Pregnancy Outcomes Comparing Low Molecular Weight Heparin vs. Unfractionated Heparin in Treating Thrombotic Conditions in Pregnancy

Submitted by

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We hereby recommend that the research project prepared under our supervision by Leigh Ann Lohoefener entitled Pregnancy Outcomes Comparing Low Molecular Weight Heparin vs. Unfractionated Heparin in Treating Thrombotic Conditions in Pregnancy will be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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Abstract

Introduction: The type of heparin to administer for treating thrombotic problems during pregnancy has become a debatable medical question. For years unfractionated heparin (UFH) has been the drug of choice. However, low molecular weight heparin (LMWH) has been gaining favor. Currently, the decision of which drug to use has been left up to physician preference due to the limited number of clinical trials that have been conducted during pregnancy. Methodology: A systematic review of the literature was conducted to determine whether pregnancy outcomes differ among those treated with LMWH, UFH, or both for thrombotic conditions during pregnancy. Twenty-one articles addressing LMWH, UFH, pregnancy outcomes, and thrombotic conditions in pregnancy were reviewed using evidence-based methods. Pregnancies from the first trimester through the postpartum period were included in the review. Results: After a review of the literature, it was found that LMWH is equally if not more effective in treating thrombotic conditions in pregnancy. LMWH was found to have fewer side effects and to be more convenient to administer and monitor than UFH. Conclusion: LMWH is as safe and effective as UFH for preventing and treating thrombosis in pregnancy with the added benefits of fewer side effects and convenience of administration.

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Introduction

Treating and preventing thrombotic conditions in pregnancy has become a debatable medical question. Venous thromboembolism (VTE) continues to be an important cause of maternal morbidity.[1] For many years unfractionated heparin (UFH) has been the drug of choice for treating these conditions. However, over the last few years low molecular weight heparins (LMWH) have been gaining favor due to several advantages over UFH. Some of these advantages include once daily dosing, decreased risk of heparin-induced thrombocytopenia and osteoporosis, and fewer allergic skin reactions.[2] LMWH also has an improved bioavailability and longer half-life than UFH.[3, 4]

Several thrombotic conditions can instigate problems in pregnancy. A variety of thrombotic conditions that affect pregnancy include recurrent pregnancy loss (RPL), venous thromboembolism (VTE), anti-phospholipid syndrome (APS), Factor V Leiden (FLV) mutation, deep vein thrombosis (DVT), and familial thrombophilias. All of these conditions can be treated and even sometimes prevented with the use of both UFH and LMWH heparins. The goal of the prophylaxis and treatment of the above thrombotic conditions is to reduce adverse outcomes and ultimately have a successful pregnancy. A successful pregnancy was determined to be a pregnancy that did not present with any adverse events during the pregnancy and after delivery.

It is difficult to find a large number of pregnant patients willing to participate in a randomized control study comparing UFH to LMWH. For this reason it is important to summarize the results of all well conducted and reliable studies comparing LMWH with

UFH to see if differences in pregnancy outcomes exist and to determine which anti-thrombotic therapy is the safest and most effective for both mother and fetus.

Literature Review

The prevalence of thrombotic conditions in pregnancy is a concern for practitioners in the medical field. Making a decision on appropriate treatment for these conditions has become a debatable question. Recently different treatment options have become available which include LMWH and UFH. For many years the treatment of choice for thrombotic conditions was UFH. Lately, with the development of LMWH, more specific considerations have been evaluated as to which treatment is more effective for both the mother and fetus.

Evaluating the risks and benefits of both LMWH and UFH is important in making a strong recommendation of treatment for patients with concerns of thrombotic conditions. Extensive research has shown that LMWH is as safe and effective, if not more effective, than UFH for treatment.[1-6] Various studies have been conducted evaluating several LMWHs including enoxaparin, dalteparin, and nadroparin.[3-5, 7, 8] All of these studies support safety and efficacy for treatment.

Most studies reviewed looked at the outcomes of the pregnancies regarding side effects of treatment with LMWH or UFH and the success of the pregnancies with various thrombotic conditions. These conditions included recurrent pregnancy loss (RPL), venous thromboembolism (VTE), anti-phospholipid syndrome (APS), Factor V Leiden (FLV) mutation, deep vein thrombosis (DVT), and familial thrombophilias. The major side effects that were less commonly seen with LMWH treatment included heparin-

induced osteoporosis and thrombocytopenia and allergic skin reactions. Based on the literature LMWHs also have a lower rate of adverse pregnancy outcomes.[1-4, 8-12]

Further research into the various treatments for thrombotic conditions needs to be addressed, but until larger studies are conducted it is important to evaluate the current information to help safely and effectively treat pregnant women with life-threatening thrombotic conditions.

