

**THE USAGE OF PORCINE BASE ANTICOAGULANT
DURING PREGNANCY AND PUERPERIUM FROM *FIQH*
PERSPECTIVE: LOW MOLECULAR WEIGHT HEPARIN
(LMWH) AS A CASE STUDY**

ZIZI AZLINDA BINTI MOHD YUSOF

UNIVERSITI SAINS ISLAM MALAYSIA

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Thesis submitted in fulfillment for the degree of
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AUTHOR DECLARATION

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged

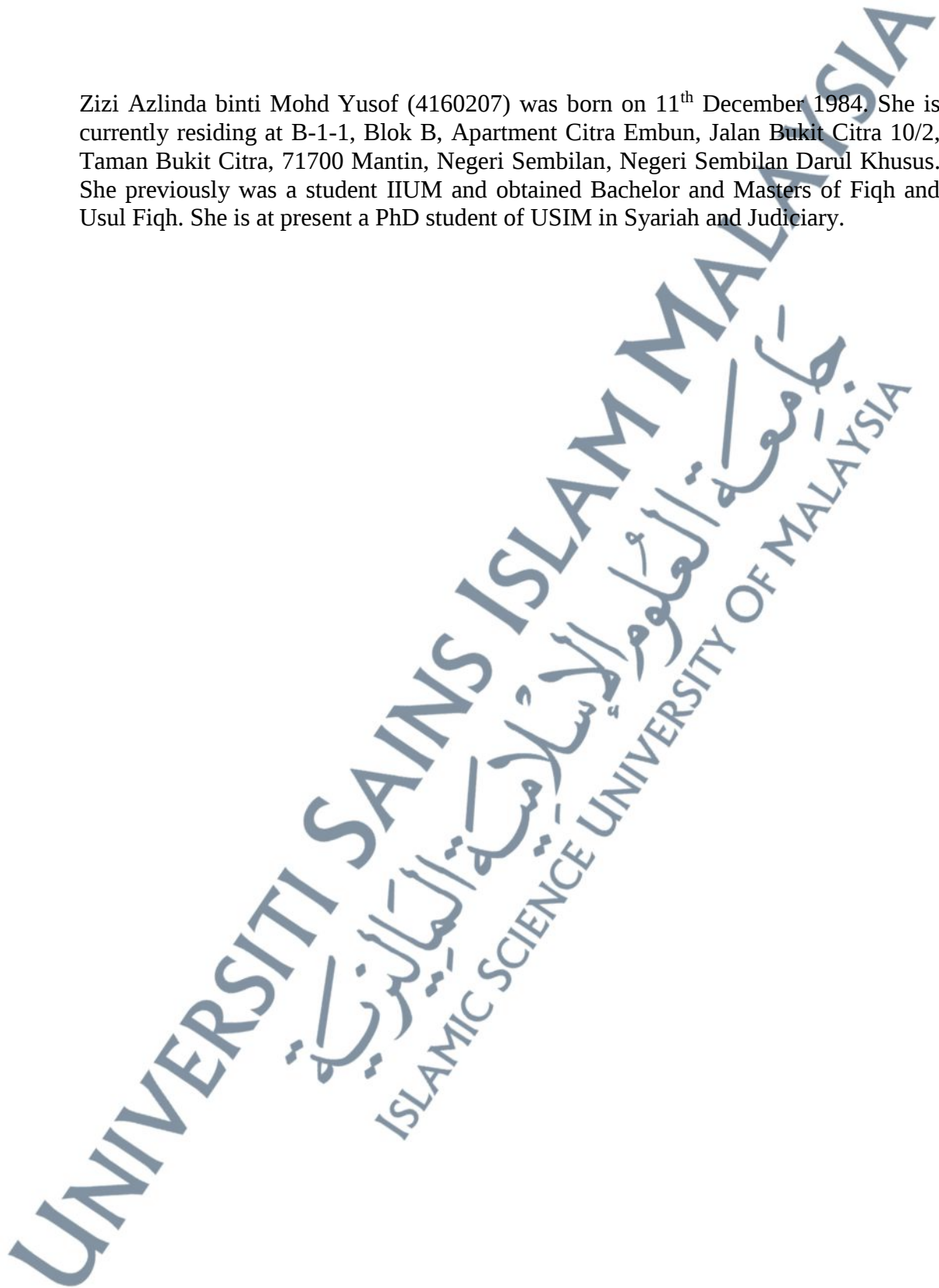
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ABSTRAK

