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REVIEW ARTICLE

Where do we go now with low molecular weight heparin use in obstetric care?

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Summary. The use of low molecular weight heparins (LMWH) in obstetric care has grown considerably since their introduction into clinical practice in the early 1990s. However, because of the physiological changes of pregnancy, the predictable pharmacokinetic profile of LMWH is lost and some uncertainty exists around the optimal dosing regimen for LMWH in obstetric care. Two recent United Kingdom prospective surveys of the management of acute venous thromboembolism (VTE) suggest that despite recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) for a twice daily LMWH regimen, a once daily regimen is acceptable for the treatment of venous thromboembolism; and that accepted thromboprophylactic doses licensed for non-pregnant individuals may not be applicable during the second and third trimester for VTE thromboprophylaxis. Accepting that randomized clinical studies are difficult in obstetric care, future advances could be made through population-based multi-center studies, coupled with pharmacokinetic modeling studies, which have the potential to determine the optimal dosing regimen for the various obstetric indications.

Keywords: heparin, low-molecular weight heparins, obstetrics, review.

Background

Since their introduction in the early 1990s, the use of low molecular weight heparins (LMWH) in clinical practice has grown exponentially and they are now the preferred option when an immediately acting anticoagulant agent is required. This is unsurprising, as they offer a predictable dose-response curve, require no routine monitoring, are less likely to cause osteoporosis and heparin-induced thrombocytopenia (HITT), making them an attractive option relative to unfractionated heparin (UFH) [1,2].

After their introduction therefore, it was only a matter of time before they were employed for the indications where anticoagulant therapy was required antenatally, namely; (i) treatment of venous thromboembolism (VTE), (ii) thromboprophylaxis (VTE and arterial), (iii) thromboprophylaxis of women with mechanical heart valves and (iv) prevention of fetal loss during the first trimester and placental dysfunction in thrombophilic women [3]. However, unlike the non-pregnant population, one key advantage is lost, the fixed dose-response curve, as a result of the physiological plasma changes of pregnancy.

Surveys of anticoagulation practice for the treatment of VTE antenatally in the UK and Ireland have found that although LMWH are widely used, the duration of treatment, the particular LMWH used, the frequency of anti-Xa monitoring and the level of anti-Xa activity aimed for are highly variable [4,5]. It would be reasonable to anticipate a similar picture when LMWH is used for other antenatal indications. In spite of this variation in practice, LMWH have been used successfully for these indications, with several large studies confirming their safety antenatally [1,6] even although the doses, the specific LMWH used and the dosing regimens have been derived from pilot studies, observational studies and expert opinion. Despite this successful use, however, some important questions still remain:

1. For many of the indications when LMWH is employed antenatally, the dose and dosing frequency of LMWH recommended is different from the non-pregnant population. Is this really necessary?
2. What level of anticoagulation with prophylactic LMWH will prevent reoccurrence of VTE and arterial thrombosis throughout pregnancy?
3. Are LMWH effective and safe for thromboprophylaxis use in pregnant women with mechanical heart valves?

Physiological changes during pregnancy affecting the pharmacokinetics of LMWH

During pregnancy, there is an expansion of intravascular plasma volume by 60%, and extravascular (breasts, uterus,

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peripheral oedema) water content [7], potentially increasing the volume of distribution of a given drug.

For drugs which are excreted renally, elimination is dependent on the glomerular filtration rate (GFR), active tubular secretion and or re-absorption. In healthy women studied during each trimester and 8–12 weeks postpartum, it has been found that the GFR increases by 50% by the end of the first trimester [8]. It is thought that this increase in GFR is maintained throughout pregnancy until the last 3 weeks, when a decrease in GFR is observed, reaching postpartum values by the last week [9].

