Tromboembolismo Venoso In gravidanza

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- **Familiarità negativa per TEV (padre IMA 58 aa fumatore, diabetico)**
- **33 aa, fumatrice 5 sig/die**
- **Portatrice di trait microcitemico (valori abituali Hb 10-11 gr/dL, MCV 65)**
- **Mai contraccezione ormonale**
- **I gravidanza a 28 anni : TC a 38 sett, F 2320 g (oligoamnios, IUGR)**

- **24^ settimana della seconda gravidanza**
- **Modesta dolenzia arto inferiore sinistro da tre giorni.**
- **Dispnea da sforzo di lieve entità**
- **Hb 8.5 gr/dL, ferritina 3 (non ha assunto trattamento marziale "in considerazione della microcitemia"**

6.1 What is the initial treatment of VTE in pregnancy?

In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. **B**

RCOG 2015

- **E’ utile la determinazione del D-dimero ?**

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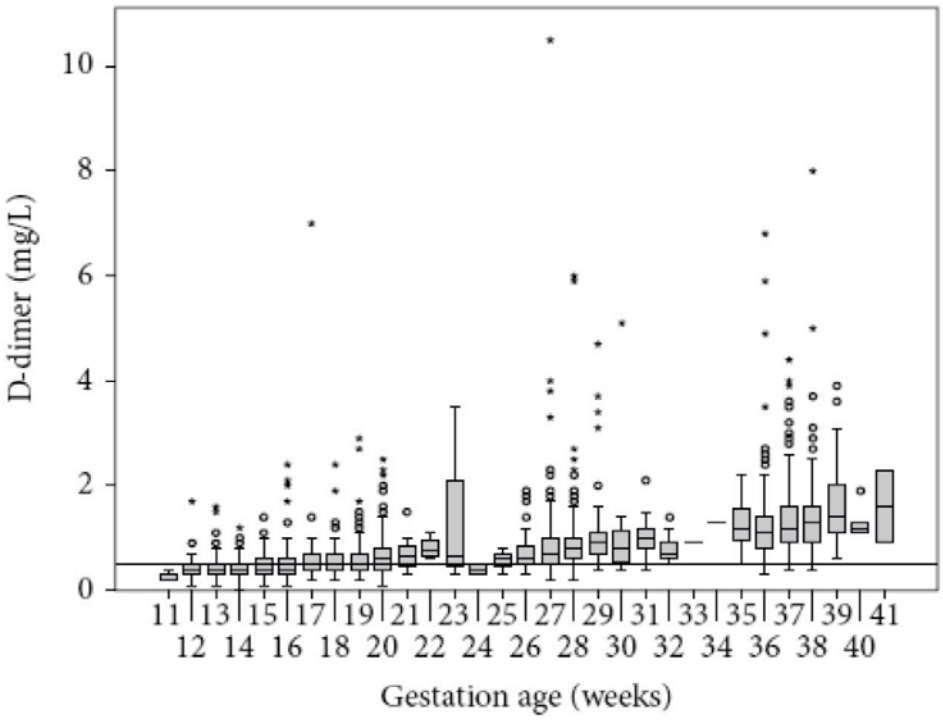
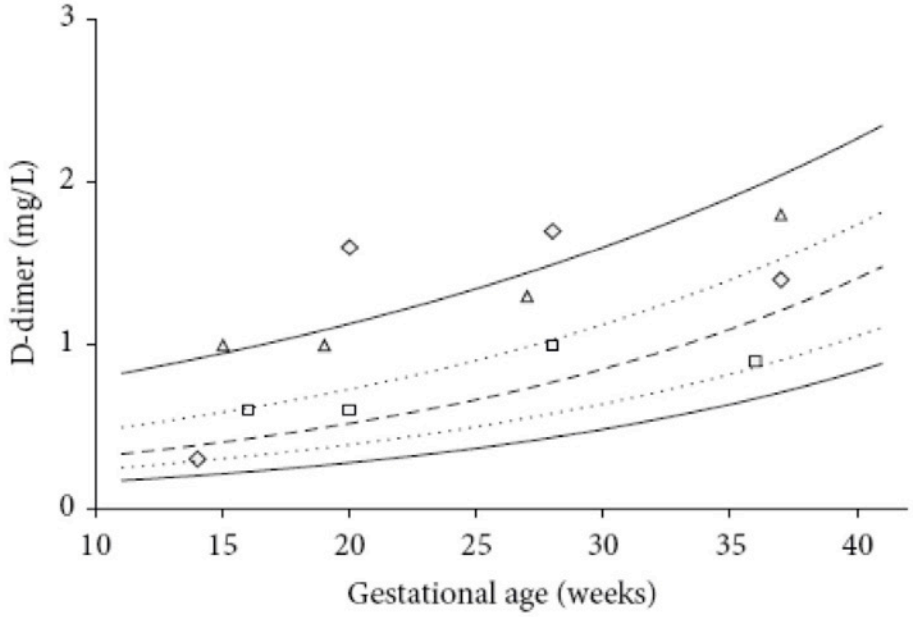
Hindawi