Ubat pencair darah berasaskan babi, heparin bermolekul rendah (LMWH) mempunyai potensi tinggi untuk mencegah penyakit mengancam nyawa yang dipanggil penyumbatan saluran darah atau Venous Thromboembolism (VTE). Ia telah diharamkan menurut keputusan Jawatankuasa Muzakarah Majlis Kebangsaan Bagi Hal Ehwal Islam Malaysia (MKI) /JAKIM pada 2009. Bagaimanapun, pengecualian penggunaan ubat pencegah itu dibenarkan bagi pesakit yang mencapai peringkat darurat sahaja, bahkan alternatif halal iaitu ubat Fondaparinux dicadangkan untuk menggantikan LMWH meskipun ubat pencair darah yang bebas derivatif binatang itu mempunyai profil keselamatan yang tidak memadai/stabil bagi wanita mengandung dan selepas bersalin. Walaupun MKI dengan jelas menyatakan, LMWH dibenarkan hanya ketika kondisi-kondisi darurat sahaja, tetapi pengecualian (*ṣiḡḡah*) itu membawa kepada kekeliruan semasa memberi preskripsi ubat tersebut kepada wanita mengandung dan selepas bersalin yang memerlukannya, yang mana ia telah menjadikan LMWH sebagai pilihan ubat yang tidak digemari. Hal ini kerana dilema penggunaannya serta pengecualian dalam kenyataan keputusan MKI. Kajian ini menggunakan metodologi kualitatif melalui teknik analisa dokumen dan temubual. Peserta kajian seramai 21 orang yang terdiri daripada sepuluh orang doctor pakar perubatan dari tiga jabatan iaitu tujuh pakar obstetrik dan ginekologi (O&G), seorang pakar kardiovaskular, seorang pakar hematologi dan seorang pakar perubatan keluarga. Tiga orang pakar farmasi dan lapan orang pakar syariah terdiri daripada mufti dan ahli akademik dari Universiti Awam juga turut ditemubual untuk kajian ini. Hasil kajian mendapati bahawa wanita mengandung melalui proses fisiologi di mana darah mereka mudah membeku dan sebilangannya mengalami penyumbatan darah beku (Venous Thromboembolism atau VTE) yang boleh membawa maut. LMWH ialah ubat pencegah terbaik kepada penyakit VTE dan penggunaannya sepatutnya diharuskan semasa mengandung dan selepas bersalin untuk mereka yang berisiko. Dengan itu, berdasarkan justifikasi kaedah fiqhiyyah seperti *Al-Ḍarar Yuzāl* dan *Al-Hājah Tunazzal Manzilah al-Ḍarūrah*, penggunaan LMWH adalah diharuskan dari sudut *fiqh* terhadap ibu mengandung dan selepas bersalin yang memerlukannya.

ABSTRACT

Porcine based blood thinners namely low molecular heparin (LMWH) drugs are known to be highly potential to prevent the life-threatening event cause by blood clotting or Venous Thromboembolism (VTE). However, its usage was clearly prohibited according to The Muzakarah (discussion) Committee of the National Council for Islamic Religious Affairs of Malaysia (MCMKI) / JAKIM National Council decision in 2009. Yet, LMWH usage is considered permissible for treatment purposes for critically ill patients in the life-threatening stage/*darūrah* stage. The halal alternative of LMWH, Fondaparinux is recommended to replace LMWH even though the animal derivative-free blood thinner drug has an inadequate / unstable safety profile for pregnant and postpartum women. The MCMKI's decision to allow exemption of LMWH usage in emergency condition (*sīghah*) creates confusion when prescribed to pregnant and postpartum women. Thus, it has made LMWH a less favorable choice due to the dilemma between its usage and the exceptions in the MCMKI's statement. This study used qualitative methodology through document analysis techniques and interviews. Twenty-one expertise consisting of ten medical consultants from three departments, namely seven obstetricians and gynaecologists (O&G), a cardiovascular specialist, a hematologist and a family physician. On the other hand, three senior pharmacists and eight shariah experts among *muftīs* and academicians from the public universities were interviewed for this study. The findings of the study revealed that pregnant women undergone physiological changes in which their blood easily clots, and some easily develop massive clotting event (Venous Thromboembolism or VTE) and can be fatal. LMWH is the best preventative medicine for VTE condition, and it should be used during pregnancy and postpartum for those who at risk. Thus, based on the justification of *fiqhiyyah* methods such as *Al-Ḍarar Yuzāl* and *Al-Hājah Tunazzal Manzilah al-Ḍarūrah*, the usage of LMWH is permissible from *fiqh* perspective upon pregnant and postpartum mothers who are indicated.

الملخص

من المعروف أن مخففات الدم المستخلص من الخنزير، وهي أدوية الهيبارين الجزيئية المنخفضة (LMWH)، ذات قدرة عالية على منع الحدث الذي يهدد الحياة الناجم عن تخثر الدم أو الجلطات الدموية الوريدية (VTE). فقد كان من الواضح أن استخدامه محظور وفقاً لقرار لجنة المذاكرة للمجلس الوطنى للأحوال الإسلامية بماليزيا فى عام 2009 ، إلا فى حالة الضرورة، ويوصى باستخدام فونداپارينوكس (Fondaparinux) كبديل حلال ليحل محل الهيبارين الجزيئية المنخفضة على الرغم من أن هذا مميح الدم الخالى من المشتقات الحيوانية يحتوى على خصائص أمان غير كافية أو غير مستقرة للنساء الحوامل وبعد الولادة. وصيغة قرار المجلس بسماع استخدام هذا الهيبارين فى حالات الضرورة والاستثنائية تخلق الارتباك عند وصفه للنساء الحوامل وما بعد الولادة ، وجعلته خياراً أقل ملائمة بسبب المعضلة الناشئة من صيغة القرار . وتستخدم هذه الدراسة المنهجية النوعية من خلال تقنيات تحليل الوثائق والمقابلات . تمت مقابلة إحدى وعشرين خبير ، ومنها عشرة استشاريين طبيين من ثلاثة اختصاصات، وهم سبعة أطباء توليد وأمراض نسائية (O&G) وأخصائى أمراض القلب والأوعية الدموية ، وأخصائى أمراض الدم وطبيب الأسرة . ومن ناحية أخرى ، تمت مقابلة ثلاثة صيادلة كبار وثمانية خبراء شرعيين من المفتين والأكاديميين من الجامعة الحكومية . كشفت الدراسة أن النساء الحوامل قد خضعن لتغيرات فسيولوجية حيث يتخثر دمهن بسهولة وبعضهن يصبون بسهولة بحدث تخثر هائل الانصمام الخثارى الوريدى (VTE) ويمكن أن يكون قاتلاً. والهيبارين الجزيئية المنخفضة هو أفضل دواء وقائى لحالة الانصمام الخثارى الوريدى ويسمح استخدامه أثناء الحمل وبعد الولادة للواتى تتعرض للخطر بناءً على القواعد الفقهية مثل الضرر يزال ، والحاجة تنزل منزلة الضرورة ، فإن استخدامه مسموح من منظور فقهي على الأمهات الحوامل وبعد الولادة اللائى يتم تحديدهن.