What does this mean for LMWH? Due to their molecular size, they are confined to the intravascular space, so the increase in plasma volume will increase their volume of distribution. The route of primary elimination is through renal excretion. If one were asked to predict what changes one would expect to observe during pregnancy regarding LMWH pharmacokinetics, considering the physiological changes which occur, one might predict a lower C_{max} (peak concentration), AUC (area under the curve – in relation to an overall exposure to the drug) and a shorter half-life.

The question is whether these changes are significant enough to warrant a different dosing strategy compared with a non-pregnant population.

Treatment of VTE

The United Kingdom Royal College of Obstetricians (RCOG) guidelines suggest that a twice daily LMWH regimen be used, preferably with enoxaparin or dalteparin [10]. Reference is made to two papers which assessed prophylactic doses of dalteparin and enoxaparin during pregnancy [11,12]. Blomback *et al*. described the pharmacokinetics of dalteparin (2500 or 5000 units once daily in 17 pregnant women during the third trimester). Although a measurable anti-Xa concentration was detectable at 16 h in the 14 women in the study receiving a 5000 unit dose once a day, the C_{max}, t_{max} and AUCs were lower compared with a study in which dalteparin was administered to 12 healthy men and women [13]. Casele *et al.* described the pharmacokinetics of enoxaparin (40 mg) in 13 women who received thromboprophylaxis throughout pregnancy and had serial pharmacokinetic parameters measured at three points (12–15 weeks gestation, 30–33 weeks and then 6–8 weeks postpartum). During early and late pregnancy, the maximum concentration and the last measurable anti-Xa activity level were lower than in the non-pregnant state. Both these papers suggest that the clearance of LMWH increased during the pregnant state. So to maintain an appropriate activity of the LMWH over a 24-h period, a twice daily regimen was suggested by RCOG in 2001 [14], and subsequently endorsed by the American College of Chest Physicians (ACCP) in 2004 [15], and reaffirmed by RCOG in 2007 [10].

However, no robust pharmacokinetic data exists for *treatment* doses of LMWH during pregnancy, so it is not known whether the same profile observed for prophylactic doses is true for treatment doses. Considering that in a non-pregnant population, it has been shown that a once daily regimen is at least as effective as a twice daily regimen [16], could a single daily dose be administered to pregnant women?

One might argue that because of the increase in volume of distribution and the increase in the GFR, the higher total daily dose and twice daily administration is justified. However, there is emerging evidence of tinzaparin being effective in this population at the dose employed in non-pregnant subjects (175 units kg^{-1} once daily). A study by Smith *et al.* [17] published data on 12 women either at high risk of VTE, or being treated for VTE, with 175 units kg^{-1} once daily tinzaparin. The authors aimed for an anti-Xa level 4-h post-dose of 0.3 to 1.0 units mL^{-1}. Although their results echoed those of Blombak and Casele, in that during the course of pregnancy the clearance of the LMWH increased, Smith *et al.* reported that the majority of women did not need their dose adjusted during pregnancy and the once daily dosing regimen appeared to be effective. One criticism of the results is the anti-Xa level aimed for; RCOG currently suggest to aim for an anti-Xa concentration 3-h post-dose of 0.5–1.2 units mL^{-1} for the treatment of VTE [10], not 0.3–1.0 units mL^{-1} 4-h post-dose. In addition, probably more importantly, it is not clear whether the *generic* target anti-Xa level can be applied to tinzaparin, for it has a different anti-Xa to anti-thrombin ratio when compared with enoxaparin and daltaparin (where most of the LMWH data in pregnancy comes from). Tinzaparin has a lower anti-Xa to anti-thrombin ratio of 1.5–2.0 compared with enoxaparin's 3.3–3.8 or dalteparin 2.8 [18], i.e. for the same target anti-Xa levels, it produces a much greater anti thrombin effect so it may have a greater anticoagulant effect for the same anti Xa activity. Also, relatively little long-term outcome data exists for tinzaparin currently, whereas it does exist for both enoxaparin and dalteparin.

The value in anti-Xa levels as a marker of efficacy?

