Progetto Ematologia Romagna

TROMBOFILIE E GRAVIDANZA

Marco Marietta - Modena

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

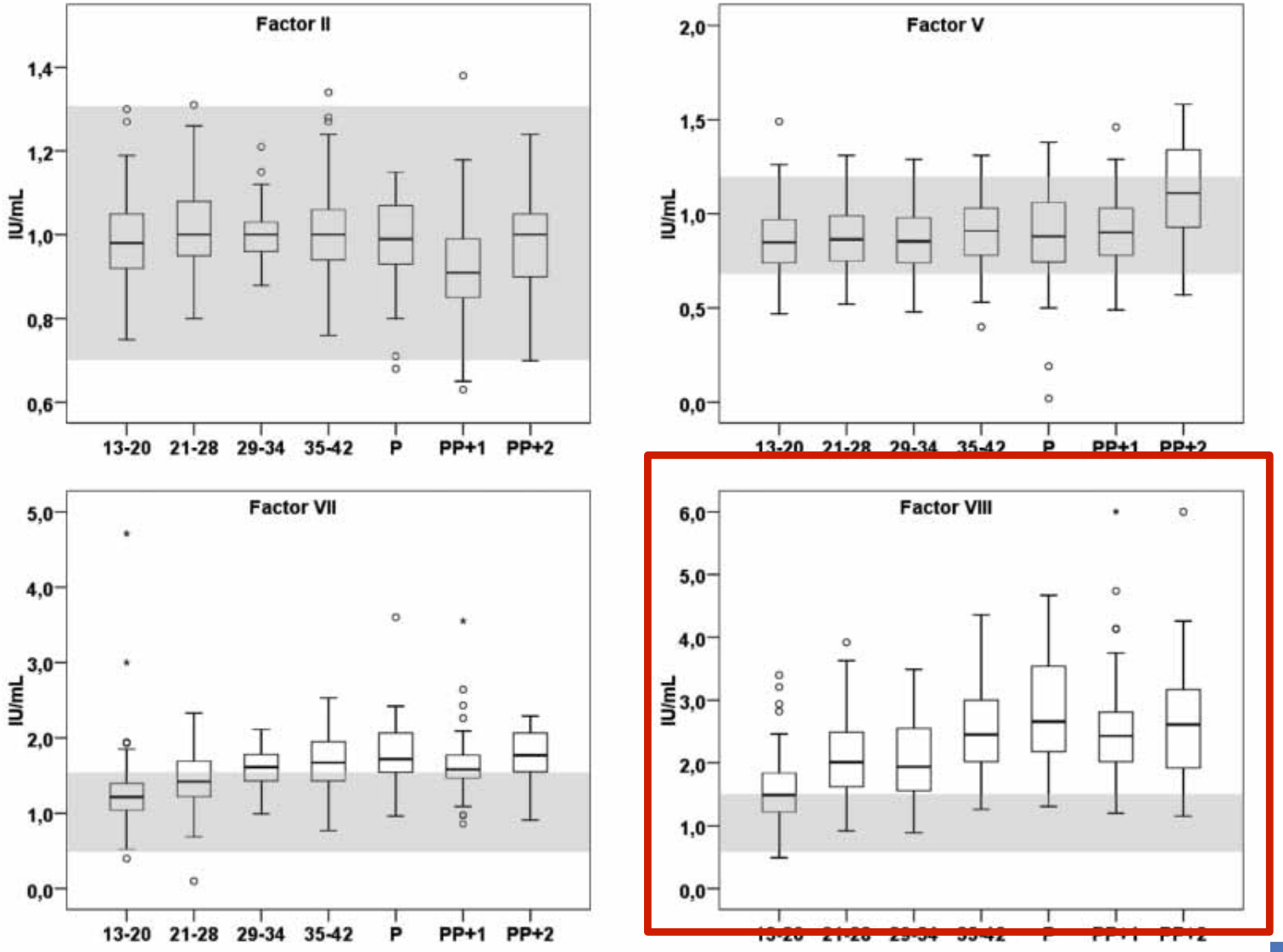
- ✓**Advisory board**: Novo-Nordisk, BioVIIIx, Bristol-Myers Squibb, Daiichi-Sankyo
- ✓**Consulenza**: Gilead, Kedrion
- ✓**Relazioni a convegni**: Novo-Nordisk, Orphan, Sanofi