TABLE OF CONTENTS

AUTHOR DECLARATION	i
BIODATA OF AUTHOR.....	ii
ACKNOWLEDGEMENT.....	iii
ABSTRAK	iv
ABSTRACT.....	v
LIST OF FIGURE	xiv
LIST OF APPENDICES	xvii
GLOSSARY.....	xviii
LIST OF TRANSLITERATION.....	xxviii
ABBREVIATION	xxxi
CHAPTER I : INTRODUCTION	1
1.1 Introduction.....	1
1.2 Background of study	6
1.2.1 Maternal Mortality in Malaysia since 1957-2016/2017	8
1.2.2 Embolism is the Significant Cause of Maternal Mortality	11
1.2.3 <i>Fatwā</i> on Clexane issued on 23rd-25th June 2009.....	14
1.3 Problem statement.....	15
1.4 Research Flow	21
1.5 Conceptual Framework.....	22
1.6 Research Questions.....	23
1.7 Research Objectives.....	23
1.8 Significant of Study	23
1.9 Research Limitation.....	24
1.9 Conclusion	26
CHAPTER II :	27
LITERATURE REVIEW	27
2.1 Introduction.....	27
2.2 The Application of <i>Ḍarūrah</i> in Islamic Ruling	28
2.3 The Position of <i>Ḥājah</i> and its Application in Determining Islamic Ruling	38
2.4 The Concept of <i>Istiḥālāh</i> as Legal Indicator in Imposing <i>Fatwā</i>	43

2.5 LMWH as Preventive Medicine from Shariah Perspective	46
CHAPTER III :	52
RESEARCH METHODOLOGY	52
3.1 Introduction.....	52
3.2 Research Design.....	52
3.3 Research Phases, Tasks and Outcomes.....	54
3.4 Sample Selection.....	57
3.5 Data Collection	58
3.1.1 Document Review	58
3.1.2 Interview	62
3.6 Data Analysis	63
3.6.1 Inductive method	63
3.6.2 Deductive method.....	64
3.6.3 Comparative Method	64
3.7 Conclusion	65
CHAPTER IV :	66
FINDINGS	66
4.1Introduction.....	66
4.2 VTE Pathophysiology during Pregnancy and Puerperium	66
4.2.1 Manifestation of VTE During Pregnancy and Puerperium	70
4.2.2 Prevention of VTE during Pregnancy and Puerperium.....	75
4.2.3 Anticoagulants for Thrombotic Treatment.....	85
4.3 Conclusion.....	101
4.4 Introduction.....	102
4.5 Definition of Medical Treatment (<i>Al-Tadāwī</i>):.....	102
4.6 Medical Treatment from Islamic <i>Fiqh</i> Scholars' Views.....	103
4.6.1 First school of Thought: Permissible (<i>Ibāḥah</i>).....	103
4.6.2 Second school of Thought: Encouraged (<i>Istiḥbāb</i>)	104
4.6.3 Third School of Thought: Permissible to receive the medical treatment, yet to leave is better	104
4.6.4 Fourth School of Thought: Incumbent (<i>Wājib</i>) for Seeking Medical Treatment.....	105
4.6.5 The Preferred (<i>Tarjīḥ</i>) Opinion:	106

4.7 Ruling of Consuming Porcine Derivative Medicine in Health Treatment	107
4.7.1 The Legal Rule of Using Porcine Derivatives Medicine in High Risk of Death (<i>Hālah Al-Darurah</i>).	112
4.8 Porcine from Islamic <i>Fiqh</i> Dimension.....	120
4.8.1 Islamic Ruling (<i>Aḥkām</i>) Regarding Porcine.....	122
4.9 Health Prevention in Islam.....	145
4.9.1 Definition of Prevention (<i>Al-Wiqāyah</i>).....	145
4.10 <i>Sharī'ah</i> Principles regarding Thromboprophylaxis with LMWH during Pregnancy and Puerperium	150
4.10.1 The Principle of <i>Istiḥālah</i> and <i>Istihlāk</i> for Thromboprophylaxis with VTE during Pregnancy and Puerperium.....	151
4.10.2 Principle of <i>Ḍarūrah</i> for Thromboprophylaxis of VTE during Pregnancy and Puerperium	183
4.10.3 The Principle of <i>Al-Ḥājah Al-Shar'īyyah</i> for Thromboprophylaxis of VTE during Pregnancy and Puerperium.....	226
4.11 Global <i>Fatwā</i> regarding LMWH.....	262
4.11.1 Part 1: <i>Fatwā</i> on LMWH over Muslim World.....	262
The <i>majma'</i> held a16th meeting	263
4.11.2 Part 2: Data from Interview Sessions	269
4.11.3 Conclusion	279
CHAPTER V : ANALYSIS AND DISCUSSION.....	280
5.1 Introduction.....	280
5.2 Data Analyzation from Interview Method.....	281
5.3 Cohen's Kappa Analyzation	293
5.4 Findings of the Study through Cohen's Kappa.....	296
5.5 Conclusion	298
5.6 Determination of Islamic legal rule on LMWH based on <i>Istiḥālah</i>	299
5.6.1 Analysis of <i>Istiḥālah</i> and <i>Istihlāk</i> Process of LMWH	299
5.7 Determination of Islamic Legal 'Rule on LMWH based on the Principle of <i>Ḍarūrah</i>	307
5.7.1 The Necessity of <i>Ahl Al-Dhikr</i> or <i>Ahl Al-Khibrah</i> in Thromboprophylaxis for Obstetric Related VTE.	309