The other uncertainty is anti-Xa monitoring, and its value as a marker of efficacy. Many of the studies which describe the pharmacokinetics of LMWH during pregnancy use the anti-Xa level as a marker of antithrombotic activity. However, the target anti-Xa level is arbitrary. A study assessing tinzaparin versus unfractionated heparin in the prophylactic treatment of VTE in patients undergoing general surgery found that anti-Xa activity correlated well with body weight, but correlated weakly with antithrombotic activity and with the incidence of hemorrhage [19]. This coupled with Smith *et al.*'s results of tinzaparin use during pregnancy, does raise the question of what the correlation is between anti-Xa levels and anti-thrombotic activity. The key question is not what the target anti-Xa levels should be, but what dose of a LMWH prevents thrombosis in clinical trials.

Additionally, a study from the UK national external quality assessment scheme (NEQAS) has demonstrated poor performance of anti-Xa assays in diagnostic laboratories, with extremely wide coefficients of variation [20]. This may in part explain some of the inconsistencies observed in published

literature. For example, Nelson-Piercy *et al*. [21] and Ellison *et al*. [22] both assessed enoxaparin 40 mg for antenatal VTE prophylaxis and found no correlation between the woman's gestational stage and anti-Xa levels measured in several laboratories. However, Hunt *et al*. [23], in a single center study, assessed the efficacy of dalteparin in 34 high-risk pregnancies, found that most women required 5000 IU once daily until week 20, when a dose increase was necessary to 5000 IU twice a day in order to maintain the 2-h post-injection anti-Xa level of 0.4–0.6 units mL^{-1}.

Current practice of antenatal VTE management within the UK

Voke *et al*. [5] recently surveyed antenatal VTE practice in 25 centers in the UK and Ireland (126 patients) and found that 97% of patients were treated with LMWH. Of those on LMWH, 66% received a once daily regimen (Table 1). Anti-Xa monitoring was performed at 90% of centers, with a wide range of target values.

More recently, Knight *et al*. [24] has published the results of a population-based national case–control study, evaluating the incidence and management of obstetric pulmonary embolism in the UK. In their study (143 patients), 134 (97%) women were treated with LMWH, with 49% on a once daily regimen (Table 2).

Voke's and Knight's studies suggest that despite the updated RCOG guidelines for the management of VTE, there is no consensus around the optimal anticoagulant management of these patients, with many clinicians favoring a once daily approach.

Prevention of VTE

Pulmonary embolism remains the most common direct cause of maternal death in the UK [25]. Since the RCOG guidelines for thromboprophylaxis after cesarean section were published in 1995 [26], the number of maternal deaths as a result of VTE has fallen substantially, suggesting that thromboprophylaxis is effective. However, most VTE occur antenatally, hence the importance of individual risk assessment and prophylaxis during the antenatal period. Both the Scottish Intercollegiate Guidelines Network (SIGN) and the RCOG have published guidelines for thromboprophylaxis during pregnancy [27,28]; Table 3 lists the RCOG dosing recommendations. Both sets of guidelines state the importance of individual risk assessment and tailoring of the appropriate level of thromboprophylaxis according to risk.

A Cochrane review has highlighted the lack of evidence from randomized trials evaluating different strategies for the prevention of VTE during pregnancy [29]. While we know that thromboprophylaxis has a role to play, what is not so clear is the optimal dose and dosing frequency for patients antenatally in the different risk categories of patients.

