Venous Thromboembolism Prevention in Obstetric Practice

Torri Metz, MD, MS
Division Chief, Maternal-Fetal Medicine
Vice-Chair for Research, Department Ob/Gyn
University of Utah Health
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No relevant disclosures

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Objectives

- Describe current prevalence of VTE in obstetric patients
- Identify patients at increased risk for VTE requiring thromboprophylaxis
- Describe available literature surrounding VTE prophylaxis postpartum

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Maternal Morbidity & Mortality

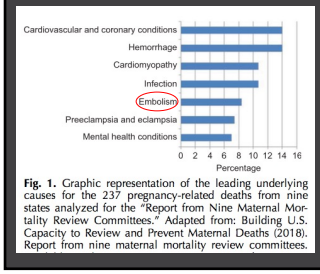

Fig. 1. Graphic representation of the leading underlying causes for the 237 pregnancy-related deaths from nine states analyzed for the "Report from Nine Maternal Mortality Review Committees." Adapted from: Building U.S. Capacity to Review and Prevent Maternal Deaths (2018). Report from nine maternal mortality review committees.

- Venous thromboembolism (VTE)
  - Includes deep vein thrombosis (DVT) & pulmonary embolism (PE)
  - Contributes to 9.3% of maternal deaths
- Significant morbidity
  - Post-thrombotic syndrome
  - Pulmonary hypertension
  - Anticoagulation

Clark et al. Obstet Gynecol 2017; 130(1): 198-202.
Metz et al. Obstet Gynecol 2018; 132(4): 1014-1045
ACOG. Obstet Gynecol 2018; 132(1): e1-e17.

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The first two weeks postpartum are "peak" risk period for VTE in obstetric population

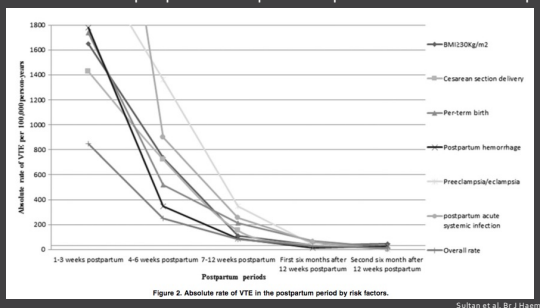

Figure 2. Absolute rate of VTE in the postpartum period by risk factors.

Sultan et al. Br J Haematol 2011; 156:366
Sultan et al. Blood 2014; 124(18): 2877

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37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

Pregnancy history:
- Conception by IVF
- Antepartum admission for non-obstetric surgery (cholecystectomy)

Medical history includes:
- Crohn's Disease (well-controlled, no recent flares)
- Obesity (body mass index 39 kg/m^2)

What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

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Current Intervention Model in Obstetrics

Hypercoagulable + Risk Factors → Venous Thromboembolism → Maternal Morbidity & Mortality

Interventions
- Mechanical prophylaxis
- Chemical prophylaxis

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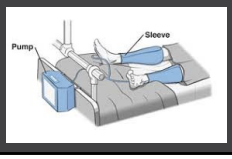
Interventions

Low-molecular weight heparin
- Enoxaparin preferred
  - Bioavailability
  - Safety profile
  - Cost & availability (in United States)

LOVENOX® (enoxaparin sodium injection)

Sequential compression devices
- Non-invasive
- Low risk
- During cesarean & postpartum



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Evidence for thromboprophylaxis

- Efficacious in reducing post-operative VTE in non-obstetric surgical fields
  - Orthopedic surgery → general surgery

Prevention of VTE in Nonorthopedic Surgical Patients

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

Michael K. Gould, MD, FCCP · David A. Garcia, MD · Sherry M. Wren, MD · ...
Juan I. Arcelus, MD, PhD · John A. Heit, MD · Charles M. Samama, MD, PhD, FCCP · Show all authors

Cochrane Database of Systematic Reviews · Review - Intervention

Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery

Seth Felder, Morten Schnack Rasmussen, Ray King, Bradford Sklow, Mary Kwaan, Robert Madoff, Christine Jensen

Bates et al. Chest 2012 ; 141(2 Suppl):e691S-e736S.
Bates et al. J Thromb Thrombolysis 2016;41(1):92-128.
Felder et al. Cochrane Database Syst Rev. 2019; 3(3):CD004318.

