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SS Risk Management
ASL5 Liguria
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TEV e Gravidanza

9º Corso Incontri Pratici Di Ematologia

SAVONA
9-10-11 novembre 2017
Hotel NH Darsena
Via Chiodo 9

Responsabile scientifico del progetto

Dott. Rodolfo TASSARA
S.C. Medicina Interna, Savona



Il testo guida

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Pregnancy Complicated by Venous Thrombosis

Ian A. Greer, M.D.

N ENGL J MED 373;6 NEJM.ORG AUGUST 6, 2015

"Limited data are available from randomized trials involving pregnant women to guide the prevention, diagnosis, and treatment of venous thrombosis in pregnancy. Evidence to guide decision making is derived largely from trials involving nonpregnant persons and from observational studies"



AGENDA

- Rapporto fra TEV e gravidanza
- Diagnosi di TEV in gravidanza
- Trattamento del TEV in gravidanza
- Trombofilia e gravidanza
- Tromboprofilassi in gravidanza



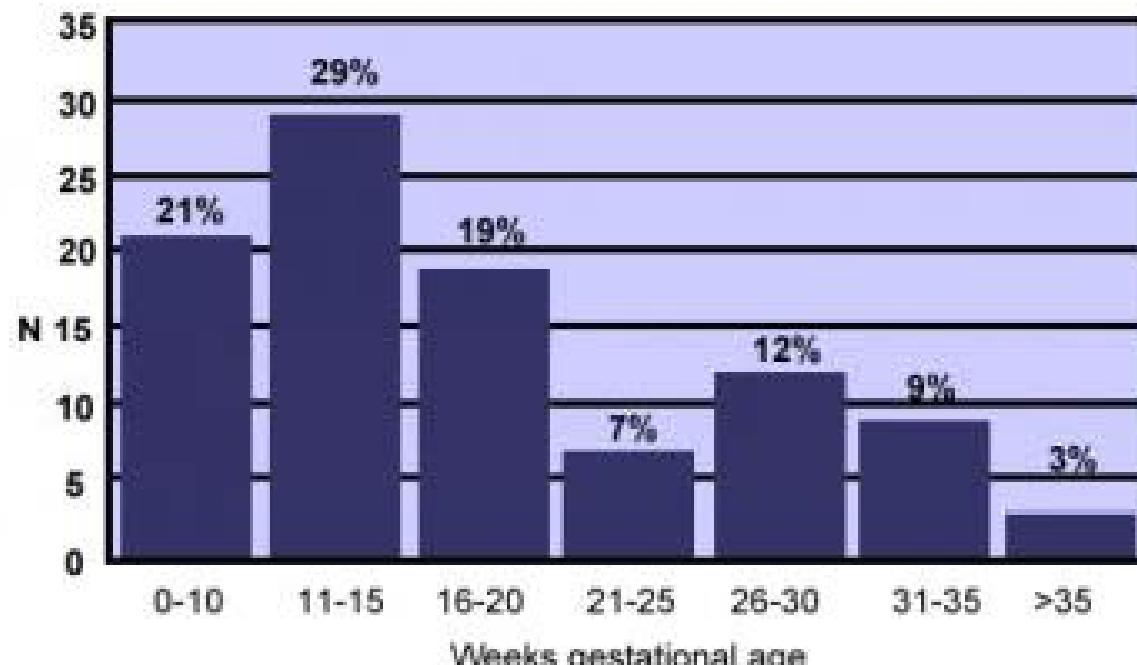
Le donne gravide hanno un rischio aumentato di tromboembolismo venoso (TEV)



1-2 episodi ogni 1000 gravidanze



>50% degli episodi si verificano nelle prime 20 settimane



Estimated gestational age at time of diagnosis of
antepartum deep venous thrombosis (n=94).



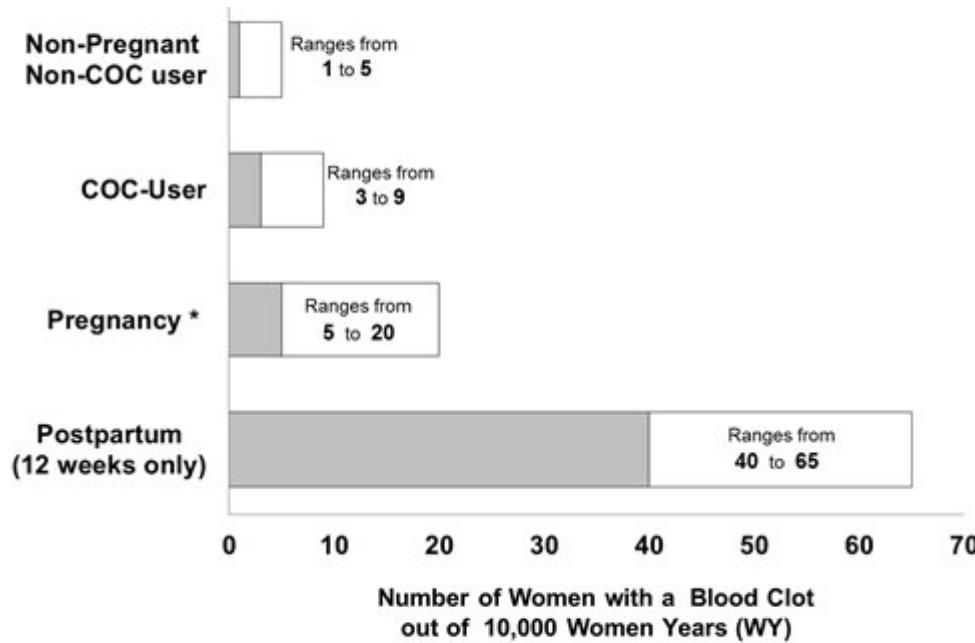
Il rischio di TEV si modifica in rapporto alla modalità di espletamento del parto

Complicanze tromboemboliche in gravidanza

| | TEV /N.ro gravidanze | Rischio/mille gravidanze (95%CI) |
|----------------------------------|-------------------------|-------------------------------------|
| Parto Vaginale | 125 / 556040 | 0.22 (0.19-0.96) |
| Taglio Cesareo Elettivo | 23 / 33779 | 0.68 (0.40-0.96) |
| Taglio Cesareo in Urgenza | 47 / 55839 | 0.84 (0.60-1.01) |
| Tutti i Tagli Cesarei | 70 / 89618 | 0.78 (0.60-0.96) |

Macklon NS, Greer I. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scot Med J 1996;41:83-6

Post partum vs antepartum



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Il rischio giornaliero è massimo nel post partum

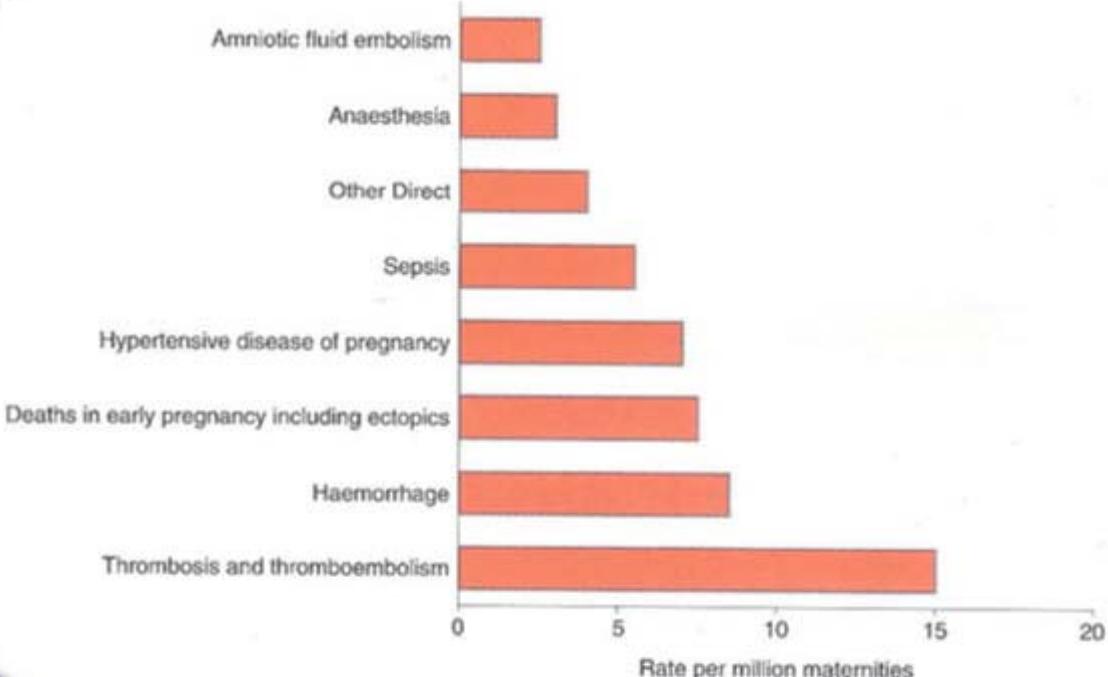
DISTRIBUZIONE RELATIVA DEL TEV

- Periodo: gravidanza: 280 giorni
puerperio: 42 giorni
- Distribuzione relativa di 100 TEV:
gravidanza: 0.15 per giorno
puerperio: 1.36 per giorno