In Voke's recent study of the treatment of VTE, 16 mothers had a history of a previous VTE, of whom only four were on antenatal thromboprophylaxis. In Knight's study of obstetric PE, nine women who had suffered a PE should have received antenatal thromboprohylaxis with LMWH according to the RCOG guidelines – only three of them did (with one receiving a lower dose than that recommended). In addition, six women (4%) suffered a PE despite antenatal prophylaxis with LMWH; all of these women were of booking weights between 56–89 kg and treated with a once daily dose of LMWH [dalteparin 2500 (2), enoxaparin 20 mg (1) and enoxaparin 40 mg (3)]. These results clearly highlight the importance of identifying patients at risk and starting thromboprophylaxis, but also that inadequate dosage can lead to failed thromboprophylaxis, and the need to judge the effective degree of anticoagulation in these women. Of the six thromboprophylactic failures in Knight's study, the three patients on enoxaparin 40 mg daily suffered their pulmonary embolism late in the third trimester. Of the remaining three patients on suboptimal thromboprophylaxis, two suffered their pulmonary embolism in the second trimester and one in the third trimester (M. Knight, personal communication). In Voke's study, of the four thromboprophylactic failures at the time of the second event, three patients were receiving enoxaparin 40 mg daily with two patients experiencing the VTE in the third trimester and the remaining enoxaparin patient experiencing the VTE in the second trimester. The remaining failed thromboprophylaxis patient in Voke's study was on dalteparin 2500 IU daily prior to the second VTE at 15 weeks.

The results of Knight's and Voke's studies tend to agree with the findings of Casele, Blomback and Hunt [11,12,23], that during the course of pregnancy, the physiological changes which occur might warrant a higher dosing strategy compared with a non-pregnant population for thromboprophylaxis – particularly as the pregnancy progresses. The current RCOG guidelines

Table 1 Regimen (once or twice daily) and which heparins were found to be used by Voke *et al*.

Heparin	Number of patients treated	Initial twice a day LMWH	Transferred to once daily	Initial once a day LMWH	Transferred to twice a day
Dalteparin	32	9	7	23	11
Enoxaparin	59	27	5	32	7
Tinzaparin	31	3	1	28	1
UFH	4	–	–	–	–
Total	126	39 (31%)	13	83 (66%)	19

Table 2 Regimen (once or twice daily) and which heparins were found to be used by Knight *et al.*

Heparin	Once daily regime (%)	Twice daily regime (%)	Total (%)
Enoxaparin	32 (39)	51 (61)	83 (62)
Dalteparin	11 (44)	14 (56)	25 (19)
Tinzaparin	23 (88)	3 (12)	26 (19)

suggest a prophylactic dose of enoxaparin 40 mg daily or dalteparin 5000 IU daily or tinzaparin 4500 IU daily for a woman of normal booking weight (50–90 kg). The treatment failures in Voke and Knight's studies are concerning and suggest that the optimal dosing strategy for women with a normal booking weight is at least 40 mg enoxaparin daily (or dalteparin 5000 IU daily or tinzaparin 4500 IU daily) in the first trimester and then 40 mg enoxaparin twice daily (or dalteparin 5000 IU twice daily or tinzaparin 4500 IU twice daily) during the second and third trimester. However, before such a change in practice can be recommended more evidence is required.

Thromboprophylaxis for a previous arterial thrombosis

Very little has been published on the use of LMWH for arterial thrombosis prophylaxis during pregnancy. The majority of patients who fall into this category are those with the antiphospholipid syndrome (APS). For the non-pregnant population, study results assessing anti-thrombotic therapy in APS with arterial thromboembolism have been conflicting [30–35] and there is even less clarity on the optimal anti-thrombotic strategy during pregnancy for this indication. Where studies have assessed anti-thrombotic use (including aspirin) in APS during pregnancy, the primary outcomes have usually assessed prevention of recurrent fetal loss, as opposed to recurrence of arterial thrombosis [36,37]. Although the optimal anti-thrombotic strategy is likely to consist of aspirin plus a LWMH, the dose of LMWH which would prevent arterial thrombosis recurrence in this population is yet to be determined.

Prophylaxis of women with mechanical heart valves

The approach to this indication is also controversial and patients should be risk assessed on a case-by-case basis.