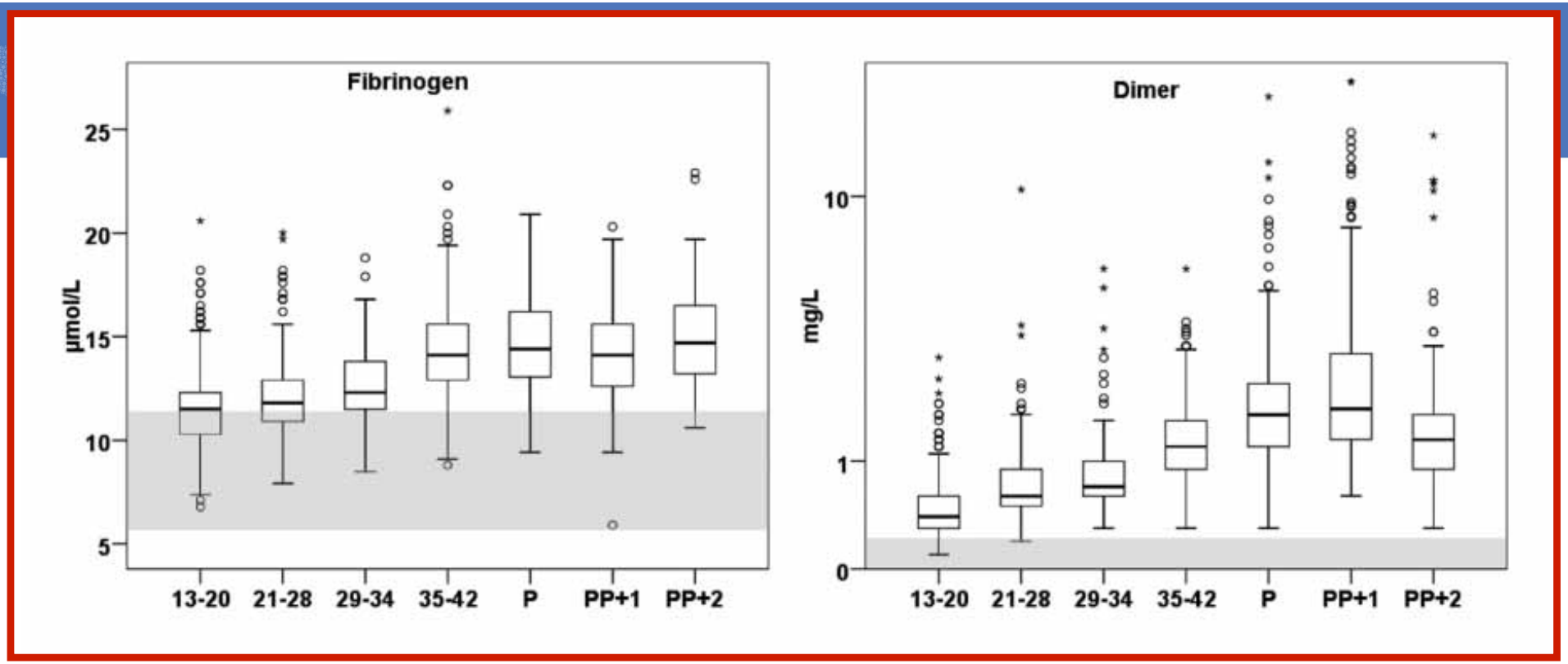
Che ci azzecca…

…la trombofilia con la gravidanza?

Haemostatic reference intervals in pregnancy

Pal B. Szecsi[1]; Maja Jørgensen[2]; Anna Klajnbard[3]; Malene R. Andersen Thromb Haemost 2010; 103: 718–727