La probabilità di TEV (per giorno) è circa 9 volte più elevata nel puerperio rispetto alla gravidanza

Martinelli, Thromb Haemost, 2002

L'EP è la maggiore causa non ostetrica di morte materna



2/100 000 gravidanze



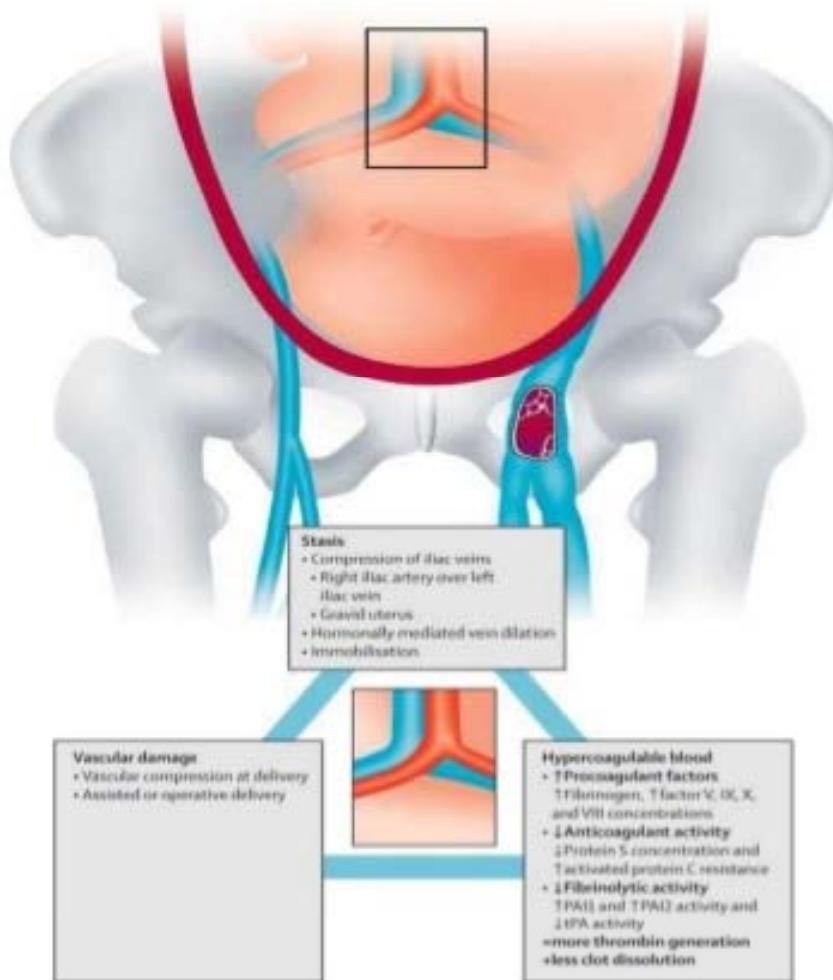
TEV E GRAVIDANZA: PECULIARITA'

- Le TVP associate alla gravidanza si verificano prevalentemente sul lato sinistro (85% vs 55% nelle non gravide)
- Sono spesso prossimali (TVP iliaco-femorale nel 72% vs 9% nelle non gravide)
- Una quota significativa di TVP in gravidanza si verifica a livello delle vene pelviche e perciò sfugge ai test routinari
- Possono esserci casi di trombosi ovariche
- Maggiore incidenza di EP e Sdr. Post-trombotica

Greer I.A. NEJM 2017



Why pregnancy has a greater risk?



FATTORI DI RISCHIO



| Pre-existing | PreviousVTE | |
|------------------------|--|---|
| | Thrombophilia | <p><i>Heritable</i> Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene mutation</p> <p><i>Acquired</i> Antiphospholipid antibodies Persistent lupus anticoagulant and/or persistent moderate/high titre anticardiolipin antibodies and/or β_2-glycoprotein I antibodies</p> |
| | ★ | Medical comorbidities e.g. cancer; heart failure; active SLE, inflammatory polyarthropathy or IBD; nephrotic syndrome; type 1 diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user |
| | Age > 35 years | |
| | Obesity ($BMI \geq 30 \text{ kg/m}^2$) either prepregnancy or in early pregnancy | ★ |
| | Parity ≥ 3 (a woman becomes para 3 after her third delivery) | |
| | Smoking | |
| | Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes) | |
| | Paraplegia | |
| Obstetric risk factors | Multiple pregnancy Current pre-eclampsia Caesarean section Prolonged labour (> 24 hours) Mid-cavity or rotational operative delivery Stillbirth Preterm birth Postpartum haemorrhage (> 1 litre/requiring transfusion) | |
| | ★ | |
| New onset/transient | Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation Bone fracture Hyperemesis, dehydration Ovarian hyperstimulation syndrome (first trimester only) Admission or immobility (≥ 3 days' bed rest) Current systemic infection (requiring intravenous antibiotics or admission to hospital) Long-distance travel (> 4 hours) | |
| | ★ Assisted reproductive technology (ART), invitro fertilisation (IVF) e.g. pelvic girdle pain restricting mobility e.g. pneumonia, pyelonephritis, postpartum wound infection | |

IMPATTO DEI FATTORI DI RISCHIO



Appendix II: Adjusted odds ratios for risk factors for VTE

| Risk factor | aOR ^a | 95% CI | Comment |
|--|-------------------|------------|---------------|
| Previous VTE ^{b,c,d} | 26.8 | 17.1–36 | |
| Age > 35 ^{c,d,e,f} | 1.3 ^d | 1.0–1.7 | n = 603 |
| | 1.4 ^d | 1.0–2.0 | pn = 256 |
| | 1.2 ^d | 1.1–1.4 | DVT |
| Obesity | 2.0 ^d | 1.09–6.45 | n = 143 an PE |
| BMI >/≥ 30 ^{c,d,p} ^{f,g} | 5.3 ^d | 2.1–13.5 | n = 129 |
| | 4.4 ^d | 3.4–5.7 | |
| | 1.7 ^d | 1.1–2.6 | pn = 256 |
| | 1.8 ^d | 1.2–2.6 | DVT |
| | 2.7 ^d | 1.6–4.4 | PE |
| BMI >/≥ 25 ^{d,g} | 1.8 ^d | 1.3–2.4 | an n = 268 |
| | 2.4 ^d | 1.7–3.3 | pn n = 291 |
| | 1.7 ^d | 1.2–2.4 | pn = 256 |
| Weight 90–120 kg ^d | 1.93 | 1.10–3.39 | an |
| Weight > 120 kg | 4.32 | 1.26–14.84 | |
| Weight gain in pregnancy > 21 kg ^d (compared to 7–21 kg) | 1.6 | 1.1–2.6 | pn n = 291 |
| Parity 1 ^d | 4.03 | 1.6–9.84 | n = 143 an PE |
| 2 ^d | 1.5 | 1.1–1.9 | n = 603 |
| ≥ 3 ^d | 2.4 | 1.8–3.1 | n = 603 |
| Smoking | 2.1 ^d | 1.3–3.4 | an n = 268 |
| 10–30/ day ^{d,g,h} | 3.4 ^d | 2.0–5.5 | pn n = 291 |
| | 1.4 ^d | 1.1–1.9 | n = 603 |
| | 2.5 ^d | 1.3–4.7 | n = 90 |
| Current smoker ^d | 2.7 ^d | 1.5–4.9 | n = 129 |
| Sickle cell ^{j,k,l} | 6.7 ^d | 4.4–10.1 | |
| | 2.5 ^d | 1.5–4.1 | DVT |
| | 1.7 ^d | 0.9–3.1 | PE |
| Heart disease ^{k,l,m} | 7.1 ^d | 6.2–8.3 | |
| | 5.4 ^d | 2.6–11.3 | pn n = 256 |
| | 3.2 ^d | 2.2–4.6 | DVT |
| | 43.4 ^d | 35.0–53.9 | PE |
| Systemic lupus erythematosus ^{k,l} | 8.7 ^d | 5.8–13 | |
| | 2.3 ^d | 1.1–4.8 | DVT |
| | 3.9 ^d | 1.9–7.8 | PE |
| Anaemia ^{m,n} | 2.6 ^d | 2.2–2.9 | |
| | 1.6 ^d | 1.4–1.9 | DVT |
| | 1.7 ^d | 1.3–2.2 | PE |
| Varicose veins ⁱ | 2.4 | 1.04–5.4 | |
| Immobility ^d | 7.7 | 3.2–19 | an |
| | 10.8 | 4.0–28.8 | pn |
| Pre-eclampsia ^{i,j} | 2.9 ^d | 2.1–3.9 | |
| | 3.1 ^d | 1.8–5.3 | pn |
| Pre-eclampsia plus FGR ⁱ | 5.8 ^d | 2.1–16 | |
| Hyperemesis ^{m,n} | 2.5 ^d | 2–3.2 | |
| | 4.4 ^d | 2.4–8.4 | DVT |

