Anticoagulazione in gravidanza: serve monitorare l'eparina a basso peso molecolare?

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Policlinico S. Orsola – Malpighi, Bologna

Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pr

Betul Oran[1], Aviva Lee-Parritz[2], Jac

Thromb Haemost 2004; 9

Table I: Articles of the use of Low Molecular Weight Heparin in women with prosthetic heart valves during pregnancy.

Author	Year	No. of pregnancies	Drug	Dose	Anti-Xa monitoring	Maternal event	Fetal event	Comment
Harenberg [23]	1997	2	Enoxaparin	adj*	All monitored	-	-	
Arnaout [22]	1998	10	Nadroparin	7500 u bid	Not monitored-	1 peripartum hemorrhage, 2 valve thrombosis	1 spontaneous abortion, 1 stillbirth	
Elkayam [12]	1999	2	NA	NA	NA	-	-	
Abildgaard [28]	1999	1	NA	NA	Monitored	-	-	
Lev Ran [15]	2000	1	Enoxaparin	40 mg qd	Not monitored	Valve thrombosis	-	
Lee [19,25]	2000	9	Nadroparin	adj*	All monitored	-	-	
Oles [13]	2001	1	Enoxaparin	1 mg/kg bid	Not monitored-	Valve thrombosis	1 spontaneous abortion	
Rowan [16]	2001	14	Enoxaparin	adj*	All monitored	1 valve thrombosis	2 spontaneous abortions	The patient with valve thrombosis had lowest anti-Xa activity among group
Ellison [17]	2001	1	Enoxaparin	adj*	Monitored	-	-	
Roberts [18]	2001	3	Tinzaparin	175 U/kg qd	1 monitored	2 CVA		Events occurred in the patients not monitored
Lindhoff-Last [27]	2001	7	NA	NA	NA	-	-	
Leyh [14]	2002	1	Reviparin	3500 U tid	Not monitored	Valve thrombosis	-	
Mahesh [20]	2002	1	Enoxaparin	40 mg bid	Not monitored	Valve thrombosis	-	The event occurred a week after switching to LMWH from UFH
Izaguirre [21]	2002	9	Enoxaparin	adj*	All monitored	-	-	
Meschengieser [26]	2003	14	1 Enoxaparin 2 Nadroparin 11 Dalteparin	adj*	All monitored	2 hematomas at the cesarean wound	1 spontaneous abortion	
Vural [24]	2003	5	Enoxaparin	60 mg bid	Not monitored	1 embolism	1 spontaneous abortion	
Total		**81**				**7 valve thrombosis (8.6%); 2 CVAs (2.5%); Total thromboembolism (12.3%)**	**6 spontaneous abortions (7.4%)**	

NA, non-applicable; CVA, cerebrovascular accident; LMWH, low molecular weight heparin; UFH, unfractionated heparin
*Dose adjustments were made to maintain a therapeutic post-injection anti-factor Xa level

9 eventi tromboembolici in 30 gravidanze trattate con dosi di LMWH in base al peso
1 evento tromboembolico in 51 gravidanze monitorate con anti-Xa

Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy

Betul Oran[1], Aviva Lee-Parritz[2], Jack Ansell[1]

Thromb Haemost 2004; 92: 747–51

In pregnant women with mechanical heart valves, LMWH appears to be a suitable option to a vitamin K antagonist. The use of LMWH warrants monitoring and appropriate dose adjustments to maintain a 4-6 hr post-injection anti-factor Xa level at a minimum of 1.0 U/ml to decrease the incidence of TEC.

Protesi valvolari meccaniche e gravidanza

	N. complicanze tromboemboliche/ N. gravidanze
Elkayam et al, J cardiovasc Pharmacol Therapeut 2004; 9: 107	2/5
Descarries et al, J Heart Valve Dis 2006; 15: 679	1/5
Quinn et al, Haematologica 2009; 94: 1608	1/12
Yinon et al, Am J Cardiol 2009; 104: 1259	1/23
Abildgaard et al, Thromb Res 2009; 124: 262 ($)	2/12
McLintock et al, BJOG 2009; 116: 1585 (#)	5/47

Totale gravidanze seguite: 104
Timing controllo anti-Xa: variabile da 1 a 4 settimane
Target anti-Xa: intorno a 1.0-1.2 anti-Xa IU/ml a picco (# 0.4-0.7 anti-Xa IU/ml a valle)
Modifica posologia LMWH: $ media n=3 (1-6)

11/12 complicanze tromboemboliche attribuite a livelli anti-Xa subterapeutici e/o scarsa compliance

Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience

John Quinn,[1] Kate Von Klemperer,[2] Ruth Brooks,[2] Donald Peebles,[3] Fiona Walker,[2] and Hannah Cohen[1]

Haematologica 2009. 94:1608-1612.

