the appropriate dose for the prevention of pregnancy-related recurrent venous thromboembolism.

Table 2: Therapeutic interchangeable LMWH for DVT prophylaxis in pregnancy

Medicine	Daily dose: <100kg	Daily dose: ≥100kg	Indication	Evidence
Enoxaparin	4000 IU	6000 IU	DVT prophylaxis in pregnancy	Bistervels et al 2022(11)
Dalteparin	5000 IU	7500 IU		
Nadroparin	2850 IU	3800 IU		

Source: Bistervels IM, et al; Highlow Block writing committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Oct 28:S0140-6736(22)02128-6.

Conclusion

- **Warfarin use during weeks 12 to 36 of pregnancy in women requiring VTE prophylaxis for reasons other than mechanical cardiac lesions is not recommended due to concerns for fetal safety.**
- **LMWH is safe for VTE prophylaxis in women with a prior VTE event, and the optimal dose is evidence based.**

Budget impact analysis

Refer to the costing analysis report: Comparative cost analysis of anticoagulants (LMWH/warfarin) as secondary VTE prophylaxis in pregnancy, 22 November 2022.

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Declarations: GSG (University of Stellenbosch) and TL (Right-To-Care Secretariat to the National Department of Health, Essential Drugs Programme) have no interests related to heparins or warfarin.

NEMLC RECOMMENDATION – MEETING OF 8 DECEMBER 2022:

NEMLC acknowledged the lack of local data for the risk of thrombosis in pregnancy and that no available evidence could be sourced for the risk of mortality, premature births or congenital anomalies associated with warfarin. However, this was likely to be a small patient population. NEMLC recommended that LMWH (e.g. enoxaparin) be recommended for VTE prophylaxis in pregnant women with a prior VTE.

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