IMPATTO DEI FATTORI DI RISCHIO

| | | | |
|--|--|--|-------------------------|
| Assisted reproductive technology ^{a,b,c,d} | 4.3 ^a 4.2 ^b 1.8 ^c | 2.0–9.4 1.5–11 1.4–2.2 | an |
| Twins ^{a,b,c} | 2.6 ^a 1.8 ^b | 1.1–6.2 1.1–3.0 | an n = 603 |
| Multiple pregnancy ^{a,b} | 4.2 ^b 1.7 ^a | 1.8–9.7 1.3–2.2 | an n = 109 DVT |
| Preterm delivery < 37 weeks ^{a,b} | 2.4 ^b 2.69 ^a | 1.6–3.5 1.99–3.65 | pn n = 256 |
| Stillbirth (IRR) ^a | 6.24 ^a | 2.77–14.1 | |
| Antepartum haemorrhage ^a | 2.3 | 1.8–2.8 | |
| Emergency caesarean section ^a | 2.7 | 1.8–4.1 | |
| Any caesarean section ^{a,b,c,d,e,f,g,h,i,j,k,l,m} | 7.6 ^a 2.1 ^a 2.0 ^b 1.8 ^a 2.9 ^a 3.4 ^a | 3.0–4.3 1.8–2.4 1.5–2.7 1.6–2.0 2.4–3.5 1.3–9.0 | pn n = 256 DVT PE |
| PPH > 1 litre ^a | 4.1 ^a | 2.3–7.3 | |
| PPH unspecified ^a | 1.2 ^a 1.3 ^a | 1.0–1.4 1.0–1.7 | DVT PE |
| PPH + surgery ^a | 12 | 3.9–36.9 | |
| Obstetric haemorrhage ^a | 9 | 1.1–71 | |
| Postpartum infection ^{a,b} | 4.1 ^a 6.1 ^a 4.1 ^a | 2.9–5.7 5.0–7.5 3.0–5.6 | DVT PE |
| Postpartum infection + caesarean section ^a | 6.2 | 2.4–16.2 | |
| Transfusion ^{a,b} | 7.6 ^a 3.6 ^a 4.5 ^a | 6.2–9.4 2.8–4.7 3.3–6.2 | DVT PE |

Abbreviations: an antenatal; aOR adjusted odds ratio; CI confidence interval; DVT deep venous thrombosis; FGR fetal growth restriction; IRR incidence rate ratio; n number of cases in case-control study; PE pulmonary embolism; pn postnatal; PPH postpartum haemorrhage; VTE venous thromboembolism.



PRESENTAZIONE CLINICA INSIDIOSA

- Dolore toracico, dispnea e sintomi relativi agli arti inferiori sono comuni in gravidanza
 - Edema, dolorabilità, discromie cutanee, termo-tatto aumentato, rigidità inusuale, cordoni venosi, dolore alla dorsiflessione
- Spesso si manifesta con dolore addominale
- La tachicardia può essere una normale risposta fisiologica
- Esame emogasanalisi e gradiente A-a sono spesso normali (<3% delle gravide con EP SaO₂ <90%, RCOG Green-top Guideline No. 37b, 2015)



TEV in gravidanza: una sfida diagnostica

- La diagnosi clinica di per sè è inaffidabile
- TVP e PE risultano meno frequenti nelle gravide sintomatiche rispetto alle non gravide
- Il trattamento anticoagulante è efficace, ma si accompagna a rischi maggiori
- Una TVP non trattata può tradursi in una EP fatale
- Pertanto, quando si sospetta la presenza di TEV in gravidanza, è essenziale diagnosticarlo se è presente ed escluderlo se è assente.



Clinical Prediction Rules: LEft score

Table 5. Frequency and Prevalence of DVT for the LEft Variables

| Variable Present | Frequency of Variable, n (%) | Prevalence of DVT (95% CI) | P Value* |
|--------------------------------------|------------------------------|----------------------------|----------|
| Symptomatic leg | | | |
| Left leg | 90 (46.4) | 17.8 (11.3–27.0) | <0.001 |
| Bilateral or right leg | 104 (53.6) | 1.0 (0.1–5.2) | |
| Calf circumference difference | | | |
| ≥2 cm | 25 (16.9) | 44.0 (26.6–63.1) | <0.001 |
| <2 cm | 123 (83.1) | 2.4 (0.9–6.9) | |
| Trimester | | | |
| First | 9 (4.6) | 55.6 (26.2–81.3) | <0.001 |
| Second or third | 185 (95.4) | 6.5 (3.8–11.0) | |
| LEft variables | | | |
| 0 or ≥1 | | | |
| 0 | 88 (45.8) | 0 (0–4.2) | <0.001 |
| ≥1 | 105 (54.2) | 16.4 (10.5–24.6) | |
| ≤1 or >1 | | | |
| ≤1 | 158 (86.8) | 0.6 (0.1–3.5) | <0.001 |
| >1 | 25 (13.2) | 58.3 (35.8–75.5) | |
| Overall | 194 (100) | 8.8 (5.5–13.6) | |

DVT = deep venous thrombosis; LEft = left leg symptoms (L) and ≥2-cm calf circumference difference (E) presented in the first trimester (Ft).

* The P value reflects the significant difference between the 2 variables used for comparison.

Table 4. Subjective Pretest Probability Assessment and Performance of the LEft Variables in Predicting DVT in Pregnant Patients*

| Variable | DVT Present, n | DVT Absent, n | Sensitivity (95% CI), % | Specificity (95% CI), % | NPV (95% CI), % | Positive LR (95% CI) | Negative LR (95% CI) |
|---------------------------------------|----------------|---------------|-------------------------|-------------------------|-----------------|----------------------|----------------------|
| Pretest probability assessment | | | | | | | |
| Low | 2 | 129 | 88 (62–98) | 74 (66–80) | 98.5 (95–100) | 3.4 (2.5–4.5) | 0.16 (0.04–0.59) |
| Moderate or high | 15 | 46 | — | — | — | — | — |
| Low or moderate | 7 | 167 | 59 (36–78) | 95 (91–98) | 96.0 (92–98) | 12.9 (5.9–28.2) | 0.43 (0.24–0.76) |
| High | 10 | 8 | — | — | — | — | — |
| LEft variables | | | | | | | |
| 0 | 0 | 89 | 100 (81–100) | 50 (43–58) | 100 (96–100) | 2.0 (1.7–2.3) | 0 (0–0) |
| ≥1 | 17 | 88 | — | — | — | — | — |

DVT = deep venous thrombosis; LEft = left leg symptoms (L) and ≥2-cm calf circumference difference (E) presented in the first trimester (Ft); LR = likelihood ratio; NPV = negative predictive value.

* Observations with missing data points were excluded from the analysis.

Context

The clinical predictors of deep venous thrombosis (DVT) are well known in the general population but not in pregnant women.

Contribution

In 7 years, 5 centers enrolled 194 pregnant women with suspected DVT. Clinical thrombosis experts evaluated the women and did leg vein compression ultrasonography. Seventeen (8.8%) women had DVT. Clinical predictors of DVT were left leg symptoms, difference in calf circumference of 2 cm or more, and presentation during the first trimester of pregnancy. All 17 women with DVT had at least 1 of these predictors.

Caution

Too few women had DVT to independently validate the findings.

Implication

Presentation during the first trimester of pregnancy and a symptomatic left leg should raise suspicion of DVT in pregnancy.