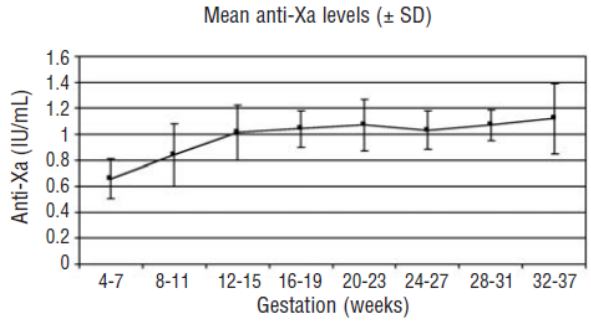


Figure 1. Mean anti-Xa levels during all pregnancies (±SD)

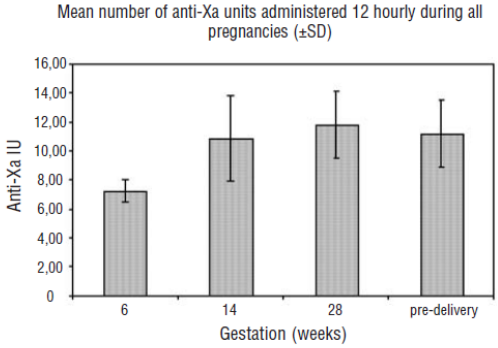


Figure 2. Mean number (±SD) of anti-Xa IU LMWH administered 12 hourly SC during all pregnancies

Large increases in the doses of LMWH were required to achieve effective anticoagulation during pregnancy, with mean doses pre-delivery showing an approximately 54% increase over initial dose.

Current clinical practice guideline recommandations for anticoagulation management in pregnant women with MHV

Recommendation	American College of Cardiology/American Heart Association (ACC/AHA) 2008[35]	American College of Chest Physicians (ACCP) 2012[4]	European Society of Cardiology (ESC) 2011[5]
Dosage recommendations for LMWH	• LMWH should be administered twice daily SC and the dose adjusted to maintain the anti-Xa level between 0.7-1.2 U/mL 4 hours after administration (Class I, level C)	• Suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 hours pos SC injection (Grade 1A)	• LMWH should be administered twice daily with dose adjustment according to weight and target anti-Xa level 4–6 hours post-dose 0.8-1.2 U/mL (Class IIa, level C)
Monitoring (levels/ timing/frequency)	• LMWH should not be administered to pregnant patients with MHV unless anti-Xa levels are monitored 4–6 hours after administration (Class III, level C) • No additional comments regarding frequency or timing of levels relative to time throughout pregnancy	• If LMWH is used, it should be administered BID (evidence summary, not included in official recommendation) • No additional comments or recommendations regarding frequency or timing of levels relative to time throughout pregnancy	• In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly (Class I, level C) • LMWH should be avoided, unless anti-Xa levels are monitored (Class III, level C)

FCSA
XIV edizione 2015

Nelle donne con protesi valvolari cardiache meccaniche viene raccomandata una delle tre seguenti procedure:

1) EBPM sottocute ogni 12 ore a dosi terapeutiche, preferibilmente aggiustate tramite periodico controllo dell'attività anti-FXa per mantenere un valore di circa 0.8-1.0 U/ml a 4 ore dall'iniezione;

Protesi valvolari meccaniche e gravidanza
Dosaggio anti-Xa a picco e/o a valle?

Alcuni lavori hanno evidenziato che i livelli anti-Xa in range terapeutico a picco sono associati nella maggior parte dei casi a livelli subterapeutici a valle (< 0.50 anti-Xa IU/ml)

- numerosi casi (Rowan et al, Am J Obstet Gynecol 2001; 185: 633)
- ≈ 70% dei casi (McLintock et al, BJOG 2009; 116: 1585)
- 91% dei casi (Barbour et al Am J Obstet Gynecol 2004; 191: 1024)
- 73% dei casi (Friedrich et al, J Perinatol 2010; 30: 253)
- 50% dei casi (Fan et al, Circulation 2011; 122: A18219)
- 46% dei casi (Berresheim et al, Thromb Res 2014; 134: 1234)

Enoxaparin treatment in women with mechanical heart valves during pregnancy

Janet A. Rowan, FRACP,[a] Lesley M.E. McCowan, MD,[a] Peter J. Raudkivi, FRACS,[b] and Robyn A. North, PhD[a]

(Am J Obstet Gynecol 2001;185: 633-7.)

