

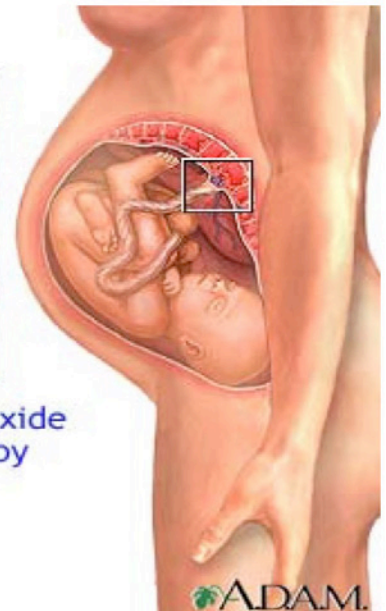
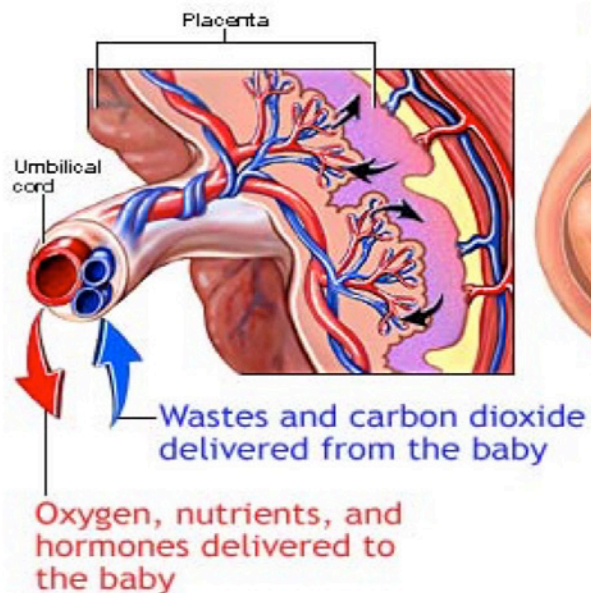
Trombofilia e aborti ricorrenti

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3° convegno *Adi anticoagulazione.it*
"Anticoagulazione: Attualità cliniche e
di laboratorio. Aspetti sociali"

Bologna, 25-26 gennaio 2018



3° CONVEGNO DI ANTICOAGULAZIONE.it

“ ANTICOAGULAZIONE | Attualità cliniche e di laboratorio. Aspetti sociali ”

BOLOGNA 25-26 GENNAIO 2018 Savoia Hotel Regency - Via del Pilastro 2, 40127 Bologna

Obstetrical complications

- ✓ Embryo/Fetal death:
 - early → miscarriage
 - late → stillbirth

- ✓ Preeclampsia / eclampsia / HELLP syndrome
- ✓ Intra-uterine growth restriction (IUGR)
- ✓ Placental abruption

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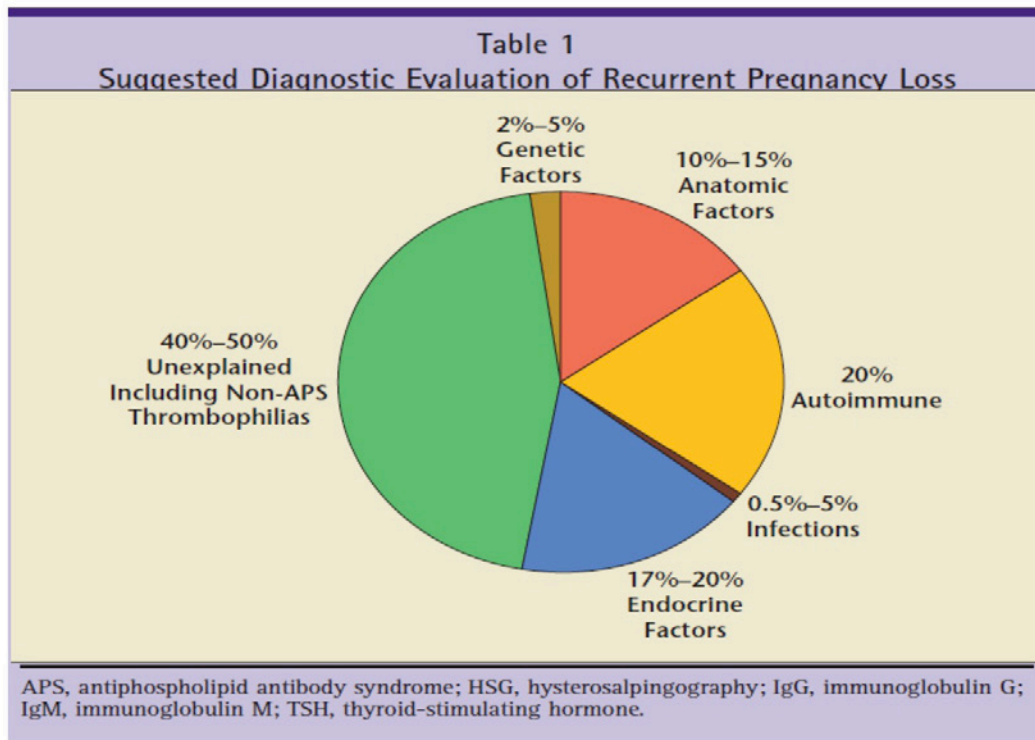
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Recurrent miscarriage