Research Article

Large D-Dimer Fluctuation in Normal Pregnancy: A Longitudinal Cohort Study of 4,117 Samples from 714 Healthy Danish Women

Katrine K. Hedengran, Malene R. Andersen, Steen Stender, and Pal B. Szecsi


D-dimer (mg/L)
0
2
4
6
8
10
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Gestation age (weeks)


D-dimer (mg/L)
0
1
2
3
10
15
20
25
30
35
40
Gestational age (weeks)

bjh research paper

2018

The DiPEP (Diagnosis of PE in Pregnancy) biomarker study: An observational cohort study augmented with additional cases to determine the diagnostic utility of biomarkers for suspected venous thromboembolism during pregnancy and puerperium

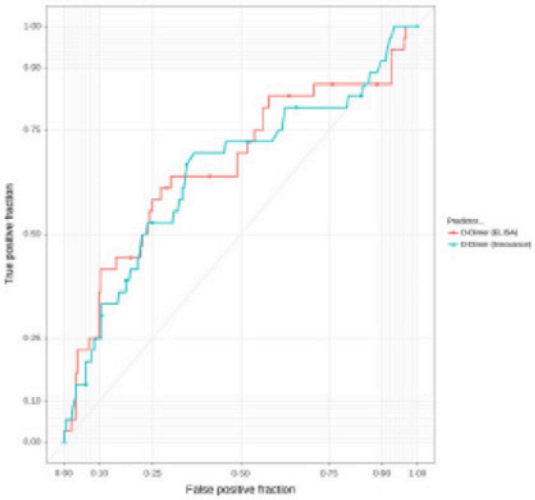


Fig 1. Receiver operator characteristic curves for D-dimer biomarkers. ELISA, enzyme-linked immunosorbent assay.

4.3 Should D-dimer testing be performed prior to objective diagnosis?

D-dimer testing should not be performed in the investigation of acute VTE in pregnancy. D

RCOG 2015

In a prospective cohort study of 221 pregnant women who presented with suspected DVT, the sensitivity of serial compression ultrasonography with Doppler imaging was 94.1% (95% CI 69.2– 99.7%), the negative predictive value was 99.5% (95% CI 96.9–100%) and the negative likelihood ratio was 0.068 (95% CI 0.01–0.39) (Chan, 2013)

When iliac vein thrombosis is suspected (back and buttock pain and swelling of the entire limb), Doppler ultrasound of the iliac vein, magnetic resonance venography or conventional contrast venography may be considered, although in practice, because of the extensive nature of these thrombi, ultrasound venography will often suffice (RCOG 2015).

What investigations are needed for the diagnosis of an acute DVT?

Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT. B

If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued. If ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound should be repeated on days 3 and 7. [*New 2015*] C

RCOG 2015

Scenario A

- D-dimero: 2.0 mg/L (v.n. <0.5)

- Doppler venoso:
  TVP popliteo-femoro-iliaca sx

- E' presente un'embolia polmonare ?