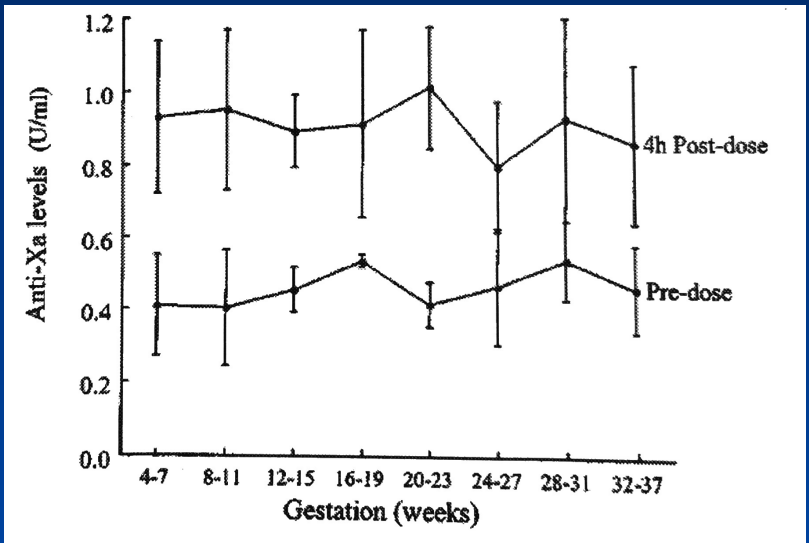
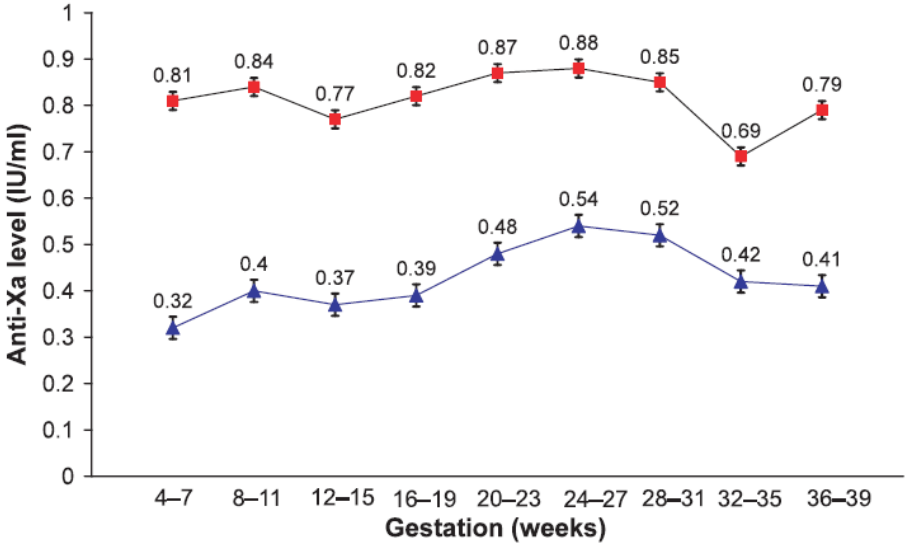


Fig 1. Anti-Xa levels and enoxaparin dose through pregnancy. Anti-Xa levels and enoxaparin dose are shown as mean (SD).

Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin

C McLintock,[a] LME McCowan,[b] RA North[c]

BJOG 2009;116:1585–1592.



Mean (SE) pre-dose (▲) and 4-hour post-dose (■) anti-Xa levels

A case series of LMWH use in pregnancy: Should trough anti-Xa levels guide dosing?

Michelle Berresheim [a], Jodi Wilkie [a], Kara A. Nerenberg [b], Quazi Ibrahim [c], Tammy J. Bungard [c,*]

Thrombosis Research 134 (2014) 1234–1240

Fig. 2. Comparison of LMWH dosing strategies in wom
anti-Xa guided vs calculated weight based.

