

## LOW MOLECULAR WEIGHT HEPARIN (LMWH) AS A PROPHYLAXIS FOR VENOUS THROMBOEMBOLISM IN PREGNANCY AND POSTPARTUM

### Executive Summary

[Adapted from the report by DR NUR FARHANA MOHAMAD]

#### Review Group Membership

##### MaHTAS Reviewer:

Dr. Nur Farhana Mohamad  
Dr. Junainah Sabirin

##### External Reviewer:

Dr. Ravichandran a/l Jeganathan  
Professor Dr. Sharifah Ezat Wan Puteh

##### Disclaimer:

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It is subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

For further information please contact:

Health Technology Assessment  
Section (MaHTAS)  
Medical Development Division  
Ministry of Health Malaysia  
Level 4, Block E1, Precinct 1  
Government Office Complex  
62590 Putrajaya.

Tel: 603 8883 1246

Fax: 603 8883 1230

Available at the following website:  
<http://www.moh.gov.my>

#### Background

According to World Health Organization (WHO), maternal mortality is unacceptably high with more than half of these deaths occurred in sub-Saharan Africa and almost one third occurred in South Asia. Venous thromboembolism is a leading cause of severe maternal morbidity and mortality, particularly in the developed world as well as in Malaysia. A systematic review of maternal deaths performed by WHO in 2014 implicated embolism in 13.8% of maternal deaths in developed countries. In Malaysia, pulmonary thromboembolism remains as one of the leading cause of direct maternal death with an incident ranging from 1.5 to 5.1 per 100,000 live births from the year of 2001 till 2016. Pulmonary embolism and deep-vein thrombosis are the two main components of venous thromboembolism. Additional risk factors for venous thromboembolism other than pregnancy alone include obesity, maternal age more than 35 years old, smoking, pre-eclampsia, postpartum haemorrhage and prolonged labour.

Effective primary prevention or thromboprophylaxis is therefore deemed vital in reducing maternal morbidity and mortality resulted from venous thromboembolism. Originally, unfractionated heparin (UH) was the standard anticoagulant used in pregnancy until recently appears to have been greatly superseded by low molecular weight heparins (LMWH). LMWH is a new class of anticoagulants derived from unfractionated heparin. Currently, LMWH is widely used in the United Kingdom, Europe and Australasia for the prevention and management of thromboembolism in pregnancy. Several guidelines have been published from major societies covering on criteria for identifying patients that should receive prophylaxis with UH or LMWH.

LMWH is thought to have the advantages of reduced risk of bleeding, more stable and predictable pharmacokinetics without the need for monitoring compared to the unfractionated heparin. The use of LMWH has become more extensive, both for thromboprophylaxis and treatment of venous thromboembolism, and more recently for the prevention of adverse pregnancy outcome.

This technology review was requested by Public Health Physician & Senior Principle Assistant Director, Family Health Development Division, Ministry of Health Malaysia to review the evidence on the use of LMWH as prophylaxis for venous thromboembolism in pregnancy and postpartum before its adoption into the national maternal health programme in Malaysia.

#### Objective/Aim

To assess the effectiveness, safety and cost-effectiveness of LMWH as a prophylaxis for venous thromboembolism in pregnancy and postpartum

#### Results and Conclusions

A total of 194 titles were identified through the OVID interface and PubMed. There were one systematic review and meta-analysis, one non-RCT, one cost-utility analysis and one cost-analysis included in this review.

#### Effectiveness

There was limited fair level of retrievable evidence to suggest that the use of LMWH as a prophylaxis for venous thromboembolism was comparable to UH/placebo in reducing the rates of symptomatic venous thromboembolism among women who are at increased risk antenatally [RR 0.47; 95% CI: 0.09, 2.49 (four trials, 404 women)] and postpartum [RR 0.33; 95% CI: 0.01, 7.99 (three trials, 217 women)]. Limited fair level of retrievable evidence to suggest that bemparin (OR = 0.106; 95% CI: 0.013, 0.838) was associated with decreased incidence of postpartum venous thromboembolism in women at increased risk compared to placebo.

#### Safety

There was limited fair level of retrievable evidence to suggest that the use of LMWH as a prophylaxis for venous thromboembolism in pregnancy and postpartum was safe and associated with less adverse effects included bruising, allergic reactions, fetal losses, bleeding episodes, haematomas and bleeding during delivery compared to UH when given antenatally. No significant difference were detected between LMWH and UH/placebo groups in bleeding episodes (major bleeding; major bruising; bleeding/bruising reported at discharge) when given postpartum.

#### Cost/ cost-effectiveness

Based on one cost-utility analysis, for high risk women with prior idiopathic venous thromboembolism or known thrombophilic condition, LMWH was more cost-effective than expectant management (no prophylactic anticoagulation and no care beyond that provided during routine prenatal visits). However, based from the cost-analysis, the use of LMWH according to the RCOG guidelines 2009 was associated with annual cost of approximately £4,484 for every delivery and £2.6 million for each life saved that may indicate overmedicalization of pregnancy.

#### Organizational

##### Guidelines

RCOG, ACOG and Ministry of Health, Malaysia have issued guidelines on thromboprophylaxis in pregnancy and postpartum recommending the use of LMWH in pregnant women who are at increased risk of venous thromboembolism with varying criterias.

##### Social implication

The Fatwa Committee National Council of Islamic Religious Affairs Malaysia in 2009 has decided that the use of LMWH is forbidden due to its porcine nature origin except in a situation where there is no other lawful source. As for pregnancy, LMWH is the treatment of choice as arixtra (fondaparinux) is not recommended in pregnancy as it may cross the placenta.

2017

#### Economic implication

Based on the analysis, the use of LMWH as a prophylaxis for venous thromboembolism in pregnancy and postpartum is estimated to have an economic implication of approximately between RM 119 million to RM 139 million per year. Thromboprophylaxis with LMWH is estimated to result in approximately total cost of RM 5 million to RM 6 million per confirmed death averted.

#### Methods

Literature search was done to search for published articles to assess the effectiveness, safety and cost-effectiveness of LMWH as a prophylaxis for venous thromboembolism in pregnancy and postpartum. The following electronic databases were searched via OVID Interface: MEDLINE (1946 to present), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2017), EBM Reviews-Cochrane Central Register of Controlled Trials (February 2017), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2016), EBM Reviews-Health Technology Assessment (4th Quarter 2016) NHS economic evaluation database (1st Quarter 2016), Pubmed and INAHTA database. The last search was run on 20th March 2017.