

**Test Genetici Predittivi nelle Trombofilie Ereditarie:
quali, quando e perché
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Rapporto costo beneficio del controllo coagulatorio e del trattamento anticoagulante in medicina riproduttiva

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PHLOGOSE UND THROMBOSE IM GEFÄSSESYSYSTEM

(R. Virchow. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Staatsdruckerei, 1856)

Virchow postulated three causes of thrombosis:

STASIS OF BLOOD FLOW

CHANGES IN THE VESSEL WALL

CHANGES IN BLOOD COMPOSITION

VENOUS THROMBOSIS

THE KNOWN RISK FACTORS FOR VENOUS THROMBOSIS ARE STASIS OF BLOOD FLOW AND CHANGES IN THE COMPOSITION OF BLOOD

A DIFFERENT CLASSIFICATION COULD ALSO BE MADE INTO GENETIC AND ACQUIRED RISK FACTORS

VENOUS THROMBOSIS IN PREGNANCY

- IN PREGNANCY, THERE IS STASIS OF BLOOD IN THE INTERVILLOUS SPACE**
- IN PREGNANCY, THERE IS AN INCREASED CONCENTRATIONS OF CLOTTING FACTORS**
- IN PREGNANCY, THERE MAY ALSO BE ENDOTHELIAL DAMAGE DUE TO PLACENTAL AGING OR ACQUIRED PATHOLOGY**

VENOUS THROMBOSIS IN PREGNANCY

HIGH RISK OF THROMBOSIS WAS FOUND IN PREGNANCY AND THE PUERPERIUM IN THROMBOPHILIC FAMILIES WITH DEFICIENCIES OF PROTEIN C, S OR ANTITHROMBIN

PRESENCE OF FACTOR V LEIDEN WAS MORE COMMON THEN IN THE GENERAL POPULATION IN UNSELECTED WOMEN WITH THROMBOSIS DURING PREGNANCY.

ABNORMALITIES OF THE CLOTTING SYSTEM PREDISPOSING TO VENOUS THROMBOSIS

- HEREDITARY DEFICIENCY OF ANTITHROMBIN
- RESISTANCE TO ACTIVATED PROTEIN C DUE TO MUTATION OF THE CLEAVAGE SITES (FACTOR V_{R506Q} OR V LEIDEN)
- HETEROZYGOUS DEFICIENCY OF PROTEIN C OR PROTEIN S
- ANTITHROMBIN DEFICIENCY
- MUTATION OF PROTHROMBIN (FACTOR II) GENE LEADING TO INCREASED CONCENTRATION OF PROTHROMBIN
- HIGH CONCENTRATION OF FACTOR VIII
- HYPERHOMOCYSTEINAEMIA

PREVALENCE OF CONGENITAL ABNORMALITIES OF THE CLOTTING SYSTEM AND INCIDENCE OF VENOUS THROMBOSIS

RISK FACTOR	% POPULATION	%THROMBOSIS
Protein C deficiency	0.2 - 0.4	3
Protein S deficiency	not known	1 - 2
Antithrombin deficiency	0.02	1
Factor V Leiden	5	20
Prothrombin 20210A	2	6
>1500 IU/L of factor VIII	11	25
Hyperhomocysteinemia	5	10

RISK OF VENOUS THROMBOSIS IN WOMEN (PER 10000 PEOPLE PER YEAR)

WOMEN WITHOUT FACTOR V LEIDEN WHO DO NOT USE OC HAVE A RISK OF 0.8

WOMEN WITH FACTOR V LEIDEN WHO DO NOT USE OC HAVE A RISK OF 5.7 (RR 6.9)

WOMEN WITHOUT FACTOR V LEIDEN WHO USE OC HAVE A RISK OF 3.0 (RR 3.7)

WOMEN WITH FACTOR V LEIDEN WHO USE OC HAVE A RISK OF 28.5 (RR 34.7)

A WOMAN'S THROMBOSIS POTENTIAL IS A DYNAMIC AGE-DEPENDENT MODEL OF INTERACTION BETWEEN GENETIC[↑] AND ACQUIRED[♥] RISK FACTORS

- ↑ BELONGING TO A THROMBOPHILIC FAMILY
- ↑ HISTORY OF THROMBOSIS
- ↑ PRESENCE OF GENETIC DEFICIENCY OF ANTITHROMBOTIC FACTORS