Predicting deep venous thrombosis in pregnancy: external validation of the LEFT clinical prediction rule

Marc Righini,¹ Christelle Jobic,² Françoise Boehlen,¹ Jean Broussaud,³ François Becker,¹ Morgan Jaffrelot,⁴ Marc Blondon,¹ Bruno Guias,⁵ Grégoire Le Gal,² and the EDVIGE study group

Table 3. Diagnostic performances of the “LEFt” rule.

| | N. (%) | Proportion of DVT N. (%) | P |
|----------------------------|------------|-----------------------------|---------|
| LEFt score (points) | | | |
| 0 | 46 (29.3) | 0 (0.0) | < 0.001 |
| 1 | 83 (52.9) | 4 (4.8) | |
| 2 | 24 (15.3) | 7 (29.2) | |
| 3 | 4 (2.5) | 2 (50.0) | |
| LEFt score | | | |
| 0 (unlikely) | 46 (29.3) | 0 (0.0) | 0.002 |
| ≥1 (likely) | 111 (70.7) | 13 (11.7) | |

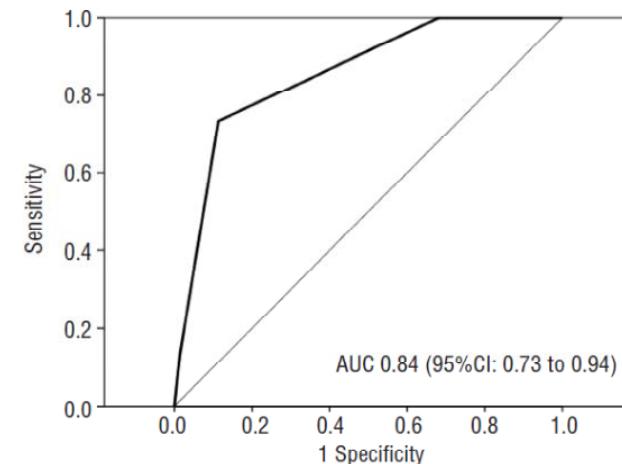


Figure 1. The “LEFt” score for DVT in pregnant women: ROC curve analysis.

In conclusion, our study suggests that the LEFt rule accurately identifies pregnant patients at very low risk of DVT. Further studies need to be performed to clarify its role in the diagnostic management of pregnant women with suspected DVT.

RESEARCH ARTICLE

The application of a clinical risk stratification score may reduce unnecessary investigations for pulmonary embolism in pregnancy

Clare O'Connor¹, John Moriarty², Jennifer Walsh³, John Murray⁴, Sam Coulter-Smith⁵ & William Boyd⁵

Table I. Modified Wells score [21].

| | |
|---|-----|
| Clinical evidence of a DVT | 3.0 |
| Other diagnosis less likely | 3.0 |
| Tachycardia | 1.5 |
| Immobilization or Surgery in past 4 weeks | 1.5 |
| History of DVT or PE | 1.5 |
| Haemoptysis | 1.0 |
| Malignancy(treatment in past 6months) | 1.0 |

Score > 6 = High (59% probability based on pooled data)

Table II. Results of the modified Wells score (MWS).

| | Sensitivity | Specificity | Positive | Negative | p value |
|-----|-------------|-------------|------------|------------|---------|
| | | | predictive | predictive | |
| MWS | 100% | 90% | 36% | 100% | <0.001 |

Table III. Results of other commonly used tests.

| | Sensitivity | Specificity | Positive | Negative | p value |
|----------|-------------|-------------|------------|------------|---------|
| | | | predictive | predictive | |
| D-dimers | 0% | 74% | 0% | 93% | N/S |
| CXR | 0% | 87% | 0% | 98% | N/S |
| ECG | 50% | 85% | 10% | 98% | N/S |
| ABG | 50% | 92% | 10% | 98% | <0.05 |

ABG: arterial blood gas; CXR: chest X-ray; ECG: electrocardiogram.

We identified a MWS of 6 or greater to be 100% sensitive for PE on CTPA. Significantly no patients with a low MWS (less than 6) were positive for PE on CTPA, giving a negative predictive value of 100%. The results demonstrate that by applying the MWS during a patients work up and eliminating those who are at low risk the number of negative CT PA s being carried out would be reduced by one third.

The MWS has been shown to be a useful tool in aiding the diagnosis of PE in the non-pregnant population by stratifying risk our study suggests that it would be equally useful in the maternity setting.

Test diagnostici

D-dimero

| Pregnancy | | D-dimer Result | | |
|--------------|---------------------------|----------------------------|-----------------------------|--------|
| Status | Negative (≤ 250 ng/ml) | Moderate (250-500ng/ml) | Significantly >500ng/ml) | Raised |
| | N (%) | N (%) | N (%) | |
| Pregnant | 9 (12) | 18 (24) | 48 (64) | |
| Non-Pregnant | 0 (0) | 25 (100) | 0 (0) | |

Test diagnostici

CUS

BMJ

BMJ 2012;344:a2635 doi: 10.1136/bmj.a2635 (Published 24 April 2012)

Page 1 of 9

RESEARCH

What is already known on this topic

Diagnostic value of single complete compression ultrasonography in pregnant and postpartum women with suspected deep vein thrombosis: prospective study

- Single complete compression ultrasonography is widely used to rule out deep vein thrombosis in everyday clinical practice
- No data are available to support this finding in the setting of pregnancy and the postpartum period

What this study adds

- Single complete compression ultrasonography may safely rule out deep vein thrombosis in pregnant and postpartum women
- Of 177 women without deep vein thrombosis and who did not receive full dose anticoagulant therapy, two experienced an objectively confirmed deep vein thrombosis during follow-up

Safety of withholding anticoagulation in pregnant women with suspected deep vein thrombosis following negative serial compression ultrasound and iliac vein imaging

Wee-Shian Chan MD, Frederick A. Spencer MD, Agnes Y. Y. Lee MD, Sanjeev Chunilal MB ChB,
James D. Douketis MD, Marc Rodger MD, Jeffrey S. Ginsberg MD

Table 3: Deep vein thromboses identified among 221 symptomatic pregnant women by serial compression ultrasonography and Doppler imaging

**Negative Predictive Value
99.5%**

| Test result | Thrombosis absent | Thrombosis present | Total |
|-------------|-------------------|--------------------|-------|
| Positive | 0 | 16 | 16 |
| Negative | 204 | 1 | 205 |
| Total | 204 | 17 | 221 |

Test diagnostici

If deep-vein thrombosis is detected, further radiologic studies do not have to be performed to confirm a pulmonary embolism.

However, a negative result on ultrasonography cannot rule out pulmonary embolism.

Greer I.A. NEJM 2017



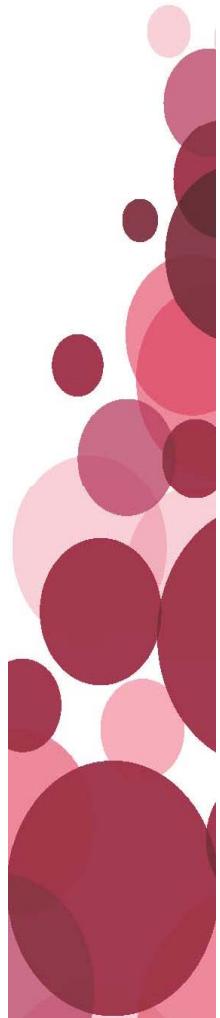
TEV in gravidanza: una sfida diagnostica

“The danger of maternal and foetal death secondary to maternal PE and unnecessary anticoagulation far outweighs the risk of radiation involved in scanning”

Mallick S, Respir Med 2006

“It is important to avoid ionizing radiation exposure whenever possible during pregnancy, but the risks of an undiagnosed PE are much greater than any theoretical risk to the fetus from diagnostic imaging”

Scarsbrook AF, Eur Radiol 2007



Test diagnostici

Scintigrafia polmonare

- Elevato valore predittivo positivo
- Bassa prevalenza di coesistenti patologie polmonari che conducono a test non diagnostici o falsamente negativi
- La fase ventilatoria può essere omessa per ridurre le esposizioni

Angio TC polmonare

- Meno utilizzata nelle gravide
- Può essere usata in caso di Rx anormale o scintigrafia non conclusiva
- La fase ventilatoria può essere omessa per ridurre le esposizioni
- Uno studio di confronto con la scintigrafia per la diagnosi di EP nelle gravide ha evidenziato uguale VPN e % di esami non conclusivi
- Può evidenziare dg alternative

Sicurezza dei test diagnostici per EP in gravidanza: dosi di radiazioni

| Test | Dose di radiazioni stimata (mSievert) | |
|--------------------------------------|---------------------------------------|---------|
| | Fetale | Materna |
| Scintigrafia perf. ^{99m}Tc | 0.2-0.6 | 1.0 |
| Scintigrafia vent. ^{81m}Kr | 0.0001 | 0.2 |
| Scintigrafia vent. ^{99m}Tc | 0.3-1.2 | 0.5 |
| AngioTC singolo strato | 0.03-0.06 | 1.6-4.0 |
| AngioTC multi strato | 0.01-0.02 | 4.0-6.0 |
| Angiografia | >0.5 | 5-30 |