The risk of valve thrombosis appears to be least with the use of coumarin anticoagulation throughout pregnancy (4%) and increases markedly with the use of unfractionated heparin (UFH) alone, with a risk of life-threatening thrombosis of 29–33% and mortality of 7–15%, respectively [38,39]. The observation that most reported valve thrombosis during pregnancy has occurred with the use of UFH, has raised the question of the effectiveness of the UFH for this indication during pregnancy [38].

In the past, various prophylactic regimens have been used for women with mechanical heart valves during pregnancy; (i) oral anticoagulation throughout pregnancy (accepting the concerns of adverse outcomes e.g. warfarin embryopathy [40,41]), (ii) oral anticoagulation until week 6, replaced by UFH until week 12 (to minimize the risk of warfarin embryopathy), followed by oral anticoagulation and (iii) UFH throughout pregnancy. All these regimens are sub-optimal: use of warfarin, because of the concerns for fetal abnormality, and use of heparin because of the greater risk of valve thrombosis and maternal complications. Clinicians are faced with a conflict between the risk to the fetus and the risk to the mother. With the advent of the use of LMWH for the antenatal indications, it was hoped that they might be more efficacious than UFH for this indication, based on the assumption that they provide a more predictable anticoagulant effect. However, after a number of reports of valve thrombosis and stroke, their use has been discouraged [42]. In 2002, Sanofi Aventis Pharmaceuticals changed the warnings labeling for enoxaparin, stating that it is not recommended in patients with prosthetic heart valves [43]. This warning was prompted from a South African study, which compared the effectiveness of enoxaparin with a combination of warfarin and UFH. The safety committee terminated the study after only 12 patients were enrolled as a result of two deaths from prosthetic valve thrombosis in the enoxaparin group, prompting concerns about its use during pregnancy for this indication, and implying the same for the other LMWH.

A recent study by James *et al.* [44] reported their experience and that in the literature of using LMWH for this indication during pregnancy in 76 women. Of those 76 women treated with LMWH, 17 experienced a thrombotic event (22%). Thirteen were valve thromboses, two were strokes and two were myocardial infarctions. There were three deaths (4%). Some of the data in James *et al.* study are not complete, so it is difficult to draw any firm conclusions. However, they do seem to suggest that LMWH is by no means inferior to UFH and could be used, echoing Ginsberg *et al.*'s conclusion in 2003 [45]. In 2004, the ACCP issued the following guidance for this indication, suggesting that any one of the three regimens below would be appropriate [15]:

Table 3 Antenatal prophylactic and therapeutic doses of low molecular weight heparin

Prophylaxis	Enoxaparin (100 units/mg)	Dalteparin	Tinzaparin
Normal body weight (50–90 kg)	40 mg daily	5000 units daily	4500 units daily
Body weight < 50 kg	20 mg daily	2500 units daily	3500 units daily
Body weight > 90 kg	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Higher prophylactic dose	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Therapeutic dose	1 mg kg^{-1} 12-hourly	90 units kg^{-1} 12-hourly	90 units kg^{-1} 12-hourly

1. Adjusted dose bid LMWH throughout pregnancy in doses adjusted either to keep a 4-h post injection anti-Xa heparin level of 1.0–1.2 units mL^{-1} (preferable) or adjusted according to weight.
2. Aggressive adjusted dose UFH throughout pregnancy, i.e. administered SC q12h in doses adjusted to keep the mid-interval aPTT at least twice control or to attain an anti-Xa heparin level of 0.35 to 0.70 units mL^{-1}.
3. UFH or LMWH (as above) until the 13 weeks changing to warfarin until the middle of the third trimester, and then restarting UFH or LMWH.

In all of the suggested regimens, the guidance suggests the addition of low-dose aspirin, 75–162 mg day^{-1}, in those patients considered at high risk (although what this means is not defined), along with restarting usual oral anticoagulation postpartum. Ginsberg *et al.* [45] define higher risk patients as those with a history of systemic embolism or atrial fibrillation.