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Sequential Compression Devices

- Retrospective observational cohort
- Hospital Corporation of America (~6% deliveries in U.S.)
- Evaluated maternal death pre- and post-implementation of pneumatic compression device protocol for individuals undergoing cesarean
- Significant decrease in post-cesarean fatal pulmonary embolism

Category of Death	2000-2006 (Pre) n = 1,461,270	2007-2012 (Post) n = 1,256,020	p
Post-cesarean pulmonary embolism	7	1	0.038

Clark et al. AJOG 2014; 211(1):32.e1-9

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Low molecular weight heparin prophylaxis

- Confidential Enquiries – UK tracking of maternal deaths
- Decline in thromboembolic deaths following 2004 introduction of RCOG thromboprophylaxis guidelines

Table 2.1. *Direct* deaths from thrombosis and thromboembolism and rates per 100 000 maternities; UK: 1985–2008

	Pulmonary embolism			Cerebral vein thrombosis			Thrombosis and thromboembolism		
	n	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI
1985–87	30	1.32	0.83–1.89	2	0.09	0.02–0.32	32	1.41	1.00–1.99
1988–90	24	1.02	0.68–1.51	9	0.38	0.20–0.72	33	1.40	1.00–1.96
1991–93	30	1.30	0.91–1.85	5	0.22	0.09–0.51	35	1.51	1.09–2.10
1994–96	46	2.09	1.57–2.79	2	0.09	0.02–0.33	48	2.18	1.65–2.90
1997–99	31	1.46	1.03–2.07	4	0.19	0.07–0.48	35	1.65	1.19–2.29
2000–02	25	1.25	0.85–1.85	5	0.25	0.11–0.59	30	1.50	1.05–2.14
2003–05	33	1.56	1.11–2.19	8	0.38	0.19–0.75	41	1.94	1.43–2.63
2006–08	16	0.70	0.43–1.14	2	0.09	0.02–0.35	18	0.79	0.49–1.25

8th Report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011; 118:51

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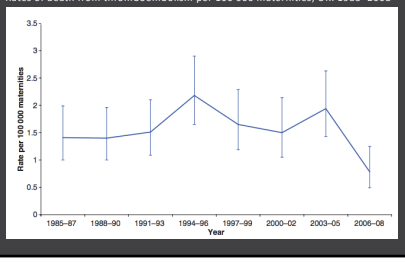
UK epidemiologic data – basis for widespread LMWH use for prophylaxis in obstetrics

Rates of death from thromboembolism per 100 000 maternities; UK: 1985–2008



8th Report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011; 118:51

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Guidelines Abound

Table. Society guidelines for postpartum risk stratification and recommendations for thromboprophylaxis

Guideline	Population & Recommendations
Royal College of Obstetricians and Gynaecologists (RCOG)	In individuals undergoing any mode of delivery: ▪ Recommend LMWH prophylaxis for 10 days in those with 1 major or 2 (or more) minor risk factors. ▪ Recommend LMWH prophylaxis for 6 weeks in those with high risk conditions including: previous VTE, requiring antenatal LMWH, high-risk thrombophilia, or low-risk thrombophilia with family history
American College of Obstetricians and Gynecologists (ACOG)	In individuals undergoing cesarean delivery: ▪ Recommend mechanical prophylaxis at delivery and postpartum until ambulatory. ▪ If additional risk factors present, may consider chemical prophylaxis. ▪ Each institution should review and select a protocol for implementation.
American College of Chest Physicians (CHEST)	In individuals undergoing cesarean delivery: ▪ Recommend LMWH prophylaxis in the hospital in those with 1 major or 2 (or more) minor risk factors. ▪ If 'very high risk' use combination LMWH and mechanical prophylaxis. ▪ If significant risk factors persist after delivery, consider LMWH for up to 6 weeks.