- ✓ HISTORICAL DEFINITION:
3 consecutive pregnancy losses prior to 20 (or 24) gestational week
- ✓ INCIDENCE: one loss = 1 in 5 pregnancies (15-20%)
recurrent = 1 in 300 pregnancies (0.3%)
- ✓ RISK OF MISCARRIAGE: 30% after 2 losses
33% after 3 losses



This strongly suggests a role for evaluation after just 2 losses
(American Society of Reproductive Medicine)



Questions

- ✓ Is thrombophilia associated with RPL?
- ✓ If yes, what is the strength of the association and the magnitude of the risk?
- ✓ Is antithrombotic prophylaxis with LMWH ± ASA useful to prevent RPL in women with or without thrombophilia?

Caso clinico

33 anni, G2, P0

✓ 1° scenario: APS

✓ 2° scenario: inherited thrombophilia

✓ 3° scenario: no thrombophilia

ASA
LMWH
ASA + LMWH

Antiphospholipid antibodies

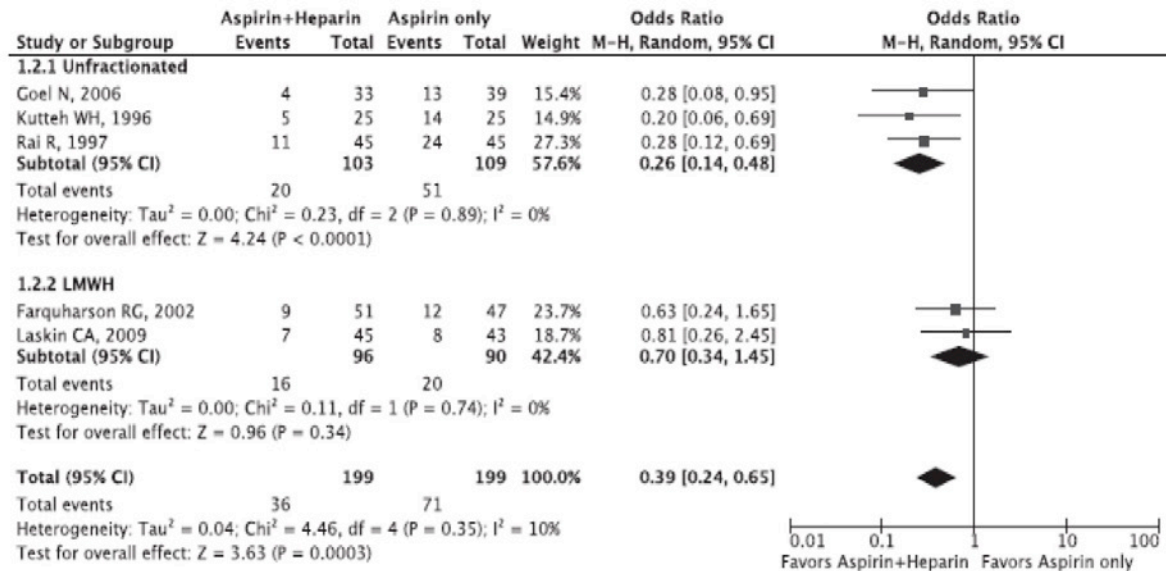
Recurrent miscarriage

Late obstetrical complications

Thrombosis
Autoimmunity
Inflammation/complement
Inhibition trophoblast proliferation