Scarsbrook et al, Clin Radiol 2006

Dosi di esposizione fetale ben al di sotto della soglia di teratogenicità
Con la TC Rischio di ipotiroidismo fetale nel primo trimestre



Tecniche per ridurre l'esposizione alle radiazioni

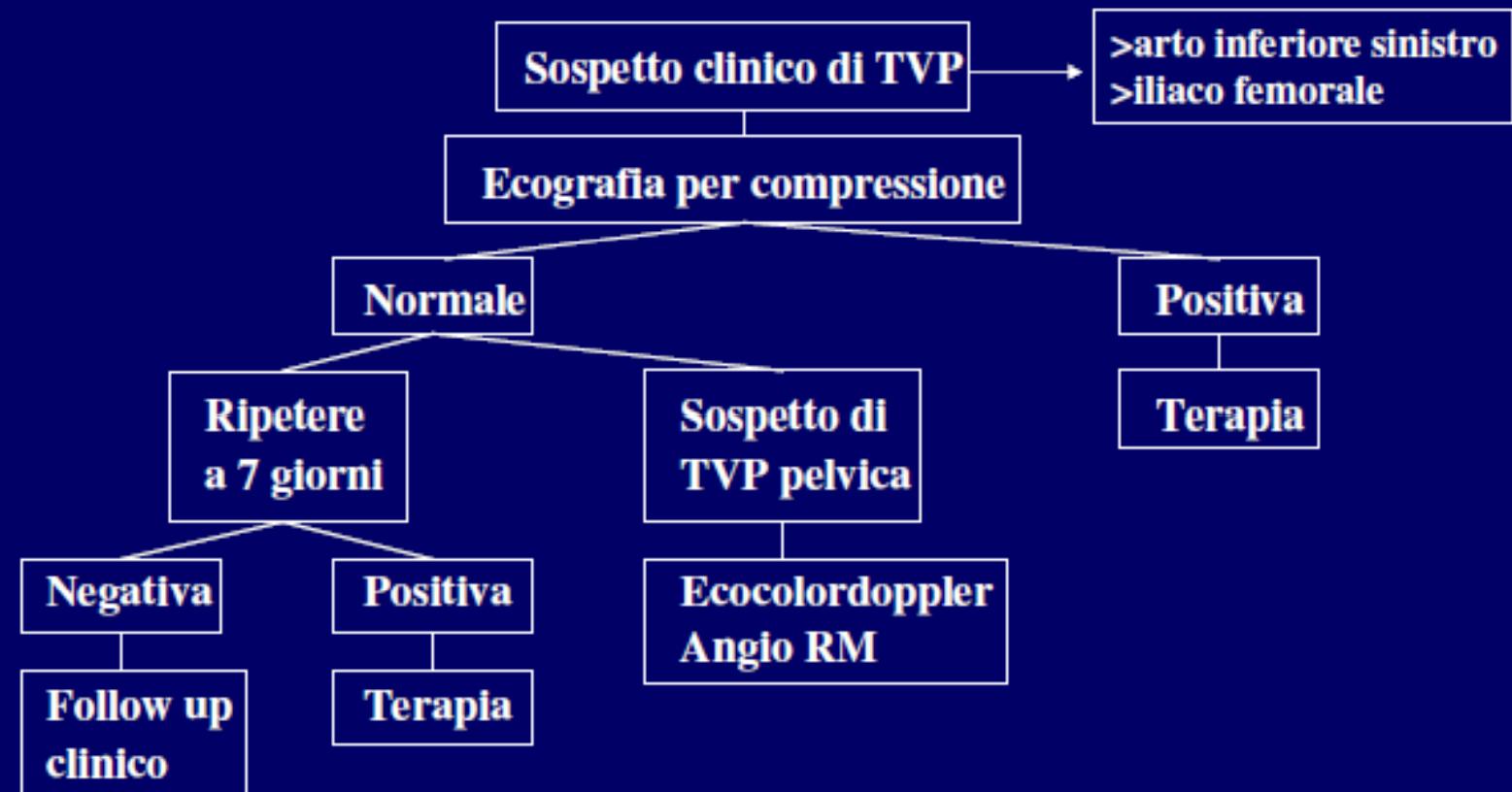
- Screening circonferenziale dell'addome e della pelvi (CTPA)
- Riduzione della durata dell'esame (CTPA)
- Dose dimezzata (VQ scan)
- Omissione della fase ventilatoria, se perfusione ok (VQ scan)
- Approccio brachiale e screening addomianle (Angiografia polm)
- Schermi di bismuto per i seni riducono esposizione del 40%

Nota bene: se una gravida esegue RX torace e a seguire scintigrafia ventilaz/perfusione, angio TC e angiografia polmonare la dose di radiazioni al feto rimane al disotto della dose derivata dall'esposizione ambientale durante i 9 mesi di gravidanza!

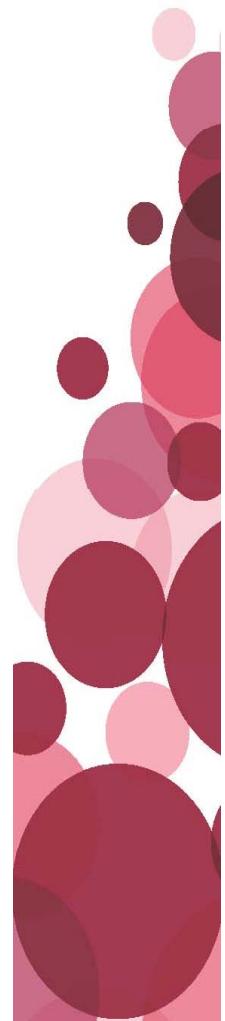
“What the radiologists need to know, Pahade JK, Radiograph



Algoritmo diagnostico nel sospetto di TVP



Da Walter Ageno



Algoritmo diagnostico nel sospetto di EP

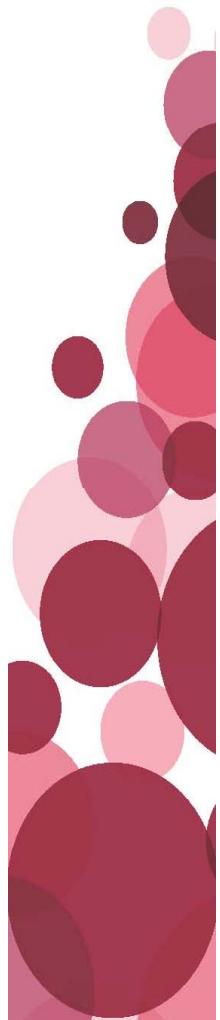
**Ecografia per compressione arti inferiori,
se negativa opzioni 1 o 2**

**In base alle disponibilità locali ed all'esperienza, iniziare con
uno dei 2 algoritmi a scelta:**

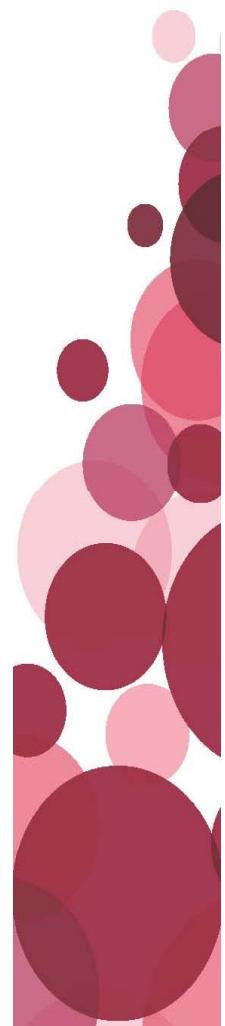
- 1) Angio TC, se positiva terapia, se negativa EP esclusa, se
non conclusiva CUS seriata o angiografia**
- 2) Scintigrafia, se positiva terapia, se negativa EP esclusa,
se non conclusiva a scelta tra CUS seriata, angio TC o
angiografia**