Society for Maternal-Fetal Medicine · Royal College of Obstetricians and Gynaecologists · CHEST American College of Chest Physicians · ACOG · SOAP Society for Obstetric Anesthesia and Perinatology

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University of Utah Postpartum Prophylaxis Guidelines

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- SCDs recommended for all undergoing cesarean
- LMWH prophylaxis for 14 days postpartum with 1 major or ≥ 2 moderate risk factors
- Enoxaparin dosing
  - BMI <40: 40mg SQ every 24 hours
  - BMI ≥ 40: 40mg SQ every 12 hours

Major Risk Factors	Moderate Risk Factors
History of VTE BMI ≥ 40 kg/m² High-risk thrombophilia: ▪ Antiphospholipid Syndrome ▪ Antithrombin deficiency ▪ Factor V Leiden homozygote ▪ Prothrombin gene mutation homozygote ▪ Compound heterozygote for Factor V Leiden and Prothrombin gene mutation Medical comorbidities ▪ Heart disease ▪ Cancer ▪ Systemic Lupus Erythematosus (SLE) ▪ Inflammatory Bowel Disease (IBD) or inflammatory polyarthropathy ▪ Sickle cell disease (SCD) ▪ Intravenous drug use Nephrotic range proteinuria Cesarean hysterectomy Cesarean section in labor	BMI ≥ 30 kg/m² Multi-fetal gestation PPH (>1L or blood transfusion) Tobacco use Elective cesarean Preeclampsia Infection Preterm delivery <37 weeks Age > 35 years Family history of VTE Varicose veins Stillbirth Prolonged labor (>24 hours) Low-risk thrombophilia: ▪ Factor V Leiden heterozygote ▪ Prothrombin gene mutation heterozygote ▪ Protein C deficiency ▪ Protein S deficiency

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37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

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Medical history includes:
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What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

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Cochrane Systematic Review, 2014

- From 10 postpartum trials: prophylaxis vs no prophylaxis
  - Included < 1000 individuals
  - Only 1 trial reported on maternal deaths (none)
  - No differences in symptomatic VTE
  - One trial with increased bleeding complications (unfractionated heparin)
  - Low quality studies

"There is ***insufficient evidence …***Large scale, high-quality randomised trials …are warranted."

Bain et al. Cochrane Database Syst Rev 2014; 11(2):CD001689.

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Risk of Harm

- Single center retrospective cohort study
  - Implemented institutional prophylaxis protocol in 2016
  - Compared VTE & wound hematomas pre-protocol (2013-2015) to post-protocol (2016-2018)
  - Unchanged VTE rates & increased wound complications post-protocol

Outcome	Preprotocol (n=11,799)	Postprotocol (n=12,430)	OR (95% CI)*	aOR (95% CI)*
Efficacy outcomes				
Diagnosis of VTE	15 (0.1)	16 (0.1)	1.01 (0.50–2.05)	—
DVT	8/15 (53.3)	5/16 (31.3)	0.40 (0.09–1.72)	0.50 (0.11–2.37)
PTE	5/15 (33.3)	8/16 (50.0)	2.00 (0.47–8.56)	1.25 (0.22–7.23)
Other	2/15 (13.3)	3/16 (18.8)	1.50 (0.21–10.52)	3.68 (0.23–58.98)
Safety outcomes				
Any wound hematoma	50 (0.4)	90 (0.7)	2.61 (1.74–3.90)	2.34 (1.54–3.57)
Superficial wound hematoma	36 (0.3)	76 (0.6)	2.98 (1.91–4.64)	2.55 (1.61–4.02)
Deep wound hematoma	15 (0.1)	18 (0.1)	1.37 (0.67–2.78)	—

Lu et al. Obstetrics & Gynecology 2021;138:530–8

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No shortage of dissent

Editorial Headlines:

Postpartum Heparin Thromboprophylaxis
More Harm Than Good

Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens

Pharmacologic Thromboprophylaxis in Obstetrics
Broader Use Demands Better Data

Warn against widespread pharmacologic prophylaxis implementation given unproven efficacy & risk of harm

Kotaska A. BJOG 2018; 125(9):1109-1116
Sibai & Rouse. Obstetrics & Gynecology 2016; 128(4):681-4.
Kotaska A. Obstetrics & Gynecology 2021; 138(4): 527-29.