Prevention of recurrent miscarriage in women with APS and RPL

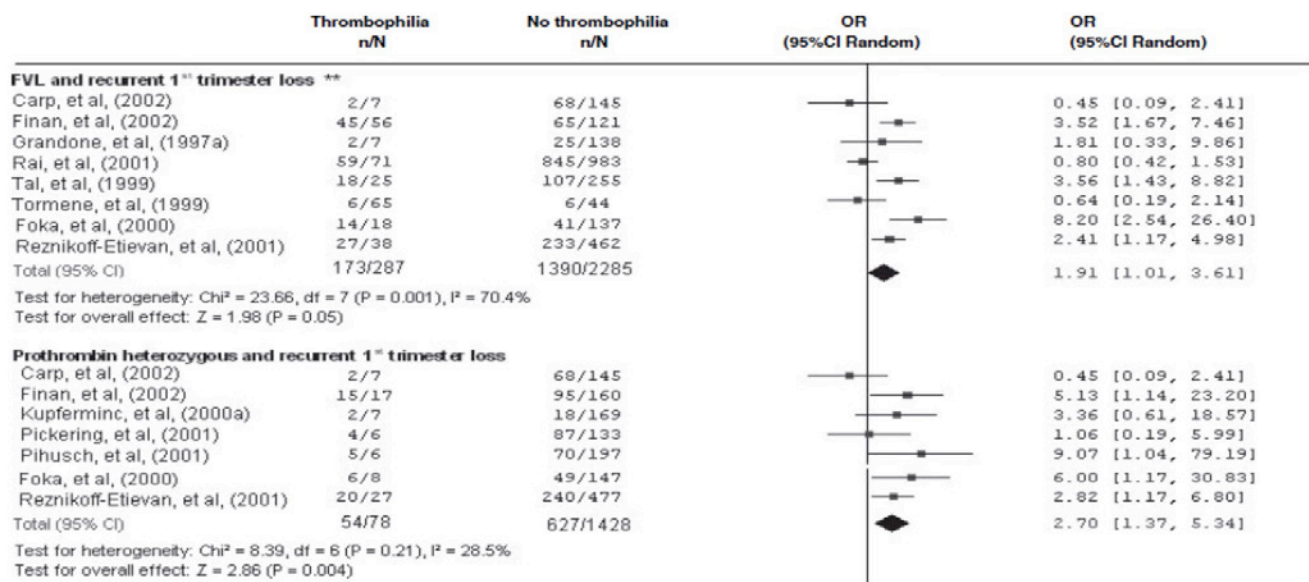
Ziakas PD et al, Obstet Gynecol 2010



ASA + LMWH
Grade 2B - ACCP 2012

Thrombophilia in pregnancy. A systematic review.

Robertson L et al, Br J Haematol 2006



Thrombophilia in pregnancy. A systematic review.

Pritchard AM et al, Clin Obstet Gynecol 2016

TABLE 1. Association Between Hereditary Thrombophilias and Selected Pregnancy Complications

	Nonrecurrent Pregnancy Loss	Late Nonrecurrent Pregnancy Loss*	Recurrent First Trimester Loss†	Recurrent Pregnancy Loss† ‡
FVL	1.52 (1.06-2.19) ^{12‡}	2.06 (1.1-3.86) ²³	1.91 (1.01-3.61) ²³	3.04 (2.16-4.3) ¹⁰
PGM	1.13 (0.64-2.01) ^{12‡}	2.66 (1.28-5.53) ²³	2.70 (1.37-5.34) ²³	2.05 (1.18-3.54) ¹⁰
Protein C deficiency	1.4 (0.9-2.2) ¹⁴	2.3 (0.6-8.3) ¹⁴	N/A	1.57 (0.23-10.54) ¹⁰
Protein S deficiency	1.3 (0.8-2.1) ¹⁴	7.39 (1.28-42.83) ¹⁰	N/A	14.72(0.99-218.01) ¹⁰
Antithrombin deficiency	2.1 (1.2-3.6) ¹⁴	5.2 (1.5-18.1) ¹⁴	N/A	N/A

Questions

- Is thrombophilia associated with RPL? **Yes.**
- If yes, what is the strength of the association and the magnitude of the risk? **The association is weak.**
- Is antithrombotic prophylaxis with LMWH ± ASA useful to prevent RPL in women with thrombophilia?

Pregnancy outcome in thrombophilic women with recurrent pregnancy loss treated with LMWH (LIVE-ENOX)

Brenner B et al, JTH 2005

	No. (%) live birth
40 mg/day enoxaparin (n=89)	70 (84%)
80 mg/day enoxaparin (n=91)	65 (78%)
placebo or no drug	?????

Thrombophilia and pregnancy complications: association not proven causal and antithrombotic prophylaxis is experimental.