Understanding the mechanism of action of LMWH and UFH is important to help determine which drug is more appropriate for treatment of each pregnant patient. LMWH is derived from depolymerization of standard heparin (UFH) and exerts its anticoagulant effect by inhibiting factor Xa.[13] On the other hand, UFH inhibits factor IIa through formation of a tertiary complex. Both UFH and LMWH bind to plasma proteins, endothelium, and macrophages thus affecting bioavailability. LMWH does not bind as easily so it has a higher bioavailability than UFH.[13] Eldor states that LMWH has a bioavailability of 85% and UFH's bioavailability is 10%.[2]

Determining an effective dose of LMWH and UFH can be more difficult during pregnancy. The dosing of anticoagulants in pregnant women is determined by the severity of the thromboembolic disease.[2] To help determine more effective doses, lab values are sometimes obtained. Since LMWH inhibits factor Xa, a specific anti-Xa assay is used for dose adjustments of LMWH. UFH is measured and dose adjusted using activated partial thromboplastin time (aPTT), which measures the anti-factor IIa activity.[13]

A major issue concerning anticoagulants such as LMWH and UFH is cost. One of the main disadvantages of LMWH is that it is more expensive than UFH. Cost is a

factor that practitioners must consider when deciding which treatment to give their pregnant patients, but they also must factor in the advantages of LMWH versus UFH as well. Exact costs of each drug depend on the dose and pharmacy.

Purpose of Study

The use of UFH versus LMWH to treat thrombotic conditions in pregnancy has left health care providers with the open-ended question of which treatment is more beneficial to pregnant women and their fetuses. With ongoing research this question continues to gain answers to which treatment is more safe and effective.

The purpose of this study was to compile as much evidence regarding the comparison of LMWH versus UFH in treating thrombotic conditions in pregnancy and to determine which treatment has the least amount of side effects and the most successful pregnancy outcomes.

Methodology

A systematic review of the literature using evidence based techniques was conducted and included studies regarding the comparison of LMWH versus UFH in treating thrombotic conditions in pregnancy. The outcomes of each treatment were considered for safety and efficacy of the pregnant women and their fetuses. A literature review of articles from the Medline database from 1983-current literature was completed. This search was conducted using the following mesh terms: heparin, clinical trials, pregnancy outcomes, venous thrombosis, low molecular weight heparin, and pregnancy. The articles were evaluated to ensure they were from accredited journals and contained information regarding LMWH and UFH with regards to pregnancy outcomes. A total of twenty-one articles were reviewed. Each article was then further evaluated for inclusion

criteria based on whether the article contained information regarding the comparison of LMWH versus UFH and how each of these drugs affected the treatment of thrombotic conditions in pregnancy. Information from thirteen articles was used to determine whether differences in pregnancy outcomes exist between the two types of heparin. The information collected included the number of pregnancies involved, the type of heparin administered, the percentage of successful pregnancies, and adverse events for each type of heparin.

Results

Twenty-one articles were reviewed concerning information about LMWH, UFH, thrombotic conditions, and pregnancy outcomes. According to evidence-based medicine, these articles included seven level 1 grade A evidence, twelve level 2 or 3 grade B evidence, and two articles of level 4 grade C evidence. Of these twenty-one articles, thirteen articles met the inclusion criteria for the comparison of LMWH verses UFH with regards to pregnancy outcomes (see Table 1). These articles contained three level 1 grade A evidence, nine level 2 or 3 grade B evidence, and one level 4 grade C evidence.[1, 3-7, 9-11, 14-17] Two articles also were included that contained background information concerning the mechanism of action, bioavailability, dosing, monitoring, and cost of LMWH and UFH.[2, 13]

These studies revealed that LMWH is as safe and effective in treating thrombotic conditions during pregnancy as UFH. Based on the literature from the thirteen articles that met inclusion criteria, 69.2% of the articles state LMWH is as effective if not more effective than UFH in treating women with thrombosis during pregnancy. The following table summarizes the information obtained from the articles reviewed (see Table 1).

Table 1

Successful Pregnancies and Adverse Outcomes of LMWH vs. UFH

Type of Heparin Administered	Total # of Pregnancies Involved	*Successful # of Pregnancies	**Adverse Outcomes
LMWH	3765 (97%)	3099 (82.3%)	666 (17.6%)
UFH	118 (3%)	66 (55.9%)	52 (44.1%)

* A successful pregnancy was determined to be a pregnancy that did not present with any adverse events during the pregnancy or after delivery.