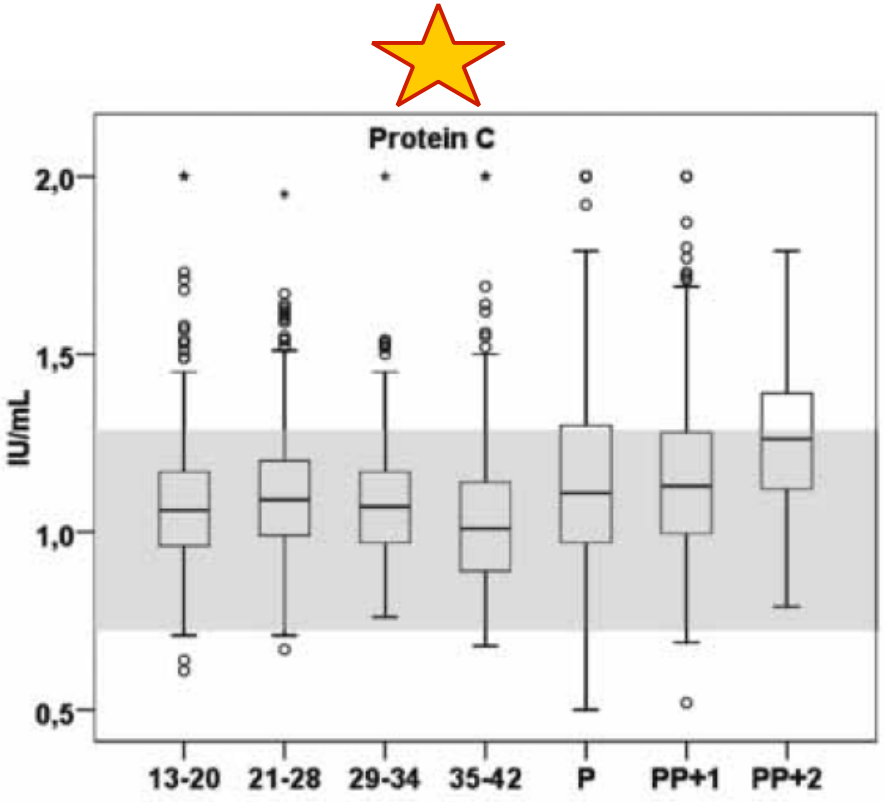


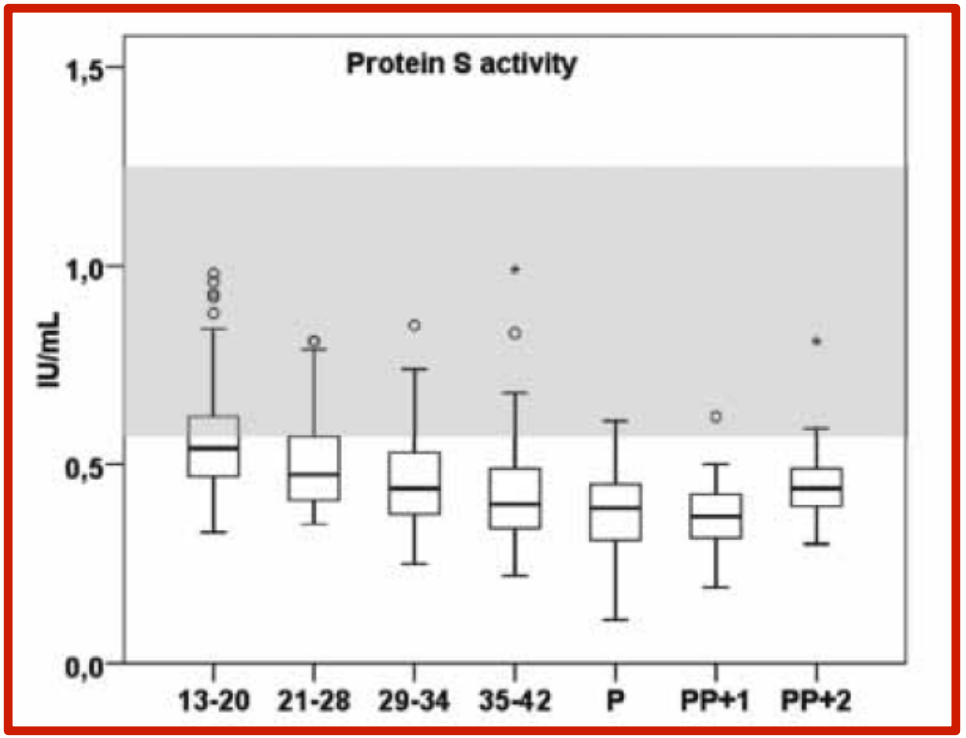


Fibrinogeno (mg/dl) e gravidanza

13-20 sett.	21-28 sett.	29-34 sett.	35-42 sett.	P	PP+1 gg	PP+2 gg	No gravida
289-527	299-571	323-568	350-649	350-642	343-642	391-670	197-401

Szecsi PB et al. Thromb Haemost 2010; 103: 718–727





Szecsi PB et al. Thromb Haemost 2010; 103: 718–727

What does this paper add?

- Here, we report gestational age-specific reference intervals for 18 haemostatic laboratory tests in 391women during uncomplicated pregnancy, delivery, and puerperium according to IFCC guidelines.
- Coagulation factors II, V, X, XI, XII, PT, aPTT, antithrombin, protein C are fairly stable during uncomplicated pregnancy, delivery, and puerperium.
- D-dimer, fibrinogen, and coagulation factors VII, VIII, and IX increase so much during uncomplicated pregnancy that gestational age-specific reference values are mandatory for correct evaluation.
- The usefulness of measuring fibrinogen and D-dimer during pregnancy is doubtful.

Szecsi PB et al. Thromb Haemost 2010; 103: 718–727

Classic thrombophilic gene variants

Thromb Haemost 2015; 114: 885–889

Pier Mannuccio Mannucci[1]; Massimo Franchini[2]

Thrombophilia is defined as a hypercoagulable state leading to a thrombotic tendency (1–3). In 1856, Rudolf Virchow conceived

With this background, the term thrombophilia is now employed to describe a tendency to develop VTE (not arterial thrombosis), owing to abnormalities of blood coagulation that can be inherited, acquired or mixed (both congenital and acquired). In-

Classic thrombophilic gene variants

Thromb Haemost 2015; 114: 885–889

Pier Mannuccio Mannucci[1]; Massimo Franchini[2]

Table 1: Prevalence of thrombophilia abnormalities and relative risk of venous thromboembolism (VTE).

Thrombophilia abnormality	Prevalence (%)		Relative risk	
	General population	Patients with VTE	First VTE	Recurrent VTE
Antithrombin deficiency	0.02–0.2	1	50	2.5
Protein C deficiency	0.2–0.4	3	15	2.5
Protein S deficiency	0.03–0.1	2	10	2.5
Factor V Leiden (heterozygous)	5	20	7	1.5
Factor V Leiden (homozygous)	0.02	1.5	80	-
Prothrombin G20210A (heterozygous)	2	6	3–4	1.5
Prothrombin G20210A (homozygous)	0.02	<1	30	-
Non-O blood group	55–57	75	2	2

Review Article

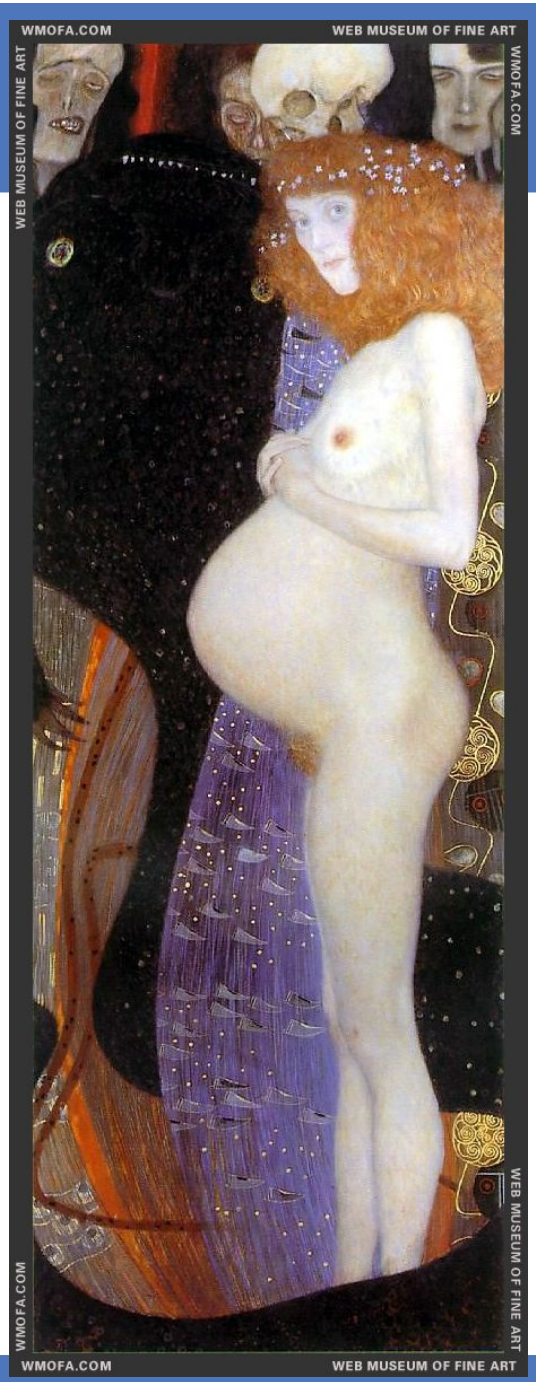
Thromb Haemost 2016; 115: 25–30

Uncertain thrombophilia markers

Massimo Franchini[1]; Ida Martinelli[2]; Pier Mannuccio Mannucci[3]