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Full Length Article

Diagnosis of venous thromboembolism in pregnancy

Wee-Shian Chan

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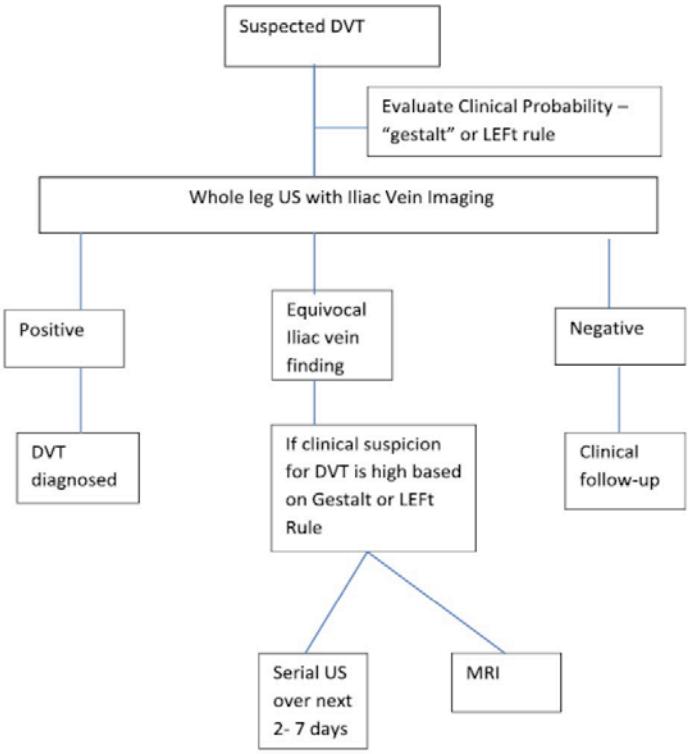
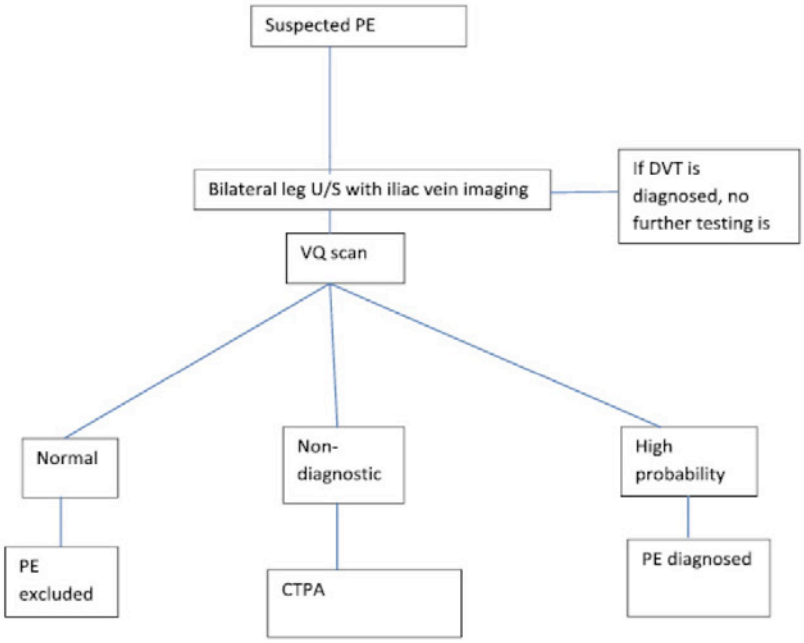

Suspected DVT
Evaluate Clinical Probability – "gestalt" or LEFt rule
Whole leg US with Iliac Vein Imaging
Positive
Equivocal Iliac vein finding
Negative
DVT diagnosed
If clinical suspicion for DVT is high based on Gestalt or LEFt Rule
Clinical follow-up
Serial US over next 2- 7 days
MRI


Suspected PE
Bilateral leg U/S with iliac vein imaging
If DVT is diagnosed, no further testing is
VQ scan
Normal
Non-diagnostic
High probability
PE excluded
CTPA
PE diagnosed