5.7.2	High Risk Group (Scored 4 onwards) of VTE During Pregnancy and Puerperium.....	312
5.8	Determination of Islamic Legal Rule on LMWH based on the Principle of <i>Al-Hājah Tunazzal Manzilah al-Darūrah</i>	315
5.8.1	Moderate Risk with Score 3 during Pregnancy and Low Risk with Score 2 during Puerperium Shall Offer for Thromboprophylaxis with LMWH	317
5.8.2	<i>Dar' u Al-Mafsadah Awlā min Jalbi Al-Maṣlahah</i> in Moderate Risk Group (Score 3) during Pregnancy.	319
5.9	Integrated Medical-Shariah Parameter to Receive Thromboprophylaxis with LMWH during Pregnancy and Puerperium	321
5.9.1	Pregnancy Risk (score 1, 2, 3, 4 and above).....	321
5.9.2	Puerperium Risk (Score 2).....	327
5.9.3	Conclusion	331
CHAPTER VI :		333
CONCLUSIONS AND RECOMMENDATIONS		333
6.1	Introduction.....	333
6.2	Implications	336
6.2.1	Implication to Organizational Authorities in Malaysia particularly JAKIM, MCMKI and MOH.....	336
6.2.2	Implication to the front liners in dealing with patients such as medical doctors and pharmacist	337
6.2.3	Implication to Women in Pregnancy and Puerperium	337
6.2.4	Implication to Islamic Academic Researcher and Students	338
6.2.5	Implication to Pharmaceutical <i>Halāl</i> Industry	338
6.3	Contributions of the Study.....	338
6.3.1	Practical Knowledge	338
6.3.2	Methodological Knowledge	339
6.3.3	Theoretical Knowledge	340
6.4	Future Recommendation.....	340
BIBLIOGRAPHY		342
APPENDIX 1		379
APPENDIX 2		381
APPENDIX 3		384

APPENDIX 4.....	390
APPENDIX 5.....	410
APPENDIX 6.....	411
APPENDIX 7.....	412
APPENDIX 8.....	413
APPENDIX 9.....	416
APPENDIX 10.....	420
APPENDIX 11.....	422
APPENDIX 12.....	428

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LIST OF TABLES

Table 1.1:	Maternal Mortality due to Obstetric Embolism: Malaysia from 2006-2015	10
Table 1.2:	Common causes of maternal mortality case in Malaysia	10
Table 1.3:	The causes of maternal death: Malaysia 2015.	12
Table 1.4:	Risk groups and indications for antenatal thromboprophylaxis	77-78
Table 1.5:	Risk groups and indications for postnatal thromboprophylaxis	79-80
Table 1.6:	The Duration of Thromboprophylaxis during Pregnancy and Puerperium.	84
Table 1.7:	Pharmacokinetic features compare between UFH, LMWH and Fondaparinux	100
Table 1.8	The comparison of composite between primate animal, pig and human.	128
Table 1.9:	Shafi'ite jurists mentions in their books about the principle of purity and impurity of living creature.	135
Table 2.0:	Malikite jurists quote in their books about all living things are pure	136
Table 2.1:	The differences between <i>lā ḍarar wa lā dirār</i>	184
Table 2.2:	Data on Fatwa of LMWH collected all over Fatwa Organizational Councils internationally and nationally	267-268
Table 2.3:	Data obtained from medical experts	269-272
Table 2.4:	Data obtained from pharmaceutical experts	273-274

Table 2.5:	Data obtained from Shariah experts	275-278
Table 2.6:	Formula to calculate using Cohen's Kappa	293
Table 2.7:	Cohen's Kappa Indicator on Level of Agreement	294
Table 2.8:	Experts Evaluation Form	294-295
Table 2.9:	Experts who verify the integrated medical-shariah parameter of this research	295
Table 3.0:	Verification for Integrated Medical-Shariah Parameter of Using LMWH, porcine base anticoagulant as thromboprophylaxis during Pregnancy and Puerperium	296
Table 3.1:	Checklist of <i>Istiḥālah</i> steps of LMWH (Enoxaparin or Clexane)	302
Table 3.2	Guideline of using unlawful sources in medicines under <i>istiḥālah</i> process	304
Table 3.3:	Examples of few risk factors associated with the score point of each risk extracted from the manual training produced by MOH in 2018	317-318