** Adverse outcomes include pulmonary embolism, VTE, significant bleeding complications, antenatal bleeding, wound hematomas, skin reactions, osteoporitic fractures, thrombosis, miscarriage, preterm infants, and fetal malformations.[1, 3-7, 9-11, 14-17]

Anticoagulant therapy is used for the treatment of a variety of thrombotic conditions. Ten articles discussed the use of LMWH for the treatment of venous thromboembolism (VTE) in pregnancy, whereas one article supported UFH for the treatment of VTE in pregnancy.[1-6, 9, 12, 18-20] The ten articles supporting LMWH for VTE had three level 1 grade A recommendations, six level 2 or 3 grade B recommendations, and one level 4 grade C recommendation while the article supporting UFH for VTE had a level 3 grade B recommendation. Furthermore, one article reviewed discussed the treatment of recurrent pregnancy loss (RPL) with LMWH.[21] The use of LMWH being a better choice of treatment for deep vein thrombosis (DVT) was discussed in two articles and three articles looked at LMWH for the treatment of anti-phospholipid syndrome (APS).[7, 8, 10, 11, 15] The article by D. Cochran discussed Factor V Leiden (FVL) and UFH for treatment.[17] Another article discussed familial thrombophilias being treated with LMWH and one article looked at UFH for the treatment of pregnant women with lupus

anticoagulant or anticardiolipin antibodies.[11, 14] Two articles reviewed did not specify whether anticoagulant treatment was better with LMWH or UFH for the treatment of VTE and APS.[16, 22]

Discussion

Evidence in Literature

The issue of thrombotic conditions causing a high incidence of morbidity and mortality in pregnant women is of great concern. More studies continue to be developed comparing LMWH and UFH for determination of which treatment has the most successful outcomes in pregnancies with thrombotic conditions. Many of these studies support the use of LMWH over UFH due to decreased side effects such as heparin-induced thrombocytopenia and osteoporosis, bleeding complications, and fewer allergic skin reactions. However, until more studies are completed comparing the two types of heparin, the ultimate decision of which treatment pregnant women with thrombotic conditions receive is still left up to the practitioner. The purpose of this paper was to organize the studies available to determine which treatment, LMWH or UFH, seems to be the most successful at this time in reducing maternal morbidity and mortality.

After reviewing the literature, it was found that LMWH has been used for the treatment of a variety of thrombotic conditions including women with recurrent pregnancy loss (RPL), venous thromboembolism (VTE), anti-phospholipid syndrome (APS), Factor V Leiden (FLV) mutation, deep vein thrombosis (DVT), and familial thrombophilias. Sanson et al. studied 486 pregnancies with LMWH as the sole anticoagulant including 290 women with comorbid conditions. They observed only 3

thromboembolic complications out of 486 pregnancies when LMWH was used as the sole treatment.[9]

Recurrent pregnancy loss due to thrombotic conditions during pregnancy is an important topic of discussion due to high rates of morbidity and mortality. Not only are these conditions dangerous for the mother, but also for the fetus. Several studies have been conducted to assess how to treat these serious conditions in pregnancy. Greer and Nelson-Piercy reviewed 64 studies and 2777 pregnancies. They found LMWH to be effective for prophylaxis and treatment of women with RPL (85.4%) and VTE (96.6%) due to its decreased side effects of bleeding and heparin-induced thrombocytopenia. No maternal deaths were reported.[4]

Women who suffer with APS are at high risk for an unsuccessful pregnancy. Stone et al studied women suffering from APS and treated with LMWH plus low dose aspirin (LAD) and found a 91% live birth rate in those who had a significant past pregnancy morbidity and/or thrombosis.[15] The first randomized trial comparing dalteparin to UFH for the treatment of APS in pregnancy was conducted by Stephenson et al. They found patients taking LMWH or UFH plus aspirin (ASA) to have a higher live birth rate.[7]

A study reviewed by D. Cochran discussed a pregnant woman diagnosed in her eighth week of pregnancy with deep vein thrombosis (DVT). This patient was found to have a FVL mutation and was treated successfully throughout her pregnancy with UFH.[17] Ulander and colleagues conducted non-randomized clinical trials on patients with lower limb DVT during pregnancy. It was discovered that LMWH has several advantages over

UFH including a decreased risk of heparin-induced thrombocytopenia and a lower risk of osteoporosis.[8]

The natural physiologic changes occurring with a pregnant woman increase her risk for thromboembolism, especially if she has a history of familial thrombophilias. LMWH, nadroparin, has been found to have a 92.3% success rate in treating pregnant women with familial thrombophilia according to a review by Makatsaria, whereas UFH only had a success rate of 72.7%.[11]

Weakness in the Literature

Unfortunately with the limited number of studies ethically allowed to be conducted on pregnant women there is a lack of conclusive evidence to be collected comparing LMWH versus UFH. Many of the studies currently available comparing these treatments have a limited sample size. More studies need to be conducted using a larger sample size of pregnant women with thrombotic conditions. Until these studies are completed, physicians must determine based on current literature which treatment they feel is most suitable in treating their pregnant patients with thrombotic conditions.