Scenario B

- **D-dimero: 2.0 mg/L (v.n. <0.5)**

- **Doppler venoso:**
  non evidenza di TVP

- **E' presente un'embolia polmonare ?**

Risk of radiologic procedures to the fetus

- Radiation exposure of up to 0.05 Gy (5 rad) in utero:
  - Oncogenicity
    - Relative risks of 1.2-2.4
    - Absolute risk of malignancy (baseline) in fetus is estimated to be 0.1%.
  - Tetratogenicity
    - No increase in pregnancy loss, growth or mental retardation

Table 1. Estimated fetal radiation exposure with radiologic procedures

Radiologic procedure	Estimated fetal radiation exposure, rad
Bilateral venography without abdominal shield	0.628
Unilateral venography without abdominal shield	0.314
Limited venography	< 0.05
Pulmonary angiography via femoral route	0.221-0.374
Pulmonary angiography via brachial route	< 0.05
Perfusion lung scan using ^{99m}Tc-MAA	
3 mCi	0.018
1 to 2 mCi	0.006-0.012
Ventilation lung scan	
Using ^{133}Xe	0.004-0.019
Using ^{99m}Tc-DTPA	0.007-0.035
Using ^{99m}Tc-SC	0.001-0.005
Chest radiograph	< 0.001

Xe indicates xenon; DTPA, diethylenetriamine penta-acidic acid; Tc, technetium.

CT angiography: 0.013- 0.0026 (rads)

Techniques to lower radiation exposure during

- Circumferential screening of the abdomen and pelvis (CTPA)
- Duration of scanning reduced (CTPA)
- Half-dose (perfusion) techniques (VQ scan)
- If perfusion is normal, then ventilation scan unnecessary (PE excluded)

***Please note that even if a pregnant woman underwent a CXR, followed by a VQ scan, then CTPA, and then pulmonary angiogram, the combined fetal radiation dose would still be less than that obtained via background radiation during the nine months of pregnancy!

What investigations are needed for the diagnosis of an acute pulmonary embolism (PE)?

Women presenting with symptoms and signs of an acute PE should have an electrocardiogram (ECG) and a chest X-ray (CXR) performed. [*New 2015*] **C**

In women with suspected PE who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue. [*New 2015*] **C**

In women with suspected PE without symptoms and signs of DVT, a ventilation/perfusion (V/Q) lung scan or a computerised tomography pulmonary angiogram (CTPA) should be performed. [*New 2015*] **C**

When the chest X-ray is abnormal and there is a clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan. [*New 2015*] **D**

Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal but the clinical suspicion of PE remains. Anticoagulant treatment should be continued until PE is definitively excluded. **C**

Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small. [*New 2015*] **D**

RCOG 2015

CTPA has potential advantages over V/Q imaging including: CTPA is more readily available,[37,38] delivers a low radiation dose to the fetus (see section below) and can identify other pathology including pneumonia (5–7%), pulmonary oedema (2–6%) and rarely aortic dissection.[5,35] Despite these potential advantages of CTPA, many authorities continue to recommend V/Q scanning as first-line investigation in pregnancy because of its high negative predictive value in this situation and its substantially lower radiation dose to pregnant breast tissue (see section below).[39,40]

RCOG 2015

Scenario A

- **D-dimero: 2.0 mg/L (v.n. <0.5)**

- **Doppler venoso:**
  TVP popliteo-femoro-iliaca sx

Treatment of acute VTE during pregnancy

- **adjusted-dose subcutaneous LMWH over adjusted-dose UFH** (Grade 1B)**, over vitamin K antagonist treatment antenatally** (Grade 1A)**.**

- **for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months)** (Grade 2C)**.**

- **discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section** (Grade 1B)**.**

ACCP 2012

6.2 What is the therapeutic dose of LMWH in pregnancy?

LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. C

During pregnancy, changes in volume of distribution and renal glomerular filtration rate result in alterations in the pharmacokinetics of LMWHs.

Previous editions of the RCOG guideline (2001 and 2007) recommended a twice-daily dosage regimen for enoxaparin and dalteparin in the treatment of VTE in pregnancy (enoxaparin 1 mg/kg twice daily; dalteparin 100 units/kg twice daily). This recommendation was based on anti-Xa activity and a paucity of reports on safety and efficacy of once-daily dosing.

