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

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
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DISCLOSURE

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EXECUTIVE SUMMARY

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heparin (UH) was the standard anticoagulant used in pregnancy until recently appears to have been greatly superseded by low molecular weight heparins (LMWH).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 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 bemiparin (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.

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 issues
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.

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.

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

1. INTRODUCTION

An estimated 303,000 maternal deaths occurred worldwide in 2015, most of which were in developing countries and most could have been prevented.[1] 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.[1] The global maternal mortality ratio (the number of maternal deaths per 100 000 live births) declined by only 2.3% per year between 1990 and 2015.[1] However, increased rates of accelerated decline in maternal mortality were observed from 2000 onwards.[1]

Venous thromboembolism is a leading cause of severe maternal morbidity and mortality, particularly in the developed world as well as in Malaysia.[2,3] A systematic review of maternal deaths performed by WHO in 2014 implicated embolism in 13.8% of maternal deaths in developed countries.[3] 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.[4] In the Confidential Enquiries into Maternal Death in Malaysia (CEMD) report for 2006 to 2008, pulmonary thromboembolism is the third commonest cause of direct maternal deaths after postpartum haemorrhage and hypertensive disorders of pregnancy.[5] Accurate data on the incidence of venous thromboembolism in Malaysia is lacking however, it has been estimated that the rate of thromboembolic event averages about 1.3 per 1000 pregnancies.[5]

Venous thromboembolism is observed to be more common in postpartum compared to antepartum.[6] Pulmonary embolism and deep-vein thrombosis are the two main components of venous thromboembolism.[7] 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.[7] Two major risk factors identified among maternal deaths due to pulmonary embolism in Malaysia from 2010 to 2015 were caesarean section and obesity with BMI > 30, followed by parity > 3, age > 35, immobilisation and hospitalisation.[4]

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 it appears to have been greatly superseded by low molecular weight heparin (LMWH). LMWH is a new class of anticoagulants derived from unfractionated heparin.[8] 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.[9]

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.[8] 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.

2. OBJECTIVE / AIM

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

3. TECHNICAL FEATURES

3.1 What is LMWH?

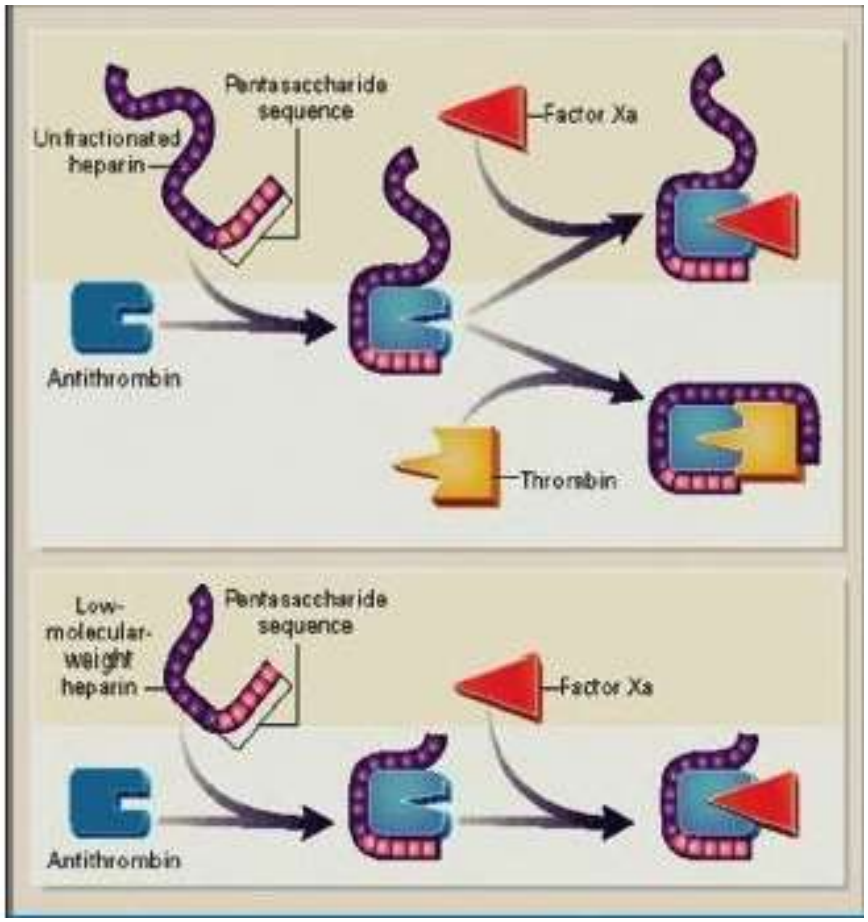
Low molecular weight heparin is a class of anticoagulants derived from unfractionated heparin. It is produced by enzymatic or chemical cleavage of the heparin molecule. It is about one third of the size of heparin, with a mean molecular weight of 4000 to 6000 daltons, compared with 12000 to 14000 daltons for unfractionated heparin. The concentration of LMWH is referenced to an international standard and usually expressed as anti-Xa U / mL. The main route for administering LMWH is via subcutaneous injection.[8] Low molecular weight heparin that is available in Malaysia include enoxaparin sodium 20 mg injection, enoxaparin sodium 40 mg injection, enoxaparin sodium 60 mg injection, tinzaparin sodium 10,000 Anti-Factor Xa IU/ml injection and tinzaparin sodium 20,000 Anti-Factor Xa IU/ml injection.[10]

Low molecular weight heparin is indicated in prophylaxis and treatment of pulmonary embolism or deep vein thrombosis as well as in unstable angina or non Q wave myocardial infarction with dosage varies accordingly. For thromboprophylaxis in pregnancy, all women should be assessed at antenatal booking as well as postpartum and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate. Low molecular weight heparin used antenatally and postpartum for thromboprophylaxis in Malaysia included enoxaparin 1 mg/kg daily or tinzaparin 4500 units daily.[2] Women who are considered high risk and intermediate risk will require thromboprophylaxis antenatally and up to six weeks postpartum.[2] It is contraindicated to use LMWH in active major bleeding, hypersensitivity to the drugs, thrombocytopenia due to the drugs and acute gastrointestinal ulcer. Known adverse reactions for LMWH are haemorrhagic symptoms, thrombocytopenia, haematomas and skin necrosis at injection site, skin allergies or systemic allergic reactions.[10]

3.2 Mechanism of action

Heparin acts as an anticoagulant by binding and catalyzing antithrombin III, a plasma serine protease inhibitor. The heparin-antithrombin III complex inhibits several procoagulant serine proteases, including factors IIa (thrombin), IXa, Xa, XIa, and XIIa. Low molecular weight heparin demonstrates greater anti-factor Xa activity compared to anti-factor IIa (thrombin) activity. In consequence, the ratio of anti-factor Xa (antithrombotic) to anti-factor IIa activity (anticoagulant) is higher.[8]

The bioavailability and anticoagulant effect of UH is reduced due to binding of UH by plasma and platelet proteins, endothelial cells, and vascular wall matrix proteins. Many of these plasma proteins increase with illness as acute phase reactants which accounts in part for the large interpatient variability in the anticoagulant response to unfractionated heparin. In contrast, LMWH has much lower affinity for plasma and matrix proteins that result in greater than 90% bioavailability after subcutaneous administration and a very predictable and reproducible anticoagulant response when dosed on a weight-adjusted basis. Consequently, neither laboratory monitoring of the anticoagulant response to LMWH nor dose adjustment is necessary.[9]



4. METHODS

4.1 Searching

Electronic databases searched through the Ovid interface:

- MEDLINE (R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews- Cochrane Central Register of Controlled Trials- February 2017
- EBM Reviews- Database of Abstracts of Review of Effects- 1st Quarter 2016
- EBM Reviews- Cochrane Database of Systematic Reviews- 2005 to March 2017
- EBM Reviews- Health Technology Assesment- 4th Quarter 2016
- EBM Reviews- NHS Economic Evaluation Database- 1st Quarter 2016

Other databases:

- Embase
- Pubmed
- Other websites: INAHTA, FDA

Additional articles were identified from reviewing the references of retrieved articles. General search engine was used to get additional web based information. The search was limited to articles on human. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on 20th March 2017.

4.2 Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Pregnant women, postpartum women
Interventions	LMWH
Comparators	Placebo, UH, no comparator
Outcomes	Mortality and morbidity, symptomatic thromboembolic events, symptomatic pulmonary embolism and symptomatic deep venous thrombosis, asymptomatic thromboembolic events Complications, adverse events Cost, cost-effectiveness, cost utility, cost-analysis and economic evaluation

	Organizational – hospital stay, guidelines
Study design	Health Technology Assessment (HTA) reports, Systematic review (SR) and Meta-analyses, SR, Randomised Controlled Trials (RCT), Non-randomised controlled trials,

Exclusion criteria

i) Animal study / laboratory study, other study design
ii) Narrative review
iii) Non English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2)

5. RESULTS AND DISCUSSION

A total of 194 records were identified through the Ovid interface and PubMed, and 12 were identified from other sources included from references of retrieved articles. After removal of 58 irrelevant or duplicates, 148 records were screened and 113 were excluded. Of these, 35 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 35 full text articles, six full text articles were included and 29 full text articles were excluded. The articles were excluded due to the study was already included in systematic review and meta-analysis (n=16), irrelevant study design (n=12) and irrelevant population (n=3). Flow chart of included studies is shown in Figure 1.