The recommendations from the ACCP are helpful, although anecdotally many clinicians are uneasy with the LMWH option during pregnancy for this indication, and a similar question arises as to that in VTE treatment and prophylaxis: if the target anti-Xa level is 1.0–1.2 units mL^{-1} 4-h post injection for enoxaparin and dalteparin, could this be achieved with a once daily regimen or would a twice daily regimen need to be employed?

Since Ginsberg's call for tackling this problem [45], little has been published in the literature to move the problem forward and provide clinicians with any firm reassurance. This illustrates the complexity of the problem and the difficulties in recruiting patients in such studies.

We conclude that each case should be considered on an individual basis depending on the patient's personal risk factors (age, smoking, hypertension, diabetes, hyperlipidemia, type and severity of valve lesion, presence of atrial fibrillation, heart failure or low cardiac output, size of the left atrium, previous thromboembolism, and thrombophilia) and valve risk factors i.e. the type and location of prostheses implanted. First generation mechanical valves e.g. the Starr–Edwards caged ball valve and Bjork–Shiley standard valves, have a high thromboembolic risk; single tilting disc valves have an intermediate thromboembolic risk; and the newer (second and third generation) bileaflet valves have low thromboembolic risks [46].

Considering the lack of reassuring information within the area, a multi-disciplinary approach to managing this population involving obstetricians, hematologists and cardiologists would seem prudent.

Conclusions and the future

The questions discussed here will only be answered by conducting clinical trials in pregnant women, for the various indications, randomized to a once daily or twice daily LMWH, with and without monitoring of anti-Xa levels, with and without subsequent dose adjustment. The ethical considerations surrounding this patient population and the number of patients that would need to be recruited are extremely challenging and may be insurmountable. An alternative strategy is through population-based multi-center studies, coupled with pharmacokinetic studies and modeling, as demonstrated by Green and Duffull [47]. They determined a dosing strategy for obese patients requiring enoxaparin using this technique. Such studies have the potential to answer some of the uncertainties and inform best practice in this area.

In the future, other agents such as fondaparinux could supersede LMWH use antenatally. Fondaparinux is a synthetic pentasaccharide which binds to antithrombin and inhibits factor Xa without inhibiting thrombin [48]. Fetal safety is always a crucial consideration when considering maternal anticoagulation. Initially, it was thought that fondaparinux would be safe to use antenatally – based on an *in vitro* a human cotyledon model, which suggested that fondaparinux does not cross the placenta [49]. However, an *in vivo* study in five infants whose mothers had received 2.5 mg fondaparinux daily, found low but detectable concentrations of anti-Xa in the umbilical cord blood [50]. To date, the limited clinical experience of fondaparinux during pregnancy [51–53] suggests that it may be a valuable alternative to danapariod when heparin is contra-indicated along with danaparoid. More safety data are required, particularly around fetal safety, before its use is likely to become wide spread. Therefore, for the medium term the research priorities should focus on LMWH and should look to address the following:

1. What are the outcomes of those patients managed with once daily LMWH compared with those managed on a twice daily regimen for the acute management of VTE?
2. Is there a need to suggest a higher prophylactic dose during the second and third trimester for VTE prophylaxis?
3. What are the outcomes of those women with a mechanical heart valve managed on a LMWH antenatally?

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References

1 Greer IA, Nelson-Piercy C. Low-molecular weight heparins for prophylaxis and treatment of venous thromboembolism during pregnancy: a systematic review of safety and efficacy. *Blood* 2005; **106**: 401–7.
2 van Dongen CJJJ, van den Belt AGM, Prins MH, Lensing AWA. Fixed dose subcutaneous low molecular weight heparin versus adjusted dose unfractionated heparin for venous thromboembolism (review). *Cochrane Database Syst Rev* 2004; **4**: CD001100.
3 Greer IA, Hunt BJ. Low molecular weight heparin in pregnancy: current issues. *Br J Haematol* 2005; **128**: 593–601.
4 Copplestone JA, Pavord S, Hunt BJ. Anticoagulation in pregnancy: a survey of current practice. *Br J Haematol* 2004; **124**: 123–5.
5 Voke KM, Keidan J, Parvod S, Spencer NH, Hunt BJ. The management of antenatal venous thromboembolism in the UK and Ireland: a prospective multi-centre survey. *Br J Haematol* 2007; **139**: 545–58.
6 Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, Brenner B, Dulitzky M, Nielsen JD, Boda Z, Turi S, Mac Gillavry MR, Hamulyák K, Theunissen IM, Hunt BJ,

