EVALUATION OF THERAPEUTIC ENOXAPARIN IN A PREGNANT POPULATION AT A TERTIARY HOSPITAL

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ABSTRACT:

BACKGROUND: Therapeutic anticoagulation with enoxaparin in pregnancy is complex due to varying pharmacokinetics and the increasing prevalence of obesity. There is limited evidence to support current dosing and monitoring strategies of enoxaparin in this population.

AIM: To describe the current practice in therapeutic anticoagulation in the pregnant population at a tertiary institution.

METHODS: A retrospective study of pregnant women on therapeutic enoxaparin between January 2007 and December 2011.

RESULTS: Forty-four pregnant women requiring therapeutic anticoagulation were identified, and divided into two groups monitored with anti-factor Xa (AXA) concentrations and unmonitored. Fifty-five percent of monitored women were initiated on the recommended 1mg/kg twice a day (bd) enoxaparin dose-strategy. Eighty-two percent of women were monitored, however there was variability regarding the timing, frequency and subsequent dose adjustments from monitoring. Overall as pregnancies progressed there was both increasing dose adjustments, and increasing frequency of monitoring. Fourteen women had a BMI over 30kg/m^2 and thirteen of these women were monitored. Nine monitored obese women required doses less than 1mg/kg/bd to maintain a therapeutic AXA level. Management appeared to be individualized. There were small numbers of toxicity events.

CONCLUSION: Variation exists in dosing and monitoring practices for therapeutic enoxaparin in the pregnant population. Dosing obese patients using 1mg/kg twice daily can lead to toxic AXA concentrations, and dose reductions are required to maintain a therapeutic range. A larger prospective study reviewing dose, AXA concentrations, and outcome data is necessary to make dosing recommendations in this group.

INTRODUCTION

The need for therapeutic anticoagulation in pregnancy is increasing due to more women with complex co-morbidities embarking on pregnancy, and the increased prevalence of venous thromboembolic events in pregnancy [1]. However, anticoagulating this group remains challenging due to altered pharmacokinetics (PK) related to the physiological changes of pregnancy itself.

The most common condition requiring therapeutic anticoagulation in pregnancy is venous thromboembolism (VTE). VTE has an incidence ranging from 0.6 to 1.3 per 1000 deliveries, which is a 5-10 fold increase compared to matched non-pregnant women, and attributed to the changes in coagulation physiology and venous stasis of pregnancy [1-9]. It is the leading cause of maternal mortality in developed countries [7, 10]. Low molecular weight heparins (LMWH) are now widely recommended for the treatment of VTE in this population [11]. They do not carry the teratogenic risk of vitamin K antagonists, and compared to unfractionated heparin have a longer half-life, more predictable PK, and less

risk of heparin-induced thrombocytopenia or osteoporosis [1, 2, 11, 12]. Anti-coagulation in pregnancy for non-VTE indications has been widely debated in the literature due to the potentially critical maternal and fetal outcomes [5, 8, 13, 14]. Recent consensus guidelines recommend that anticoagulation should be dose-individualized for each woman, however little data exists regarding how to achieve specific and safe dosing and monitoring strategies [11, 15]. Therapeutic drug monitoring using anti-Factor Xa (AXA) concentrations has recently become available to obstetric teams, although the clinical relevance of this surrogate marker has never been studied in the pregnant population.

During pregnancy, physiological changes may alter the PK of LMWHs, potentially rendering standard weight-based dosing (mg/kg) unsuitable, and place the patient at-risk of bleeding or another embolic event. Specifically, increased plasma volume and glomerular filtration rate (GFR) (in the second trimester (T2)) leads to a higher clearance and larger volume of distribution (Vd) for hydrophilic drugs (e.g. enoxaparin) compared to non-pregnant women [5, 8, 15, 16]. This may result in lower serum concentrations when standard dosing recommendations are used. While studies have shown mixed results, it is clear there are progressive and variable changes in the PK of LMWHs throughout the trimesters of pregnancy [11, 15-20]. Barber et al demonstrated that in T2 the increase in Vd and GFR resulted in reduced peak concentrations of LMWH and increased rates of drug clearance [15]. Gibson et al established that weight based dosing of LMWHs was insufficient to maintain therapeutic AXA concentrations through increasing trimesters.