LIST OF FIGURE

Figure 1.1:	Pie chart shows the population of religions in Malaysia	3
Figure 1.2:	Percentage distribution of the population by ethnic groups, 2014-2016	3
Figure 1.3:	Halal consumerism in Malaysia	5
Figure 1.4:	Maternal Mortality Ratio in Malaysia: 1991-2015	7
Figure 1.5:	Number of maternal mortality due to obstetric embolism by type of Emboli, 2009-2015	9
Figure 1.6:	Causes of Maternal Deaths: Malaysia 2015	12
Figure 1.7:	Concept mapping of the research	21
Figure 1.8:	Conceptual Framework of this research	22
Figure 1.9:	Research phases and task of this research	56
Figure 2.0:	Virchow's Triad; three broad categories of factors that disturb normal haemostasis and contribute to thrombosis	68
Figure 2.1:	Swollen leg due to DVT during pregnancy	72
Figure 2.2:	Deep vein Thrombosis in left leg	73
Figure 2.3:	The migration of a thrombosis into pulmonary embolism	73
Figure 2.4:	VTE Risk assessment in Pregnancy and Puerperium	83
Figure 2.5:	The steps to use LMWH (Enoxaparin sodium) subcutaneously	98
Figure 2.6	The component of <i>al-khinzīr</i> in <i>al-najāsāt</i> and embedded in <i>al-muḥarramāt</i>	107
Figure 2.7	Hadith regarding medical treatment with <i>ḥarām li dhātihi</i> and <i>ḥarām li ghayrihi</i>	109

Figure 2.8:	Enoxaparin Sodium or trade name is Clexane. One of the brands that is imported into Malaysia	125
Figure 2.9:	Wild boar found throughout the countries	127
Figure 3.0:	Landrace	127
Figure 3.1:	Enoxaparin Sodium is extracted from porcine intestine mucosal. The figure shows where the mucosa layer situated in large intestine. Mucosa is added in remaining food in large intestine	152
Figure 3.2:	The study conducted on the stages of decomposition of a summer carrion of the baby pig <i>Sus Scrofa</i> Linnaeus	156
Figure 3.3:	The acceptance upon <i>istiḥālah</i> in the shed of <i>fiqh</i> and jurists' scholars of sect	167
Figure 3.4:	Theory of <i>istiḥālah</i> structure	174
Figure 3.5:	The figure shows the depolymerization process from heparin source either bovine or porcine	177
Figure 3.6:	Different ways to obtain LMWH either with enzymatic method or chemical method or physical method and main chemical structures to each method.	177
Figure 3.7:	<i>Istiḥālah</i> structural theory of LMWH manufacture	179
Figure 3.8:	The percentage of the knowledge of occurrences according to Al-Shanqīṭiyy	192
Figure 3.9:	The process removal of DNA porcine in the purification chemical step is formed by <i>istihlāk</i> and <i>istiḥālah</i> pertains to LMWH manufacturing process.	300
Figure 4.0:	Purification chemical steps to remove DNA	301
Figure 4.1:	<i>Ḍarūrah</i> definition based on <i>fiqh</i>	307
Figure 4.2:	The diagram shows the emergence of few <i>mafsadah</i> that could occur amongst pregnant women and puerperium.	313

Figure 4.3:	The diagram shows the emergence of few <i>mafsadah</i> that could occur amongst pregnant women and puerperium without effective preventative medicine	319
Figure 4.4	Parameter standard to each stage VTE risk assessment in pregnancy with the legal proof in shariah based on <i>qawā'id fiqhiyyah</i> on the left side	322
Figure 4.5:	The general big picture of parameter of the need of LMWH usage as prevention VTE during pregnancy only. The parameter intended to assist Malaysian Muftis to impose fatwa regarding VTE related obstetric.	324
Figure 4.6:	Each condition in puerperium or postnatal supported with <i>qawā'id fiqhiyyah</i>	330

LIST OF APPENDICES

Appendices	Item	Page
Appendix 1	Manufacturing flow chart of the heparin sodium starting material & Manufacturing Flow chart of the Enoxaparin Sodium Drug substance	379-380
Appendix 2	Description of Porcine Content Free in Clexane & lab certificate	381-383
Appendix 3	Interview Questions Set of Medical Practitioners, Interview Questions Set of Syariah experts, Interview Questions Set of pharmaceutical experts.	384-389
Appendix 4	Invitation Letter for Interview's participants	390-409
Appendix 5	Green top guideline of thromboprophylaxis of VTE	410
Appendix 6	Adjusted odd ratio for risk factor VTE	411
Appendix 7	VTE Risk assesement in Pregnancy and Puerperium	412
Appendix 8	Price list of medicine by Beraeu Pharmaceutical National Service, MOH	413-415
Appendix 9	Evaluation shariah experts form (Cohen's Kappa)	416-419
Appendix 10	Slides maternal death in Sarawak	420-421
Appendix 11	Evaluation shariah experts form (workshop)	422-427
Appendix 12	Transcription of interviews	428-461

GLOSSARY

Al-Ḥājah tunazzal manzilah al-ḍarūrah: A *qāʿidah fiqhiyyah juzʿiyyah* under *al-ḍarār yuzāl* which means assumption that *ḥājah* could place as *ḍarūrah* role in excusing the obligatory and permitted the act of doing or consuming the forbidden.

Al-Ḍarār Yuzāl: A *qāʿidah fiqhiyyah kubrā* refers to an action of removing the harmful.

Anticoagulant: Agents that prevent blood clotting.