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But also calls for more widespread use

Editorial Headlines:

Maternal risk from thromboembolism needs to be reduced

Pregnancy–related venous thromboembolism: Progress but questions remain

Call for more widespread implementation of prophylaxis protocols & additional research

Friedman & D'Alton. AJOG 2020;223(6):794-795.
Bates. Eur J Intern Med. 2022;97:32-33.

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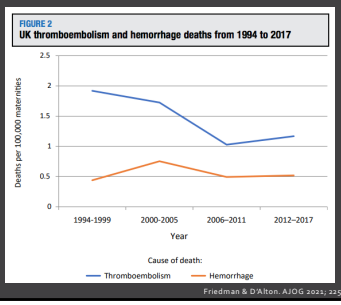
But continued population level decrease in UK…

UK population level data continue to demonstrate decline in VTE (1994-2017)

Decrease maternal mortality due to VTE without increase in hemorrhage-attributed deaths



Friedman & D'Alton. AJOG 2021; 225(3):228-236.

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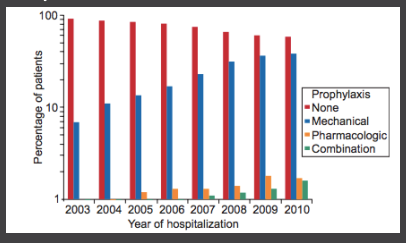
Institutional/Population Level Implementation



- US data, 2003-2010
- Post-cesarean
- Over 1 million deliveries
- 22.1% receiving mechanical prophylaxis
- 1.3% receiving LMWH prophylaxis

Friedman et al. Obstet & Gynecol 2013; 122(6): 1197-1204

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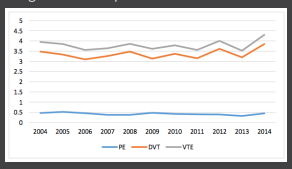
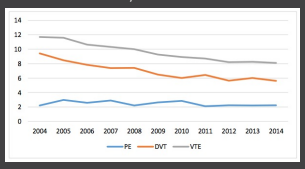
Similar U.S. Population level data?

Rates of venous thromboembolism per 10,000 delivery hospitalizations from the Nationwide Inpatient Sample, 2004-2014.

Vaginal Delivery



Cesarean Delivery



Abe et al. Semin Perinatology 2019; 43(4):200-204.

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Current Intervention Model in Obstetrics

Hypercoagulable + Risk Factors → Venous Thromboembolism → Maternal Morbidity & Mortality

Interventions

- Mechanical prophylaxis
- Chemical prophylaxis

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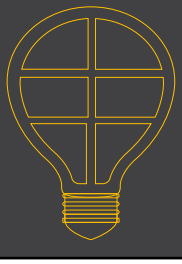
Why not conduct a large RCT?



- LARGE sample size
- Multiple unanswered questions
  - Target population – who is 'at risk'?
  - Enoxaparin dose
  - Enoxaparin length of therapy
  - Surrogate outcome
  - Compliance/Willingness to use

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Variable uptake across U.S.

- Use of VTE prophylaxis continues to vary widely across the U.S.
  - Cross sectional study at single tertiary hospital
  - Assessment of patient risk factors and rates of chemical (LMWH) prophylaxis by varying guidelines post-cesarean:
    - RCOG – 85% (95% CI 80.5-88.6%)
    - ACOG – 1% (95% CI 0.3-3.0%)
    - CHEST – 34.8% (95% CI 29.6-40.4%)

Palmerola et al. BJOG 2016;123(13):2157-2162.