Validity of the Review Section

This review of LMWH versus UFH in treating thrombotic conditions in pregnancy is valid based on constructive evidence-based medicine and graded levels of evidence.

Conclusion

As physician assistants, it is important to continuously review peer-reviewed articles and carefully assess the data available to accurately treat our patients. When treating pregnant women with thrombotic conditions concern should be placed on both

the mother and fetus. After reviewing the current literature, practitioners should understand that LMWH is as safe and effective for the treatment of thrombotic conditions as UFH with the added benefit of fewer side effects and should be considered as the drug of choice for treatment. Many of the clinical studies already completed regarding LMWH conclude that further randomized clinical trials with larger sample sizes are needed before LMWH can be considered the drug of choice for treatment of thrombosis in pregnancy.

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Appendix
Raw Data

Study (Year)	Research Addresses	Level of Evidence	Numbers and Characteristics	Pertinent findings	Supportive of Research
	1. Unfractionated Heparin 2. LMWH 3. Both 4. Background	1. Random Control Trial 2. Non-Random Control Trial 3. Observational (case control, cohort, systematic review, meta-analysis) 4. Observational (case study, cohort without control, case series) 5. Non-experimental 6. Expert Opinion	Main Data		1. Yes LMWH Tx 2. Yes UFH Tx 3. Both Helpful Tx 4. No Specified Tx 5. Background
Sanson, B (1999)	2	3	Total Pregnancies (**n=486)** LMWH sole anticoagulant from 21 different studies: Results: Pregnancies **290 (60%)** had maternal comorbid conditions and **196 (40%)** non-comorbid conditions. LMWH associated with only 3 thromboembolic complications out of 486.	Women without comorbid conditions **(31%)** implies use of LMWH not associated with adverse fetal/infant outcomes. Long term use of LMWH safe because complications associated with these meds (i.e.osteoporosis, thrombocytopenia, bleeding) occurred infrequently.	1
Barbour (2004)	2	2	Total **n=138** peak and **n=112** through anti-Xa levels obtained for **n=13** pregnancies in 12 women; **n=250** pregnancies used dalteparin.	Recommended BID dose of 100 u/kg: 54% received therapeutic dose initially, 30% required initial dose of 140 u/kg; at 30 weeks gestation: 12% = 100 u/kg, 35% = 120 u/kg, 50% = 140 u/kg. None of the women had recurrent DVT's on dalteparin treatment. Results show 85% of the pregnant women using 100 u/kg BID was not sufficient to achieve peak therapeutic anticoagualant levels. There were no significant changes from heparin-induced osteopenia.	1