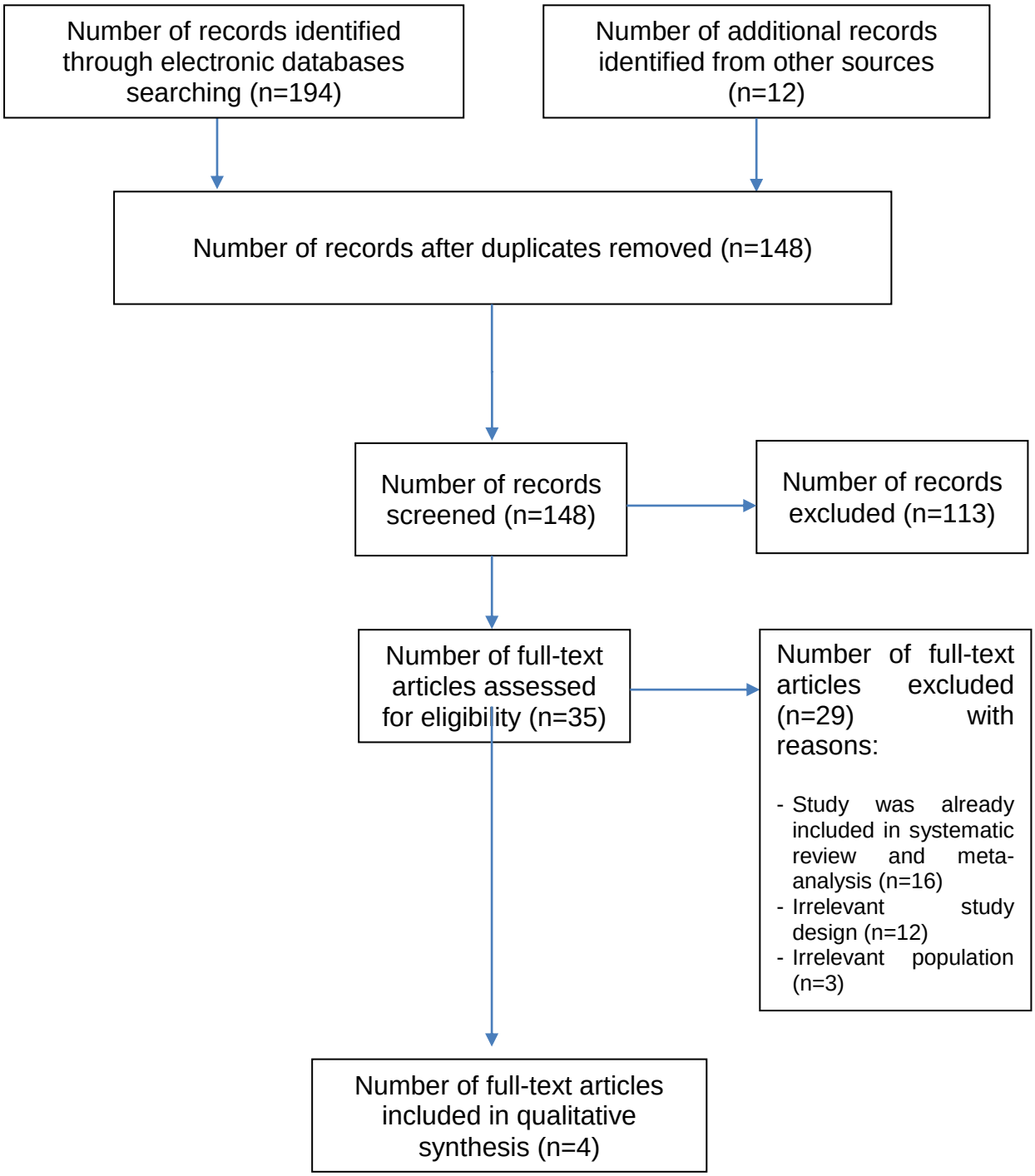


Figure 1. Flow chard of included studies

The four full text articles finally selected for this review comprised of one systematic review and meta-analysis, one non-RCT, one cost-utility analysis and one cost-analysis.

Assessment of risk of bias in included studies

Two authors assessed each study independently. Disagreements were resolved by concensus. Risk of bias was assessed using Critical Appraisal Skills Programme (CASP) checklist for SR, using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008) for RCT, using Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomised experimental studies), and using NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with no control group. Review authors judgements of risk of bias involved answering specific questions and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The assessment of risk of bias revealed that the only SR is considered to have low risk of bias, similar with the cost-utility analysis. However, there was no mention of participants in the non-RCT receiving similar treatment or care, other than the exposure or intervention of interest.

The results of risk of bias of included studies are summarised as follows.

Assessment of risk of bias of systematic review (CASP)

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Bain E et al.[9]	+	+	+	+

Assessment of risk of bias of quasi experimental studies (non-RCT) (JBI)

Criteria assessed	Alalaf S K et al.[10]
Clear what is the cause and what is the effect?	+
Participants included in any comparisons similar?	+
Participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	?

Was there a control group?	+
Multiple measurements of outcome pre and post the intervention/ exposure?	+
Follow-up complete, and if not was follow-up adequately reported and strategies to deal with the loss to follow-up employed?	+
Outcomes of participants included in any comparisons measured in the same way?	+
Outcome measure in reliable way?	+
Appropriate statistical analysis used?	+

Assessment of risk of bias of economic evaluation (CASP)

Criteria assessed	Johnston J A et al.[13]
A well-define question posed?	+
Comprehensive description of competing alternative given?	+
Effectiveness established?	+
Effects of intervention identified, measured and valued appropriately?	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	+
Results of the evaluation?	+
Incremental analysis of the consequences and costs of alternatives performed?	+
Sensitivity analysis performed?	+

5.1 EFFICACY / EFFECTIVENESS

5.1.1 Antenatal prophylaxis

Low molecular weight heparin versus UH

Bain E et al. (2014) conducted a systematic review and meta-analysis to assess the effects of thromboprophylaxis on the incidence of venous thromboembolism and adverse effects of the treatment in women who were pregnant or have recently given birth in the previous six weeks and at increased risk of venous thromboembolism. This includes women who had a caesarean section, had previously had venous thromboembolism, had an acquired or inherited thrombophilia, and other risk factors for venous thromboembolism. Sixteen RCTs involving 2592 women, assessing a range of methods of thromboprophylaxis were included in the review. Six trials compared methods of antenatal prophylaxis: four trials compared LMWH with UH, one compared LMWH with placebo and one compared LMWH with no treatment in the antenatal period. Nine trials assessed prophylaxis after caesarean section: two trials compared LMWH with placebo; one trial compared UH with placebo; one trial compared UH with physiotherapy compared with physiotherapy alone; three trials compared LMWH with UH; one trial compared UH with hydroxyethyl starch (HES); and one trial compared a 10-day bemiparin (LMWH) regimen with a five-day regimen. The primary outcomes of interest were maternal death, symptomatic thromboembolic events, symptomatic pulmonary embolism and symptomatic deep venous thrombosis. The secondary outcomes of interest included asymptomatic thromboembolic events, blood transfusion, bleeding episodes, serious wound complications, adverse effects sufficient to stop treatment, adverse effects not sufficient to stop treatment, symptomatic osteoporosis, fetal loss, thrombocytopenia and fetal anomalies. Risk of bias for each study was independently assessed by two review authors using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The trials included were judged to be of a moderate risk of bias. The review found that for antenatal prophylaxis, there were no trials which reported on maternal mortality. There were no significant differences detected for the symptomatic thromboembolic events, symptomatic pulmonary embolism and symptomatic deep venous thrombosis when LMWH was compared with UH. The risk ratios (RR) for symptomatic thromboembolic events were antenatal LMWH versus UH, RR 0.47; 95% CI: 0.09, 2.49 (four trials, 404 women).[11 Level I]

Low molecular weight heparin versus no treatment/placebo

Bain E et al. (2014) found that there were no significant differences detected for the symptomatic thromboembolic events, symptomatic pulmonary embolism and symptomatic deep venous thrombosis when LMWH or UH was compared with no treatment/placebo. Risk ratios for symptomatic thromboembolic events antenatal LMWH/UH versus no heparin were 0.33; 95% CI: 0.04, 2.99 (two trials, 56 women).[11 Level I]

5.1.2 Postpartum prophylaxis

Low molecular weight heparin versus UH

For post-caesarean/postnatal prophylaxis, a systematic review and meta-analysis conducted by Bain E et al. (2014) found only one trial comparing five-day LMWH

versus 10-day LMWH after caesarean section which reported on maternal mortality, observing no deaths. There were no statistically significant differences detected across any of the comparisons for the other primary outcomes (symptomatic thromboembolic events, symptomatic PE and symptomatic DVT). The RRs for symptomatic thromboembolic events were: post-caesarean LMWH versus UH, RR 0.33; 95% CI: 0.01, 7.99 (three trials, 217 women); post-caesarean five-day LMWH versus 10-day LMWH, RR 0.36; 95% CI: 0.01, 8.78 (one trial, 646 women); postnatal UH versus no heparin, RR 0.16; 95% CI: 0.02, 1.36 (one trial, 210 women).[11 Level I]

Low molecular weight heparin versus no treatment/placebo

Bain E et al. (2014) found that there were no statistically significant differences detected across any of the comparisons for the other primary outcomes (symptomatic thromboembolic events, symptomatic PE and symptomatic DVT) between post-caesarean LMWH/UH versus no heparin with RR 1.30; 95%CI: 0.39, 4.27 (four trials, 840 women). The authors concluded that there was insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period, with the small number of differences detected in this review being largely derived from trials that were not of high methodological quality. Large scale and high-quality randomised trials of currently used interventions are warranted.[11 Level I]

Alalaf S K et al. (2015) conducted a non-randomised controlled trial in Iraq between May 2012 to November 2013 to determine the ability of bemiparin and enoxaparin, relative to no intervention, to reduce the incidence of post-partum venous thromboembolism in women at risk of venous thromboembolism. Risk factors for venous thromboembolism after vaginal and abdominal deliveries were determined based on the Royal College of Obstetricians and Gynaecologists (RCOG) 2009 Green-top Guideline. Women who delivered vaginally were included in the study if they had two or more persistent risk factors for venous thromboembolism. Women who delivered by elective caesarean section were included if they had one or more additional risk factors, whereas all women who delivered by emergency caesarean section were included in the study. Postpartum haemorrhage and severe preeclampsia were two risk factors for venous thromboembolism and LMWH was indicated for patients with postpartum haemorrhage and severe preeclampsia after stabilization of the condition. Seven thousands and twenty women aged ≥15 years with risk factors for venous thromboembolism who delivered vaginally or by emergency or elective caesarean section were recruited and assigned at a ratio of 1:1:1 using sequential group allocation method to the three study groups; no-intervention group (control), bemiparin group, and enoxaparin group (n = 2340 per group). Women who were recruited to the enoxaparin group received injections of pre-filled syringes of enoxaparin sodium 40 mg (Clexane Sanofi-Aventis; equivalent to 4000 IU anti-Xa activity) in 0.4 mL water while women who were recruited to the bemiparin group received injections of 3500 IU bemiparin (Hibor, Laboratories Fco ROVI, SA, Madrid, Spain) in 0.2 mL water. The first dose of bemiparin (3500 IU/) or enoxaparin (4000 IU) was injected subcutaneously six hours after vaginal delivery or caesarean section under general anaesthesia. In women who were administered spinal anaesthesia, the first dose was administered eight hours after delivery. The second dose (3500 IU bemiparin or 4000 IU enoxaparin) was delivered 24 hours

later, and then daily up to a total of seven doses. Women with severe preeclampsia or postpartum haemorrhage received the first dose of LMWH eight to 24 hours after delivery. All women were encouraged to mobilize during labour and the early postpartum period. Women were examined on the seventh day postpartum and six weeks after delivery, and were regarded as free of venous thromboembolism if there was no sign of symptomatic venous thromboembolism 40 days postpartum. The primary outcome measures of interest were the incidence of symptomatic venous thromboembolism in the three groups. Secondary outcome measures included the incidence of side effects and wound complications in the two intervention groups. The study found that symptomatic venous thromboembolism, was observed in one (0.043%) woman in the bemiparin group, two (0.085%) in the enoxaparin group, and nine (0.384%) in the control group (P = 0.017) for the three modes of delivery. Regression analysis showed that women on bemiparin (OR = 0.106; 95% CI: 0.013, 0.838) and enoxaparin (OR = 0.226; 95% CI: 0.049, 1.049) were at lower risk of developing venous thromboembolism than control women. The incidence of symptomatic venous thromboembolism was significantly lower in the two combined intervention groups (0.64 per 1000 deliveries) than in the control group (3.8 per 1000 deliveries) (RR 0.166; 95% CI: 0.045, 0.614; P = 0.004). The incidence of symptomatic venous thromboembolism was 0.5% in women with a body mass index (BMI) < 25 kg/m2, 0% in women with a BMI of 25–30 kg/m2, and 0.2% in women with a BMI >30 kg/m2 (P = 0.003). No other factor was significantly associated with the incidence of venous thromboembolism. All cases of venous thromboembolism occurred within the first week after delivery. The authors concluded that postpartum bemiparin and enoxaparin are both effective as prophylaxis for venous thromboembolism.[12] Level II-1