Nijkeuter et al JTH 2006

Da Walter Ageno

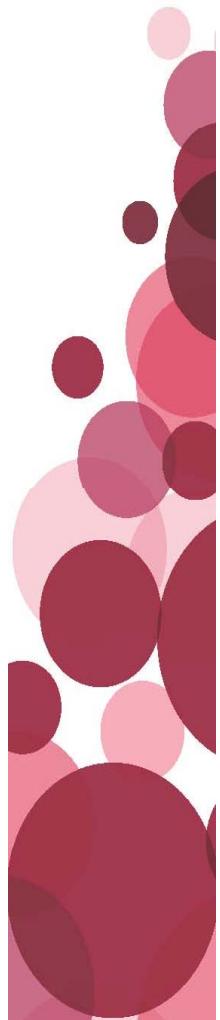


Trattamento del TEV



Trattamento del TEV

- EBPM farmaco di scelta per migliore profilo di sicurezza, farmacocinetica più affidabile, maggiore praticità ed efficacia sovrapponibile a ENF
 - Uso prevalentemente basato su studi in donne non gravide
 - L'utilizzo diffuso negli ultimi 20 anni in donne gravide ha dimostrato che le EBPM sono efficaci quanto ENF, ma più sicure (meno HIT e meno osteoporosi)
 - Non attraversano la placenta!
 - Non aumentano il rischio di emorragia postpartum
 - Uguale efficacia e sicurezza con mono e bisomministrazione
 - Non indicato monitoraggio attività anti-Xa



Eparine e gravidanza

Revisione sistematica della letteratura sul trattamento del TEV in gravidanza

| | |
|-------------------------|-------|
| N° studi (>10 pazienti) | 18 |
| N° pazienti | 981 |
| Età (range) | 17-43 |
| EBPM | 822* |
| UFH | 155 |

* In 6 studi è stato riportato l'aggiustamento della dose con il dosaggio dell'attività anti-Fattore Xa in alcuni pazienti

Revisione sistematica della letteratura sul trattamento del TEV in gravidanza: metanalisi eventi clinici antepartum

| | |
|--------------------------|---------------------|
| Emorragie totali | 3.28% (2.10%-4.72%) |
| Emorragie maggiori | 1.41% (0.6%-2.41%) |
| Emorragie maggiori <7 gg | 1.0% (0.4%-2.0%) |
| Recidive TEV | 1.97% (0.88%-3.49%) |
| Recidive TEV <7 gg | 1.41% (0.44%-2.90%) |

Altre opzioni

- ENF
 - Inizialmente ENF ev seguita da ENF sottocute bid (controlli settimanali PTT target 60-80 sec 6h dopo l'ultima iniezione

ANTAGONISTI VIT k

- Teratogenicità (Embriopatia: ipoplasia nale e/o); se assunto nelle prime 6-12 settimane (Chan et al)
- Alterazioni SNC in qualsiasi trimestre (agenesia del corpo calloso; atrofia cerebellare) molto rare
- Complicanze emorragiche fetali specialmente al parto per l'immaturità epatic neonato



Altre opzioni

- Fondaparinux
 - Attività anti Xa trovata nel plasma del cordone ombelicale di 6 donne trattate con fondaparinux
 - Per ora, riservarne l'uso alle donne con HIT o allergie alle eparine
- Inibitori diretti della trombina e anti-Xa
 - Da non utilizzare: attavversano la placenta





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Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

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

**For pregnant women with acute VTE,
we recommend therapy with:**

- **adjusted dose LMWH over adjusted-dose UFH**

(Grade 1B)

THE ACUTE MANAGEMENT OF THROMBOSIS AND EMBOLISM DURING PREGNANCY AND THE PUERPERIUM

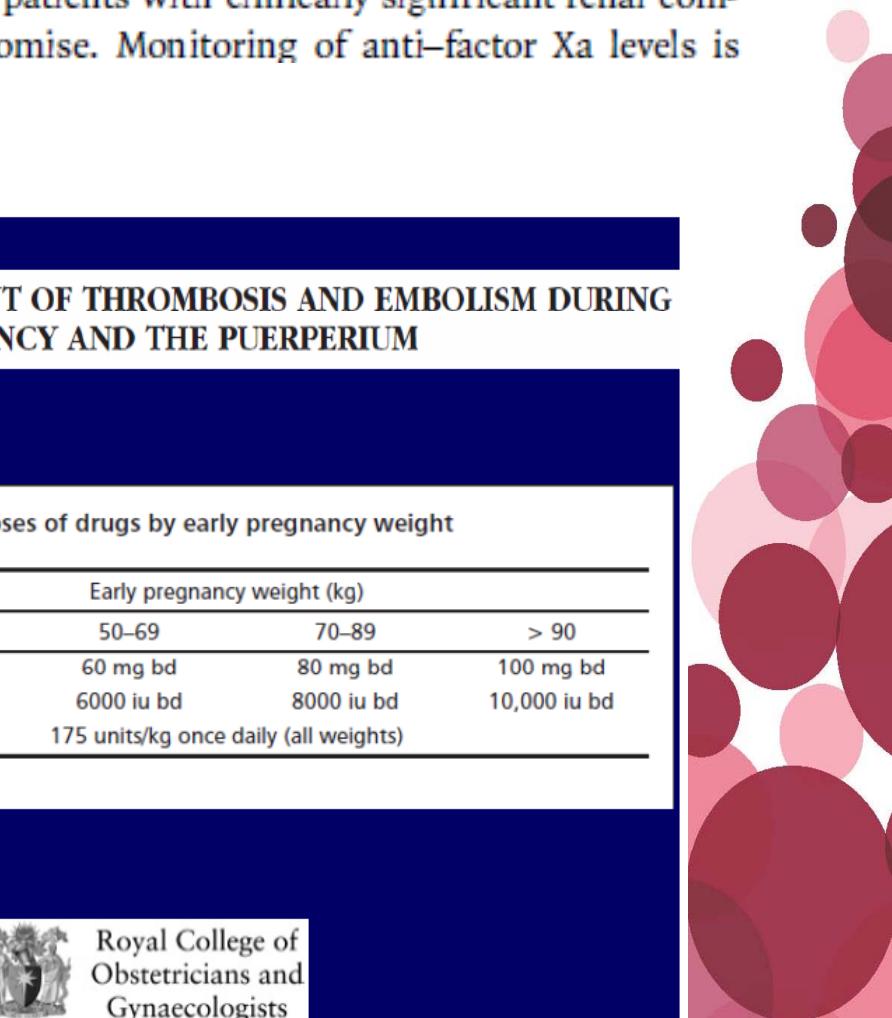
Table 1. Calculation of initial doses of drugs by early pregnancy weight

| 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



Royal College of
Obstetricians and
Gynaecologists



Aggiustate per quale peso?

istered²⁰; either early or current pregnancy weight is used, since data are lacking to support the use of one weight over the other. Doses are adjusted in patients with clinically significant renal compromise. Monitoring of anti-factor Xa levels is



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7.1.3. 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).



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It remains unclear whether the dose of LMWH can be reduced (e.g. 75% of the full dose) after an initial phase of therapeutic anticoagulation

A modified dosing regimen may be useful in pregnant women at increased risk of bleeding or osteoporosis

Al momento del parto

- Sospendere EBPM (or ENF sc) 24 ore prima di un parto in elezione
- Se si verifica un parto spontaneo durante l'assunzione di ENF sc, monitorare aPTT e se prolungato somministrare solfato di protamina
- Se si verifica un parto spontaneo durante l'assunzione di EBPM, l'effetto anticoagulante dipende dall'ora dell'ultima dose
 - Evitare partoanalgesia
 - Ev. Solfato di protamina



Situazioni particolari



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- Women with a **very high risk for recurrent VTE** (eg, proximal DVT or PE close to the expected date of delivery) may benefit by having a **planned delivery** by induction or cesarean section, as appropriate, so that the duration of time without anticoagulation can be minimized.
- Those at the highest risk of recurrence (eg, proximal DVT or PE within 2 weeks) can be **switched to therapeutic IV UFH**, which is then discontinued 4 to 6 h prior to the expected time of delivery or epidural insertion.



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- A temporary **inferior vena caval filter** can be inserted and removed postpartum.
- However, the latter may be best **restricted** to women with proven DVT who have recurrent PE despite adequate anticoagulation because experience with these devices during pregnancy is limited, and the risk of filter migration and inferior vena cava perforation may be increased during pregnancy.