Consolidated evidence	Weak evidence	Lack of evidence
Loss-of-function mechanisms • Antithrombin deficiency • Protein S deficiency • Protein C deficiency Gain-of-function mechanisms • Factor V Leiden • Prothrombin G20210A • Non-O blood group • High levels of FVIII • Dysfibrinogenaemia • Hyperhomocysteinaemia	• High TAFI plasma plasma levels • High coagulation factor levels (fibrinogen, FIX, FXI) • EPCR polymorphisms **HR 2-3**	• Plasminogen deficiency • High PAI-1 levels • FXIII leu34val • Lp(a) • MTHFR C677T and A1298C polymorphisms • Low TFPI levels • High coagulation factor levels (FV, FVII, FX) • Thrombomodulin polymorphisms • ACE polymorphisms • PZ/ZPI polymorphisms • ADAMTS13 polymorphisms

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; Lp(a), lipoprotein a; EPCR, endothelial protein C receptor; ACE, angiotensin-converting enzyme; ADAMTS, A Disintegrin And Metalloprotease with ThromboSpondin-1-like domains; PZ, protein Z; ZPI, protein Z-dependent protease inhibitor.



La trombofilia per la mamma

Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis

BMJ 2017;359:j4452 doi: 10.1136/bmj.j4452

Thrombophilia	Thrombophilic VTE/Total*	Controls VTE/Total*	ODDS RATIO (95% CI)			
			All	Case-control	Cohort	High quality
AT	48/153	710/2178	9.5 (1.6 to 31.9)	5.0 (0.6 to 24.7)	25.9 (0.0 to 176.3)	8.9 (0.3 to 34.7)
PC	49/180	691/2024	9.3 (2.1 to 43.1)	12.3 (0.0 to 139.8)	5.9 (0.0 to 49.6)	7.7 (0.0 to 48.1)
PC	53/192	700/2212	7.0 (1.3 to 21.9)	6.7 (0.2 to 34.7)	7.2 (0.0 to 35.4)	6.9 (0.2 to 24.6)
Heterozygous FV	305/3345	923/34 626	6.4 (4.0 to 9.7)	7.2 (4.3 to 12.6)	3.9 (0.2 to 11.9)	6.4 (3.9 to 10.6)
Homozygous FV	27/80	919/26 906	35.8 (0.4 to 137.8)	128.9 (3.0 to 3093.9)	12.0 (0.0 to 69.9)	46.7 (4.1 to 193.1)
Heterozygous FII	94/1433	1002/21 736	5.1 (2.6 to 9.8)	4.9 (2.0 to 11.4)	4.9 (0.0 to 23.7)	4.3 (2.0 to 8.8)
Homozygous F II	4/5	559/19 692	21.1 (0.0 to 727.4)	18.2 (0.0 to 1073.7)	NA	13.4 (0.0 to 584.2)
Compound FV / FII	45/242	803/2652	21.2 (1.6 to 89.0)	45.4 (0.6 to 478.6)	8.6 (0.5 to 62.3)	26.9 (1.1 to 147.1)

Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis

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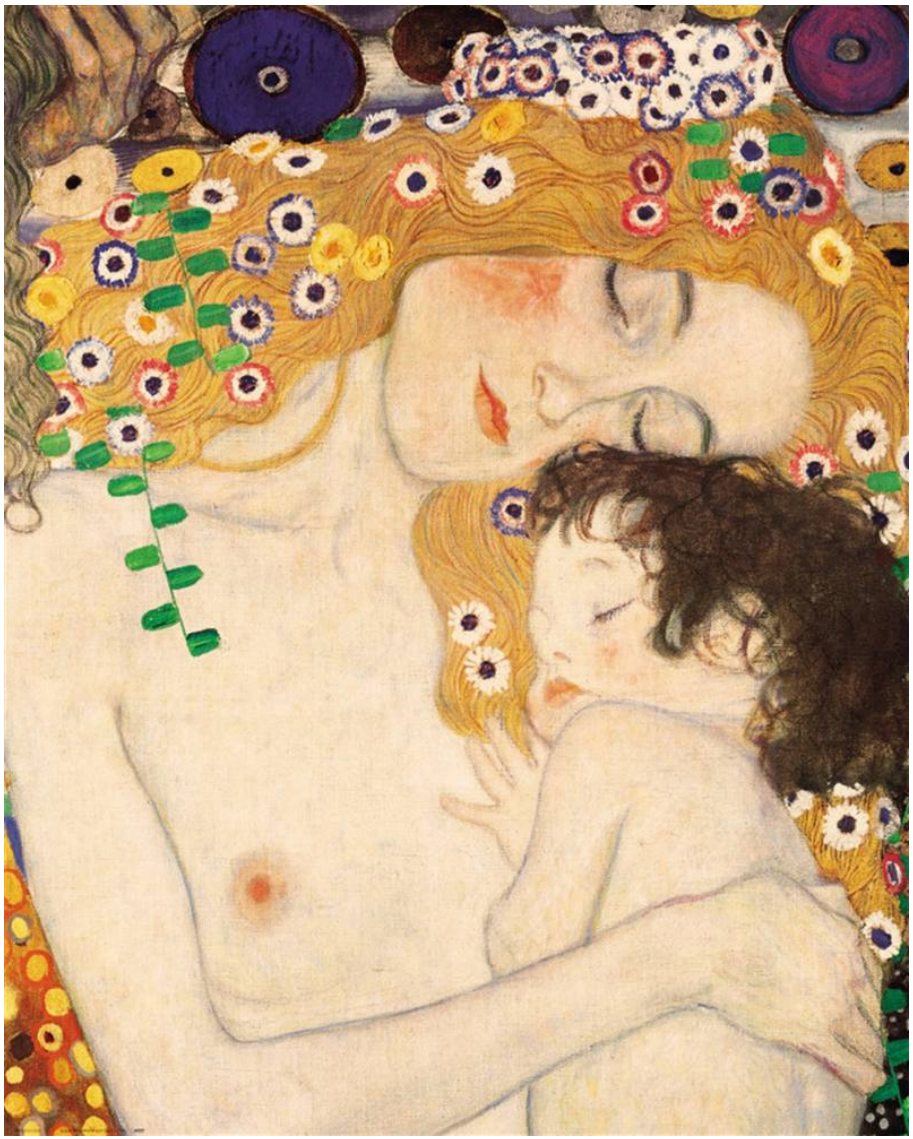
Thrombophilia	VTE/Total*	AR of VTE, all studies, % pregnancies (95% CrI) Baseline risk: 0.5% (family), 0.1% (non-family)		
		Overall	Antepartum	Post partum
Antithrombin (family)	23/125	16.6 (0.0 to 45.1)	7.3 (1.8 to 15.6)	11.1 (3.7 to 21.0)
Protein C (family)	10/137	7.8 (0.0 to 33.8)	3.2 (0.6 to 8.2)	5.4 (0.9 to 13.8)
Protein S (family)	7/135	4.8 (0.0 to 20.0)	0.9 (0.0 to 3.7)	4.2 (0.7 to 9.4)
Heterozygous FV Leiden				
Overall	**45/3031**	**1.1 (0.3 to 1.9)**	0.4 (0.1 to 0.9)	2.0 (0.9 to 3.7)
Family	**35/1359**	**2.4 (0.9 to 4.4)**	0.4 (0.0 to 0.9)	2.5 (1.2 to 4.4)
Non-family	**10/1672**	**0.4 (0.0 to 0.9)**	0.7 (0.0 to 2.6)	0.4 (0.0 to 1.8)
Homozygous FV Leiden				
Overall	5/58	6.2 (0.0 to 18.0)	2.8 (0.0 to 8.6)	2.8 (0.0 to 8.8)
Family	4/35	8.3 (0.0 to 29.6)	NA	NA
Non-family	1/23	5.6 (0.0 to 34.3)	NA	NA
Heterozygous FII				
Overall	**14/1322**	**0.9 (0.2 to 2.0)**	0.0 (0.0 to 0.2)	0.9 (0.2 to 2.0)
Family	**11/998**	**1.0 (0.0 to 2.5)**	NA	NA
Non-family	**3/324**	**0.8 (0.1 to 2.0)**	NA	NA
Heterozygous FV / FII				
Family	5/199	2.5 (0.0 to 9.5)	NA	NA

Croles FN. BMJ 2017;359:j4452

Thrombophilia	VTE/Total*	AR of VTE, % pregnancies (95% CrI) NON CARRIERS: 0.5% (family), 0.1% (non-family)		
		Overall	Antepartum	Post partum
Antithrombin (family)	**23/125**	**16.6 (0.0 to 45.1)**	7.3 (1.8 to 15.6)	11.1 (3.7 to 21.0)
Protein C (family)	**10/137**	**7.8 (0.0 to 33.8)**	3.2 (0.6 to 8.2)	5.4 (0.9 to 13.8)
Protein S (family)	**7/135**	**4.8 (0.0 to 20.0)**	0.9 (0.0 to 3.7)	4.2 (0.7 to 9.4)
Heterozygous FV Leiden				
Overall	45/3031	1.1 (0.3 to 1.9)	0.4 (0.1 to 0.9)	2.0 (0.9 to 3.7)
Family	35/1359	2.4 (0.9 to 4.4)	0.4 (0.0 to 0.9)	2.5 (1.2 to 4.4)
Non-family	10/1672	0.4 (0.0 to 0.9)	0.7 (0.0 to 2.6)	0.4 (0.0 to 1.8)
Homozygous FV Leiden				
Overall	**5/58**	**6.2 (0.0 to 18.0)**	2.8 (0.0 to 8.6)	2.8 (0.0 to 8.8)
Family	**4/35**	**8.3 (0.0 to 29.6)**	NA	NA
Non-family	**1/23**	**5.6 (0.0 to 34.3)**	NA	NA
Heterozygous FII				
Overall	14/1322	0.9 (0.2 to 2.0)	0.0 (0.0 to 0.2)	0.9 (0.2 to 2.0)
Family	11/998	1.0 (0.0 to 2.5)	NA	NA
Non-family	3/324	0.8 (0.1 to 2.0)	NA	NA
Heterozygous FV + FII				
Family	5/199	2.5 (0.0 to 9.5)	NA	NA

Croles FN. BMJ 2017;359:j4452

2018



La trombofilia per il prodotto del concepimento

Un popolo che ignora il proprio passato non saprà mai nulla del proprio presente

Indro Montanelli

Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant

(AM. J. OBSTET. GYNECOL. 142:829, 1982.)