5.2 SAFETY

With regards to safety, enoxaparin and dalteparin have been approved by United States Food and Drug Administration (USFDA) as thromboprophylaxis.[13,14]

5.2.1 Antenatal prophylaxis

Low molecular weight heparin versus UH

Bain E et al. (2014) reported in their systematic review that for antenatal prophylaxis, LMWH was associated with fewer adverse effects sufficient to stop treatment which included excess bruising/allergic rashes (RR 0.07; 95% CI: 0.01, 0.54; two trials, 226 women), and fewer fetal losses (RR 0.47; 95% CI: 0.23, 0.95; three trials, 343 women) when compared with UH. In two trials, antenatal LMWH compared with UH was associated with fewer bleeding episodes (defined in one trial of 121 women as bruises > 1 inch (RR 0.18, 95% CI: 0.09, 0.36); and in one trial of 105 women as injection site haematomas of ≥2 cm, bleeding during delivery or other bleeding (RR 0.28, 95% CI: 0.15, 0.53), however in a further trial of 117 women no difference between groups was shown for bleeding at delivery. The review reported that these results for the secondary outcomes should be interpreted with caution as they were derived from small trials that were not of high methodological quality.[11] Level I

5.2.2 Postpartum prophylaxis

Low molecular weight heparin versus no treatment/placebo

For prophylaxis after caesarean section, in two trials, that compared LMWH with placebo, no difference between groups in bleeding episodes (major bleeding; major bruising; bleeding/bruising reported at discharge) were detected. No other differences in secondary outcomes were shown when LMWH was compared with UH post-caesarean, nor when post-caesarean five-day LMWH was compared with 10-day LMWH or when UH was compared to no heparin.[11] Level I

Alalaf S K et al. (2015) reported in their non-randomised controlled trial that the proportion of women experiencing mild side effects which included pain and ecchymosis was significantly lower in the bemiparin group than in the enoxaparin group. Wound dehiscence, hematoma, and separation were observed in six women in the enoxaparin group, but in no women in the bemiparin group (P = 0.031).[12] Level II-1

5.3 COST-EFFECTIVENESS

Johnston J A et al. (2005) conducted a cost-utility study using a Markov state transition decision analytic model to compare prophylactic LMWH to expectant management (no prophylactic anticoagulation and no care beyond that provided during routine prenatal visits) for pregnant women with a single prior venous thromboembolism. A societal perspective and a lifetime time horizon were assumed. Model parameters were based on literature review. Three base case scenarios were considered which corresponded to different assumptions regarding the underlying patient samples; "unselected" women without stratification into different clinical risk groups, "low-risk" women with a prior venous thromboembolism associated with a transient risk factor and no known thrombophilic condition, and "high-risk" women with prior idiopathic venous thromboembolism or known thrombophilic condition. Outcomes were expressed as U.S. dollars per quality-adjusted life-year (QALY). The study showed that for "low-risk" women with a prior venous thromboembolism associated with a transient risk factor and no known thrombophilic condition (recurrence risk 0.5%), expectant management was both more effective (24.16 QALYs versus 24.14 QALYs) and less costly than prophylaxis ($2879 versus $6875). For "high-risk" women with prior idiopathic venous thromboembolism or known thrombophilic condition (recurrence risk 5.9%), prophylaxis was associated with a reasonable cost-effectiveness ratio ($38,700 per QALY) given a risk of bleeding complications <1.0% (base case 0.5%). The authors concluded that for low-risk women with prior venous thromboembolism, expectant management during pregnancy leads to better outcomes than administration of prophylactic low molecular weight heparin. For high-risk women, antepartum thromboprophylaxis is a cost-effective use of resources.[15]

A cost-analysis was conducted by Bond C et al. (2011) to assess the likely cost of consumables to the maternity service and the impact of recent guidance documents on provision of thromboprophylaxis have been published by the RCOG (2009) and National Institute for Health and Clinical Excellence (NICE) (2010). One hundred consecutive live and stillbirths were identified using the maternity database and 97 case records were obtained. Risk factors were identified and individual scores were

calculated. From these scores, the proportion of women who would have extended measures [LMWH and antiembolic stockings (AES)], antenatally and postnatally were calculated. Annual cost of these preventive measures per 1000 maternities was calculated. The cost calculations were based on hospital drug costs for enoxaparin, and women being supplied with two thigh-length pairs of AES, at October 2010 prices. The results showed that antenatally, 2.1% had a RCOG risk score of three or more and would have been advised to have LMWH throughout pregnancy and the puerperium. Postnatally, 40.1% had an RCOG score of two or more and would have required enoxaparin for one to six weeks. The annual cost of stockings, LMWH and sharps bins were approximately £44,847 for every one thousand deliveries (£4484 for a delivery) and £2.6 million for each life saved. About 10% of normal-weight postnatal women who achieved a vaginal birth had a risk score prompting thromboprophylaxis for at least seven days. The authors concluded that these data suggest that the current guidance might represent overmedicalization of pregnancy and that the criteria for thromboprophylaxis should be refined further.[16]

The cost of enoxaparin sodium 20 mg injection, 40 mg injection and 60 mg injection is approximately RM 13.50, RM 19.20 and RM 23.20 per vial, respectively.[17] The cost of heparin 1000 units/ml injection and 5000 units/ml injection is approximately RM 1.23 and RM 1.53 per vial, respectively.[17]

5.4 ORGANIZATIONAL ISSUES

5.4.1 Guidelines / Recommendations

Royal College of Obstetricians and Gynaecologists (RCOG)

In updated guidelines by RCOG on Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium, Green Top Guideline No. 37a, April 2015, the recommendations stated that:

- LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis
- Any woman with four or more current risk factors shown in Table 1 (other than previous venous thromboembolism or thrombophilia) should be considered for prophylactic LMWH throughout the antenatal period and will usually require prophylactic LMWH for six weeks postnatally
- Any woman with three current risk factors shown in Table 1 (other than previous venous thromboembolism or thrombophilia) should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks postnatally
- Any woman with two current risk factors shown in Table 1 (other than previous venous thromboembolism or thrombophilia) should be considered for prophylactic LMWH for at least 10 days postpartum
- Women with previous venous thromboembolism (except those with a single previous venous thromboembolism related to major surgery and no other risk factors) should be offered thromboprophylaxis with LMWH throughout the antenatal period

- All women with class 3 obesity (BMI greater than or equal to 40 kg/m2) should be considered for prophylactic LMWH in doses appropriate for their weight for 10 days after delivery
- Women with two or more persisting risk factors listed in Table 1 should be considered for LMWH in prophylactic doses appropriate for their weight for 10 days after delivery
- All women with a previous history of confirmed venous thromboembolism should be offered thromboprophylaxis with LMWH or warfarin for at least 6 weeks postpartum regardless of the mode of delivery
- All women who have had caesarean sections should be considered for thromboprophylaxis with LMWH for 10 days after delivery apart from those having an elective caesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional risk factors
- Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women[18]

Table 1. Risk factors for venous thromboembolism in pregnancy and the puerperium

See also Appendix I and Appendix II		
Pre-existing	Previous VTE	
	Thrombophilia	*Heritable* Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene mutation
		Acquired Antiphospholipid antibodies Persistent lupus anticoagulant and/or persistent moderate/high titre anticardiolipin antibodies and/or β_2-glycoprotein 1 antibodies
	Medical comorbidities e.g. cancer; heart failure; active SLE, inflammatory polyarthropathy or IBD; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease;[49] current intravenous drug user	
	Age > 35 years	
	Obesity (BMI ≥ 30 kg/m²) either prepregnancy or in early pregnancy	
	Parity ≥ 3 (a woman becomes para 3 after her third delivery)	
	Smoking	
	Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)	
	Paraplegia	
Obstetric risk factors	Multiple pregnancy Current pre-eclampsia	
	Caesarean section Prolonged labour (> 24 hours) Mid-cavity or rotational operative delivery Stillbirth Preterm birth Postpartum haemorrhage (> 1 litre/requiring transfusion)	
New onset/transient *These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve and therefore what is important is an ongoing individual risk assessment*	Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation Bone fracture	
	Hyperemesis, dehydration	
	Ovarian hyperstimulation syndrome (first trimester only)	Assisted reproductive technology (ART), in vitro fertilisation (IVF)
	Admission or immobility (≥ 3 days' bed rest)	e.g. pelvic girdle pain restricting mobility
	Current systemic infection (requiring intravenous antibiotics or admission to hospital)	e.g. pneumonia, pyelonephritis, postpartum wound infection
	Long-distance travel (> 4 hours)	

American College of Obstetricians and Gynecologists (ACOG)

In the ACOG Practice Bulletin published in September 2011 on "Thromboembolism in Pregnancy", the recommendations stated that:

Level B ACOG recommendations and conclusions (based on limited or inconsistent scientific evidence) include the following:

- Heparin compounds are the preferred anticoagulants in pregnancy
- To minimize postpartum bleeding complications, a reasonable strategy is to resume anticoagulation therapy no sooner than 4 to 6 hours after vaginal delivery, or 6 to 12 hours after cesarean delivery
- Warfarin, LMWH, and unfractionated heparin are compatible with breast-feeding because they do not accumulate in breast milk and do not lead to anticoagulation in the infant

Level C ACOG recommendations (based primarily on consensus and expert opinion) include the following:

- Women with a history of thrombosis who have not been thoroughly evaluated for possible underlying causes should receive testing for antiphospholipid antibodies, as well as for inherited thrombophilias
- For women with acute thromboembolism during the current pregnancy, or for those at high risk for venous thromboembolism, including women with mechanical heart valves, therapeutic anticoagulation is recommended
- For women in whom restarting anticoagulation is planned after delivery, pneumatic compression devices should be left in place until the woman is ambulatory and anticoagulation therapy is resumed
- In the last month of pregnancy, or sooner if delivery appears imminent, women receiving either therapeutic or prophylactic anticoagulation may be converted from LMWH to unfractionated heparin, which has a shorter half-life
- Neuraxial blockade should be withheld for 10 to 12 hours after the last prophylactic dose of LMWH, or 24 hours after the last therapeutic dose of LMWH
- For all women not already receiving thromboprophylaxis, placement of pneumatic compression devices before cesarean delivery is recommended. However, an emergency cesarean delivery should not be delayed for the placement of compression devices[19]

Clinical Practice Guidelines (CPG), Ministry of Health, Malaysia

In the CPG published in 2013 on "Prevention and Treatment of Venous Thromboembolism", it is recommended that:

- All women should be assessed at booking and after delivery and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate
- This assessment should be repeated if the woman is admitted to the hospital for any reason or develops other intercurrent problems during the antenatal and postpartum period
- All women should be assessed after delivery and stratified into risk groups according to risk factors and offered thromboprophylaxis with LMWH where appropriate[2]