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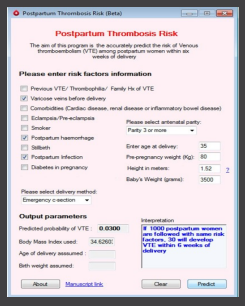
Defining 'at risk'

- No validated prediction model in clinical practice
- CHEST/RCOG use risk algorithm
  - Additive? Multiplicative?
- What risk threshold should we use?



Sultan et al. BMJ 2016; 355: i6253

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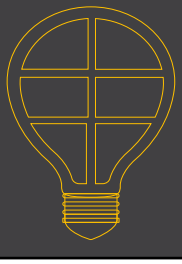

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Enoxaparin Dosing

- Current guidelines – 'fixed' dosing
  - Society for Maternal-Fetal Medicine (SMFM) / American College of Obstetricians & Gynecologists (ACOG)
    - BMI <40 kg/m^2: Enoxaparin 40 mg once daily
    - BMI ≥ 40 kg/m^2: Enoxaparin 40 mg every 12 hours
- Expert opinion & extrapolation from non-obstetric surgical fields

ACOG. Obstet Gynecol 2018;132(1):e1-e17.
Pacheco et al. SMFM. Am J Obstet Gynecol 2020;223(2):811-17.

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Enoxaparin Dosing

- Weight-based enoxaparin dosing superior to fixed dosing in non-pregnant individuals with obesity

Table. Prior Studies of LMWH Dosing in Postpartum Women

Author	Study Type and N	Findings
Hiscock et al	Prospective cohort, N=80	Weight-based dosing* achieved prophylactic anti-Xa levels in 72% of participants, no comparison (POD #1 and #3)
Overcash et al	Prospective cohort BMI ≥ 40 kg/m^2, N=85	Weight-based dosing* achieved prophylactic anti-Xa levels in 85% compared to 26% fixed dose LMWH (POD #2)
Stephenson et al	Randomized controlled trial BMI ≥ 35 kg/m^2, N=84	Weight-based dosing* achieved prophylactic anti-Xa levels in 88% compared to 14% fixed dose LMWH (POD #2)

*Weight-based dosing strategy differed by trial. For Hiscock, weight-based dosing was stratified by 40kg weight increments as in the RCOG guidelines. Overcash and Stephenson utilized 0.5 mg/kg twice daily.

- No change in national guidelines based on results

Hiscock et al. Int J Obstet Anesth 2013; 22(4): 280-8
Overcash et al. Obstet Gynecol 2015; 125(6): 1371-6.
Stephenson et al. J Perinatol 2016; 36(2): 95-9.

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Enoxaparin Dosing – RCT @ UUH

- **Objective**: To evaluate fixed versus weight-based enoxaparin dosing to achieve prophylaxis in individuals following cesarean delivery across all body mass index (BMI) categories.
- Included: Age 18+, cesarean delivery, met institutional criteria for postpartum enoxaparin prophylaxis
- Excluded: contraindication to prophylaxis, plan for postpartum therapeutic anticoagulation, known renal dysfunction

Bruno et al Obstet Gynecol 2023

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Enoxaparin Dosing – RCT @ UUH

- Randomization arms
  - Weight-based enoxaparin
    - 0.5 mg/kg every 12 hours
  - Fixed enoxaparin
    - BMI <40 kg/m^2 – 40 mg daily
    - BMI ≥40 kg/m^2 – 40 mg every 12 hours
- LMWH inpatient & through 14 days post-discharge
- Followed through 6 weeks postpartum

Bruno et al Obstet Gynecol 2023

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Enoxaparin Dosing – RCT @ UUH

- Primary outcome – prophylactic peak anti-Xa level
  - At steady state – after at least third dose enoxaparin
  - Peak – 4-6 hours after enoxaparin dose
  - Prophylactic range – 0.2-0.6 units/mL
- Secondary outcomes
  - Sub-prophylactic peak level (<0.2 units/mL)
  - Supra-prophylactic peak level (>0.6 units/mL)
  - Outpatient peak anti-Xa level (Between postoperative day 10-18)
  - VTE within 6 wks postpartum
  - Wound complications within 6 wks postpartum

Bruno et al Obstet Gynecol 2023

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Enoxaparin Dosing – Work @ UUH