AGE-DEPENDENT WEAR-AND-TEAR OF VESSELS

- ♥ IMMOBILISATION
- ♥ USE OF ORAL CONTRACEPTIVES
- ♥ PREGNANCY AND PUERPERIUM

Risk factors for venous thromboembolism in pregnancy and the puerperium

Pre-existing	New onset or transient
<p>Previous VTE</p> <p>Thrombophilia congenital antithrombin deficiency protein C deficiency, protein S deficiency, Factor V Leiden prothrombin gene variant acquired (antiphospholipid syndrome) lupus anticoagulant anticardiolipin antibodies</p> <p>Age over 35 years</p> <p>Obesity (BMI > 30 kg/m²) either pre-pregnancy or in early pregnancy</p> <p>Parity > 4</p> <p>Gross varicose veins</p> <p>Paraplegia</p> <p>Sickle cell disease</p> <p>Inflammatory disorders e.g. inflammatory bowel disease medical disorders, e.g. nephrotic syndrome, certain cardiac diseases</p> <p>Myeloproliferative disorders, e.g. essential thrombocythaemia, polycythaemia vera</p>	<p>Surgical procedure in pregnancy or puerperium, e.g. evacuation of retained products of conception, postpartum sterilisation</p> <p>Hyperemesis</p> <p>Dehydration</p> <p>Ovarian hyperstimulation syndrome</p> <p>Severe infection, e.g. pyelonephritis</p> <p>Immobility (> 4 days bed rest)</p> <p>Pre-eclampsia</p> <p>Excessive blood loss</p> <p>Long-haul travel</p> <p>Prolonged labour c</p> <p>Midcavity instrumental delivery c</p> <p>Immobility after delivery</p>

Thromboprophylaxis during pregnancy and the puerperium

- Regardless of their risk of VTE, immobilisation of women during pregnancy, labour and the puerperium should be minimised and dehydration should be avoided.
- Women with previous VTE should be offered postpartum thromboprophylaxis with LMWH. It may be reasonable not to use antenatal thromboprophylaxis with heparin in women with a single previous VTE associated with a temporary risk factor that has now resolved
- Women with previous recurrent VTE or a previous VTE and a family history of VTE in a first-degree relative should be offered thromboprophylaxis with LMWH antenatally and for at least six weeks postpartum.

THROMBOPROPHYLAXIS DURING PREGNANCY

- Pregnancy is a risk factor for VTE and is associated with a ten-fold increase compared with the risk for nonpregnant women.
- Pulmonary thromboembolism (PTE) is the a common direct cause of maternal death

O TEMPORA O MORES

- B.C. & A.D.

- B.LMWH & P.LMWH

“LMWHs are the agents of choice for antenatal thromboprophylaxis.

They are as effective as and safer than unfractionated heparin in pregnancy “

RISK OF BLEEDING

- Worldwide the most common cause of maternal mortality is haemorrhage, but the proportion due to each cause varies between regions.

Table 1: Causes of Maternal Mortality

Haemorrhage 24%

Infection 15%

Unsafe Abortion 13%

Hypertensive disorders of pregnancy 12%

Obstructed Labour 8%

Other direct causes* 8%

Other indirect causes**20%*

*Other direct causes include: ectopic pregnancy, embolism, anaesthesia-related causes

** Indirect causes include: anaemia, malaria, heart disease

- The confidential enquiry into maternal deaths report recommends all women should undergo an assessment of risk factors for VTE in early pregnancy or before pregnancy.
- It recommends women should be reassessed before or during labour for risk factors for VTE. Age over 35 years and BMI greater than 30 or a body weight greater than 90Kg are important independent risk factors for postpartum VTE even after vaginal delivery.
- The combination of either of these risk factors with other risk factors for VTE, such as pre-eclampsia or immobility should lead the clinician to consider the use of LMWH for three to five days postpartum.

RISK OF HAEMATOMA FORMATION

- *There is an increased risk of around 2% of wound hematoma following caesarean section with both unfractionated heparin and LMWH.*

RISK OF HAEMATOMA FORMATION

- A retrospective analysis of the relation between time interval from prophylactic administration of low molecular weight heparin (LMWH) to delivery and the occurrence of wound haematoma was performed
- After administration of LMWH within 2 hours of caesarean section , the percentage of women with a wound haematoma was significantly larger (12%vs 3%).
- Multivariate regression analysis, including other risk factors for wound haematoma, indicated administration of LMWH within 2 hours prior to delivery as the only statistically significant factor, which influenced the development of wound haematoma (odds ratio = 5.3, 95% CI = 1.2–22.8).