Anti-thrombin: endogenous factors and drugs that directly inhibit the action of thrombin, usually by blocking its enzymatic activity they are distinguished from indirect thrombin inhibitors such as heparin, which act by enhancing the inhibitory effects of antithrombins.

Anti-thrombosis: is thrombotic drug which comprises two types of drugs, namely anticoagulant and antiplatelet. The anticoagulant works to slow down clot formation by reducing fibrin and preventing clots from forming. Meanwhile, the antiplatelet agent prevents platelet from clumping and thereby inhibiting it from growing and forming the clot.

Argatroban: is an anticoagulant that is a small molecule and direct thrombin inhibitor.

Arixtra: a type of anticoagulant, is used to treat serious blood clots in the legs and/or lungs. It is usually used with another “blood thinner” medication.

Aspirin Antiplatelet (ASA): an anticoagulant which reduces the risk of serious vascular events by reducing platelet activity, in patients at high risk of such an event by about a quarter.

Bovine: relating to the subfamily Bovinae, which includes cattle, buffalo, oxlike and cowlike.

Clexane: an anticoagulant. Clexane (trade name) contains a medicine called enoxaparin sodium. This belongs to a group of medicines called Low Molecular Weight Heparin which marketed in certain countries including Malaysia used to prevent and treat VTE.

Clinical Practical Guideline (CPG): statements that include recommendations intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

Cohen's Kappa: is a verification process that uses Kappa's formula to measure inter-rater reliability and intra-rater reliability for qualitative categorical items.

Dar'u al-mafsadah awlā 'alājalbi al-maṣlaḥah: Blocking the evils is prioritized over seeking the benefits.

Darūrah: An emergency situation which threatens any of the objectives of shariah (*maqasid al-shariah*) either religion, life, intellectual, lineage and wealth. Some shariah scholars include dignity in *maqāsid al-shariah* as well.

Deep Venous Thrombosis (DVT): is blood clot which forms deep in human veins in the lower leg or thigh. The swollen leg is a hint of that disease. DVT can lead to serious problems in the lung which can cause death.

Department of Islamic Development Malaysia (JAKIM): popularly known as JAKIM is a federal government agency in Malaysia that administers Islamic affairs in Malaysia.

Direct Oral Anticoagulants (DOAC): These medications directly inhibit the blood's ability to form blood clots. Several direct oral anticoagulants (DOACs) have been

approved by the United States Food & Drug Administration (FDA) since 2010. Unlike warfarin, these drugs do not require regular blood monitoring.

DNA: Deoxyribonucleic acid is cell in living organisms which stores all the information on genetics, characteristics and traits of the owner. The existence of DNA in things reveal who they are.

Embolism: Obstruction or impediment of an artery or venous typically by a blood clot or an air bubble.

Enoxaparin Sodium: Type of anticoagulant in the LMWH group and manufactured through chemical steps to prevent and treat blood clot or VTE event. Its trading name in Malaysia is Clexane produced by Sanofi Aventis SDN BHD.

Factors VIII, IX, X: These factors influence the blood system to circulate in a good flow. Any decrease in coagulation factors means severe effect to the blood flow such as embolism.

Fatwā: rulings on a point of Islamic law given by a recognized Islamic authority.

Fondaparinux: Anticoagulant for prevention and treatment of VTE. It is manufactured chemically and synthetically with free of animal derivatives. Fondaparinux is approved for use in certain amounts but in certain cases, clinicians prefer to choose natural sources due to its limited advantages.

Graduated compression stocking: a special stocking that help to promote good circulation in the legs with designed to give different pressure over different part of lower limb. Thus, creates a pumping mechanism to enhance circulating blood flow over the legs. It is also called as elastic thrombo-embolic deterrent stocking.

Hemorrhage: an escape of blood out of a ruptured blood vessel and causes bleeding.

Hājah: A situation which puts people in bare difficulty and hardship if the need is denied or cannot be obtained. *Hājah* situation do not obstruct the *maqāṣid al-shariah*,

instead places people who are involved through a long, hard life. However, this situation can be ranked as *ḍarūrah* in certain cases especially in medical issues, *mu'amalat* issues and the sort.

Halal: According to JAKIM definition, “*halal originates from an Arabic phrase that means allowed or permitted by Islamic Law*”

Half-life: The concept of time consumption that requires for a quantity to reduce to half of its initial value.

Ḥarām lidhātihi: Things which are determined as *ḥaram* due to internal factors, solely because of itself which is mentioned clearly in Al-Quran or hadith.

Ḥarām li ghairihi: Things which are determined as *ḥaram* due to external factors, not because of itself.

Ḥaram: *Ḥaram* is the opposite of *halal* which originates from an Arabic phrase that means prohibited by Islamic law.

Heparin induced thrombocytopenia (HIT): A situation where antibody binds to heparin and platelet causing blood clot formation inside a blood vessel occurs thus further leading to thrombosis.

Heparin: A compound occurring in the liver and other tissues which inhibits blood coagulation. A sulphur-containing polysaccharide, it is used as an anticoagulant in the treatment of thrombosis.

High-risk group: The most crucial group of patients which require thromboprophylaxis with LMWH with VTE score 4 and above.

Hyper allergic: Hypersensitive reaction to certain substances which need other alternatives.

Hypercoagulability: Is a state referring to an abnormally increased tendency for blood clotting in the veins or arteries.