Each of the four pregnant women with MHV required higher than weight-based enoxaparin dosing to achieve target anti-Xa levels, with an overall mean increase to 1.35 mg/kg every 12 hours compared with 1 mg/kg every 12 hours (Table 3). In all four cases, achieving target peak anti-Xa levels did not ensure maintenance of a minimal trough level. In order to sustain the minimum target trough anti-Xa level (>0.6 U/mL), peak levels exceeded the upper target of 1.2 U/mL in the majority of women.

Target a picco 1.0-1.2 anti-Xa IU/ml
Target a valle: > 0.6 anti-Xa IU/ml

Anticoagulation in Pregnancy

Sorel Goland, MD[a,*], Uri Elkayam, MD[b]

Cardiol Clin 30 (2012) 395–405

Table 2
Recommended approach for anticoagulation in women with MHV during pregnancy

	Higher Risk	Lower Risk
Definition	First-generation PHV (eg, Starr-Edwards, Bjork-Shiley) in the mitral position, MHV in the tricuspid position, AF, history of TE on anticoagulation	Second-generation PHV (eg, St Jude Medical, Medtronic-Hall) in the mitral position and any mechanical PHV in the aortic position
Treatment	Warfarin (INR 2.5–3.5) for 35–36 wk, followed by UFH[a] (aPTT ≥2.5) to parturition + ASA 80–100 mg every day or LMWH (trough anti-Xa ≥0.7, peak ≤ 1.5) or UFH[a] (aPTT ≥2.5) for 12 wk, followed by warfarin (INR 2.5–3.5) to 35–36 wk, then IV UFH[a] (aPTT >2.5) to parturition +ASA 80–100 mg every day	LMWH (trough anti-Xa ≥0.6, peak ≤ 1.5) to 35–36 wk then IV UFH (aPTT ≥2.0) to parturition or LMWH (trough anti-Xa ≥0.6, peak ≤1.5) for 12 wk, or UFH[a] (aPTT ≥2.0) followed by warfarin (INR 2.5–3.0) for 35–36 wk, then IV UFH (aPTT ≥2.0) to parturition

Tromboembolismo venoso in gravidanza

- Vari studi osservazionali hanno mostrato un basso rischio di complicanze trombotiche ed emorragiche nelle donne in gravidanza con TEV trattate con LMWH in base al peso e senza nessun monitoraggio
  (Lepercq et al, BJOG 2001; 108: 1134 - Voke et al, Br J Haematol 2007; 139: 545 - Knight BJOG, 2008; 115: 453)

- Altri studi hanno dimostrato che per mantenere il corretto livello di anticoagulazione (misurato con l'anti-Xa) non è necessario nessun aggiustamento della dose di LMWH
  (Rey et al Int J Gynaecol Obstet 2000; 71: 19 - Rodie et al BJOG; 2002; 109: 1020 - Smith et al Am J Obstet Gynecol 2004; 190: 495)

Tromboembolismo venoso in gravidanza

Altri studi hanno invece mostrato che:

- nelle donne con TEV in gravidanza la somministrazione della LMWH in base al peso determina un livello di anticoagulazione (misurato con l'anti-Xa) più basso dell'atteso
- le modificazioni fisiologiche indotte dalla gravidanza richiedono un aumento della dose di LMWH

(Casele et al Am J Obstet Gynecol 1999; 181: 1113 - Jacobsen et al BJOG 2003; 110: 139 - Barbour et al Am J Obstet Gynecol 2004; 191: 1024 - Ni Ainle et al Blood Coagul Fibrinol 2008; 19: 689 - Friedrich et al J Perinatol 2010; 30: 253 - Gibson et al Thromb Res 2013; 131: e71)

Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin

E. Rey[a,*], G.E. Rivard[b]

International Journal of Gynecology & Obstetrics 71 (2000) 19–24

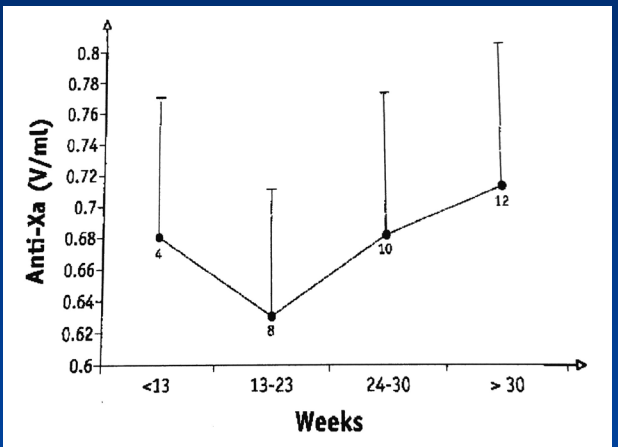


Fig. 2. Mean peak anti-Xa activity levels throughout pregnancy in women on a therapeutic dose. Numbers indicate the number of patients included in each data point.