FRANK DE WOLF, M.D.
LUIS O. CARRERAS, M.D.
PHILIPPE MOERMAN, M.D.
JOS VERMYLEN, M.D.
ANDRÉ VAN ASSCHE, M.D.
MARCEL RENAER, M.D.
Leuven, Belgium

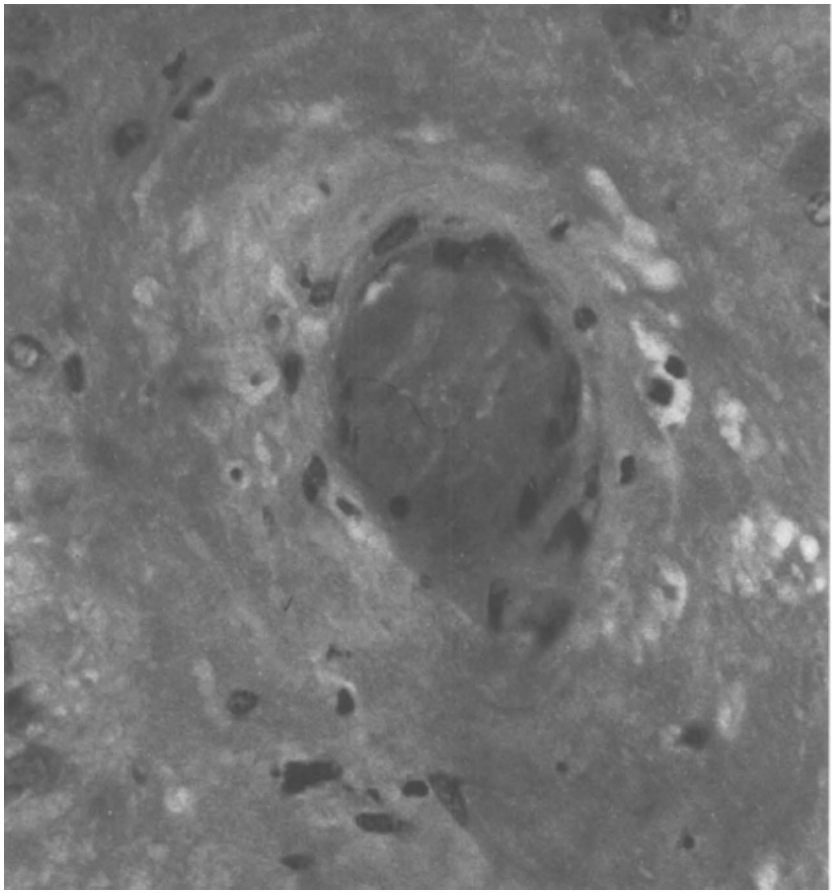


Fig. 2. Decidual segment of a spiral artery in the basal plate of the placenta. Absence of physiologic changes. Intraluminal thrombosis. Necrosis of the vessel wall. (X 530.)

OBSTETRIC COMPLICATIONS ASSOCIATED WITH THE LUPUS ANTICOAGULANT

D. Ware Branch, M.D., James R. Scott, M.D., Neil K. Kochenour, M.D., and Edward Hershgold, M.D.

Abstract We identified eight patients with the lupus anticoagulant (an autoantibody acquired by some patients with systemic lupus erythematosus), by observation of an increased activated partial thromboplastin time and abnormal results on a tissue thromboplastin–inhibition test. The patients had experienced a total of 30 spontaneous abortions and fetal deaths in 31 previous pregnancies (96.8 per cent). During their next pregnancy, the patients were treated with 40 to 50 mg of prednisone per day and 81 mg of aspirin per day. The therapy shortened their activated partial thromboplastin times, produced normal values for tissue thromboplastin inhibition, and reduced the rate of pregnancy loss to 37.5 per cent. However, preeclampsia developed in the five patients who gave birth to live infants, and fetal growth retardation occurred in three cases. The corticosteroid and low-dose aspirin regimen appears to improve perinatal outcome in cases in which the mother has the lupus anticoagulant, but such practices as careful fetal surveillance and preterm delivery when appropriate are also important to successful obstetric management of such cases. (N Engl J Med 1985; 313:1322-6.)

Table 1. Previous Obstetric Histories of Eight Women with the Lupus Anticoagulant.

Patient	Pregnancies	Spontaneous Abortions (at <12 wk)	Fetal Deaths (at >12 wk)	Live-Born Infants
A	5	3	2	0
B	2	0	2	0
C	7	5	2	0
D	1	0	0	1
E	7	4	3	0
F	4	4	0	0
G	3	0	3	0
H	2	0	2	0
	31	16 (51.6%)	14 (45.2%)	1 (3.2%)

Thromb Haemost 2000; 84: 228–36

Antiphospholipid and Antiprotein Syndromes in Non-thrombotic, Non-autoimmune Women with Unexplained Recurrent Primary Early Foetal Loss

Odds ratio (95% CI) for early foetal loss and type of positive marker in women

	Univariate conditional logistic regression			Multivariate conditional logistic regression		
	Odds ratio	95%CI	p	Odds ratio	95%CI	p
Conventional phospholipid-dependent assays						
Lupus Anticoagulant (1)	4.2	1.9-9.3	0.003	3.0	1.3-6.8	0.009
Anticardiolipin antibodies, IgG	0.86	0.29-2.6	0.79 NS	-	-	-
Anticardiolipin antibodies, IgM	1.8	0.61-5.5	0.29 NS	-	-	-
Non-conventional phospholipid-containing assays						
Anti phosphatidylethanolamine, IgM (2)	6.8	2.6-17.6	0.0001	6.0	2.3-15.7	0.0003
Anti phosphatidylethanolamine, IgG	1.1	0:12-2.9	0.85 NS	-	-	-
Phospholipid-free assays						
Anti-β2-glycoprotein I antibodies, IgG (3)	5.9	2.2-15.4	0.0003	4.4	1.6-11.7	0.0035
Anti-β2-glycoprotein I antibodies, IgM	1.1	0.12-2.9	0.85 NS	-	-	-
Anti-annexin V antibodies, IgG (4)	4.9	1.6-7.9	0.0028	3.2	1.2-8.1	0.015
Anti-annexin V antibodies, IgM	1.8	0.61-5.5	0.29 NS	-	-	-
Anti-prothrombin antibodies, IgG (5)	2.9	1.2-7.0	0.015	2.1	0.8-5.2	0.12 NS
Anti-prothrombin antibodies, IgM	0.86	0.29-2.6	0.79 NS	-	-	-
(1) and/or (2) and/or (3) and/or (4) and/or (5)	3.4	2.3-5.3	< 0.0001			

Best Practice & Research Clinical Haematology
Vol. 16, No. 2, pp. 211–225, 2003
doi:10.1053/ybeha.2003.247

BEST PRACTICE & RESEARCH

6

Antiphospholipid antibodies and pregnancy

Monica Galli* MD, PhD

Tiziano Barbui MD

Table 2. Epidemiology and timing of pregnancy loss in different clinical conditions.