5.5 SOCIAL IMPLICATIONS

Low molecular weight heparin is a porcine-based medicinal product while UH is a bovine-based medicinal product. The 87th Conference of the Fatwa Committee National Council of Islamic Religious Affairs Malaysia which was held in June 2009 had discussed the ruling on using clexane and fraxiparine medicines (LMWHs). The Committee has decided that Islam prohibits using medicine derived from unlawful sources as a cure, except in a situation where there is no other lawful source and the amount used according to the prescribed dosage only. The *haram* based medicine is only permitted to be used limitedly. The permissibility of using *haram* based medicine is annulled when the *halal* alternative is found. Thus, with regards

to clexane and fraxiparine that are urgently needed by patients who are in critical condition to prevent sudden clotting of the blood, the Committee has decided that the medicines are forbidden. It is due to the availability of alternative medicine namely arixtra (fondaparinux) that is produced from lawful sources which has the same function and efficiency as clexane and fraxiparine.[20] However for pregnancy, LMWH is the treatment of choice as arixtra (fondaparinux) is not recommended in pregnancy as it may cross the placenta.[2]

Health professionals must be aware that LMWH are of animal origin and this may be of concern to some patients. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement and after discussing their suitability, advantages and disadvantages with the patient.[2]

5.6 ECONOMIC IMPLICATIONS

Budget Impact Analysis

The use of LMWH as antenatal and postnatal prophylaxis has been suggested by The National Technical Committee Confidential Enquiries Into Maternal Death and Clinical Practice Guidelines entitled Prevention and Treatment of Venous Thromboembolism.[2,21] Hence, this analysis was undertaken as simplified budget impact analysis to determine the financial implication of implementing thromboprophylaxis for prevention of venous thromboembolism among antenatal and postnatal mothers using LMWH. Two types of LMWH were included in this analysis based on its availability in the Ministry of Health Medicines Formulary; Enoxaparin and Tinzaparin.

The risk assessment and categorisation should be done prior to start thromboprophylaxis either antenatally or post natal. Women whom were categorised as high risk antenatally will require thromboprophylaxis with LMWH antenally and six weeks postpartum. Those women with intermediate risk antenatally should be offered LMWH for six weeks postpartum. Meanwhile, any postpartum women categorised as high risk will require six weeks postnatal prophylactic LMWH while intermediate risk requires seven days postnatal prophylactic LMWH if < 3 risk factors.[21] (Refer appendix 4)

The dosage of prophylactic LMWH is recommended based on the women's body weight. The published mean body weight of Malaysian women is approximately 58 kg.[22] In order to match the dosage calculation based on the available data, body weight of 50-90kg was assumed as normal and overweight group while 91-130kg is categorised as obese. Other category of body weight was not included in this analysis .The duration and recommended dosages of thromboprophylaxis are illustrated in Table 1 and 2.

There were no retrievable local data with regards to the number of eligible patient in high and intermediate risk group for thromboprophylaxis in Malaysia. Therefore, the number of patient who may be eligible for this prophylaxis was estimated based on deliveries in relation to colour coded risk level at booking in year 2012. Firstly, red coded risk level at booking represent immediate referral to hospital under shared

care of O&G Specialist and Family Medicine Specialist. Secondly, yellow coded risk level at booking represent the need of referral hospital (O&G Specialist) or Family Medicine Specialist and a shared care by medical officer and health nurses. Finally green coded risk level at booking represent the management at health clinics by medical officers and health nurses.[23] In this analysis, antenatal LMWH thromboprophylaxis was assumed to be started at week 12 until week 40. As labour/emergency caesarean section is one of the intermediate risk factor, those women who undergone caesarean section in green colour coded group was also included in a separate analysis since there was lack of available information on the current practice of using LMWH in caesarean section patient in Malaysia. Other related statistics were estimated from the National Obstetrics Registry and National Health Morbidity Survey 2015.[24-26] (Refer appendix 5)

Table 1: Duration of thromboprophylaxis according to risk assessment

Risk assessment	Duration of thromboprophylaxis	Source
High risk	Antenally and 6 weeks postpartum	21,2
Intermediate risk (antenal assessment)	6 weeks postpartum	21,2
Intermediate risk (postpartum)– labour/emergency caesarean section	7 days postpartum	21,2

Table 2: Doses of prophylactic LMWH according to women's weight

Body weight (kg)	Type of thromboprophylaxis		Source
	Enoxaparin	Tinzaparin	
50-90kg	40mg daily	4500 units daily	21
91-130kg	60mg daily	7000 units daily	21

Table 3: Input parameters

Parameter	Value	Source
Total deliveries 2016	461,561	24
High risk (red coded)	2.51%* (11,585)	25
Intermediate risk (yellow coded)	15.15%* (69,926)	25
Caesarean section (green coded)	14.053%* (64,863)	25
Prevalence of obesity in females	33.6%	26
No. of maternal death due to pulmonary embolism 2015	24	27

***** percentage of patient from total deliveries who were eligible for thromboprophylaxis

The cost inputs for Enoxaparin and Tinzaparin were taken from the procurement price by the Ministry of Health Malaysia in the year 2015 and 2016 respectively. No other treatment costs such as thromboembolism deterrent (TED) and intermittent pneumatic compression were included as it is regarded as the standard management of venous thromboembolism with or without the LMWH. Human resource and monitoring costs were also not included as LMWH requires minimal monitoring compared with heparin and absence of the local data. Furthermore no comparison between LMWH and heparin was made in this analysis following the recommendation in the reference documents.[2,21] Summary of the input parameters and costs were shown as Table 3 and 4.

Table 4: Cost parameters

Type of thromboprophylaxis	Cost/Unit	Source
Enoxaparin 40mg pre-filled syringe	RM 19.45	28
Enoxaparin 60mg pre-filled syringe	RM 23.84	
Tinzaparin Sodium 10,000 anti factor XaIU/ml injection pre-filled syringe	RM 16.60	29
Tinzaparin Sodium 20,000 anti factor XaIU/ml injection pre-filled syringe	RM 34.15	

Results:

Based on the budget impact analysis, Enoxaparin had the lowest total cost of thromboprophylaxis with a total cost of approximately between RM119 million to RM128 million when thromboprophylaxis were given to 146,000 pregnant women a year. Meanwhile, the use of Tinzaparin as a thromboprophylaxis of venous thromboembolism will increase the total cost to RM128 million to RM139 million per year. Additionally, analyses of the combination between the coverage of Enoxaparin and Tinzaparin were also performed and resulted with an incremental cost of approximately between RM4 million to RM5 million. The results is summarized and illustrated as in Table 5 and Figure 1.

It has been reported that the Malaysian maternal deaths caused by pulmonary embolism in 2015 were the highest with the number of deaths of 24. Thus, by using this data, thromboprophylaxis are estimated to result in approximately total cost of RM5 million to RM6 million per death averted. However, these estimations have not factored in the cost implications of the near miss cases.

Table 5: Total cost (RM) of thromboprophylaxis per year (base case)

Treatment	Total cost high risk+intermediate risk	Incremental cost	Total cost high risk+ intermediate risk +CS	Incremental cost
Enoxaparin	RM 119,151,064		RM128,651,881	
Tinzaparin	RM 128,100,958	RM8,949,893.39*	RM139,174,644	RM10,522,762*
50%Enoxaparin +50%Tinzaparin	RM123,626,011	RM4,474,946.69*	RM133,913,262	RM5,261,381*

*compared with 100% use of Enoxaparin
*CS = Caesarian section

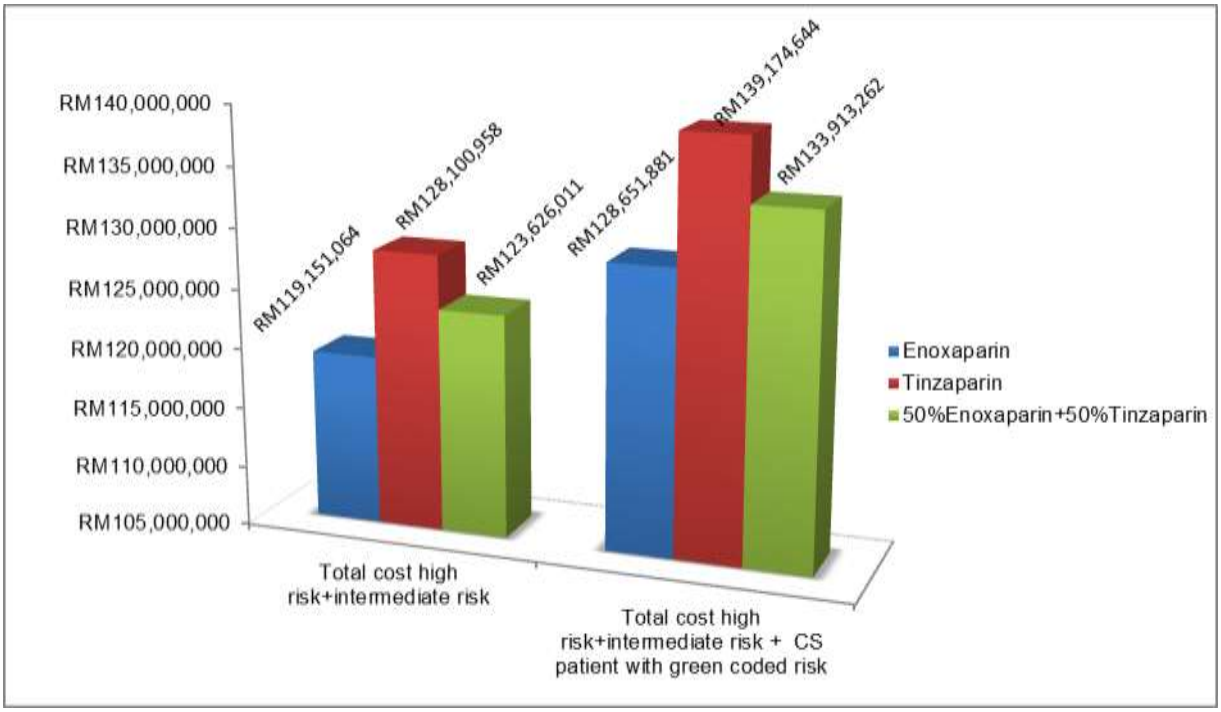


Figure 1: Comparison of total cost according to type of thromboprophylaxis

*CS = Caesarean section

UNCERTAINTY ANALYSIS

One way sensitivity analysis was performed to determine the robustness of the results by varying the input parameters as ± 20% from the base case values. The changes in percentage of obesity risk were shown to result in a minimal differences in total cost compared to base case. In contrast, other parameters significantly changed the total costs of all types of thromboprophylaxis. In the event of LMWH are being used as a thromboprophylaxis for antenatal and post natal patients, potential

cost savings of approximately between RM 20 million to RM 30million are estimated if the price of LMWH could be further reduced by 20%.