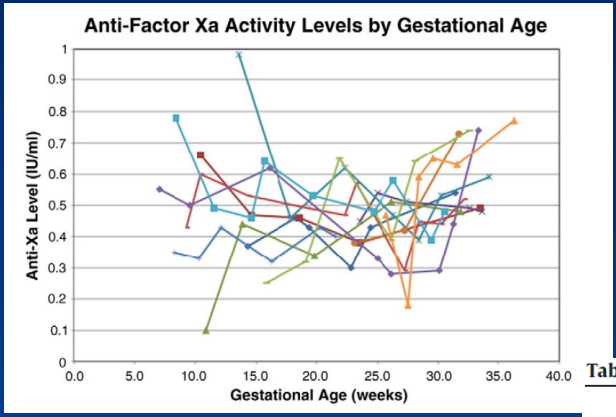
Among the 15 women on the adjusted-weight therapeutic dosage, 34 anti-Xa activity levels were available. Anti-Xa activity measurements were in the expected therapeutic range throughout pregnancy (Fig. 2).

Target range: 0.5 – 1.0 anti-Xa IU/ml

Weight-adjusted dosing of tinzaparin in pregnancy☆

P.S. Gibson [a,b,*], K. Newell [b], D.X. Sam [a,b], A. Mansoor [c], X. Jiang [c], S. Tang [b], S. Ross [b]

Thrombosis Research 131 (2013) e71–e75



Target range: 0.5 – 1.2 anti-Xa IU/ml

Table 2 Outcomes.

	N = 12	Statistical result*
Primary Outcome		
Maintained therapeutic anticoagulation on weight-based dosing throughout pregnancy	1 (8%)	95% CI (0.2% to 38.5%)
Secondary Outcomes†		
Estimated dose requirement (IU)		p<0.001
Trimester 1 (<=12 wks)	14255 (SE 890)‡	
Trimester 2 (13–27 wks)	16533 (SE 854)§	
Trimester 3 (28–40 wks)	17828 (SE 857)**	

A case series of LMWH use in pregnancy: Should trough anti-Xa levels guide dosing?

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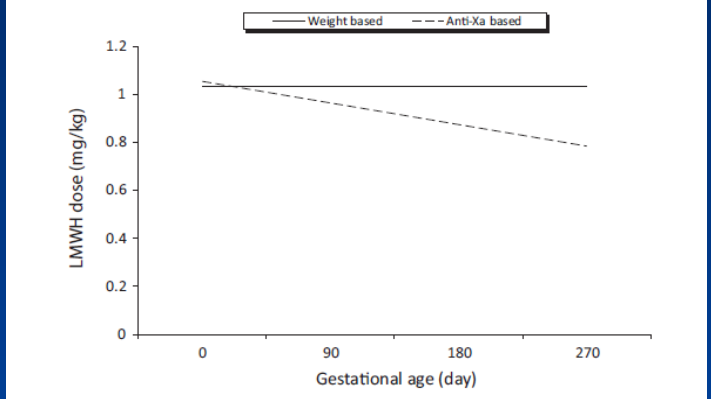

Fig. 3. Comparison of LMWH dosing strategies in women with VTE: peak anti-Xa guided vs calculated weight-based.

Target a picco 0.5-1.0 anti-Xa IU/ml

The dose of enoxaparin remained fairly steady throughout the pregnancy, and by delivery had decreased to slightly lower (0.96 mg /kg) than the traditional weight-based dosing (1 mg/kg).

Parenteral Anticoagulants

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

David A. Garcia, MD; Trevor P. Baglin, MBChB, PhD; Jeffrey I. Weitz, MD, FCCP; and Meyer Michel Samama, MD

CHEST 2012; 141(2)(Suppl):e24S–e43S

1.2.3 Monitoring Antithrombotic Effect: LMWHs are typically administered in fixed or weight-adjusted doses for thromboprophylaxis and in weight-adjusted doses for therapeutic purposes. Coagulation monitoring is not generally necessary, but some authorities suggest that monitoring be done in obese patients and in those with renal insufficiency.[129-131] Monitoring may also be advisable when treatment doses of LMWH are given during pregnancy.[132]