Rowan (2003)	2	3	**Prophylactic Group: n=26** pregnancies in 24 women plus 8 pregnant women on low dose ASA. Enoxaparin therapy started at 10.7 weeks gestation. Median duration of treatment with enoxaparin = 24.1 weeks. Enoxaparin ceased at 44 hours prior to delivery; **p=0.002** **Therapeutic Group: n=32** pregnancies in 28 women plus 15 pregnant women also on low dose ASA. Enoxaparin started at 13.7 weeks gestation. Median duration of therapy = 12.9 weeks. 27 pregnancies > 20 weeks. In 6 pregnancies enoxaparin decreased to 40 mg qd in 3rd trimester, 3 changed to UFH at 36-38 weeks, and 18 continued enoxaparin until delivery; **p=0.004**.	**Prophylactic Group:** None of women on enoxparin for prophylactic therapy had antepartum hemorrhage, thromboembolic events, skin allergies, or developed thrombocytopenia. **Therapeutic Group:** None of the women on therapeutic enoxaparin had complications of antepartum hemorrhage, thrombocytopenia, skin allergies or clinical evidence of fracture. Therapeutic enoxaparin used BID (1 mg/kg) can be safely used during pregnancy, carefully managed at delivery, and continued for 3 months after pregnancy to prevent long-term risks of recurrent DVT. **Overall conclusion:** Women can be safely managed on enoxaparin for prophylactic and therapeutic therapy during pregnancy.	1
Greer (2005)	2	3	**Total Analysis: n=64** studies, **n=2777** pregnancies **Treatment of VTE: n=15** studies, **n=174** patients; therapy: enoxaparin; **LMWH** administered BID in **n=153** cases **Treatment of thromboprophylaxis: n=30** studies, **n=1348** pregnancies, **n=1321** pregnancies; **LMWH** administered for risk factors (previous VTE or thrombophilia) **Treatment for prevention of adverse pregnancy outcomes: n=15** studies, **n=447** pregnancies; **LMWH** used for primary prevention of recurrent pregnancy loss (RPL); **n=5** studies, **n=88** pregnancies; **LMWH** used for prevention of preeclampsia, fetal growth restriction, and other adverse pregnancy outcomes.	No maternal deaths. Overall successful pregnancies = live births: **n=2215** pregnancies **(94.7%)** successful outcomes; subdivided: LMWH for RPL = **n=370** pregnancies **(85.4%)** successful outcomes; LMWH for thromboprophylaxis or treatment of VTE = **n=1845** pregnancies **(96.6%)** successful outcomes. **Conclusions:** No maternal deaths. LMWH effective for thromboprophylaxis in pregnancy. LMWH has advantages over UFH with reduced risk of bleeding. LMWH has decreased risk of heparin-induced thrombocytopenia (HIT): **n=2777** pregnancies with no HIT associated with thrombosis reported. **Overall:** LMWH is safe and effective for preventing and treating thrombosis in pregnancy.	1
Stephenson (2004)	3	1	Total **n=28** pregnant women: **n=14** LMWH (dalteparin), **n=14** UFH; all patients received ASA 81 mg; LMWH dosed every 24 hours and UFH dosed every 12 hours (BID); smaller does of LMWH needed vs. UFH. **Results:** LMWH - **n=13** conceived, **n=9** live births **(69%, CI 95%)**; UFH - **n=13** conceived, **n=4** live births **(31%, CI 95%)**.	First randomized trial comparing dalteparin to UFH for treatment of antiphospholipid syndrome (APS) in pregnancy. Patients taking LMWH/UFH plus ASA have a higher live birth rate. Treatment with dalteparin and ASA is equal to UFH plus ASA for treatment of APS in pregnancy.	Both helpful but LMWH better.

Sorensen (2000)	2	3	Total of **n=66** pregnant women (**n=60** dalteparin, **n=4** enoxaparin, **n=2** tinzaparin); controls (n=17,259 single pregnancies) receiving no prescriptions in the same period as LMWH mothers.	LMWH doesn't cross placenta so no teratogenic side effects on fetus. Non-significant increase in pre-term deliveries (7/66 pregnancies). No evidence stating LMWH used in pregnancy is associated with increased risk of malformations, low birth weight, or stillbirth. Therefore, LMWH is safe alternative to UFH for treating obstetric thromboprophylaxis.	1
Rosove (1990)	1	2	**n=15** pregnancies treated with UFH starting at average of 10.3 weeks gestation continued through pregnancy; given subcutaneous UFH every 12 hours; average UFH dose was 24, 700 plus/minus 7400 units; 14/15 live births with 1 miscarriage at 12 weeks after 6 weeks of treatment with UFH, 5/14 placentas examined showing minimum infarction, 13/14 pregnancies had normal neonatal outcome.	UFH valuable in decreasing placental infarcts, birth weights improved, increased live births in women with two or more previous fetal losses, previous 2nd and 3rd trimester losses, SLE, lupus anticoagulants, and anticardiolipin antibody titers of five or more standard deviations. 9 preterm C-section deliveries.	2
Ginsberg (1989)	UFH + Coumadin UFH alone Coumadin alone	3	**n=1325** pregnancies associated with anticoagulant therapy. **A: n=355** heparin alone, **78.6%** receiving heparin for prevention of VTE; **B n=578** oral anticoagulants alone, **33.4%** receiving oral anitcoags for prevention of VTE; **C n=392** both heparin and oral anticoagulants, **39.8%** receiving heparin + anticoags for preventing VTE. Maternal comorbid conditions: **A:** 77/355 - excluded decrease of 10.4% for rate of adverse outcomes, premature infants <37 weeks had decrease of 10.4% to 3.6%, death rate of 2.5%. **A -** rate of adverse outcomes falls dramatically **B & C** - no change; **A** death rate lower than **B & C**.	High rate of adverse fetal outcomes associated with heparin therapy in pregnancy. This is largely due to comorbid conditions suffered by mother rather than heparin therapy. Oral anticoagulants cause adverse fetal/infant outcomes. Heparin therapy should be recommended for thrombotic preventional treatment in pregnancy.	2
Ulander (2003)	3	2	**n=35** patients with lower limb DVT during pregnancy. 1st week: **n=10** UFH, **n=25** LMWH, then **n=35** patients treated with LMWH (dalteparin or enoxaparin) for secondary prophylaxis until delivery. Anti-Xa levels measured to achieve therapeutic levels of LMWH. Post-thrombotic symptoms measured with questionaire by Villalta et al. **(n=35)**.	Prevalence of post-thrombotic symptoms (PTS) not statistically different in comparison of proximal and distal DVT. Prevalence of PTS 51% in study. Overall location of DVT does not predict PTS. LMWH has advantages over UFH: decreased risk factors and heparin-induced thrombocytopenia. Prevalence of PTS in pregnant women doesn't seem to be higher than non-pregnant women. LMWH is as safe and effective as UFH.	1