Iḥtiyāt: It is a legal level of judgment which usually refers to extreme caution towards imposing legal law in Islam.

Ijtihād: Process of legal reasoning through which the jurist or people who have the ability and authority (*mujtahid*) to derive or rationalise law in the virtues of Al-Quran and hadith.

Inhibitor of factor Xa: a type of anticoagulant that work by selectively and reversibly blocking the activity of clotting factor Xa, preventing clot formation. They affect both factor Xa within the blood and within a preexisting clot. Apixaban, edoxaban, fondaparinux, and rivaroxaban are all Factor Xa inhibitors.

Intermittent pneumatic compression (IPC): device that is used to help prevent blood clots in the deep veins of the legs. The devices use cuffs around the legs that fill with air and squeeze the lower limbs. This increases blood flow through the veins of your legs and helps prevent blood clots mechanically.

Intra venous infusion (IV): The term intravenous means “into the vein”. A thin plastic tube called an IV catheter is inserted into the vein to give medication to the patient. Intravenous can be given either through injection or infusion. Using needle means intravenous by injection while using plastic tube means intravenous by infusion.

Istiḥālah kuliyyah: Transformation process of a certain material from one form into another form that produces new characteristics and names until the no residual of the DNA traced in the latter one.

Istiḥālah saḥīḥah: Transformation process of a material into another form with new characteristics and names by using the right structure theory of *istiḥālah* process. The process is approved by shariah.

Istiḥālah tāmmah: Transformation process of material into another form with new characteristics and names until the DNA of the first material is unable to be traced in the latter one.

Istiḥālah: Transformation or conversion of substance which involves changes in its compositions and properties.

Istihlāk: decomposition or extreme dilution or damage or decay into another form and its compositions and properties untraceable and totally depleted.

Low Molecular Weight Heparin (LMWH): Low-molecular-weight heparin is a class of anticoagulant medications. They are used in the prevention of blood clots and treatment of venous thromboembolism and in the treatment of myocardial infarction. It is measured in Dalton (Da).

Low risk group: The group that needs continuation of non-pharmacological prevention such as elastic stockings for VTE sufferers, mobilization, and avoiding dehydration. Its scores are 1 and 2 according to VTE Risk assessment provided by the MOH.

Maḥṣadah: Evil upon people in relation to objectives of shariah.

Maṣlaḥah: Benefit upon people in relation to objectives of shariah.

Malaysian National Fatwa Council (MCMKI): Malaysian main council of issuing fatwa to contemporary issues which is responsible to standardize the *fatwā* produced by the Fatwa Council of States in Malaysia.

Maqāṣid al-Sharī'ah: The objective of shariah being sent down to humankind including to attain well-being, benefits, and warding off evil. The shariah is to preserve five elements of Muslims such as religion, life, intellect, lineage and wealth. At the same time, to block all means of evil which can obstruct those five elements.

Maternal morbidity: A term typically referring to any physical or mental illness or disability directly related to pregnancy or childbirth. These illnesses or disabilities do not obstruct lives but impaired the quality of life.

Maternal mortality rate (MMR): key performance indicator (KPI) or efforts to improve the health and safety of mothers before, during, and after childbirth per country worldwide.

Maternal mortality: WHO defines it as “the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes”.

Millennium Development Goals (MDGs): The United Nations which includes 191 UN members championed eight goals targeted to be achieved in the year 2015. They agreed to combat eight types of threats which degrade the quality of human lives such as poverty, hunger disease, illiteracy, environmental degradation, and discrimination against women. MDG has its own target and indicator regardless if the mission is accomplished or not.

Ministry of Health (MOH): A Ministry in the government of Malaysia that is responsible for the health system such as health behaviour, cancer, public health, health management, health promotion and healthcare tourism.

Moderate group: The crucial group of patients which require thromboprophylaxis with LMWH. It is scored as 3 points according to VTE Risk assessment provided by the MOH.

Non-vitamin K Antagonist Oral Anti-Coagulants (NOACs): Oral anticoagulant such as dabigatran, which inhibits thrombin, and apixaban, betrixaban, edoxaban and rivaroxaban, which inhibit factor Xa. Increasingly, NOACs is preferable than VKA like

warfarin even though NOACs were least effective in stroke treatment but associated with less intracranial bleeding. However, NOACs are not preferable for pregnant women due to cross placenta.

Porcine: Pig-based derivate which is usually used in medical and pharmaceutical term.

Pregnancy: the condition or period of being pregnant. It also known as gestation; the time during which one or more fetuses develops inside a woman's uterus within 9 months normally. Pregnancy results from sexual intercourse or is assisted by reproductive technology (IVF).

Prophylaxis: Prevention of diseases

Puerperium: The period of about six weeks or around a month and a-half after delivery, where the mother's reproductive organs return to its original non-pregnant condition.

Pulmonary Embolism (PE): A blockage or congestion in the artery of the lungs by thrombus from elsewhere in the body that flows through the bloodstream. Usually, PE is a result of DVT at the legs due to long haul travel, pregnancy and puerperium in women.

Qawā'id Fiqhiyyah: An Arabic term which means Islamic legal maxims in plural. *Qā'idah fiqhiyyah* is the singular. The *qawā'id fiqhiyyah* are the body of abstract rules and theoretical guidelines produced by Islamic *Fiqh* scholars to solve novel issues that neither happened in previous times nor enunciated in Al-Quran or Hadith.