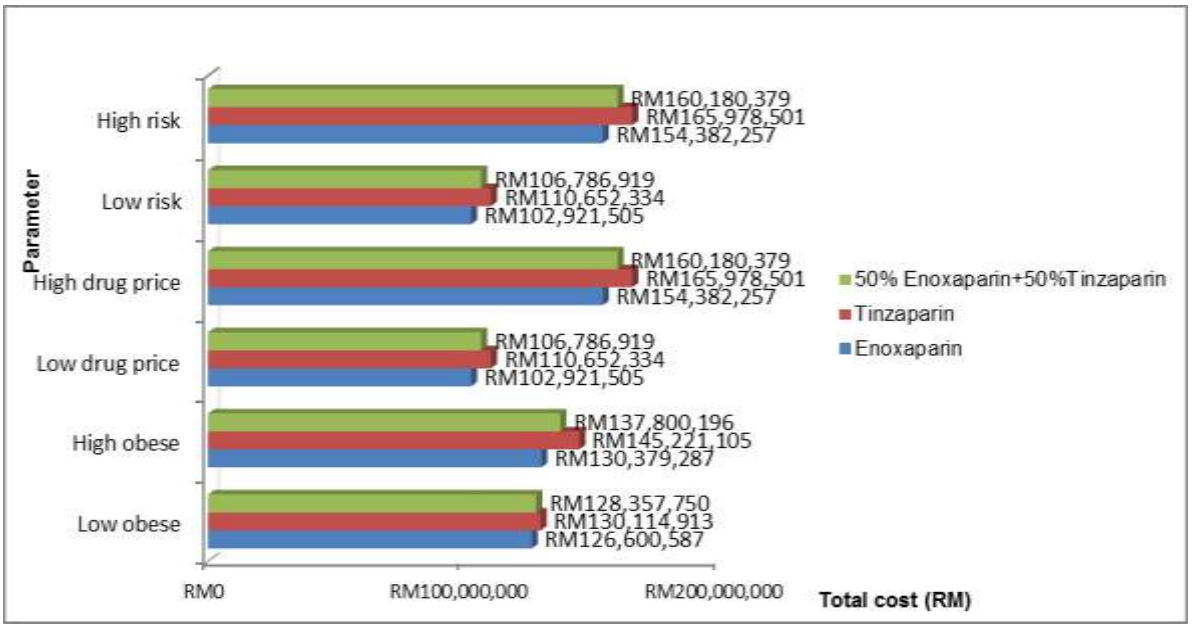


Figure 2: Sensitivity analysis results (financial implication with inclusion of caesarean section patient with green coded risk according to type of thromboprophylaxis)

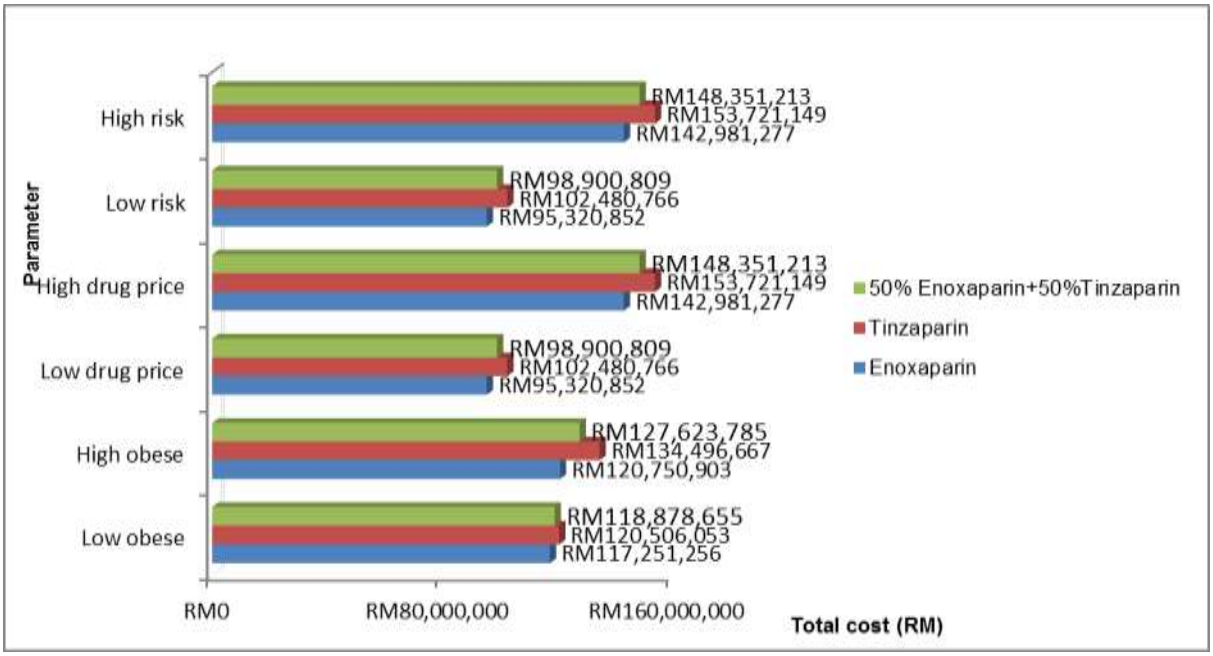


Figure 3: Sensitivity analysis results (financial implication without inclusion of caesarean section patient with green coded risk according to type of thromboprophylaxis)

Lack of data on the morbidity of venous thromboembolism has been the major limitation in this analysis. There is expected uncertainty in the number of patient who may be eligible for the prophylaxis due to the unavailability of local data. However, the approximated financial implication may be useful as guidance for the decision makers on the requirement of the budget increment. Moreover, the sensitivity

analysis that has been conducted by varying the input parameters may provide additional information on the financial implication in various scenarios.

5.7 LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this report.

6. CONCLUSION

6.1 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 in reducing the rates of symptomatic venous thromboembolism among women who are at increased risk antenatally and postpartum. Limited fair level of retrievable evidence to suggest that bemiparin was associated with decreased incidence of postpartum venous thromboembolism in women at increased risk compared to placebo.

6.2 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.

6.3 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.

6.4 Organizational issues

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.

6.5 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.

6.6 Economic implication

Based on the budget impact 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.

7. REFERENCES

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8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Pregnancy/
2 Gestation.tw.
3 pregnanc*.tw.
4 Pregnant Women/
5 (pregnant adj1 (woman or women)).tw.
6 Postpartum Period/
7 Postpartum.tw.
8 (postpartum adj1 period).tw.
9 (postpartum adj1 (women or woman)).tw.
10 puerperium.tw.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 Heparin, Low-Molecular-Weight/
13 (heparin adj1 low molecular weight).tw.
14 (heparin adj1 low-molecular-weight).tw.
15 lmwh.tw.
16. thromboprophylaxis.tw.
17 Anticoagulants/
18 (agents adj1 (anticoagulant or anticoagulation)).tw.
19 anticoagulant*.tw.
20 (anticoagulant adj1 drugs).tw.
21 (inhibitors adj1 indirect thrombin).tw.
22 thrombin inhibitors, indirect.tw.
23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 Thromboembolism/
25 Thromboembolism*.tw.
26 Venous Thromboembolism/
27 (venous adj1 thromboembolism).tw.
28 Venous Thrombosis/
29 ((deep vein or deep-vein or deep-venous) adj1 thrombos*).tw.

30 phlebothrombos*.tw.

31 (venous adj1 thrombos*).tw.

32 (deep adj1 (vein thrombos* or venous thrombos*)).tw.

33 Pulmonary Embolism/

34 (pulmonary adj1 embolism*).tw.

35 (pulmonary adj1 thromboembolism*).tw.

36 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

37 11 and 23

38 36 and 37

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Health Technology Assessment	
EBM Reviews- NHS economic evaluation database	
PubMed	
INAHTA	LMWH

8.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3. Appendix 3

Evidence Table : Efficacy / Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689 .	Systematic review and meta-analysis **Aim:** To assess the effects of thromboprophylaxis in women who are pregnant or have recently given birth and are at increased risk of VTE on the incidence of VTE and adverse effects of treatment **Method:** -The Cochrane Pregnancy and Childbirth Group's Trials Register were searched for randomised trials comparing one method of thromboprophylaxis with placebo or no treatment, and randomised trials comparing two (or more) methods of thromboprophylaxis -Population: Women who were pregnant or had given birth in the previous six weeks	I	19 RCTs were included in this review but only 16 trials with 2592 women who are pregnant or have recently given birth could be included in the analysis	Any intervention: Pharmacological interventions • Unfractionated heparin (UFH); • low molecular weight (LMWH); • aspirin; • warfarin; •hydroxyethyl starch (HES); • other Non-pharmacological interventions •Graduated compression stockings; •intermitted pneumatic compression •early mobilisation; •surveillance	Any intervention: Pharmacological interventions • Unfractionated heparin (UFH); • low molecular weight (LMWH); • aspirin; • warfarin; •hydroxyethyl starch (HES); • other Non-pharmacological interventions •Graduated compression stockings; •intermitted pneumatic compression •early mobilisation; •surveillance		**Results:** 16 trials, involving 2592 women, assessing a range ofmethods of thromboprophylaxis; Six trials compared methods of antenatal prophylaxis: -heparin versus no treatment/placebo (two trials), and low molecular weight heparin (LMWH) versus unfractionated heparin (UFH)(four trials). Nine trials assessed prophylaxis after caesarean section: -four compared heparin with placebo; -three compared LMWH with UFH; -one compared hydroxyethyl starch (HES) with UFH; -and one compared five-day versus 10-day LMWH -One study examined prophylaxis with UFH in the postnatal period (including following vaginal births). -the studies included were overall moderate risk of bias	Cochrane review Moderate risk of bias

Evidence Table : Efficacy / Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689 .	-Primary outcomes 1. Maternal death; 2. symptomatic thromboembolic events; 3. symptomatic PE; 4. symptomatic DVT. -19 RCTs were included in this review but only 16 trials with 2592 women could be included in the analysis -Trials were of a moderate quality, and assessed drugs including unfractionated heparin and low molecular weight heparin in pregnancy and after caesarean birth -Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*						**<u>For antenatal prophylaxis</u>**: -None of the included trials reported on maternal mortality. -No differences were detected for the other primary outcomes of symptomatic thromboembolic events, symptomatic pulmonary embolism (PE) and symptomatic deep venous thrombosis (DVT) when LMWH or UFH was compared with no treatment/placebo or when LMWH was compared with UFH. -RR for symptomatic thromboembolic events were: ▪ Antenatal LMWH/UFH versus no heparin, RR 0.33; 95%CI 0.04 to 2.99 (two trials, 56 women); ▪ Antenatal LMWH versus UFH, RR 0.47; 95% CI 0.09 to 2.49 (four trials, 404 women). -No differences were shown when antenatal LMWH or UFH was compared with no treatment/placebo for any secondary outcomes.	

Evidence Table : Efficacy/Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689					,		**For post-caesarean/postnatal prophylaxis:** -One trial comparing five-day versus 10-day LMWH after caesarean section reported on maternal mortality, observing no deaths. -No differences were seen across any of the comparisons for the other primary outcomes (symptomatic thromboembolic events, symptomatic PE and symptomatic DVT). -RRs for symptomatic thromboembolic events were: ▪ post-caesarean LMWH/UFH versus no heparin, RR 1.30; 95%CI 0.39 to 4.27 (four trials, 840 women); ▪ post-caesarean LMWH versus UFH, RR 0.33; 95% CI 0.01 to 7.99 (three trials, 217 women); ▪ post-caesarean five-day versus 10-day LMWH, RR 0.36; 95%CI 0.01 to 8.78 (one trial, 646 women); ▪ postnatal UFH versus no heparin, RR 0.16; 95% CI 0.02 to 1.36 (one trial, 210 women).	