Stone (2004)	3	3	**n=33** pregnant women with primary APS; treatment is low dose ASA (LAD) plus LMWH (dalteparin).	91% live birth rate can be achieved in women with primary APS with significant past pregnancy morbidity and/or thrombosis; antithrombotic drugs increase the outcome of pregnancies complicated by APS; exact dosages yet to be determined.	1
Noble (2005)	3	3	**n=50 (n=25** UFH plus LDA and **n=25** LMWH + LDA); LMWH = enoxaparin.	Obstetric Outcome: 21/25 (84%) LMWH had a viable infant; 4/25 (16%) LMWH miscarried; 20/25 (80%) UFH had a viable infant; 5/25 (20%) UFH miscarried; miscarriages in LMWH group occurred significantly later than UFH (8.7 plus or minus 1.2 weeks vs. 7.2 plus or minus 1.3 weeks, $p<0.05$); **Conclusion:** LDA + LMWH and LDA + UFH provide similar obstetric outcomes.	3
Di Nisio (2005)	2	1	2 studies, **n=242** participants included in study. Interventions = ASA, UFH, and LMWH. Primary outcome measured = live birth > 37 weeks gestation. **n=54** women negative for anticadiolipin antibodies and no obvious cause for previous pregnancy losses. Of **n=54**, **n=27** ASA and **n=27** placebo.	Both ASA and placebo groups had 81% of pregnancies with outcome of live births. Enoxaparin prophylaxis increased live birth rate compared to ASA alone. (0/10 losses for enoxaparin and 9/10 losses for ASA). **Conclusion:** At present, use of ASA or LMWH to prevent pregnancy loss in women with greater than or equal to 2 miscarriages or 1 later intrauterine fetal death without apparent cause other than thrombophilia, not based on firm evidence.	1
Eldor (2002)	2	4	Several case studies and non-randomized clinical trials supporting LMWH in treating VTE in pregnancy. N=210 for LMWH. 119 successful pregnancies 26 adverse events and 65 unknown outcomes. N= 115 for UFH. Not enough info to determine pregnancy outcomes and adverse events.	**Conclusions:** LMWH is safe and effective in pregnancy. ACCP has recognized advantages of LMWH. LMWH is emerging treatment of choice.	1