Risk for thrombo-embolism in caesarean section*

Risk level	Risk factors	Management
Low risk	<ul style="list-style-type: none"> •Elective caesarean section with uncomplicated pregnancy and no other risk factors 	Early mobilisation and hydration
Moderate risk	<ul style="list-style-type: none"> Age >35 Obesity BMI>30 Para 4 or more Gross varicose veins Current infection Pre-eclampsia Immobility prior to surgery (>4days) Major systemic illness, eg. heart/lung disease, inflammatory bowel disease: nephritic syndrome Nephrotic syndrome, sickle cell disease Emergency caesarean in labour 	Low molecular weight heparin prophylaxis
High Risk	<ul style="list-style-type: none"> Patients with 3 or more risk factors Extended surgery, e.g. caesarean hysterectomy Personal or family history of deep vein thrombosis; pulmonary embolism or thrombophilia; paralysis of lower limbs Patients with antiphospholipid antibody (cardiolipin antibody or lupus anticoagulant) 	Low molecular weight heparin prophylaxis +/- leg stockings *RCOG guidelines

RISK OF URINARY TRACT INFECTION AFTER CATHETERIZATION

- Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection. Each year, more than 1 million patients in U.S. acute-care hospitals and extended-care facilities acquire such an infection; the risk with short-term catheterization is 5% per day. CAUTI is the second most common cause of nosocomial bloodstream infection, and studies suggest that patients with CAUTI have an increased institutional death rate, unrelated to the development of urosepsis

INEXPESIVE MEASURE TO REDUCE THE RISK OF VT

- CORRECT POSITIONING OF THE PATIENT DURING SURGERRY
- AVOIDING DEHYDRATION
- AVOIDING IMMOBILIZATION ON A STRETCHER
- AVODING BLADDER CATHETERIZATION
- COMPRESSIVE STOCKINGS
- EARLY MOBILIZATION

VENOUS THROMBOEMBOLISM AND ORAL CONTRACEPTION

- Most women opt for combined oral contraception (COC) and only 5% of women choose progestogen-only pills.
- Use of COC is associated with an increased risk of VTE. The incidence of VTE increases with age but it is uncommon in women of reproductive age (5–21 per 100000 women per year) and thus the absolute risk remains small.

VENOUS THROMBOEMBOLISM AND ORAL CONTRACEPTION

- COC containing levonorgestrel or norethisterone are associated with a lower risk of venous thromboembolism than those containing desogestrel or gestodene.
- A levonorgestrel- or norethisterone-containing COC should be advised as a pill of first choice
- The RR of venous thromboembolism increases in the first 4 months after starting COC . This risk decreases with increasing duration of use, (remaining above that of non-users). After discontinuation, VTE risk falls to that of non-users within 3 months

VT AND OC

- *Cyproterone acetate: it is not licensed as a contraceptive but for treatment of acne or hirsutism.*
- *A case-control study used data after adjustment for body mass index (BMI), smoking and androgenic disorders, showed a four-fold increase in the risk of VTE with Diane® compared with a COC containing levonorgestrel (OR 3.9, 95% CI 1.1–13.4).*

Eligibility to OC

WHO categories for hormonal methods of contraception in relation to venous thromboembolism: adapted from the WHO Medical Eligibility Criteria for Contraceptive Use⁶¹

WHO Category 1: unrestricted use		WHO Category 2: benefits outweigh risks	
COC	POC	COC	POC
Postpartum \geq 21 days in non-breastfeeding women Immediately after first- or second-trimester Minor surgery without immobilisation Varicose veins	Postpartum < 21 days in non-breastfeeding women (injectable and implant) a Immediately after first-trimester BMI \geq 30 Family history of VTE in a first-degree relative superficial thrombophlebitis Sickle cell disease	Obesity BMI \geq 30 Family history of VTE in a first-degree relative Major surgery without prolonged immobilisation Superficial thrombophlebitis Sickle cell disease	History of VTE Major surgery with prolonged immobilisation Known thrombogenic mutations
WHO Category 3: risks outweigh benefits		WHO 4: unacceptable health risk	
COC	POC	COC	POC
Postpartum < 21 days in non-breastfeeding women	Current VTE < 4 weeks postpartum	History of VTE Current VTE Major surgery with prolonged immobilisation Known thrombogenic mutations	