Evidence Table : Efficacy / Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689							**Conclusion:** There is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period, with the small number of differences detected in this review being largely derived from trials thatwere not of high methodological quality. Large scale, high-quality randomised trials of currently used interventions are warranted	

Evidence Table : Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	Nonrandomised controlled trial **Aim:** To determine the ability of bemiparin and enoxaparin, relative to no intervention, to reduce the incidence of postpartum VTE in women at risk of VTE. This trial also aimed to compare the incidence of adverse events in the two interventional groups. **Method:** -women aged ≥15 years with risk factors for VTE who delivered vaginally or by emergency or elective CS at the Maternity Teaching Hospital, Kurdistan Region, Erbil City, Iraq, between May 1, 2012, and November 1, 2013 -VTE risk factors after vaginal and abdominal deliveries were determined based on the RCOG 2009Green-top Guideline.	III	7020 haemodynamically stable women delivered vaginally or abdominally, were included	Bemiparin Enoxaparin	Bemiparin Enoxaparin No control	40 days postpartum	**Results:** -VTE occurred in 1 (0.042%) woman in the bemiparin group, two (0.085%) women in the enoxaparin group, and nine (0.384%) women in the control group (P = 0.017). -Regression analysis showed that women on bemiparin (OR = 0.106; 95% CI = 0.013–0.838) and enoxaparin (OR = 0.226; 95% CI = 0.049–1.049) were at lower risk of developing VTE than control women. -The primary outcome, symptomatic VTE, was observed in one (0.043%) woman in the bemiparin group, two (0.085%) in the enoxaparin group, and nine (0.384%) in the control group (P = 0.017) -The incidence of symptomatic VTE was 0.5%in women with a body mass index (BMI) < 25 kg/m2,0% in women with a BMI of 25–30 kg/m2, and 0.2% in women with a BMI >30 kg/m2 (P = 0.003). -No other factor was significantly associated with the incidence of VTE. -All cases of VTE occurred within the first week after delivery	-Sequence allocation method -No blinding

Evidence Table : Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	-Women who delivered vaginally were included in the study if they had two or more persistent risk factors for VTE. -Women who delivered by elective CS were included if they had one or more additional risk factors, whereas all women who delivered by emergency CS were included in the study -Other inclusion criteria included the absence of active bleeding and haemodynamic stability (pulse <100 beats per min and systolic blood pressure >100 mmHg). -LMWH was indicated for patients with PPH or severe PE after stabilization of the condition.						-Women on bemiparin were at lower risk of developing symptomatic VTE than women in the control group (OR 0.106; 95% CI: =0.013–0.838. However, BMI was not significantly associated with the incidence of VTE - The incidence of symptomatic VTE was significantly lower in the two combined intervention groups (0.64 per 1000 deliveries) than in the control group (3.8 per 1000 deliveries) (relative risk = 0.166; 95% CI = 0.045–0.614; P = 0.004 by Fisher's exact test). <u>Safety:</u> -Proportion of women experiencing mild side effects (pain and ecchymosis) was significantly lower in the bemiparin group than in the enoxaparin group. -Wound dehiscence, hematoma, and separation were observed in six women in the enoxaparin group, but in no women in the bemiparin group (P = 0.031) - Eighteen women in the control group developed wound infection leading to separation of the edges at 5–10 days post caesarean section	

Evidence Table : Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	-These women had risk factors for VTE and were allocated to the following groups: treatment with 3500 IU/day of bemiparin, 4000 IU/day of enoxaparin, or no intervention (control). -The first dose was administered 6 hours after vaginal or abdominal delivery, or 8 hours after delivery in women receiving spinal anaesthesia. -Women already taking an anticoagulant or having any contraindication to LMWH, such as antenatal or postpartum active bleeding requiring blood transfusion, placenta previa, thrombocytopenia (platelet count <75 × 108/μl), severe renal disease (glomerular filtration rate <30 ml/minute), severe liver disease, or uncontrolled hypertension (>200/120 mmHg), were excluded.						**Conclusion:** Postpartum bemiparin and enoxaparin are both effective as prophylaxis for VTE. Wound complications develop after enoxaparin, but not after bemiparin use.	

Evidence Table : Effectiveness
Question : Is LMWH effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	-Subsequent doses were administered daily for up to 6 days. The incidence of VTE was assessed for up to 40 days postpartum. -Data were analyzed using the Statistical Package for Social Sciences version 19. -Proportions were compared using the chi square test of association or Fisher's exact test. Binary logistic regression analysis was used with VTE as the dependent variable							

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689 .	Systematic review and meta-analysis **Aim:** To assess the effects of thromboprophylaxis in women who are pregnant or have recently given birth and are at increased risk of VTE on the incidence of VTE and adverse effects of treatment **Method:** -The Cochrane Pregnancy and Childbirth Group's Trials Register were searched for randomised trials comparing one method of thromboprophylaxis with placebo or no treatment, and randomised trials comparing two (or more) methods of thromboprophylaxis -Population: Women who were pregnant or had given birth in the previous six weeks	I	19 RCTs were included in this review but only 16 trials with 2592 women who are pregnant or have recently given birth could be included in the analysis	Any intervention: Pharmacological interventions • Unfractionated heparin (UFH); • low molecular weight (LMWH); • aspirin; • warfarin; •hydroxyethyl starch (HES); • other Non-pharmacological interventions •Graduated compression stockings; •intermitted pneumatic compression •early mobilisation; •surveillance	Any intervention: Pharmacological interventions • Unfractionated heparin (UFH); • low molecular weight (LMWH); • aspirin; • warfarin; •hydroxyethyl starch (HES); • other Non-pharmacological interventions •Graduated compression stockings; •intermitted pneumatic compression •early mobilisation; •surveillance		**Results:** <u>Safety:</u> -Antenatal LMWH was associated with fewer adverse effects sufficient to stop treatment (RR 0.07; 95% CI 0.01 to 0.54;two trials, 226 women), and fewer fetal losses (RR 0.47; 95% CI 0.23 to 0.95; three trials, 343 women) when compared with UFH. -In two trials, antenatal LMWH compared with UFH was associated with fewer bleeding episodes (defined in one trial of 121 women as bruises > 1 inch (RR 0.18, 95% CI 0.09 to 0.36); and in one trial of 105 women as injection site haematomas of ≥2 cm, bleeding during delivery or other bleeding (RR 0.28; 95% CI 0.15 to 0.53)), however in a further trial of 117 women no difference between groups was shown for bleeding at delivery. -The results for these secondary outcomes should be interpreted with caution, being derived from small trials that were not of high methodological quality	Cochrane review Moderate risk of bias

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Bain E, Wilson A, Tooher R et al. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2014;(2):CD001689 .	-Primary outcomes 1. Maternal death; 2. symptomatic thromboembolic events; 3. symptomatic PE; 4. symptomatic DVT. -19 RCTs were included in this review but only 16 trials with 2592 women could be included in the analysis -Trials were of a moderate quality, and assessed drugs including unfractionated heparin and low molecular weight heparin in pregnancy and after caesarean birth -Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*						-For prophylaxis after caesarean section, in one trial (of 580 women), women receiving UFH and physiotherapy were more likely to have bleeding complications ('complications hémorragiques') than women receiving physiotherapy alone (RR 5.03; 95% CI 2.49 to 10.18). -In two additional trials, that compared LMWH with placebo, no difference between groups in bleeding episodes (major bleeding; major bruising; bleeding/bruising reported at discharge) were detected. -No other differences in secondary outcomes were shown when LMWH was compared with UFH post-caesarean, nor when post-caesarean HES was compared with UFH, post-caesarean five-day LMWH was compared with 10-day LMWH, or when UFH was compared to no heparin postnatally.	

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	Nonrandomised controlled trial **Aim:** To determine the ability of bemiparin and enoxaparin, relative to no intervention, to reduce the incidence of postpartum VTE in women at risk of VTE. This trial also aimed to compare the incidence of adverse events in the two interventional groups. **Method:** -Women aged ≥15 years with risk factors for VTE who delivered vaginally or by emergency or elective CS at the Maternity Teaching Hospital, Kurdistan Region, Erbil City, Iraq, between May 1, 2012, and November 1, 2013 -VTE risk factors after vaginal and abdominal deliveries were determined based on the RCOG 2009Green-top Guideline.	III	7020 haemodynamically stable women delivered vaginally or abdominally, were included	Bemiparin Enoxaparin	Bemiparin Enoxaparin No control	40 days postpartum	**Results:** <u>Safety:</u> -Proportion of women experiencing mild side effects (pain and ecchymosis) was significantly lower in the bemiparin group than in the enoxaparin group. -Wound dehiscence, hematoma, and separation were observed in six women in the enoxaparin group, but in no women in the bemiparin group (P = 0.031) - Eighteen women in the control group developed wound infection leading to separation of the edges at 5–10 days post caesarean section	

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	-Women who delivered vaginally were included in the study if they had two or more persistent risk factors for VTE. -Women who delivered by elective CS (category 4) were included if they had one or more additional risk factors, whereas all women who delivered by emergency CS (category 1, 2, or 3) were included in the study -Other inclusion criteria included the absence of active bleeding and haemodynamic stability (pulse <100 beats per min and systolic blood pressure >100 mmHg). -LMWH was indicated for patients with PPH or severe PE after stabilization of the condition. Women already taking an anticoagulant or							

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	having any contraindication to LMWH, such as antenatal or postpartum active bleeding requiring blood transfusion, placenta previa, thrombocytopenia (platelet count <75 × 108/μl), severe renal disease (glomerular filtration rate <30 ml/minute), severe liver disease, or uncontrolled hypertension (>200/120 mmHg), were excluded. -These women had risk factors for VTE and were allocated to the following groups: treatment with 3500 IU/day of bemiparin, 4000 IU/day of enoxaparin, or no intervention (control). -The first dose was administered 6 hours after vaginal or abdominal delivery, or 8 hours after delivery in women receiving spinal anaesthesia.							