Early studies of LMWHs did not include AXA monitoring, and therefore a suitable target range has not actually been clinically evaluated for efficacy or bleeding risk [11, 19, 21]. The prevalence of obesity (body mass index (BMI) over 30 kg/m^2) is increasing and in pregnancy further increases the risk of VTE [22, 23]. Further, extra adipose tissue has little effect on the clearance of enoxaparin, and is not adjusted for in current weight based dosing of enoxaparin [21]. Thus despite the growing use of LMWHs for therapeutic anticoagulation in pregnancy there are still many questions pertaining to optimal dosing and monitoring.

Hypothesis

Based on the known pharmacokinetic changes in pregnancy, the increased prevalence of obesity in the population, and the increased prevalence of other co-morbidities requiring therapeutic anticoagulation we hypothesized that the usual recommended dose of 1mg/kg/bd results in clinically significantly variable AXA concentrations across this population.

Aims

1. To describe the management and outcomes of pregnant women on therapeutic enoxaparin at a tertiary hospital.
2. Evaluate the current dose strategies and resultant therapeutic concentrations across the trimesters

MATERIALS AND METHODS

This was a retrospective study at the Royal Brisbane and Women's Hospital (RBWH) – a large teaching hospital in Brisbane, Queensland, Australia. This facility has a dedicated Obstetric Medicine, Cardiac Obstetric Medicine and Endocrine Obstetric Medicine teams, with support from clinical pharmacy and clinical pharmacology when required. It is one of the three-referral centers for complex pregnancies throughout Queensland and Northern New South Wales.

This study was approved by the hospital's ethics committee (HREC/12/QRBW/128). From the Hospital's Obstetric Medicine database, we collected data from all pregnant patients who had been therapeutically anti-coagulated with enoxaparin for any indication, between January 2007 and December 2011. This included patients who were already on anticoagulation (e.g. mechanical valve) or those who developed a new reason to require treatment doses of anticoagulation during pregnancy. Patients were excluded if they received only prophylactic anticoagulation, or if anticoagulation was restricted to the post-partum period. Once cases were identified their case notes and obstetric database

sheets were recalled and subjected to detailed analysis with a standardized data collection form, by two independent researchers. Information on patient's demographics, medical co-morbidities, weight, dosing of enoxaparin, and pregnancy outcomes was collected.

Monitoring of enoxaparin was measured by AXA concentrations using the Liquid Anti-XA assay by Diagnostic Stago. Within the general hospital population (and excluding valvular patients), concentrations between 0.5 and 1.0 IU/ml are considered therapeutic. For women who required anti-coagulation for MVs, they had a recommended AXA concentration of between 1-1.2 IU/ml [13]. Post dose AXA concentrations and sample times were collected from Auslab®, the statewide pathology database.

We aimed to review the indications for anticoagulation, percentage of pregnant women who have AXA concentrations performed, frequency of AXA concentrations, and appropriateness of any sequential dose adjustment as our outcome measures. Using bleeding and clotting as surrogate markers of effective dose-adjustments.

Sub-analysis: We identified all obese patients (BMI >30 kg/$m^{2)}$ and reviewed those in the morbid obesity range (BMI >40kg/m^2). BMI was calculated on either pre-pregnancy weight or first trimester (T1) weight and categorized according to the WHO guidelines.

Statistical analysis: We used descriptive statistics for describing the population and standard correlative statistics in our evaluation of the data.

RESULTS

Study population

We identified 44 pregnant women who were prescribed therapeutic anticoagulation with enoxaparin, the LMWH used at the RBWH (Appendix Table One). Women were divided into two groups, monitored with AXA concentrations and un-monitored. Eight women were unmonitored; four had had a previous VTE and two had a known thrombotic disorder. Thirty-six women were monitored; eight had had a previous VTE, four had a known thrombotic disorder, and six women had a known autoimmune disorder. Fourteen women had a BMI over 30 kg/m^2 – only one obese woman was un-monitored.