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Shannon M. Bates, MDCM; Ian A. Greer, MD, FCCP; Saskia Middeldorp, MD, PhD; David L. Veenstra, PharmD, PhD; Anne-Marie Prabulos, MD; and Per Olav Vandvik, MD, PhD

CHEST 2012; 141(2)(Suppl):e691S–e736S

7.1 Treatment of VTE During Pregnancy

Given the absence of large studies using clinical end points that demonstrate an optimal therapeutic anti-Xa LMWH range or that dose adjustments increase the safety or efficacy of therapy, the lack of accuracy and reliability of the measurement,[187] the lack of correlation with risk of bleeding and recurrence,[188] and the cost of the assay, routine monitoring with anti-Xa levels is difficult to justify.

How I treat pregnancy-related venous thromboembolism

Saskia Middeldorp[1]

(*Blood* 2011;118(20):5394-5400)

Data from pharmacokinetic studies of various LMWHs in pregnant women have shown conflicting results with regard to the need for dose escalation to maintain levels within the therapeutic range.[20-25] The American College of Chest Physicians guidelines are unable to provide a specific advice about anti-Xa level monitoring, in the absence of large studies using clinical endpoints demonstrating that there is an optimal therapeutic anti-Xa LMWH range or that dose adjustments increase the safety or efficacy of therapy.[26] Despite these uncertainties, I monitor antifactor Xa levels 4 hours after injection and target to an anti-Xa level of 0.8 to 1.6 with a once-daily regimen of LMWH (0.6-1.0 units/mL if a twice-daily regimen is used) at infrequent intervals

IL RISCHIO TROMBOEMBOLICO IN GRAVIDANZA E PUERPERIO

Prima edizione novembre 2014

Il fisiologico incremento della velocità di filtrazione glomerulare con il conseguente aumento dell'escrezione renale di eparina, l'incremento del legame proteico all'eparina e l'aumento del volume plasmatico (37) propri della gravidanza possono determinare una ridotta emivita e concentrazioni plasmatiche più basse dell'ENF e dell'EBPM rispetto alle donne non gravide. Per tale motivo può essere necessario somministrare dosi più elevate e più frequenti di farmaco per ottenerne concentrazioni plasmatiche efficaci (38,39,40). Non vi sono evidenze per suggerire l'aggiustamento della dose di EBPM in base alla determinazione dei livelli di attività anti-Xa.

SOGC CLINICAL PRACTICE GUIDELINE

Venous Thromboembolism and Antithrombotic Therapy in Pregnancy

J Obstet Gynaecol Can 2014;36(6):527–553

10. For the treatment of acute venous thromboembolism in pregnancy we recommend adhering to the manufacturer's recommended dosing for individual low molecular weight heparins based on the woman's current weight. (II-1A) Low molecular weight heparin can be administered once or twice a day depending on the agent selected. (III-C)

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b
April 2015

Royal College of Obstetricians & Gynaecologists

6.3 Should blood tests be performed to monitor heparin therapy in pregnancy?

Routine measurement of peak anti-Xa activity for patients on LMWH for treatment of acute VTE in pregnancy or postpartum is not recommended except in women at extremes of body weight (less than 50 kg and 90 kg or more) or with other complicating factors (for example, with renal impairment or recurrent VTE).

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Shannon M. Bates, MDCM; Ian A. Greer, MD, FCCP; Saskia Middeldorp, MD, PhD; David L. Veenstra, PharmD, PhD; Anne-Marie Prabulos, MD; and Per Olav Vandvik, MD, PhD

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UK NEQAS
FOR BLOOD COAGULATION

Report on Survey 213

Survey distribution date: 21st July 2015
Issued: September 2015

Sample **15/29** was a sample containing approximately 0.5u/ml enoxaparin.

Table 7. Method	Heparin Assay Kit	n	Median (u/ml)	CV (%)	Range (u/ml)
Chromgenic Assays	Biophen (Hyphen-Biomed)	37	0.52	8.4	0.40 - 0.58
	Chromogenix Coamatic Heparin	12	0.48	11.6	0.43 - 0.59
	IL HemosIL Heparin	18	0.45	12.3	0.39 - 0.60
	IL HemosIL Liquid Heparin	92	0.42	11.9	0.18 - 0.55
	Siemens Berichrom Heparin	29	0.53	23.5	0.11 - 0.70
	Stago Liquid anti-Xa	32	0.44	17.7	0.13 - 0.59
	Overall	**240**	**0.45**	**17.4**	**0.11 - 0.70**