Risk Assessment Model (RAM): Risk assessment of VTE during pregnancy and puerperium produced by the MOH in 2017 to determine which level of risk women belong to, consequently, to address the thromboprophylaxis with or without LMWH.

Skin necrosis: is a kind of unexpected death of cells and tissues including skin.

Subcutaneous (SC): To indicate something is situated under the skin. For example, subcutaneous fat. However, injection subcutaneously means that it is given in the layer of tissue just beneath the skin.

Surveillance: Medically, it is a close observation on patients' conditions to be prescribed proper medicine and treatment. It is also a monitoring of behaviors and activities for further responses.

Thrombi: plural form of thrombus. It is also called as blood clot and is the end form of blood coagulation step in hemostasis. Two components play the role in coagulation are combined platelets and red blood cells which form a plug. Secondly, a mesh of cross-linked fibrin protein.

Thromboprophylaxis: Pharmacological preventions with using anticoagulant as prevention of getting thrombus or VTE.

Thrombotic: The formation of a blood clot inside a blood vessel which obstructing the blood flow through the system of circulatory. The blood clot that can travel to lung called embolus.

Tinzaparin: Type of anticoagulant in LMWH group and manufactured through enzymatic steps to prevent and treat blood clot or VTE event. (produce by another company).

Training Manual: is a book or booklet of instructions, designed to improve the quality of a performed task. Training manual in VTE management is produced by MOH to clarify the prevention and treatment of VTE among pregnant and puerperium mothers.

Venous Thromboembolism (VTE): Blood clot disease in which could block the circulation to any system when the thrombus travels to lung or brain. It considered as life-threatening disease who diagnosed in any people either male or female, pregnancy or non-pregnancy associated with certain risk factors.

Vitamin K antagonists (VKA): is a kind of oral anticoagulant which purposely to reduce blood clotting by reducing the action of vitamin K.



LIST OF TRANSLITERATION

1. Alphabet

ARABIC WORDS TRANSLITERATION SYSTEM TRANSLITERATION TABLE			
Transliteration	Example	Latin	Arabic
fa' r	فأر	'	ء
burd	برد	b	ب
tall	تل	t	ت
thawb	ثوب	th	ث
jidār	جدار	j	ج
ḥalīb	حليب	ḥ	ح
khādim	خادم	kh	خ
dīk	ديك	d	د
dhahab	ذهب	dh	ذ
rafīq	رفيق	r	ر
zamīl	زميل	z	ز
salām	سلام	s	س
sha' b	شعب	sh	ش
ṣakhr	صخر	ṣ	ص
ḍayq	ضيق	ḍ	ض
ṭālib	طالب	ṭ	ط
ẓālim	ظالم	ẓ	ظ
ghulām	غلام	gh	غ
fīl	فيل	f	ف
qalb	قلب	q	ق

kalām	كلام	k	ك
lubb	لب	l	ل
māl	مال	m	م
najm	نجم	n	ن
waraq	ورق	w	و
yamm	يم	y	ي

2. Short Vowel

Arabic	Latin	Example	Transliteration
ا	a	كَتَبَ	kataba
ي	i	عَلِمَ	‘alima
و	u	غَلِبَ	ghuliba

3. Long Vowel

Arabic	Latin	Example	Transliteration
ي، ا	ā	فَقِي، عَالِم	‘ālim, fatā
ي	ī	دَاعِي، عَلِيم	‘alīm, da‘ī
و	ū	اَدْعُو، عُلُوم	‘ulūm, Ad‘ū

4. Diphthong

Arabic	Latin	Example	Transliteration
و	aw	نوم	Nawm
ي	ay	ليل	Layl

ي	iy	شافعي	Shāfi‘iyy (ending)
و	uww	علو	‘Uluww (ending)

5. Exemptions

5.1 Arabic letter ء (hamzah) found at the beginning of a word is transliterated to the letter “a” and not to ‘.

Example: أكبر transliterated to: akbar (not ‘akbar)

5.2 Arabic letter ة (ta marbutah) found in a word without ال (al) which is coupled with another word that contain ال (al) at the beginning of it is transliterated to the letter “t”.

Example: مكتبة الإمام transliterated to: maktabat al-Imām

However, if the Arabic letter ة (ta marbutah) found in a word with ال (al), in a single word or in the last word in a sentence, it is transliterated to the letter “h”.

Example: المكتبة الأهلية transliterated to al-maktabah al-ahliyyah

قلعة

Qal‘ah

دار وهبة

Dār Wahbah

ABBREVIATION

Abbreviations	Description
LMWH	Low Molecular Weight Heparin
UFH	Unfractionated heparin
MOH	Malaysia Ministry of Health
JAKIM	Department of Islamic Development Malaysia
MCMKI	Muzakarah (discussion) Committee of the National Council for Islamic Religious Affairs of Malaysia
DOAC	Direct oral anticoagulant
NOAC	Non-vitamin K Antagonist Oral Anti-Coagulants
RAM	Risk Assessment Model
CPG	Clinical Practical Guideline
VTE	Venous Thromboembolism
MMR	Maternal Mortality Rate
CEMD	Confidential Enquiry Maternal Death
SC	Subcutaneous
IV	Intravenous
DVT	Deep venous thrombosis
PE	Pulmonary embolism
VKA	Vitamin K antagonists
HIT	Heparin induced thrombocytopenia
ASA	Aspirin Antiplatelet
MDGs	Millennium Development Goals