Dosing

In line with product label, the recommended dose for therapeutic enoxaparin at the RBWH is 1mg/kg/bd. This study showed a mean (+/- SD) starting dose of 77.2 +/- 17mg BD for an average starting weight of 80.2kg amongst the monitored group. Only 20 (55%) of monitored patients had initial doses of 1mg/kg/bd (Figure One). In response to measured AXA concentrations, dose adjustments were variable and often deviated from standard 1mg/kg/bd regimens (Appendix Table Three). As pregnancies progressed there were increasing dose adjustments below the 1mg/kg/bd regimen.

Nine of the 13 (64%) monitored obese women required doses of enoxaparin under the standard 1mg/kg/bd regimen to maintain a therapeutic AXA level. Three (21%) required doses higher than 1mg/kg/bd. One woman required less than 1mg/kg/bd in the first trimester however by the third trimester she was managed on the 1mg/kg/bd regimen. Patients were rarely dosed over 100mg/bd of enoxaparin (even where their weight was greater than 100kg).

Monitoring

Monitoring (at least one AXA concentration during treatment period) occurred in 80% of VTE patients, all MV patients, and 13 of the 14 (93%) obese patients. Two hundred and twenty-seven AXA concentrations were performed, 86% at the recommended time of 4 hours post dose. The median (range) of timing of the AXA concentrations was 4 (2-8) hours, and an average of 7.6 concentrations performed per patient.

There was wide variability in the timing and frequency of monitoring throughout the pregnancies (Table One). Monitoring was performed in the same trimester as treatment initiation in 67% of MV patients and 79% of women with non-valvular indications for anticoagulation. All seven women who didn't have monitoring in the same trimester as treatment initiation, were either on treatment pre-pregnancy and no monitoring was performed in T1, or treatment was initiated in T1. Monitoring (adjusted for eligible trimester) was more frequent as the pregnancies progressed.

With respect to therapeutic ranges, 87% of all AXA concentrations in non-valvular patients during the third trimester were therapeutic (Table One). In patients with MVs, for all AXA concentrations through all trimesters; 49.6% were therapeutic, 26.3% were supra-therapeutic and 24% were sub-therapeutic.

Dose adjustments

In response to measured AXA concentrations, we identified variable dose adjustments made both amongst the patient group as a whole, and within individual pregnancies (Appendix Table Three). In total twenty-two women had 56 dose adjustments. All women with valvular indications had dose adjustments, 17 out of 19 appropriately reflected target AXA concentrations. In the MV population there were 5 occasions where the AXA concentration was below the recommended target, and eleven occasions where the AXA concentration was above the recommended target, and no dose adjustment was made. In the non-MV population there was a total of 37 dose adjustments, 40% appropriately reflecting target AXA concentrations.

Forty-eight percent of total dose adjustments made deviated from the recommended 1mg/kg/bd regimen. Figure two illustrates the variability in AXA concentrations in response to a weight-based dosing; for example a dose of 1mg/kg has a response that varies between approximately 0.5 to 2.0 IU/ml.

Complications

Haemorrhagic complications were seen in thirteen (29.5%) women. With the exception of two cases of minor epistaxis, all significant complications were ante-partum, intrapartum and post-partum haemorrhages. Nine of the eleven women with significant haemorrhagic complications had AXA monitoring, enoxaparin was only considered causative in two monitored cases (Appendix Table Four). In one of these cases AXA concentration was elevated without dose adjustment.

There were two patients with thrombotic complications during the study period. Both developed a suspected recurrent pulmonary embolism (PE) while having AXA concentrations at the lower end of the therapeutic range, 0.54 IU/ml and 0.58 IU/ml (Appendix Table Five).

Morbid obesity

We evaluated three women in the study with WHO obesity class III (BMI >40 kg/m^2), all were monitored.

The first patient was diagnosed with a PE in T3 and initiated on 100mg/bd of enoxaparin (weight at diagnosis 113kg). She had two AXA concentrations performed at K30 (0.74 IU/ml), and K31 (0.97IU/ml). She had no haemorrhagic or thrombotic complications after starting on enoxaparin.

The second patient was diagnosed with a PE in T2 and initiated on 120mg/bd (weight at diagnosis 150kg). Her first AXA concentration was sub-therapeutic and her dose subsequently increased to 140mg/bd. At K19 her AXA concentration was therapeutic (0.76 IU/ml). No further AXA concentrations were performed until K35 (weight T3 160kg). She maintained a therapeutic AXA concentration (0.84 IU/ml) on the dose of 140mg/bd. She had no haemorrhagic or thrombotic complications after starting on enoxaparin.