- Methods
  - Enrolled from June 19, 2020 – November 18, 2021
  - Data & Safety Monitoring Board (DSMB) – monitored adverse events & progress
  - Single interim analysis at 50% enrollment
    - Pre-specified 'stopping criteria'
    - Stopped enrollment early for efficacy
  - Modified intention-to-treat (ITT) analysis

Bruno et al Obstet Gynecol 2023

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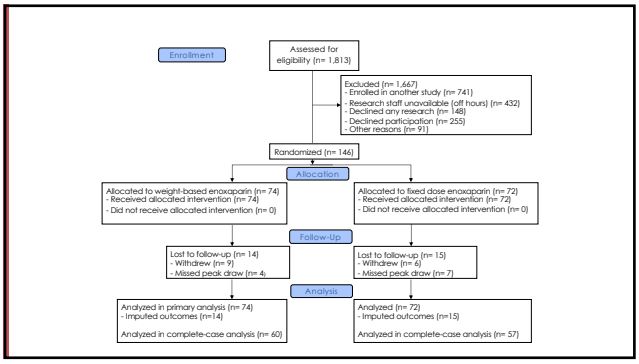

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Modified intention-to-treat analysis

Outcome	Weight-based (N=74)	Fixed (N=72)	Relative Risk (95% CI)	p
Prophylactic peak anti-Xa*	49 (66)	32 (44)	1.49 (1.10-2.02)	0.008
Sub-prophylactic peak*	24 (32)	40 (56)	0.58 (0.40-0.86)	0.005
Supra-prophylactic peak*	15 (20)	15 (21)	0.97 (0.51-1.84)	0.933
Prophylactic outpatient peak*	15 (20)	5 (7)	2.92 (1.12-7.61)	0.019
Venous thromboembolism	0 (0)	0 (0)	–	–
Any wound complication	5 (7)	1 (1)	4.86 (0.58-40.63)	0.102
Hematoma	3 (4)	0 (0)	–	0.084
Surgical site infection	2 (3)	0 (0)	–	0.160
Other	0 (0)	1 (1)	–	0.309

Data as n(%)
*Worst-case imputation for missing data

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Key Findings

- Weight-based LMWH dosing more effective than fixed dosing to achieve prophylactic peak anti-Xa levels
- Weight-based dosing remained more effective than fixed at achieving prophylactic anti-Xa level at 2-wk postpartum visit
- No postpartum VTEs in the study
- Wound complications did not differ by dosing regimen

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In Context

- Together with 3 other studies, growing pool of data supporting weight-based enoxaparin dosing
- National guidelines and institutional protocols should consider a weight-based approach to post-cesarean thromboprophylaxis dosing

Hiscock et al. Int J Obstet Anesth 2013; 22(4): 280-8
Overcash et al. Obstet Gynecol 2015; 125(6): 1371-6.
Stephenson et al. J Perinatol 2016; 36(2): 90-9.

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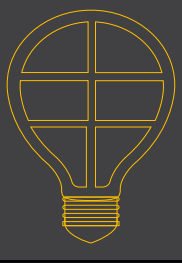
Why not conduct a large RCT?



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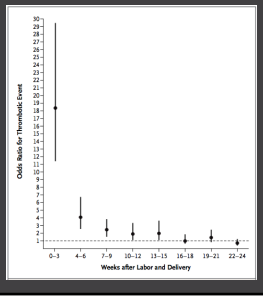
Length of Therapy



- Length of LMWH prophylaxis varies by guideline
- Risk not eliminated post-discharge
- QI/QA review – UUH (2017-19)
  - 18 VTE – range from PPD# 0-34
- 1-2 doses of enoxaparin inpatient only likely not useful

Kamel et al. NEJM 2014; 370(14): 1312

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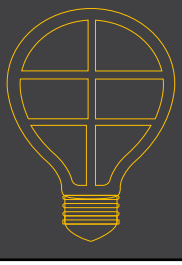