*Known thrombogenic mutations (factor V Leiden; prothrombin mutation; protein S, protein C and antithrombin deficiencies)

VENOUS THROMBOEMBOLISM & OC

- OC increase the relative risk of VTE, but the absolute risk remains very small.
- Progestogen-only methods (pills, injectables, implant and intrauterine system) do not appear to be associated with increased risk of VTE. However, evidence regarding these methods is limited and absence of evidence does not equate to absence of risk.
- Heavy smoking, obesity and underlying thrombophilia increase the risk of VTE and these factors must be taken into account when making contraceptive choices.
- Women with previous VTE should be advised against the use of COC but a progestogen-only method may be used.
- There is no place for routine screening for thrombophilia prior to contraceptive prescribing.

Arriva la pillola generica...

- **Il gestodene, sottolinea, è frutto di decenni di ricerca volta a ottimizzare la componente progestinica delle pillole anticoncezionali. "E' il progestinico più tollerato - ripete il ginecologo - che abbatte il pericolo di tromboembolismo venoso e non comporta effetti negativi sulla libido né rischi di irsutismo, acne, ritenzione idrica con gonfiore e cellulite, né di iperinsulinismo o di aumentata resistenza insulinica 'anticamera' della sindrome metabolica. Per questo prescrittori e utenza lo premiano", aggiunge**: dei 27 milioni di confezioni di pillole vendute in Italia nel 2006, l'85,6% è del tipo monofasico, il 63% è 'light' e il 40% contiene gestodene.

Is screening for thrombophilia needed before prescribing hormonal contraception?

- **Routine thrombophilia screening prior to hormonal contraceptive use is not recommended.**
- **A thrombophilia screen may be considered in a woman with a history of venous thromboembolism in a first-degree relative under the age of 45 years who, after counselling, still wishes to use combined oral contraception.**

HORMONAL REPLACEMENT THERAPY

- After 5.2 years of follow-up, the trial was stopped as there was an increased risk of coronary heart disease (hazard ratio 1.29, 95% CI 1.02–1.63), stroke (hazard ratio 1.41, 95% CI 1.07–1.85) and breast cancer (hazard ratio 1.26, 95% CI 1.0–1.59), as well as pulmonary embolism.
- The overall health risks from HRT in this study exceeded the gains from reduced hip fracture and reduced risk of colorectal cancer, indicating that such combined oral HRT should not be prescribed for the primary prevention of arterial disease.

Epidemiology of HRT and VTE

Table 1. Epidemiological studies of VTE and HRT

Authors	Study design	Relative risk	Absolute risk
Jick <i>et al.</i> ⁴	Population-based nested case-control study of idiopathic VTE in the USA 1980-94	2.1-6.9, dependent upon dose for current users for idiopathic VTE	9/100 000 versus 32/100 000 women/year for non-users/users of HRT
Daly <i>et al.</i> ⁵	UK hospital-based case-control study in women aged 45-64 years with idiopathic VTE in 1993-94	3.5 (95% CI 1.8-7.0) for idiopathic VTE in current users (note: risk appeared higher in short-term current users)	11/100 000 versus 27/100 000 women/year for non-users/users of HRT
Grodstein <i>et al.</i> ⁶	Questionnaire study on primary PTE in Nurses Health Cohort in USA 1976-92	2.1 (95% CI 1.2-3.8) for idiopathic primary PTE in current users	8/100 000 versus 14/100 000 women/year for non-users/users of HRT
Gutthann <i>et al.</i> ⁷	Population-based nested case-control in UK using the general practice research database	2.1 (95% CI 1.4-3.2) for current users for idiopathic VTE 4.6 (95% CI 2.5-8.4) during the first six months of use	11/100 000 versus 23/100 000 women/year for non-users/users of HRT
Varas-Lorenzo <i>et al.</i> ⁸	Case-control study in Italy	2.3 (95% CI 1.0-5.3) for current users for idiopathic VTE	< 20/100 000 versus < 60/100 000 women/year for non-users/users of HRT
Hulley <i>et al.</i> ⁹ Grady <i>et al.</i> ¹⁰	Randomised, double-blind placebo-controlled trial of HRT (equine conjugated oestrogens and medroxyprogesterone acetate) for secondary prevention of coronary heart disease in USA	VTE: 2.7 (95% CI 1.4-5.0) DVT: 2.8 (95% CI 1.3-6.0) PTE: 2.8 (95% CI 0.9-8.7) for current users (note: an increase was reported in risk of coronary events in women in the first four months of use followed by a reduction in risk over the last two years of this trial, which was conducted over 4.1 years)	230 versus 620/100 000 women years for non-users versus users (note: reflects older higher-risk population compared with the above studies)
Holbraaten <i>et al.</i> ¹¹	Population-based case-control study in 1990-96 for VTE in Scandinavia using oestradiol-based HRT in women aged 44-70 years	1.22 (95% CI 0.76-1.94) overall, 3.54 (95% CI 1.54-8.2) in first 12 months of use and 0.66 (95% CI 0.39-1.10) after the first year of use for primary and secondary VTE	Not available
Writing Group for the Women's Health Initiative Investigators ¹²	Randomised controlled primary prevention trial in 1993-98 with HRT (oral conjugated equine oestrogens, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day) or placebo in 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline	VTE: 2.11 (95% CI 1.58-2.50) DVT: 2.07 (95% CI 1.49-2.87) PE: 2.13 (95% CI 1.39-3.25)	VTE: 340 versus 160 per 100 000 woman-years
Scarabin <i>et al.</i> ¹³	multicentre hospital-based case-control study during 1999-2002 in women aged 45-70 years comparing oral HRT (mainly 17-beta oestradiol 0.5-2 mg/day) and transdermal HRT (50-100 micrograms/day)	Oral HRT: VTE: 3.5 (95% CI 1.8-6.8) Transdermal VTE: VTE: 0.9 (95% CI 0.5-1.6)	Not available