The third patient was initiated on enoxaparin for her MV in T1 and initiated on 100mg/bd (weight = 99kg). She had multiple peak and trough AXA concentrations throughout each trimester. Her pregnancy was complicated by a major post-partum haemorrhage (last dose of enoxaparin 172 hours prior to delivery). The initial 1mg/kg/bd dosing however resulted in a supra-therapeutic AXA concentration of 1.37 IU/ml. Progressive supra-therapeutic levels resulted in dose reductions to 90 mg/bd and subsequently 80mg/bd.

DISCUSSION

There is a paucity of large trials evaluating therapeutic anti-coagulation with LMWHs in pregnancy, with most recommendations based on case studies, expert opinions, small

observational studies or extrapolation from trials in non-pregnant populations [4, 15]. We aimed to evaluate how our hospital has managed therapeutic anticoagulation with enoxaparin during pregnancy. Although our data is sparse, particularly in the group with mechanical valves, we believe that the inconsistencies in management highlighted within this study are most likely representative of a 'real world' tertiary obstetric clinic; and have further highlighted the need for small Australasian centres to share data to enable more evidence-based guidelines in this area.

We found that 55% of monitored patients were initially dosed with enoxaparin based on the licensed dose of 1mg/kg/bd. Weights were not rounded and thus where the 1mg/kg/bd dosing was not adhered too, this usually reflected drug delivery. For example, a patient of 64kg may have been initiated on 60mg/kg/bd enoxaparin for ease of administration, rounding to the closest 10 is regarded as standard dosing. However standard dosing frequently resulted in variable AXA concentrations, and inconsistent successive dose adjustments.

This study showed wide variability in the frequency and timing of AXA monitoring, although most women with VTE, obesity or MVs were monitored in some form (mean of 7.6 AXA concentrations per patient). This illustrates physician concern regarding this population and individualization for each case. Despite being well used there is little data to guide on the most effective method to interpret concentrations and to dose-adjust.

Not all AXA concentrations were performed at four hours post-dosing, the recommended best estimate of peak effect. This affects the interpretation of results by clinicians. We also demonstrated a marked variability in AXA concentrations within individual patients, which we believe is related to changing PK during pregnancy. The changes in AXA concentrations supports Casele et. al.'s findings that clearance decreases in late pregnancy [16, 24]. Only 49.6% of all AXA concentrations in the MV population were therapeutic, indicating the difficulties in dosing this special population, and the potential risks of both thrombosis and bleeding. The wide variability in management suggests a protocol formed in collaboration with medical, obstetric, pharmacy and clinical pharmacology teams is warranted; ideally at a national level to ensure consistency across hospital sites.

In our study, we found an obesity rate similar to that of the general population (32% in our study, 34.5% in general population [25]). The study showed 70% of monitored obese women required lower doses to avoid supra-therapeutic AXA concentrations. This data suggests dosing obese patients using 1mg/kg twice daily in early pregnancy may lead to toxic concentrations, and dose reductions are required to maintain a therapeutic range, reductions that will change as the pregnancy progresses. It supports data showing that extra adipose tissue does not affect the clearance of enoxaparin [19, 26].

From this study, it is difficult to ascertain whether AXA monitoring is correlated with complication rates and larger multi-center randomized blinded control trials are warranted. Twenty-five percent of women in both monitored and unmonitored groups had a significant bleeding event. However, from the nine monitored women we suspect that enoxaparin was not causative in seven of these cases, as complications occurred over 28 hours (range 28-295 hours) from the last dose of enoxaparin. Given the 6-hour half-life of enoxaparin is related to dosing, it is possible that we have excluded some complications, which may have been related to the drug.

LIMITATIONS

The study has been limited by its retrospective nature, small sample size, and single center evaluation. As our unit is part of a large tertiary center for a wide demographic, there is a referral bias. In the original data collection the doses of enoxaparin for unmonitored patients were not recorded from case notes.