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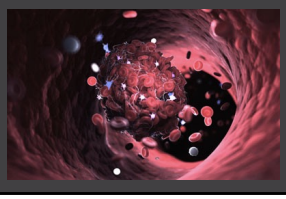
Surrogate Outcome

- Symptomatic VTE relatively rare event
- More prevalent marker of VTE ideal for trial feasibility
- Potential:
  - Lower extremity Doppler
  - Biomarker (D-dimer, other thrombosis markers)



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Surrogate Outcome

- Lower Extremity (LE) Doppler Study
  - Prospective cohort study of individuals undergoing cesarean and with obesity (defined as BMI >/= 30 kg/m^2)
  - Receive **NO** LMWH prophylaxis but otherwise standard of care
  - Primary outcome: asymptomatic deep vein thrombosis (DVT)
    - LE Doppler between postoperative day #10-18

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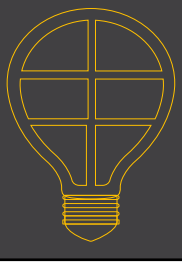
Why not conduct a large RCT?



- LARGE sample size
- Multiple unanswered questions
  - Target population – who is 'at risk'?
  - Enoxaparin dose
  - Enoxaparin length of therapy
  - Surrogate outcome
  - Compliance/Willingness to use

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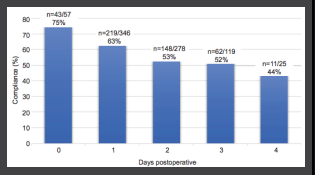
SCD Compliance

- Single center prospective study (gyn & OB)
- 4 month window with educational interventions
- 859 observations in 228 patients
- No difference in compliance over time
  - 61.3% first month
  - 60.1% last month
- Compliance decreased over course of hospitalization by day



Brady et al. Obstet Gynecol 2015; 125: 19–25.
Palmerola et al. J Matern Fetal Neonatal Med 2016; 29(19): 3072–3075.

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LMWH Compliance

- Few studies
- Single center observational study of individuals receiving postpartum thromboprophylaxis, in 67 individuals:
  - 82.4% reported no missed doses of LMWH
  - Survey data – 'Good' understanding of risks of VTE
- U of U Institutional LMWH RCT –
  - Participant report of outpatient compliance with LMWH therapy
  - Reported compliance – 79% (fixed) vs 88% (weight)

Guimicheva et al. Thrombosis Research 2019; 173:85-90.

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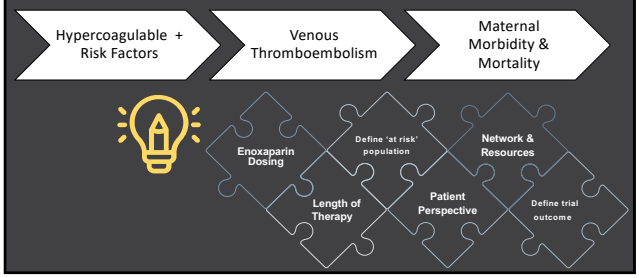
More work to do…



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Connect the Dots

- VTE significant contributor to maternal morbidity & mortality
  - Deserves our time & resources
- More work to be done to address postpartum VTE reduction
  - Better defining 'at risk' population
  - Consider implementation of weight-based enoxaparin dosing
  - Understanding of willingness to use enoxaparin & patient adherence
  - Surrogate outcomes as VTE rare event
- Need an efficacy trial: enoxaparin vs placebo

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Until then… what do we?

37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

Pregnancy history:
- Conception by IVF
- Antepartum admission for non-obstetric surgery (cholecystectomy)

Medical history includes:
- Crohn's Disease (well-controlled, no recent flares)
- Obesity (body mass index 39 kg/m^2)

What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

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Key Takeaways

- Use a standardized protocol at institutional level
  - Existing protocols focus on 'at risk' population
  - Consider use of therapy through 2 weeks postpartum – especially in higher risk
- Ongoing patient education & engagement in research

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Thank you!

Ann Bruno, MD
Associate Professor
University of Utah Health

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Questions?

torri.metz@hsc.utah.edu

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