Büller HR. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; **81**: 668–72.
7 Dawes M, Chowienczyk PJ. Pharmacokinetics in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2001; **15**: 819–26.
8 Davison JM, Nobel MCB. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. *Br J Obstet Gynaecol* 1981; **88**: 10–7.
9 Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet* 2005; **44**: 989–1008.
10 Royal College of Obstetricians and Gynaecologists. *Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management*. Guideline no.28 Update. London: RCOG Press, 2007. Available at http://www.rcog.org.uk.
11 Blomback M, Bremme K, Hellgren M, Lindberg H. A Pharmacokinetic study of Dalteparin (Fragmin) during late pregnancy. *Blood Coagul Fibrinolysis* 1998; **9**: 343–50.
12 Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low molecular weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol* 1999; **181**: 1113–7.
13 Eriksson BI, Soderberg K, Widlund W, Wandeli B, Tengborn L, Risberg B. A comparative study of three low molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers. *Thromb Res* 1995; **73**: 398–401.
14 Royal College of Obstetricians, and Gynaecologists. *Thromboembolic Disease During Pregnancy and Puerperium: Acute Management*. London: RCOG Press, 2001.
15 Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; **126**: 627–44.
16 Merli G, Spiro TE, Olsson C-G, Abildgaard U, Davidson BL, Eldor A, Elias D, Andrew Grigg A, Musset D, Rodgers GM, Trowbridge AA, Yusen RD, Zawilska K. Subcutaneous Enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001; **134**: 191–202.
17 Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J. Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. *Am J Obstet Gynecol* 2004; **190**: 495–501.
18 White RH, Ginsberg JS. Low molecular weight heparins: are they all the same. *Br J Haematol* 2003; **121**: 12–20 (Review).
19 Laizorovicz A, Bara L, Samama MM, Haugh MC. Factor Xa inhibition: correlation between the plasma levels of anti-Xa activity and occurrence of thrombosis and haemorrhage. *Haemostasis* 1993; **23**(Suppl. 1): 89–98.
20 Kitchen S, Lampietro R, Woolley AM, Preston FE. Anti-Xa monitoring during treatment of LMWH or danaparoid: inter-assay variability. *Thromb Haemost* 1999; **82**: 1289–93.
21 Nelson-Piercy C, Letsky EA, de Swiet M. Low molecular weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. *Am J Obstet Gynecol* 1997; **176**: 1062–8.
22 Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. *Br J Obstet Gynaecol* 2000; **107**: 1116–21.
23 Hunt BJ, Doughty H, Majurndar G, Copplestone A, Kerslake S, Buchanan N, Hughes G, Khamashta M. Thromboprophylaxis with low molecular weight heparin (dalteparin) in high risk pregnancies. *Thromb Haemost* 1997; **77**: 39–43.
24 Knight M, UKOSS. Antenatal pulmonary embolism: risk factors, management and outcomes. *Br J Obstet Gynaecol* 2008; **115**: 453–61.
25 CEMACH. *Why Mothers Die 2000-2002. The Sixth Report of the Confidential Enquiries Into Maternal Deaths in the United Kingdom*. London: RCOG Press, 2004.
26 Royal College of Obstetricians and Gynaecologists. *Report of the RCOG Working Party on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics*. London: RCOG press, 1995.
27 Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis During Pregnancy, Labour & After Vaginal Delivery. Guideline no.37. London: RCOG Press, http://www.rcog.org.uk, 2004.
28 Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of Venous Thromboembolism – A National Clinical Guideline (No 62), October 2002.
29 Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database Syst Rev* 2002; CD001689. DOI: 10.1002/14651858.CD001689
30 Derksen RHWM, de Groot PG, Kappelle LJ. Low dose aspirin after ischaemic stroke associated with antiphospholipid syndrome. *Neurology* 2003; **61**: 111–4.
31 Khamashta MA, Cuadrado MJ, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; **332**: 993–7.
32 Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992; **117**: 303–8.
33 Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, Laskin C, Fortin P, Anderson D, Kearon C, Clarke A, Geerts W, Forgie M, Green D, Costantini L, Yacura W, Wilson S, Gent M, Kovacs MJ. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 2003; **349**: 1133–8.
34 Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T. A randomized clinical trial of high intensity warfarin versus conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome. *J Thromb Haemost* 2005; **3**: 848–53.
35 Rickles FR, Marder VJ. Moderate dose oral anticoagulant therapy in patients with the antiphospholipid syndrome? *J Thromb Haemost* 2005; **3**: 842–3.
36 Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *Br Med J* 1997; **314**: 253–7.
37 Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol* 2002; **100**: 408–13.
38 Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves – a systematic review of the literature. *Arch Intern Med* 2000; **160**: 191–6.
39 Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *Br J Obstet Gynaecol* 2000; **107**: 245–53.
40 Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68**: 122–40.
41 Ginsberg JS, Hirsh J, Turner DC, Levine MN, Burrows R. Risks to the foetus of anticoagulation therapy during pregnancy. *Thromb Haemost* 1989; **61**: 197–203.
42 http://www.fda.gov/medwatch/SAFETY/2002/lovenox.htm (accessed 18th November 2007).
43 *Enoxaparin (Clexane) – Summary of Product Characteristics*. *Sanofi-Aventis*, March 2007 http://emc.medicines.org.uk/ (accessed 10th December 2007).
44 James AH, Brancazio LR, Gehrig TR, Wang A, Ortel TL. Low molecular weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. *J Matern Fetal Neonatal Med* 2006; **19**: 543–9.
45 Ginsberg JS, Chan WS, Bates SM, Kaatz S. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med* 2003; **163**: 694–8.
46 Goldsmith I, Turpie AGG, Lip GYH. ABC of antithrombotic therapy: valvar heart disease and prosthetic heart valves. *Br Med J* 2002; **325**: 1228–31.