CONCLUSION

Guidelines are required for the dosing and monitoring of therapeutic enoxaparin in the pregnant population. They should recommend initial dosing, how and when to measure AXA concentrations, and how to dose adjust. There should be a strong emphasis on physiological changes seen in the third trimester, which appear to affect enoxaparin PK to

a much greater extent that earlier PK. Specific populations at risk include the obese, morbid obese, multiple pregnancies, and patient with prosthetic valves, and these require closer monitoring. However more and prospective data is needed to show the relationship of concentration to toxicity or efficacy.

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Table One: AXA concentrations within the patient population – mean frequency monitoring through trimesters and percentages within therapeutic parameters

	Population	*Trimester 1*	*Trimester 2*	*Trimester 3*
Mean number of AXA concentrations performed per patient (for women with established treatment in each trimester)	All women	2	2.38	3.25
	Non-valvular patients	1.2	1.9	2.24
	MV patients	5.3	7.3	14.3
Percentage of Sub-therapeutic AXA concentrations per trimester	Non-valvular patients	0%	3%	4%
	MV patients	31%	27%	14%
Percentage of Therapeutic AXA concentrations per trimester	Non-valvular patients	72%	70%	87%
	MV patients	50%	50%	49%
Percentage of Supra-therapeutic AXA	Non-valvular	28%	27%	8%

concentration per trimester	patients MV patients	19%	23%	37%

Figure One: Initial Dose vs. Weight

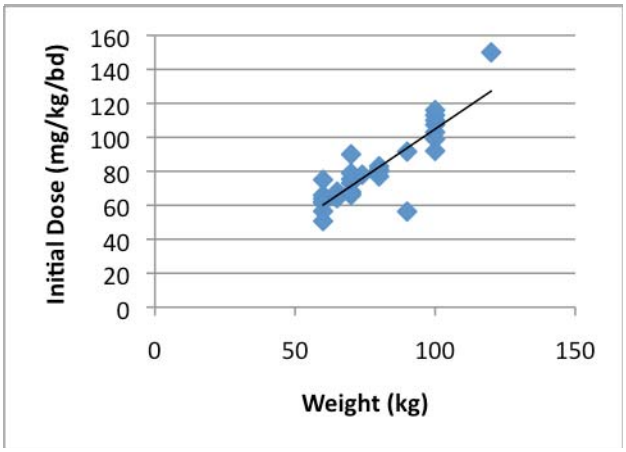
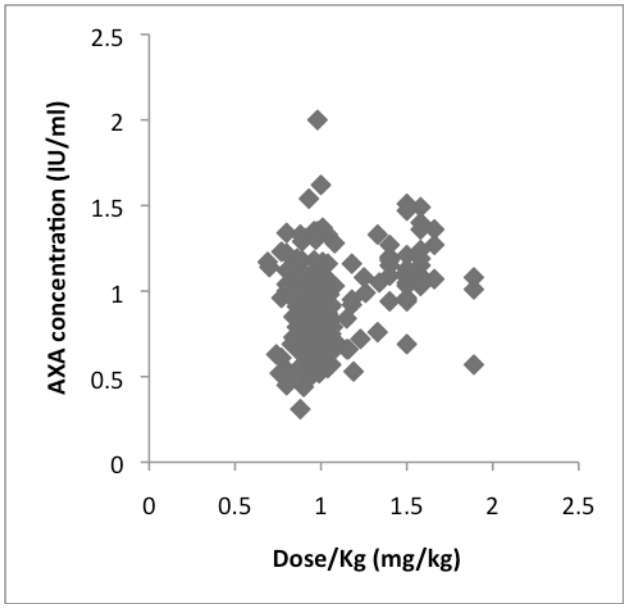


Figure Two: Plot of all recorded AXA concentrations versus dose/kg for each AXA concentration



APPENDICES.