		Pregnancy loss (%)		
	Overall prevalence (%)	< 10th week	> 10th week	Reference
General population	10–20	87	13	48
Antiphospholipid syndrome	50–75	50	50	47,52
Essential thrombocythaemia	43	83	17	51

bjh research paper © 2005 Blackwell Publishing Ltd, *British Journal of Haematology*, **132**, 171–196

L. Robertson,[1] O. Wu,[1] P. Langhorne,[1]

Thrombophilia in pregnancy: a systematic review

THROMBOFILIA	ODDS RATIO (95% CI)					
	EARLY PL (n/N)	RECURRENT EARLY PL (n/N)	LATE PL (n/N)	PREECLAMPSIA (n/N)	ABRUPTIO PLACENTAE (n/N)	IUGR (n/N)
FV HETERO	1.7 (1.1-2.6) 172/243	1.9 (1.0-3.6) 173/287	2.1 (1.1-3.9) 27/382	2.2 (1.5-3.3) 161/249	4.7 (1.1-19.6) 13/28	2.7 (0.6-12.1) 25/49
FV HOMO	2.7 (1.3-5.6) 37/76		2 (0.4-9.7) 2/118	1.9 (0.4-7.9) 4/5	-	-
FII HETERO	2.5 (1.2-5.0) 53/75	2.7 (1.4-5.3) 54/78	2.7 (1.3-5.5) 348/1134	2.5 (1.5-4.2) 42/71	7.7 (3-19.8) 10/20	2.9 (0.6-12.1) 69/323
MTHFR HOMO	1.4 (0.8-2.5) 75/110	0.9 (0.4-1.7) 22/39	1.3 (0.9-1.9) 69/323	1.4 (1.1-1.8) 221/481	1.5 (0.4-5.3) 3/14	1.2 (0.8-1.8) 62/121
HYPERHOMOCYS	6.2 (1.4-28.4) 33/37	4.2 (1.3-13.9) 33/37	1 (0.2-5.5) 2/7	3.5 (1.2-10.1) 37/41	2.4 (0.4-15.9) 32/42	-
LAC	4 (1.0-8.6) 59/107	-	2.4 (0.8-7) 22/39	1.4 (0.8-2.7) 63/89	-	-
ACA	3.4 (1.3-8.7) 127/149	5.0 (1.8-14.0) 116/120	3.3 (1.6-6.8) 52/130	2.7 (1.6-4.5) 130/217	1.4 (0.4-4.8) 6/12	6.9 (2.7-17.7) 7/60

PC, PS, AT not shown because of the small sample size (<10 cases)

bjh research paper © 2005 Blackwell Publishing Ltd, *British Journal of Haematology*, **132**, 171–196

L. Robertson,[1] O. Wu,[1] P. Langhorne,[1]

Thrombophilia in pregnancy: a systematic review

Conclusions

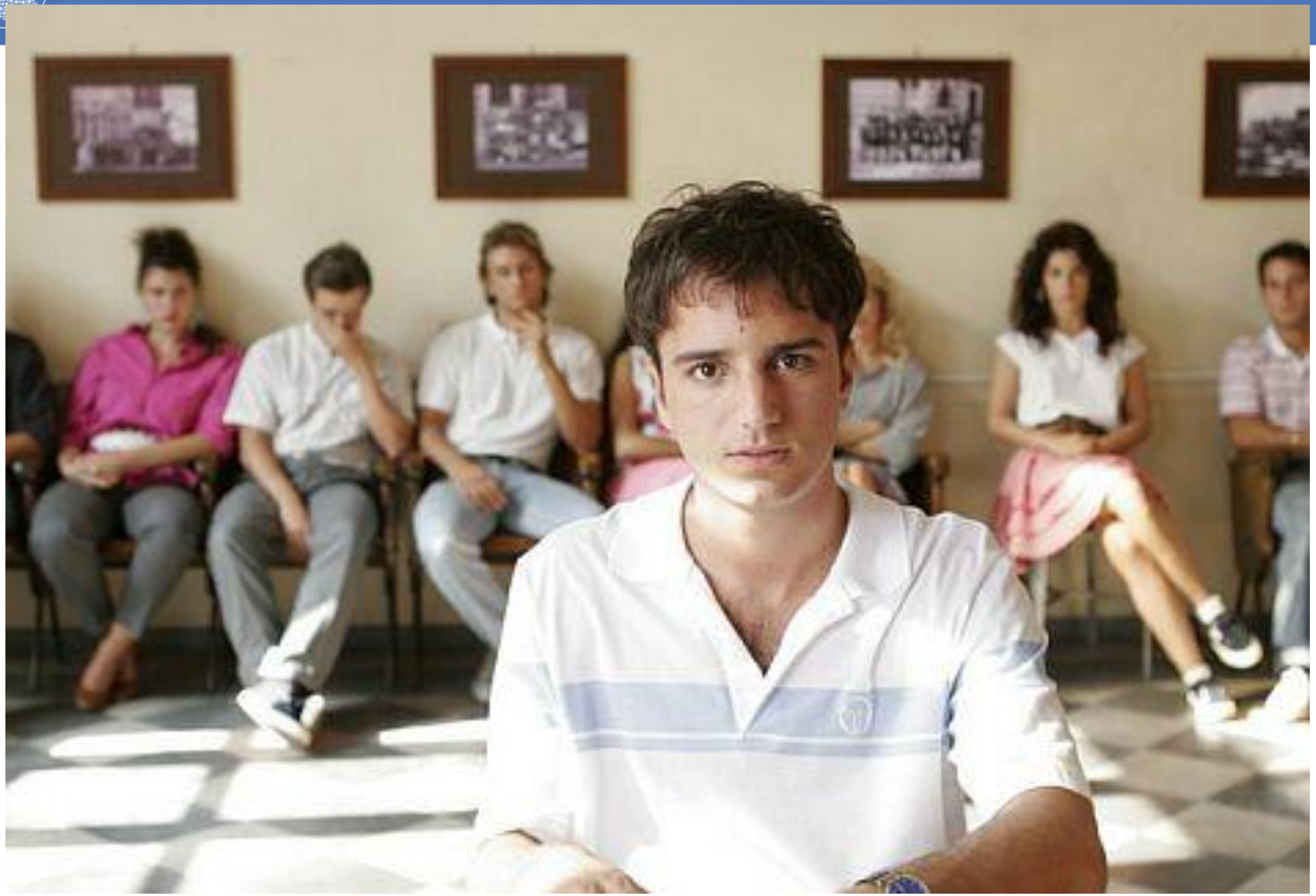
Our review has confirmed that women with thrombophilia are at increased risk of developing complications during pregnancy.