Evidence Table : Safety
Question : Is LMWH safe as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Alalaf SK, Jawad RK, Muhammad PR, et al. Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. BMC Pregnancy Childbirth. 2015;15:72	-Subsequent doses were administered daily for up to 6 days. The incidence of VTE was assessed for up to 40 days postpartum. -Data were analyzed using the Statistical Package for Social Sciences version 19. -Proportions were compared using the chi square test of association or Fisher's exact test. Binary logistic regression analysis was used with VTE as the dependent variable							

Evidence Table : Cost-effectiveness
Question : Is LMWH is cost-effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Johnston JA, Brill-Edwards P, Ginsberg JS et al. Cost-effectiveness of prophylactic low molecular weight heparin in pregnant women with a prior history of venous thromboembolism. Am J Med. 2005;118(5):503-14	Cost-utility analysis **Aim:** To compare the effectiveness and cost-effectiveness of prophylactic low molecular weight heparin with clinical vigilance and investigation of symptomatic women during the antepartum period. **Methods:** -a Markov state transition decision model examining two strategies: antepartum prophylaxis with low molecular weight heparin; and expectant management during the antepartum period without prophylaxis was constructed -a societal perspective -6-week time interval in modeling both antepartum events and future lifetime events.			LMWH	Expectant management (no prophylactic anticoagulation and no care beyond that provided during routine prenatal visits)		**Results:** For “low-risk” women with a prior venous thromboembolism associated with a transient risk factor and no known thrombophilic condition (recurrence risk 0.5%), expectant management was both more effective and less costly than prophylaxis. For “high-risk” women with prior idiopathic venous thromboembolism or known thrombophilic condition (recurrence risk 5.9%), prophylaxis was associated with a cost-effectiveness ratio ($38,700 per QALY) given a risk of bleeding complications <1.0% (base case 0.5%). **Conclusion:** For low-risk women with prior venous thromboembolism, expectant management during pregnancy leads to better outcomes than administration of prophylactic low molecular weight heparin. For high-risk women, antepartum thromboprophylaxis is a cost-effective use of resources	

Evidence Table : Cost-effectiveness
Question : Is LMWH is cost-effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Johnston JA, Brill-Edwards P, Ginsberg JS et al. Cost-effectiveness of prophylactic low molecular weight heparin in pregnant women with a prior history of venous thromboembolism. Am J Med. 2005;118(5):503-14	-Model parameters were based on a review of the existing English-language literature -Outcomes were expressed as U.S. dollars per quality-adjusted life-year (QALY).							

Evidence Table : Cost-effectiveness
Question : Is LMWH is cost-effective as prophylaxis for venous thromboembolism in pregnancy?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Bond C, O'Brien K, Draycott T et al.Financial implications and maternal impact of national recommendations for thromboprophylaxis: a retrospective cross-sectional analysis. Obstet Med. 2011;4(2):70-72	Cost-analysis **Aim:** To assess the likely cost of consumables to the maternity service and the impact of these policies on women. **Methods:** -One hundred consecutive live and stillbirths were identified using the maternity database; 97 case records were obtained. -Risk factors were identified and individual scores were calculated, together with the proportion that would have extended measures (low-molecular-weight heparin [LMWH], antiembolic stockings).		97 case records	LMWH + stockings+ sharps bins			**Results:** - Antenatally, 2.1% had a Royal College of Obstetricians and Gynaecologists (RCOG) risk score of three or more and would have been advised to have LMWH throughout pregnancy and the puerperium. -Postnatally, 40.1% had an RCOG score of two or more and would have required enoxaparin for one to six weeks. The annual cost of stockings, LMWH and sharps bins approximate to GB£44,847 for every one thousand deliveries, GB£2.6 million for each life saved. -About 10% of normal-weight postnatal women who achieved a vaginal birth had a risk score prompting thromboprophylaxis for at least seven days. **Conclusions** These data suggest that the current guidance might represent overmedicalization of pregnancy and that the criteria for thromboprophylaxis should be refined further	

9.4 Appendix 4
Prevention of Venous Thromboembolism (VTE) in pregnancy

Table 1: Risk groups and indications for antenatal thromboprophylaxis[2]

<table>
<tr><th colspan="2">Antenatal risk assessment</th></tr>
<tr><td colspan="2">❖ To be assessed at booking and with every admission into hospital
❖ Can be divided into 3 risk groups
❖ Management will depend on the risk group</td></tr>
<tr><td colspan="2">These risk groups do not include those who are sufficiently high risk(very high risk) to require anticoagulation when not pregnant(on long term warfarin)
• Previous VTE on warfarin
• APLS with previous VTE
This group requires therapeutic dose of LMWH antenatally</td></tr>
<tr><th>High Risk</th><th>Recommendation</th></tr>
<tr><th>Risk factors</th><th>Management</th></tr>
<tr><td>Any one
➢ Single previous VTE with
• Family history or
• Unprovoked / estrogen related
➢ Previous recurrent VTE >1</td><td>Requires antenatal prophylaxis with LMWH
➢ Enoxaparin 1 mg/kg daily or
➢ Tinzaparin 4500 units daily
(if BW >90kg, to dose at 75 units/kg daily)</td></tr>
<tr><th>Intermediate risk</th><th>Recommendation</th></tr>
<tr><th>A Risk factors</th><th>Management</th></tr>
<tr><td>➢ Single previous VTE with no family history
➢ Medical comorbidities e.g.
• Heart/lung disease
• SLE
• Cancer
• Inflammatory conditions
• Nephrotic syndrome
• Sickle cell disease
• Thalassaemia
• IVDU
➢ Surgical procedures e.g.
• Appendicectomy</td><td>Consider antenatal prophylaxis with LMWH
➢ Enoxaparin 1 mg/kg daily or
➢ Tinzaparin 4500 units daily
(if BW >90kg, to dose at 75 units/kg daily)</td></tr>
</table>

B Patient risk factors (see below)	
Any ≥3 ≥ 2 if admitted into hospital	
Low risk	**Recommendation**
Patient risk factors	**Management**
Any 2 or less (not admitted into hospital): ➢ Age >35 years ➢ Obesity BMI >30 ➢ Parity≥3 ➢ Smoker ➢ Gross varicose veins ➢ Current systemic infection ➢ Immobility e.g. paraplegia, longhaul travel >4 hours ➢ Preeclampsia ➢ Dehydration/ hyperemesis/ OHSS ➢ Multiple pregnancy ➢ Assisted reproductive treatment	Mobilisation Avoid dehydration

Table 2: Risk groups and indications for postnatal thromboprophylaxis[2]

Postnatal risk assessment	
❖ To be assessed in delivery suites ❖ Can be divided into 3 risk groups	
These risk groups do not include those who are sufficiently high risk(very high risk) to require anticoagulation when not pregnant(on long term warfarin) • Previous VTE on warfarin • APLS with previous VTE Switch from therapeutic LMWH to longterm warfarin postnatally	
High Risk	**Recommendation**
A Risk factors	**Management**
Any one ➢ Any previous VTE ➢ Anyone requiring antenatal prophylactic LMWH	At least 6 weeks postnatal prophylactic LMWH

Intermediate risk	Recommendations
Risk factors	**Management**
Any one ➢ **Caesarean section in labour** ➢ **BMI >40** ➢ **Prolonged hospital admission** ➢ **Medical comorbidities e.g.** • **Heart/lung disease** • **SLE** • **Cancer** • **Inflammatory conditions** • **Nephrotic syndrome** • **Sickle cell disease** • **Thalassaemia** • **IVDU**	**At least 7 days postnatal prophylactic LMWH** **If persisting or >3 risk factors, consider extending thromboprophylaxis with LMWH**
B Patient risk factors (see below)	
Any ≥ 2 risk factors	
Low risk	**Recommendations**
Patient risk factors	**Management**
Any 1 risk factor: ➢ **Age >35 years** ➢ **Obesity BMI >30** ➢ **Parity ≥3** ➢ **Smoker** ➢ **Elective CS** ➢ **Any surgical procedure in the puerperium** ➢ **Gross varicose veins** ➢ **Current systemic infection** ➢ **Immobility e.g. paraplegia, longhaul travel >4 hours** ➢ **Preeclampsia** ➢ **Midcavity rotational operative delivery** ➢ **Prolonged labour >24 hours** ➢ **Assisted reproductive treatment** ➢ **PPH >1 litre or blood transfusion**	**Mobilisation** **Avoid dehydration**

9.5 Appendix 5
Antenatal Colour Coding

5.8 PANDUAN PENGENDALIAN IBU ANTENATAL MENGIKUT SISTEM KOD WARNA

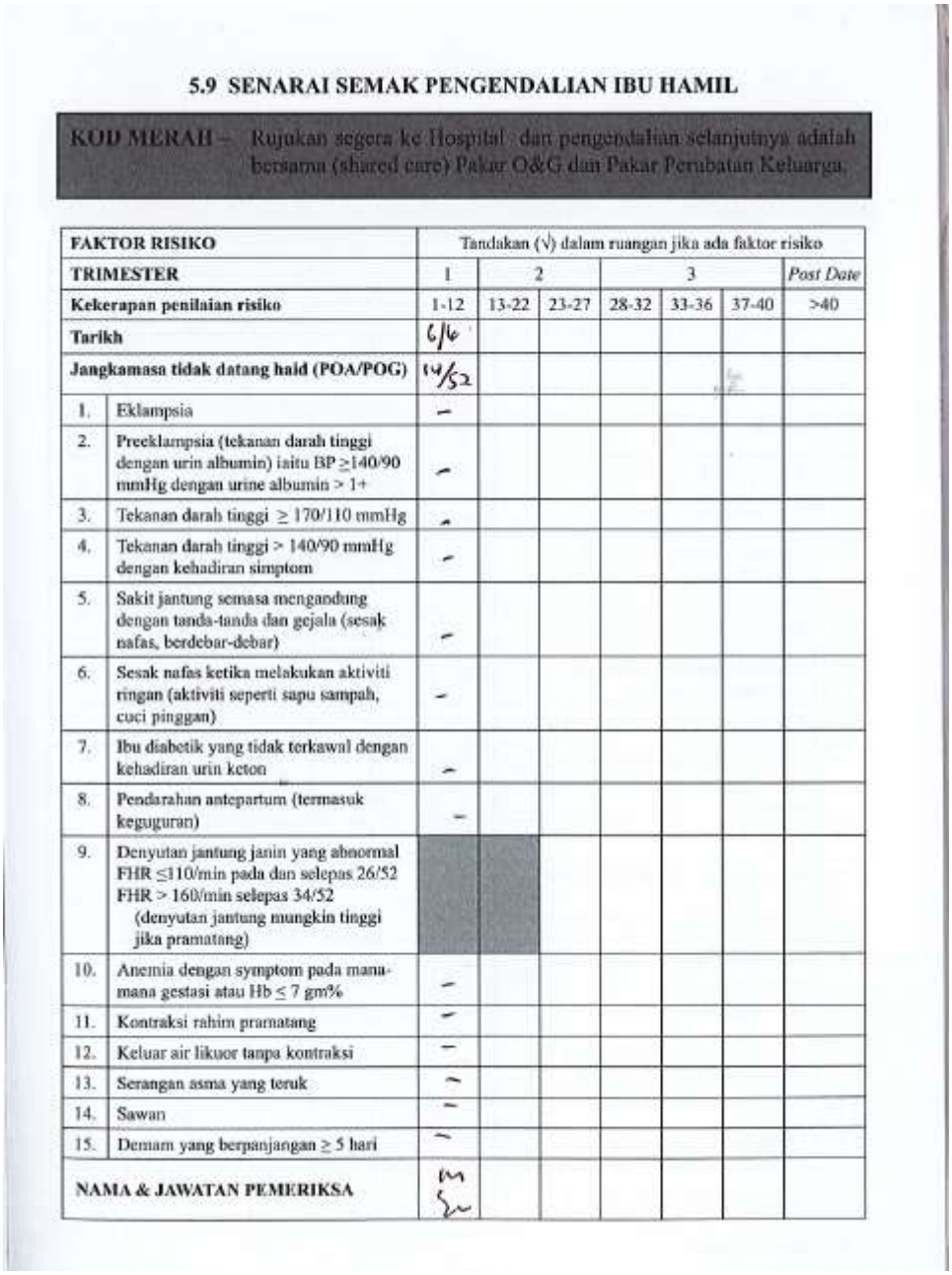
Sistem ini mempunyai penggunaan empat kod warna. Penentuan kod warna ini adalah berdasarkan kepada penilaian faktor risiko ibu semasa lawatan ke klinik/rumah. Penjagaan ibu adalah berasaskan kepada kod warna seperti berikut:-

KOD WARNA	TAHAP PENJAGAAN
Merah	Rujukan segera ke Hospital dan pengendalian selanjutnya adalah bersama *(shared care)* Pakar O&G dan Pakar Perubatan Keluarga.
Kuning	Rujukan untuk pengendalian oleh Pakar O&G Hospital/Pakar Perubatan Keluarga, dan penjagaan selanjutnya boleh dilakukan bersama *(shared care)* Pegawai Perubatan dan Jururawat Kesihatan
Hijau	Pengendalian di Klinik Kesihatan oleh Pegawai Perubatan dan Kesihatan dan pengendalian selanjutnya boleh dilakukan bersama Jururawat Kesihatan/Jururawat Masyarakat di bawah pengawasan Pegawai Perubatan
Putih	Penjagaan oleh Jururawat Kesihatan/Jururawat Masyarakat di Klinik Kesihatan dan Klinik Desa (sekiranya tiada terdapat faktor risiko yang disenaraikan dalam kod merah, kuning dan hijau, ibu diberi kod warna putih).