APPENDIX TABLE 1. PATIENT DEMOGRAPHICS

Age	*BMI*	*Body weight (Kg) at initiation enoxaparin*	*Total weight gain pre-pregnancy/T1 to T3 (Kg)*	*Co-morbidities*
28	25	71	4	Previous VTE
20	31	.	.	Previous VTE
27	.	90	.	Previous pre-term labor
28	.	83	.	Previous VTE
35	21	72	13	Previous VTE
29	25	.	16	Previous VTE
24	27	70	11	Previous VTE
25	33	99	15	Previous VTE
38	36	.	7	Previous VTE
30	38	.	0	Previous VTE *
29	32	85	7	Previous VTE *
30	22	67	.	Previous VTE
33	26	75	7	Previous VTE, APLS *
30	27	78	.	Previous VTE, APLS
20	21	.	6	Previous VTE, Factor V Leiden Deficiency
20	20	61	5	Factor V Leiden Deficiency
20	20	61	5	Factor V Leiden Deficiency
25	.	76	6	APLS, Chronic bronchiolitis
26	22	64	9	new placental thrombosis
23	18	.	6	Rheumatic Heart Disease *
31	44	106	7	Rheumatic Heart Disease
35	24	60	.	Rheumatic Heart Disease

30	36	96	0	PET/HELP, PPROM
21	34	90	3	PET/HELP
34	30	77	2	PCOS *
28	.	103	.	Seronegative RA
33	53	159	1	Auto-immune arthritis, Crohns disease, Smoker, Essential HTN
22	19	65	15	Smoker
28	22	70	8	Smoker
28	31	80	0	Smoker
36	.	67	.	Smoker
31	36	107	8	Smoker
17	21	63	10	Smoker
25	43	.	.	Smoker
21	33	116	16	Nil
31	20	52	4	Nil
29	25	83	.	Nil
38	21	64	8	Nil
28	20	77	21	Nil
31	22	.	6	Nil
28	22	67	.	Nil
35	22	61	.	Nil
28	25	80	10	Nil

* = prepregnancy anticoagulation

Appendix Table Two: Examples of heterogeneous drug adjustments in response to AXA concentrations, and/or deviation from 1mg/kg/BD regimes

Patient with AVR/MVR weight 62kg	• Initial dose enoxaparin 60mg/BD, Variability in management of supra-therapeutic AXA concentrations seen • G21+1 AXA concentration 1.36 IU/ml, no dose adjustment • G23+2 AXA concentration 1.24 IU/ml, dose decreased • G27+4 AXA concentration 1.27 IU/ml, no dose adjustment • G36+2 AXA concentration 1.27 IU/ml, no dose adjustment
Patient with DVT (T1)- weight 77kg	• Initiated on 80mg/BD enoxaparin. Variability in management of supra-therapeutic AXA concentration seen. Patient requiring dosing under 1mg/kg/BD regimen (in response to AXA concentrations) • At K8 AXA concentration 1.28 IU/ml led to dose decrease to 70mg/BD • Following 3 AXA concentrations within the therapeutic range, despite being dosed under 1mg/kg/bd regime (K11 0.82 IU/ml, K16 0.68 IU/ml, K18 0.79 IU/ml) • K21 (weight 77kg) AXA concentration 1.31 lead to dose reduction to 60mg/BD • K23 AXA concentration 1 IU/ml, no dose change

	• K26 AXA concentration 1.23 IU/ml, dose reduction to 55mg/BD • K28 AXA concentration 1.17 IU/ml, no dose adjustment made and no further AXA concentrations performed (weight 79kg in T3)

Appendix Table Three: Haemorrhagic complications

1	• Patient developed an anti-partum haemorrhage at K17, within the first few days of anticoagulation with enoxaparin for an inferior vena-cava thrombosis. • Initial dose of enoxaparin was 70mg/bd (weight 67kg) • One AXA concentration taken at 7 hours post-dose (0.55 IU/ml)
2	• Ante-partum haemorrhage at K30/40 • Initiated on enoxaparin 60mg/bd for VTE K31 (weight 51kg) • AXA concentration elevated on 3 occasions with no dose adjustment • Last dose of enoxaparin was given 17hrs prior to delivery.

Appendix Table Four: Thrombotic complications

1	• Patient with suspected recurrent PE at K23 • Initiated on 100mg/bd enoxaparin at K10 for PE (weight 107kg). • Elevated AXA concentrations led to dose reductions to 80mg mane and 85mg nocte enoxaparin. Subsequent AXA level K23 0.54 IU/ml (weight 103kg)
2	• Patient with suspected recurrent PE at K37. • Initiated on 60mg/bd enoxaparin T1 for suspected PE (weight 61.5kg). • Only one AXA concentration (0.58 IU/ml) performed in the pregnancy at K37+3, when she presented with her suspected recurrent PE