However, despite the increase in relative risk, the absolute risk of VTE and adverse outcomes in pregnancy remains low.

Furthermore, aside from recurrent pregnancy loss in antiphospholipid syndrome and prevention of VTE, there is insufficient evidence on the benefit of antithrombotic interventions to guide therapy.

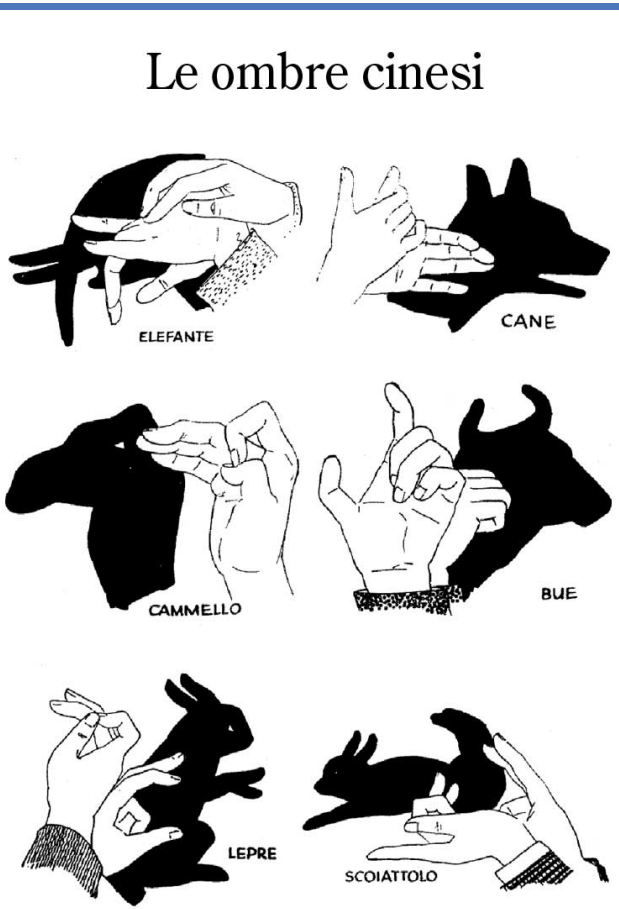
Thus, at present, universal screening for thrombophilia in pregnancy cannot be justified clinically.

2018



PROGETTO EMATOLOGIA – ROMAGNA Cesena, 15 settembre 2018

La trombofilia è quella cosa con la quale o senza la quale tutto rimane tale e quale



Guido Daniele

IL RUOLO DEL LABORATORIO

Dott. G. Poletti

2018

Dalla fisiopatologia alla clinica…

TERAPIA

Prof.ssa B. Cosmi

René Magritte – L'uso della parola I, 1928-1929

Thrombophilia Testing and Venous Thrombosis

Table 4. Diagnostic Criteria for the Antiphospholipid Syndrome.

The antiphospholipid syndrome is present if at least one of the two clinical criteria and at least one of the three laboratory criteria are met:

Clinical criteria

Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis

Pregnancy complication

- Unexplained death of a morphologically normal fetus at or beyond wk 10 of gestation
- Premature birth of a morphologically normal neonate before wk 34 of gestation as a result of eclampsia, severe preeclampsia, or placental insufficiency
- Three or more unexplained, consecutive, spontaneous abortions before wk 10 of gestation, not related to chromosomal or anatomical abnormalities in the parents

Laboratory criteria*

Lupus anticoagulant assay

IgG or IgM anticardiolipin antibody test

IgG or IgM anti–beta-2 glycoprotein 1 antibody test

Connors JM. N Engl J Med 2017;377:1177-87.

Trombofilia acquisita

ACQUISITI

- Età
- Immobilizzazione
- Ingessature
- Chirurgia maggiore /ortopedica
- Neoplasie
- Contraccettivi orali / Terapia ormonale sostitutiva
- Sindrome da ac. Antifosfolipidi
- Malattie mieloproliferative
- Malattie infiammatorie croniche intestinali
- Collagenopatie
- Obesità
- Sindrome metabolica
- Cateteri venosi centrali