Since then, a prospective multicentre observational study has found that 60% of practitioners use once-daily dosing of enoxaparin and dalteparin for treatment of VTE in pregnancy.

A national case–control study on the management of antenatal PE using the UK Obstetric Surveillance System found that 49% of women were managed with a once-daily dosage schedule.

Further, a large, international retrospective study on the use of tinzaparin in pregnancy (with 254 pregnancies receiving treatment doses and 94.1% of these in a once-daily regimen) has provided reassuring data on safety and efficacy of once-daily dosing.

Recommendations on the treatment of pregnancy-associated VTE from clinicians in New Zealand and Australia concluded that there is insufficient evidence to favour one dose regimen over the other, and that treatment of acute VTE in pregnancy can be with LMWH administered either once daily or twice daily.

A recent pharmacokinetic study involving 123 pregnant women found that the half-life of enoxaparin is prolonged with the progression of pregnancy; the authors conclude that their study provides further support for the use of once-daily enoxaparin for treatment of VTE in pregnancy.

Table 1. Calculation of initial doses of drugs by early pregnancy weight

Initial dose	Early pregnancy weight (kg)			
	< 50	50–69	70–89	> 90
Enoxaparin	40 mg bd	60 mg bd	80 mg bd	100 mg bd
Dalteparin	5000 iu bd	6000 iu bd	8000 iu bd	10,000 iu bd
Tinzaparin	175 units/kg once daily (all weights)			

bd = twice daily

Table 1a. Initial dose of enoxaparin is determined as follows:

Booking or early pregnancy weight	Initial dose of enoxaparin
< 50 kg	40 mg twice daily or 60 mg once daily
50–69 kg	60 mg twice daily or 90 mg once daily
70–89 kg	80 mg twice daily or 120 mg once daily
90–109 kg	100 mg twice daily or 150 mg once daily
110–125 kg	120 mg twice daily or 180 mg once daily
> 125 kg	Discuss with haematologist

RCOG 2015

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). C

Routine platelet count monitoring should not be carried out. D

Obstetric patients who are postoperative and receiving unfractionated heparin should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped. D

CASE-STUDY

- Peso 60 kg

- Inizia terapia con enoxaparina 6000 U x 2 / 24 h

Doppler dopo 10 giorni:
iniziali segni di ricanalizzazione

CASE-STUDY

- Peso 60 kg

- Inizia terapia con
  enoxaparina 6000 U x 2 / 24 h
- Collant elastico pressione media

Doppler dopo 10 giorni:
iniziali segni di ricanalizzazione

8. Maintenance treatment of VTE

8.1 What is the maintenance treatment of DVT or PE?

Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. **B**

7. Treatment of proven acute VTE during pregnancy

For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C)**.**

For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B)**.**

ACCP 2012

CASE-STUDY

- **Riduce enoxaparina 6000 U x 1 / 24 h alla 30^ settimana**
- **PV alla 39^ settimana**
- **Prosegue enoxaparina 4000 U x 1 fino a 6 settimane dopo**

CASE-STUDY

- **Indagini per trombofilia ?**

Thrombophilia-associated VTE

Heritable thrombophilia

Women with previous VTE associated with antithrombin deficiency (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. D

Management should be undertaken in collaboration with a haematologist with expertise in thrombosis in pregnancy and consideration given to antenatal anti-Xa monitoring and the potential for antithrombin replacement at initiation of labour or prior to caesarean section. [*New 2015*] ✓

If anti-Xa levels are measured, a test that does not use exogenous antithrombin should be used and 4-hour peak levels of 0.5–1.0 iu/ml aimed for. [*New 2015*] ✓

Other heritable thrombophilic defects are lower risk and can be managed with standard doses of thromboprophylaxis. [*New 2015*] ✓

Opinione personale

- Il dosaggio antitrombina deve essere effettuato contestualmente alla diagnosi di TVP per:
- - decidere un incremento dosaggio LMWH
- - Decidere sull'impiego di concentrati in situazioni critiche

QUESTION TIME

- Diagnosi EP
- LMWH od o bid
- Diagnosi TVP iliaca