Situazioni particolari

Table 1

Treatment of pulmonary embolism during pregnancy.

| Author | year | Treatment | Total dose | gestational week | outcome mother | outcome child* | preterm delivery* | bleeding complications |
|---|------|-----------|-------------|------------------|----------------|----------------|-------------------|------------------------|
| <i>Thrombolytic therapy</i> | | | | | | | | |
| Ahearn ¹⁷ | 2002 | rt-PA | 100 mg | 12 | good | good | no | no |
| Baldo ¹⁸ | 1990 | rt-PA | 100 mg | 35 | good | death (14 d)† | yes (20 h) | no |
| Hossdorff ¹⁹ | 1990 | rt-PA | 43 mg | 31 | good | good | yes (48 h) | yes, minor |
| Pate ²⁰ | 2003 | rt-PA | 100 mg | 20 | good | good | no | no |
| Yap ²¹ | 2002 | rt-PA | 100 mg | 30 | good | good | no | no |
| Trukhacheva ²² | 2005 | rt-PA | 100 mg | 23 | good | good | no | no |
| Fagher ²³ | 1990 | SK | 1100,000 U | 28 | good | good | yes (10 h) | yes, major |
| McTaggart ²⁴ | 1977 | SK | 2900,000 U | 34 | good | death (0-8 h)† | yes (18d) | yes, minor |
| Half ²⁵ | 1972 | SK | 1800,000 U | 32 | good | good | yes (0 h) | yes, major |
| Mazeika ²⁶ | 1994 | SK | 1400,000 U | 25 | good | good | no | yes, major |
| Te Raa ²⁷ | 2009 | SK | 2650,000 U | 25 | good | good | no | yes, major |
| Kramer ²⁷ | 1995 | UK | | 21 | good | good | no | no |
| Deklos ²⁸ | 1986 | UK | 57,200 U/kg | 28 | good | good | no | yes, minor |
| <i>Surgical embolectomy</i> | | | | | | | | |
| Blegvad ³⁵ | 1989 | SE | | 28 | good | good | no | no |
| Duff ³⁶ | 1985 | SE | | 13 | good | death (8 h)† | yes (8 h) | no |
| Cohn ³⁷ | 1973 | SE | | 1st trim | good | good | no | no |
| Marcinkevicius ³⁸ | 1970 | SE | | 24 | good | death (-1 h)† | yes (20 h) | no |
| Becker ³⁴ | 1983 | SE | | ? | good | good | no | no |
| Becker ³⁴ | 1983 | SE | | ? | good | good | no | no |
| Becker ³⁴ | 1983 | SE | | ? | good | death (?)† | yes (?) | no |
| Taniguchi ³⁹ | 2008 | SE | | 22 | good | good | yes (7 wk) | no |
| <i>Catheter embolectomy/Catheter thrombolytic therapy</i> | | | | | | | | |
| Sofocleous ⁴⁴ | 2001 | CF rt-PA | 34 mg | 15 | good | death (24 h)† | yes (24 h) | no |
| Bechtel ⁴³ | 2005 | CF rt-PA | 15.5 mg | 30 | good | good | no | no |
| Krishnamurthy ⁴⁵ | 1999 | CT UK | 55,000 U/kg | 26 | good | good | no | no |
| Rosenblum ⁴⁰ | 2008 | CE | | 26 | good | good | no | no |

Legend: rt-PA = recombinant tissue plasminogenactivator, SK = streptokinase, UK = urokinase, SE = surgical embolectomy, CE = catheter directed mechanical embolectomy, CF = catheter directed thrombolytic therapy, preceded by mechanical fragmentation of the clot, CT = catheter directed thrombolytic therapy without mechanical fragmentation, ? = unknown, *(time after intervention).

†= cause of death. Baldo et al: cesarean section was accomplished, death due to acute respiratory distress syndrome. No evidence of fetal haemorrhage at autopsy. McTaggart et al: death was thought to be resulted from maternal anoxia following massive embolism. No evidence of fetal haemorrhage at autopsy. Duff et al: death due to premature spontaneous abortion, cause of abortion was not further specified. Marcinkevicius et al: death due to anoxaemia following pulmonary embolism. Becker et al: unknown. Sofocleous et al: death due to spontaneous premature abortion, probably due to maternal haemodynamic compromise because of pulmonary embolism and not due to thrombolytic therapy.

Trombolisi

Guidelines on the diagnosis and management of acute pulmonary embolism

Thrombolysis for life-threatening PE



- Streptokinase (and probably other thrombolytic drugs) does not cross the placenta.
- In mothers, the overall incidence of bleeding is about 8%, usually from the genital tract.
- This risk does not seem unreasonable compared with the death rate seen in patients with massive PE treated with heparin alone.

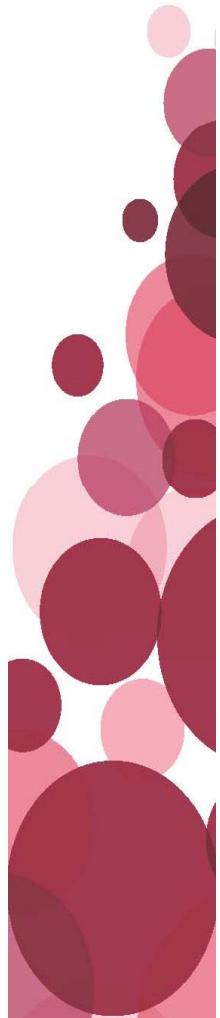
Guidelines on the diagnosis and management of acute pulmonary embolism



- At the time of delivery, thrombolytic treatment should not be used except in extremely severe cases and if surgical embolectomy is not immediately available.
- Indications for cava filters in pregnant women are similar to those in other patients with PE.

Postpartum

- Ricominciare la terapia anticoagulante entro 8-12h dal parto (consultarsi con il ginecologo)
- EBPM o coumadin per 6 settimane
- Calze a compressione graduata per riduzione del dolore; non dimostrata efficacia nella prevenzione della sdr. post-trombotica



Complicanze materne

- Sanguinamento
 - 2% con ENF
 - Molto poco frequente con EBPM
- Osteoporosi
 - 2.2% incidenza di fratture vertebrali con ENF (>1 mese)
 - poco frequente con EBPM
- HIT
 - 3% con ENF
 - Sospetto di HIT se PLT <100 o 50% del valore basale 5-15 giorni dopo inizio dell'ENF
 - poco frequente con EBPM

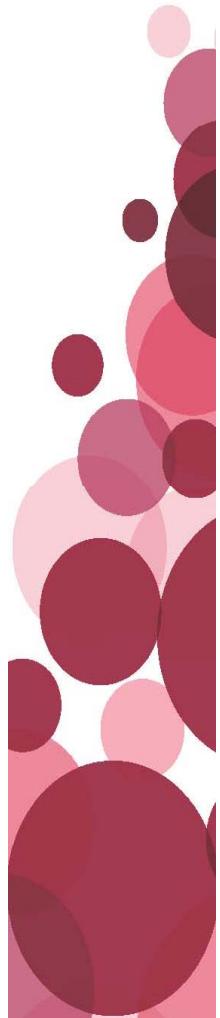
Complicanze fetali

Possibile sanguinamento uteroplacentare ma molto raro



Durante l'allattamento

- Eparina e warfarin non sono secreti nel latte materno
- EBPM: piccole quantità possono essere secrete nel latte materno ma non vengono assorbiti dal neonato che non manifesterà effetti anticoagulanti
- Fondaparinux e DTIs: non noto



Tromboprofilassi in gravidanza e nel post-partum



- Donne con storia di TEV hanno un rischio aumentato di recidiva durante la gravidanza (rischio di recidiva 1-13%)
- Tale rischio dipende dalla natura dei fattori di rischio per TEV, dalla presenza/assenza di trombofilia e dal numero di precedenti episodi di TEV

TABLE 2. RISK FACTORS AND RATE OF RECURRENT VENOUS THROMBOEMBOLIC EVENTS IN 95 WOMEN WITH PREVIOUS VENOUS THROMBOEMBOLISM.*

| VARIABLE | IDIOPATHIC CONDITION AND ABNORMAL TEST RESULTS | TEMPORARY RISK FACTOR AND ABNORMAL TEST RESULTS | IDIOPATHIC CONDITION AND NORMAL TEST RESULTS | TEMPORARY RISK FACTOR AND NORMAL TEST RESULTS |
|------------------------|--|---|--|---|
| Recurrent events (no.) | | | | |
| Total | 2 | 2 | 2 | 0 |
| Ante partum | 1 | 1 | 1 | |
| Post partum | 1 | 1 | 1 | |
| No recurrence (no.) | 8 | 13 | 24 | 44 |
| Recurrence rate | | | | |
| Percent (95% CI) | 20 (2.5–55.6) | 13 (1.7–40.5) | 7.7 (0.01–25.1) | 0 (0.0–8.0) |

*CI denotes confidence interval. Temporary risk factors were pregnancy, use of oral contraceptives, surgery, trauma, immobility, and chemotherapy. Only women in whom laboratory studies were performed are included.