Pettila (1999)	3	1	**n=105** pregnant patients: **n=50** LMWH (dalteparin) and **n=55** UFH. Primary outcome measurement includes no thrombotic complications in either group. Bleeding complications: dalteparin 0.18, UFH 0.64. 2 UFH patients suffered from lumbosacral compression fractures, no fractures in dalteparin group.	LMWH safe in treating non-pregnant patients with VTE. No reoccurrences of VTE in dalteparin group. More bleeding complications in UFH group. No thrombocytopenia in either group. **Conclusion:** LMWH is safe and effective and only needs to be administered once daily. UFH causes more bleeding complications and may require more frequent lab follow-up than LMWH.	1
Gates (2004)	2	1	**Trial 1** (Antenatal thromboprophylaxis): pregnant women are at increased risk for thromboembolic disease. **n=16** pregnant patients (**n=8** enoxaparin, **n=8** placebo). 2 interventions were being compared: enoxaparin vs placebo (normal saline). Patients were randomized as recruited. **Trial 2** (Thromboprophylaxis post C-section): cesarean delivery, **n=141 (n=70** enoxaparin, **n=71** placebo) pregnant patients. Enoxaparin vs placebo (normal saline). Patients were randomized as recruited. Patients were followed for 6 months post delivery for thrombotic events.	**Trial 1:** 1 woman in placebo group had symptomatic thromboembolic event, a PE 29 days post delivery. Sample size is too small for conclusions regarding effectiveness of enoxaparin. **Trial 2:** 1 woman in LMWH group had symptomatic thromboembolic event, a PE in 2nd week post delivery. Insufficient evidence to make recommendation for clinical practice for enoxaparin.	4
Huxtable (2005)	2	3	**n=72** patients exposed to LMWH for prophylaxis. **n=85** pregnancies (singles and multiples). **93/99** potential live births with 94% success rate. **11/12** twin pregnancies successful. **1/1** triplet pregnancy successful. 68 single births. Mean max dose of enoxaparin was 38.1 mg every 12 hours. 9 patients experienced bleeding events. 49% of pregnancies with immediate family history of TE disease or adverse obstetrical outcomes. **Adverse events: n=9** bleeding, **n=3** placental pathologies, **n=3** preeclampsia, **n=2** allergic reactions, **n=3** bleeding events requiring intervention. Average dose of enoxaparin was 30 mg SQ every 12 hours.	No thrombotic complications or osteoporosis occurred. Enoxaparin is safe and effective for preventing thromboembolism and adverse obstetrical complications in all pregnancies including 12/13 multiple pregnancies. Adjusted dose prophylaxis enoxaparin to a target anit-Xa level of 0.2-0.4 IU/mL at 5-6 hours after dose is administered = 94% success rate than previous systemic reviews with fixed doses of enoxaparin. No complications with epidurals. Singles had 94% success rate. Multiples had 92% success rate. No fetal abnormalities with enoxaparin. **Conclusion:** Enoxaparin is safe and effective for treatment and prophylaxis.	1
D. Cochran (2000)	1	4	**n=1** pregnant woman diagnosed in 8th week of pregnancy with DVT due to Factor V Leiden (FVL) mutation. In hospital UFH given, then next 7 months as outpatient patient used SQ heparin pump. 8 weeks post-partum heparin was discontinued.	UFH is a treatment for DVT's with FVL during pregnancy.	2

Makatsaria (2003)	2	3	LMWH = nadroparin. **Treatment and secondary prophylaxis of DVT's: n=18** pregnancies. Nadroparin SQ every day through pregnancy and 1 month post-partum was administered. Results: no recurrence of DVT or adverse effects. **n=17** healthy deliveries, **n=1** missed abortion. **Thromboprophylaxis for Familial thrombophilia: n=60** pregnancies in 32 thrombophilic women. 92.3% success rate with nadroparin. 72.7% success rate with UFH. 17.4% success rate with no treatment. 1 case of DVT fixed by increasing nadroparin to BID SQ. **APS: n=85** patients. 3 groups: 1) **n=26** nadroparin 2) **n=29** (**n=20** nadroparin, **n=9** UFH) 3) **n=30** nadroparin and ASA. 84/85 (98.8%) successful pregnancies. 1 fetal death in group 3. Premature delivery higher in patients receiving nadroparin from 2nd trimester (17.6% group 2) than in patients receiving nadroparin from 1st trimester (7.6% group 1).	LMWH's provide effective antithrombotic activity and have a favorable SE profile. Nadroparin is safe and effective for thromboembolic prophylaxis during pregnancies in women with familial thrombophilia and ASP. Results in APS study show early and continued use of nadroparin is effective in prevention of fetal loss and thrombotic complications. Decrease risk of premature delivery with nadroparin use in APS. Success of pregnancies with nadroparin were all >90%. Average dose for success was 0.1 mL/10 kg SQ once daily.	1