Marc A. Rodger, Michael Paidas, Claire McLintock, Saskia Middeldorp, Susan Kahn, Ida Martinelli, William Hague, Karen Montella, Ian Greer

Obstet Gynecol 2008;112 (2):320-324

“... randomized controlled trials in well-defined patient groups are urgently needed.”

The era of RCTs

2009-2015

RCTs

Country	Publ y	Acronym	Patients' selection	Recruitment
Canada	2009	pilot study*	# all late OCs	2000-2007
UK/Australia	2010	SPIN	≥2 misc <24w	2004-2008
Holland	2010	ALIFE	≥2 misc <20w	2004-2008
Finland	2010	HABENOX#	≥3 misc <13w, ≥2 13-24w, 1LFL+1 misc<13w	2002-2007
{ France	2010	NOH-AP	abruptio placentae	2000-2009
{ France	2011	NOH-PE	preeclampsia	2000-2010
Holland/Australia/Sweden	2012	FRUIT§#	early (<34w) PE/SGA	2000-2009
Italy	2012	HAPPY	all late OCs	2006-2010
Canada/Australia	2014	TIPPS§	all late OCs	2000-2012
Germany/Austria	2015	ETHIG II	≥2 misc <12w, ≥1 ≥12w	2006-2013

*only non-thrombophilic women; §only thrombophilic women #prematurely interrupted

RCTs

Acronym	Patients' selection	N	treatment	OR/HR/abs RD (95%CI)	
pilot study*	all late OCs	116	LMWH 4/5/6000	0.15 (0.03-0.7)	
SPIN	≥2 miscarriage <24w	294	LMWH 4000 + ASA 100	0.91 (0.52-1.59)	
ALIFE	≥2 miscarriage <24w	364	ASA 100 ± LMWH 2850*	2.1% (-10.8-15.0) -5.4% (-18.6-7.8)	
HABENOX	≥3 misc <13w, ≥2 13-24w, 1LFL+1 misc<13w	207	ASA 100 ± LMWH 4000, ASA 100 (ref.)	1.08 (0.83-1.39) 1.17 (0.92-1.48)	
{	NOH-AP	abruptio placentae	160	LMWH 4000	0.37 (0.18-0.77)
	NOH-PE	preeclampsia	224	LMWH 4000	0.32 (0.16-0.66)
FRUIT	early (<34w) PE/SGA	139	ASA 80 ± LMWH 5000	8.7% (1.9-15.5)	
HAPPY	all late OCs	135	LMWH 4000	2.2% (-1.6-16.0)	
TIPPS	all late OCs	289	LMWH 5000	2.6% (-6.4-11.6)	
ETHIG II	≥2 misc <12w, ≥1 ≥12w	449	LMWH 5000	-0.7 (-7.3-5.9)	

*control group receiveing oral placebo

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia.

Leslie Skeith, Marc Carrier, Risto Kaaja, Ida Martinelli, David Petroff, Ekkehard Schleußner, Carl A Laskin, Marc A Rodger

Blood 2016;127 (13):1650-1655

✓ 8 RCTs, 483 pregnant women with recurrent miscarriage <10w or ≥1 ≥10w

✓ livebirth rate: RR 0.81 (0.55-1.19)
RR 1.04 (0.93-1.16) only multicenter trials

Questions

- Is thrombophilia associated with RPL? **Yes.**
- If yes, what is the strength of the association and the magnitude of the risk? **The association is weak.**
- Is antithrombotic prophylaxis with LMWH ± ASA useful to prevent RPL in women with thrombophilia? **No.**

RCT in non thrombophilic women

Pasquier et al, Blood 2015

PREFIX study

258 non thrombophilic women ≥ 3 misc $< 15w$ (2007-2012)

Enoxaparin 40 mg vs placebo

Absolute difference -6% (95%CI -17.1 to 5.1)

Key Points

- The use of low-molecular-weight heparin did not improve live-birth rates in nonthrombophilic women with consecutive recurrent miscarriage.
- Prophylactic doses of low-molecular-weight heparin should no longer be prescribed in this clinical setting.

Take home message

- ✓ Owing the weak grade of recommendation, pregnant women with **APS** and RPL should receive ASA + LMWH
- ✓ Although **inherited thrombophilia** is weakly associated with RPL, nor ASA nor LMWH improve the live-birth rate and therefore should NOT be given.
- ✓ To date, the use of LMWH in women with RPL remains **NON** evidence based.
- ✓ Before prescribing LMWH to pregnant women in order to prevent RPL, a doctor should:
 - consider the principle of *primum non nocere*
 - consider the off-label indication
 - inform the woman about safety and side effects
 - obtain the signed informed consent



Thank you !