Brills-Edward P NEJM 2000



| Selezionare i fattori di rischio presenti | | | | | |
|---|-------------|---|-------|--|-------|
| Fattori di rischio preesistenti | Punti | Fattori di rischio ostetrici | Punti | Fattori di rischio transitori | Punti |
| Progresso TEV escluso singolo evento post-chirurgia maggiore | 4 | TC in travaglio | 2 | Immobilità ^a ex. idratazione | 1 |
| Progresso TEV post-chirurgia | 3 | Parto operativo | 1 | Sequel | 1 |
| Nota condizione trombofilica ad alto rischio | 3 | Pre-eclampsia nella gravidanza attuale | 1 | Procedure chirurgiche in gravidanza e puerperio (eccetto sutura perineale) | 3 |
| Comorbidità mediche (cancro, sospetto cardiaco, lesioni poliflogistica inflamatoria, malattia inf. cronica intestinale, sindrome nefruistica, Diabete mellito con nefropatia, anemia falciforme, abuso stupefacenti ecc.) | 3 | Gravidanza ottenuta mediante PMA (solo prima della nascita) | 1 | Sindrome da iperstimolazione ovarica (solo I trimestre) | 4 |
| Storia familiare di TEV non provocato o associato a terapia estrogenica in parente di I grado | 1 | Gravidanza multiple | 1 | Iperemesi | 3 |
| Obezità 1 se >30 2 se >40 | TC elettivo | 1 | | | |
| Parità ≥3 | 1 | Travaglio prolungato (>48h) | 1 | | |
| Abitudine al fumo | 1 | Emorragia post-partum (>1000ml) | 1 | | |
| Grosse Varicosità venose | 1 | Parto pretermine <37+0 settimane (grav attuale) | 1 | | |
| Età >35 anni | 1 | MIPI (grav attuale) | 1 | | |
| Nota condizione trombofilica a basso rischio (senza TEV)* | 1 | | | | |

*Se la condizione trombofilica a basso rischio è relativa ad una paziente con storia familiare positiva per TEV in un parente di primo grado, la profilassi deve essere proseguita per 6 settimane, durante il puerperio.

Punteggio calcolato Rischio emorragico Alto Basso (markare la voce che interessa)

Strategia di profilassi (indicare la propria scelta)

| Punteggio Prima del parto | Livello di rischio trombotico | Strategia di profilassi consigliata | Barrare la strategia scelta |
|---|-------------------------------|--|-----------------------------|
| ≥6 | Alto | Tromboprofilassi con EBPM dal I trimestre | |
| 3 | Intermedio | Tromboprofilassi con EBPM dalla 28ma settimana | |
| <3 | Basso | Multidrizzazione e idratazione | |
| Ricovero ospedaliero | | | |
| Punteggio Dopo il parto | | | |
| ≥2 dopo il parto | Alto | Tromboprofilassi per almeno 10 giorni | |
| Ricovero prolungato (≥4) o nuovo ricovero nel puerperio | Alto | Considerare la tromboprofilassi | |

Data _____ Firma del medico _____

(RCOG Green-top Guideline No.37a)

Stratificazione del rischio in gravidanza e dopo il parto



BUONE PRATICHE PER LA SICUREZZA



Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No.37a
April 2015

LA PREVENZIONE DEL TROMBOEMBOLISMO VENOSO NEI PAZIENTI OSPEDALIZZATI

a cura del GRUPPO MULTIDISCIPLINARE AZIENDALE

SETTEMBRE 2017

Coordinamento:
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SS Risk Management
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Revisione esterna:
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Università degli Studi dell'Insubria


Stratificazione del rischio in gravidanza e dopo il parto



| Peso | Dose enoxaparina | Dose dalteparina | Dose tinzaparina |
|------------|------------------|------------------|------------------|
| <50 kg | 2000 UI/die | 2500 UI/die | 3500 UI/die |
| 50-90 kg | 4000 UI/die | 5000 UI/die | 4500 UI/die |
| 91-130 kg | 6000 UI/die | 7500 UI/die | 7000 UI/die |
| 131-170 kg | 8000 UI/die | 10.000 UI/die | 9000 UI/die |
| >170 kg | 0.6 UI/kg/due | 75 mcg/kg/die | 75 mcg/kg/die |

Da RCOG: Reducing the risk of thrombosis and embolism during pregnancy and the puerperium.
Green-Top Guidelines n° 37, 2009.

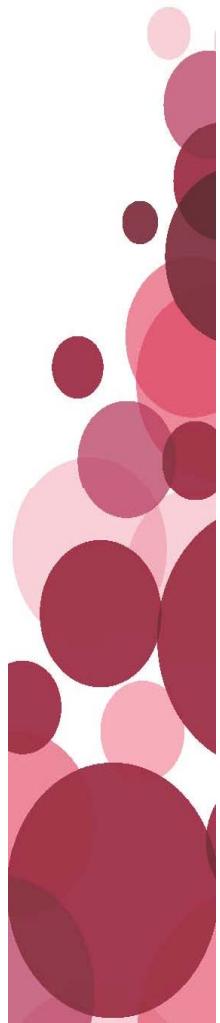


Taglio cesareo

- Eseguire stratificazione del rischio per scegliere la strategia di profilassi appropriata (grado 2C)
- EBPM o ENF a dosi profilattiche +/- calze a compressione graduata durante la degenza ospedaliera post-partum (grade 2C) da continuare fino a 6 settimane se persistono fattori di rischio importanti (grado 2C).



Trombofilia e gravidanza



Trombofilia nota e gravidanza

Lupus anticoagulant e Anticorpi Anticardiolipina

Evidenza di associazione con aumentato rischio di trombosi e aborto (meno con preeclampsia, abruptio, ritardo di crescita intrauterina)

Necessaria tromboprofilassi in gravidanza

Trombofilia non-APLAs

I dati presenti in letteratura evidenziano solo una debole associazione fra alterazioni trombofiliche come FVL o mutazioni PT e gravidanze ad esito sfavorevole

Gli studi clinici con EBPM o ENF vs. placebo in donne con storia di gravidanze ad esito sfavorevole e alterazioni trombofiliche non APLAs non hanno mostrato un miglioramento degli esiti

Tromboprofilassi se pregresso TEV o, in assenza di TEV pregresso, se alterazione trombofilica maggiore



Screening trombofilico e donne in età fertile

Pareri discordanti

3 Scenari:

Pregresso TEV in donna in età fertile:

Se TEV unprovoked o associato a fattori di rischio modesti (gravidanza, ecc) può essere indicato lo screening per definire la durata della terapia

In gravidanza è sempre indicata tromboprofilassi

Aborti ripetuti: ricerca antifosfolipidi

Donna in età fertile e TEV e/o difetto trombofilico maggiore familiare di primo grado: Screening ragionevole



Table 1. Summary of Recommendations for Which There is Consensus and Uncertainties and Variations in Guidelines for the Management of Venous Thromboembolism in Pregnancy.*

Recommendations for which there is consensus

Primary diagnostic techniques

Compression duplex ultrasonography

Ventilation–perfusion lung scanning

Anticoagulant treatment

Generally low-molecular-weight heparin (weight-based dose) instead of unfractionated heparin

Avoid the use of coumarins in antenatal period

Low-molecular-weight heparin, unfractionated heparin, and coumarins can be used in breast-feeding mothers

Graduated compression stockings for symptom relief in deep-vein thrombosis

Treatment for a minimum of 3 to 6 mo in total and until at least 6 wk post partum

Monitoring of platelet count for heparin-induced thrombocytopenia

Not recommended in women treated exclusively with low-molecular-weight heparin

Recommended in women treated with unfractionated heparin

Discontinuation of heparin for 24 hr before induction of labor or cesarean section in women receiving treatment doses to allow delivery and provision of neuraxial anesthesia

Thrombolysis reserved for massive life-threatening pulmonary embolism with hemodynamic compromise or with proximal deep-vein thrombosis threatening leg viability

Caval filters restricted to women with recurrent venous thromboembolism despite therapeutic anticoagulation, since benefits are uncertain, or in women in whom anticoagulation is contraindicated

Uncertainties and variations in guidelines regarding anticoagulant management and monitoring

Whether once-daily or twice-daily low-molecular-weight heparin administration is preferred; all guidelines indicate that both are acceptable

Whether the dose should be adjusted as pregnancy advances; only one guideline specifically recommends dose reduction to intermediate dose (50 to 75% of full treatment dose) or prophylactic dose after initial (3 mo) treatment

* Data are from Bates et al.,¹⁰ Royal College of Obstetricians and Gynaecologists,²⁰ James,⁴⁵ Chan et al.,⁴⁶ Royal College of Obstetricians and Gynaecologists,⁴⁷ and McLintock et al.⁴⁸

Strategies toward ending preventable maternal mortality (EPMM)



**Grazie per
l'attenzione**