PTE: pulmonary thromboembolism; VTE: venous thromboembolism; the evidence is consistent in demonstrating an increased relative risk of VTE, although the absolute risk, particularly in the absence of other risk factors, is low. There is some evidence that the effect is dose related, as Grodstein *et al.*⁶ found that the relative risk of VTE increased from 3.3 (95% CI 1.4-7.8) to 6.9 (95% CI 1.5-33.0) with 0.625 mg and 1.25 mg of oestrogen respectively. This is in agreement with the data of Daly *et al.*⁵ who found an increase in relative risk from 3.7 (95% CI 1.3-10.2) with 0.625 mg oestrogen to 6.6 (95% CI 2.2-19.6) with 1.25 mg oestrogen, but not all studies have shown a dose effect. There is also a clear association with duration of use (Table 2). The highest risk occurred in the first 6-12 months of use. The study by Varas-Lorenzo *et al.*⁸ reported no cases after the first 12 months of use. Although information is limited, there are some data that suggest that transdermal therapy carries a lower risk than oral therapy (Table 3), but the numbers studied were small.

WOMEN AND VT

- WOMEN HAVE AN INCREASED RISK OF VT DURING THEIR LIFE
- THIS INCREASED RISK IS BOUND TO THEIR FERTILITY
- FERTILITY CONTROL THROUGH OC IS ALSO ASSOCIATED WITH AN INCREASED RISK OF VT
- PREGNANCY AND PUERPERIUM ARE ASSOCIATED WITH INCREASED RISK OF VT
- CONTROL OF THIS INCREASED RISK IS ASSOCIATED WITH AN INCREASED RISK OF BLEEDING

WOMEN AND VT

- FAMILIAR AND PERSONAL HISTORY OF VT CARRIES AN INCREASED RISK OF SUBSEQUENT VT
- SIMPLE MEASURES TO REDUCE THE RISK OF VT SHOULD ALWAYS BE INSTITUTED
- AVOIDING ADDITIONAL RISK FACTORS FOR VT IS MANDATED
- SCREENING FOR CONGENITAL THROMBOPHILIA FACTORS IS FEASIBLE BUT ITS IMPACT ON REDUCING THE RISK OF VT IS YET UNDEFINED

CONCLUSIONS

- THE COST OF SCREENING FOR THROMBOPHILIA SHOULD BE BALANCED AGAINST ITS BENEFITS IN REDUCING THE RISK OF VT
- THE COST OF ADMINISTRATION OF ANTICLOTTING MOLECULES SHOULD BE BALANCED AGAINST ITS EFFECTIVENESS IN REDUCING A POTENTIAL INCREASED RISK OF VT AND THE PRODUCTION OF UNDESIRABLE CONSEQUENCES