47 Green B, Duffull SB. Developing a dosing strategy for enoxaparin in obese patients. *Br J Clin Pharmacol* 2003; **56**: 96–103.
48 *Fondaparinux (Arixtra) – Summary of Product Characteristics*. Glaxosmithkline, November 2007 http://emc.medicines.org.uk/ (accessed 10th December 2007).
49 Lagrange F, Vergnes C, Brun JL, Paolucci F, Nadal T, Leng JJ, Saux MC, Banwarth B. Absence of placental transfer of pentasaccharide (Fondaparinux, Arixtra) in the dually perfused human cotyledon in vitro. *Thromb Haemost* 2002; **87**: 831–5.
50 Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; **350**: 1914–5.
51 Mazzolai L, Hohlfeld P, Spertini F, Hayoz D, Schapira M, Duchosal MA. Fondaparinux is a safe alternative in case of heparin intolerance during pregnancy. *Blood* 2006; **108**: 1569–70.
52 Harenberg J. Treatment of a woman with lupus and thromboembolism and cutaneous intolerance to heparins using fondaparinux during pregnancy (letter). *Thromb Res* 2007; **119**: 385–8.
53 Gerhardt A, Zotz RB, Stockschlaeder M, Scharf RE. Fondaparinux is an effective alternative anticoagulant in pregnant women with high risk of venous thromboembolism and intolerance to low-molecular-weight heparins and heparinoids. *Thromb Haemost* 2007; **97**: 496–7.