Cochran Review Gates (2002)	3	1	**n=649** total pregnant women in 8 trials. 4 studies compared methods of prophylaxis antenatally: LMWH vs. UFH 92 studies), ASA + heparin vs. ASA alone (one study), and unfractionated heparin vs. no treatment (one study). 4 studies compared postnatal prophylaxis after C-section: hydroxyethyl starch with UFH (one study), heparin with placebo, one LMWH and one UFH (two studies), and UFH vs. LMWH (one study). **Burrows 2001: n=76** women having elective or emergency C-section; LMWH (dalteparin) vs. placebo (saline). **Gibson 1998: n=17** women having C-section; LMWH vs. UFH. **Hamersley 1998: n=61** women with APS, protein S or protein C deficiency, or idiopathic thrombophilia; LMWH vs. UFH. **Heilmann 1991: n=207** women delivered by C-section; hydroxyethyl starch vs. UFH. **Hill 1988: n=50** women delivered by C-section; UFH. **Howell 1983: n=40** women with previous TED treated with anticoagulants for at least 6 weeks; calcium heparin. **Pettila 1999: n=107** women with previous PE, VTE, protein C or S deficiency, activated protein C resistance, pregnancy, or contraceptive pills. **Rai 1997: n=90** women with 3 or more consecutive miscarriages and positive results for antiphospholipid antibodies on at least 2 or more occasions > 8 weeks apart; calcium heparin + LDA or LDA alone.	**Results of outcomes:** LMWH vs. UFH - fetal loss 1 LMWH, 1 UFH; osteoporosis 1 UFH; bleeding episodes 9 LMWH, 35 UFH; blood transfusions 2 UFH; thrombocytopenia 2 UFH. ASA + Heparin vs ASA alone - fetal loss 13 ASA + Heparin, 26 ASA; UFH vs. no treatment-symptomatic thromboembolic event 1 no treatment; symptomatic thromboembolic DVT 1 no treatment; bleeding episodes 2 UFH; osteoporosis 1 UFH; fetal loss 1 UFH, 1 no treatment. LMWH or UFH vs. placebo - symptomatic thromboembolic event 1 heparin; symptomatic thromboembolic DVT 1 heparin; blood transfusion 1 placebo. Starch vs. UFH – asymptomatic thrombo-embolic event - 7 starch, 9 UFH; blood transfusions 2 starch, 1 UFH; bleeding episodes 5 starch, 2 UFH; serious wound complications 9 starch, 6 UFH. **Conclusions:** In regards to bleeding episodes, LMWH has advantages over UFH for antenatal prophylaxis. Insufficient evidence to base recommendations for thromboprophylaxis during pregnancy and early post-natal period. Larger studies need to be conducted with randomized to assess effects of treatment methods for TE.	1

Cochran Review Empson (2005)	3	1	Outcomes of all treatments given to women for prevention of miscarriage due to antiphospholipid antibody or lupus anticoagulant to maintain pregnancy. Thirteen studies with total of **n=849** participants. UFH + ASA vs ASA alone (2 trials, **n=140**), LMWH + ASA vs. ASA alone (1 trial, **n=98**), High-dose UFH vs. Low-dose UFH (1 trial, **n=50**), ASA alone (**n=135**), Prednisone + ASA vs placeco, ASA, and Heparin + ASA (3 trials, **n=286**), Intravenous immunoglobulin +/- UFH + ASA vs UFH or LMWH + ASA (2 trials, **n=58**), intravenous immunoglobulin vs. prednisone + ASA (1 trial, **n=82**).	UFH + ASA vs. ASA = no significant reduction in pregnancy loss. LMWH + ASA vs. ASA = no significant reduction in pregnancy loss. No advantage of high-dose vs. low-dose UFH. ASA alone showed no significant decrease in pregnancy loss. Prednisone + ASA showed significant increase in prematurity when compared to placebo, ASA, or heparin + ASA. An increase of pregnancy loss or premature birth was associated with intravenous immunoglobulin +/- UFH + ASA when compared to UFH or LMWH + ASA. No significant difference in outcomes when comparing intravenous immunoglobulin to prednisone + ASA. **Conclusions:** Reduction of pregnancy loss by 54% is seen with combined UFH + ASA. Larger randomized trials need to be completed to assess the differences b/w UFH and LMWH.	4
Cochran Review Van Dongen (2004)	3	1	Objective of review is to determine effect of LMWH compared to UFH in treating VTE. 22 studies with total of **n=8867** participants. Thrombotic complications: LMWH 151/4181 (3.6%) vs. UFH 211/3941 (5.4%). Reduction of thrombosis size: LMWH 53% of participants, UFH 45% of participants. Major hemorrhages: LMWH 41/3500 (1.2%), UFH 73/3624 (2.0%). in 18 trials, 187/4193 (4.5%) LMWH patients died and 233/3861 (6.0%) UFH patients died. 9 studies (**n=4451**) examined proximal thrombosis: **n=2192** LMWH, **n=2259** UFH. End of follow-up, **n=80** LMWH (3.6%) and **n=143** (6.3%) UFH had thrombotic complications. Major hemorrhage: **n=18** (1.0%) LMWH and **n=37** (2.1%) UFH. 9 studies (**n=4157**) showed statistically significant reduction of mortality with LMWH. End of follow-up, 3.3% (70/2094) LMWH died and 5.3% (11./2063) UFH died.	In the 9 studies, subgroup analysis showed significant reductions in thrombotic conditions and major hemorrhage with LMWH when compared to UFH. **Conclusions:** LMWH is more effective than UFH for initial treatment of VTE. Significant reductions in occurrence of major hemorrhage with initial treatment and overall mortality at follow-up was seen with LMWH.	1

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