Di dalam situasi yang tertentu khususnya di kawasan pedalaman, di mana tidak terdapat Pegawai Perubatan, pengendalian boleh dilakukan oleh Jururawat Kesihatan/ Jururawat Masyarakat dengan pengawasan dari Pegawai Perubatan yang terdekat atau mudah dihubungi.

Pakar O&G/Pakar Perubatan Keluarga boleh menukarkan kod warna mengikut penilaian tahap risiko semasa ibu hamil. Tag warna yang dilekatkan dapat mempamerkan kod warna yang telah diberikan sebelumnya.

Risks factors under the category of red, yellow, green and white code[30]



5.9 SENARAI SEMAK PENGENDALIAN IBU HAMIL

KOD MERAH – Rujukan segera ke Hospital dan pengendalian selanjutnya adalah bersama (shared care) Pakar O&G dan Pakar Perubatan Keluarga.

FAKTOR RISIKO		Tandakan (√) dalam ruangan jika ada faktor risiko						
TRIMESTER		1	2		3			*Post Date*
Kekerapan penilaian risiko		1-12	13-22	23-27	28-32	33-36	37-40	>40
Tarikh		6/6						
Jangkamasa tidak datang haid (POA/POG)		14/52						
1.	Eklampsia	–						
2.	Preeklampsia (tekanan darah tinggi dengan urin albumin) iaitu BP ≥140/90 mmHg dengan urine albumin > 1+	–						
3.	Tekanan darah tinggi ≥ 170/110 mmHg	–						
4.	Tekanan darah tinggi > 140/90 mmHg dengan kehadiran simptom	–						
5.	Sakit jantung semasa mengandung dengan tanda-tanda dan gejala (sesak nafas, berdebar-debar)	–						
6.	Sesak nafas ketika melakukan aktiviti ringan (aktiviti seperti sapu sampah, cuci pinggan)	–						
7.	Ibu diabetik yang tidak terkawal dengan kehadiran urin keton	–						
8.	Pendarahan antepartum (termasuk keguguran)	–						
9.	Denyutan jantung janin yang abnormal FHR ≤110/min pada dan selepas 26/52 FHR > 160/min selepas 34/52 (denyutan jantung mungkin tinggi jika pramatang)							
10.	Anemia dengan symptom pada mana-mana gestasi atau Hb ≤ 7 gm%	–						
11.	Kontraksi rahim pramatang	–						
12.	Keluar air likuor tanpa kontraksi	–						
13.	Serangan asma yang teruk	–						
14.	Sawan	–						
15.	Demam yang berpanjangan ≥ 5 hari	–						
NAMA & JAWATAN PEMERIKSA		M Sw						

SENARAI SEMAK PENGENDALIAN IBU HAMIL

KOD KUNING – Rujukan untuk pengendalian oleh Pakar O&G Hospital/ Pakar Perubatan Keluarga, dan penjagaan selanjutnya boleh dilakukan bersama (*shared care*) Pegawai Perubatan dan Jururawat Kesihatan

FAKTOR RISIKO		Tandakan (√) dalam ruangan jika ada faktor risiko						
TRIMESTER		1	2		3			*Post Date*
Kekerapan penilaian risiko		1-12	13-22	23-27	28-32	33-36	37-40	>40
Tarikh		6/6						
Jangkamasa tidak datang haid (POA/POG)		14/0						
1	Ibu HIV positif	–						
2	Ibu Hepatitis B positif	–						
3	Ibu Tuberkulosis / Malaria / Sifilis	–						
4	Tekanan darah tinggi > 140/90 - <170/110 mmHg dengan *urin albumin negative*	–						
5	Ibu diabetik (dengan rawatan insulin)	–						
6	Pergerakan janin kurang semasa kandungan ≥ 32 minggu	–						
7	Kandungan melebihi 7 hari dari EDD	–						
8	Ibu dengan masalah perubatan yang memerlukan rawatan bersama dengan hospital	–						
9	Ibu yang terlibat dalam isu mediko-legal	–						
10	Ibu tunggal dan Ibu remaja (< 19 tahun)	–						
11	Hemoglobin 7-9 gm % atau simptomatik	–						
12	Placenta previa yang stabil – tiada pendarahan	–						
13	*Maternal pyrexia* > 38C atau > 3 hari	–						
14	*Sejarah masalah ketidaksuburan sebelum kandungan semasa (*infertility*)	–						
15	Penyakit jantung tanpa gejala	–						
16	*Ketagihan dadah/merokok	–						
NAMA & JAWATAN PEMERIKSA		[illegible]						

*Periksa sekali sahaja

SENARAI SEMAK PENGENDALIAN IBU HAMIL

KOD HIJAU –Pengendalian di Klinik Kesihatan oleh Pegawai Perubatan dan Kesihatan dan pengendalian selanjutnya boleh dilakukan bersama (*shared care*) Jururawat Kesihatan/ Jururawat Masyarakat di bawah pengawasan Pegawai Perubatan

FAKTOR RISIKO		Tandakan (√) dalam ruangan jika ada faktor risiko						
TRIMESTER		1	2		3			*Post Date*
Kekerapan penilaian risiko		1-12	13-22	23-27	28-32	33-35	37-40	>40
Tarikh		6/1						
Jangkamasa tidak datang haid (POA/POG)		14/52						
1.	*Rh *negative*	-						
2.	*Berat badan ibu sebelum mengandung atau ketika booking <45kg	-						
3.	*Masalah perubatan semasa (termasuk psikiatrik dan kecacatan fizikal) kecuali Diabetes dan H pertensi	-						
4.	*Pembedahan ginekologi yang lalu	-						
5.	*LNMP yang tidak pasti	-						
6.	*3 kali riwayat keguguran yang berturutan	-						
7.	*Riwayat obstetrik yang lalu : Pembedahan cresarean	✓	✓	✓	✓	✓	✓	✓
	Riwayat lalu PIH/eklampsia/diabetes	-						
	Kematian perinatal	-						
	Mempunyai sejarah bayi dengan berat lahir kurang daripada 2.5kg atau lebih daripada 4kg	-						
	Koyak *perineum 3rd degree*	-						
	Lekat uri	-						
	Pendarahan selepas bersalin	-						
	Kelahiran *instrumental*	-						
	Sakit bersalin lama	-						

Sambungan Kod Hijau

FAKTOR RISIKO		Tandakan (√) dalam ruangan jika ada faktor risiko						
TRIMESTER		1	2		3			*Post Date*
Kekerapan penilaian risiko		1-12	13-22	23-27	28-32	33-36	37-40	>40
Tarikh		6/6						
Jangkamasa tidak datang haid (POA/POG)		14/52						
8.	Kandungan lebih dari satu	–						
9.	Tekanan darah tinggi (140/90 mmHg) tanpa urin albumin	–						
10.	Hemoglobin kurang dari 9-<11gm %	–						
11.	Glukosuria 2 kali	–						
12.	Air kencing mempunyai albumin ≥1+	–						
13.	Pertambahan berat badan yang mendadak melebihi 2 kg dalam seminggu	–						
14.	Berat badan ibu sebelum mengandung atau *booking* melebihi 80 kg	–						
15.	Tinggi rahim (SFH) kecil atau besar dari tarikh jangka masa kandungan	–						
16.	Menyongsang/*oblique*/melintang dengan tidak ada tanda sakit bersalin pada 36 minggu kehamilan							
17.	Kepala bayi tinggi (*Head not engaged*) semasa cukup bulan (37 minggu) bagi primigravida							
18.	Ibu GDM (kawalan diet)	–						
19.	Berat badan statik atau menurun (dalam tempoh sebulan)	–						
20.	*Ibu berumur > 40 tahun	–						
21.	*Primigravida	–						
22.	*Gravida 6 dan ke atas	–						
23.	*Jarak kelahiran kurang dari 2 tahun atau melebihi 5 tahun	–						
24.	*Ibu dengan masalah tertentu : Ukuran tinggi kurang dari 145 cm	–						
NAMA & JAWATAN PEMERIKSA		[illegible]						

*Penilaian sekali sahaja
Nota : Ibu mesti diperiksa oleh Pegawai Perubatan dalam tempoh 2 minggu dari tarikh *booking*

SENARAI SEMAK PENGENDALIAN IBU HAMIL

KOD PUTIH –Penjagaan oleh Jururawat Kesihatan / Jururawat Masyarakat di Klinik Kesihatan dan Klinik Desa. Ibu hanya akan diberi kod berwarna putih setelah ia tidak mempunyai sebarang faktor risiko yang tersenarai dalam kod merah, kuning dan hijau.

IBU DIBENARKAN BERSALIN DI PUSAT BERSALIN ALTERNATIF, sekiranya memenuhi syarat-syarat berikut :-

FAKTOR RISIKO		**TANDAKAN (√) DALAM RUANGAN BERKENAAN**
TARIKH		
Jangkamasa tidak datang haid (POA/ POG)		
1.	*Gravida* 2-5	
2.	Tiada masalah obstetrik yang lalu yang mungkin berulang atau memberi kesan pada kandungan semasa	
3.	Tiada masalah perubatan yang lalu	
4.	Tiada masalah perubatan/obstetrik pada kandungan semasa	
5.	Ukuran tinggi lebih dari 145 sm	
6.	Ibu berumur lebih 18 tahun dan kurang 40 tahun	
7.	Ibu berkahwin dan mempunyai sokongan keluarga	
8.	POA >37 minggu atau <41 minggu	
9.	Anggaran berat bayi > 2 kg dan < 3.5 kg	
	NAMA & JAWATAN PEMERIKSA	

Nota: Ibu perlu diperiksa oleh Pegawai Perubatan dalam tempuh 2 minggu dari tarikh minggu *booking*.