Trombofilia e rischio abortivo

Ida Martinelli

Centro Emofilia e Trombosi A. Bianchi Bonomi
Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico
Milano

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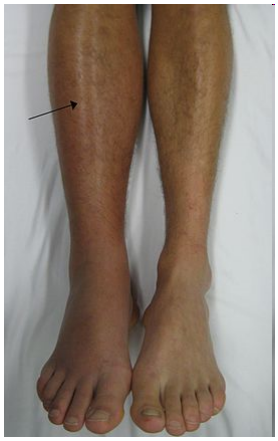
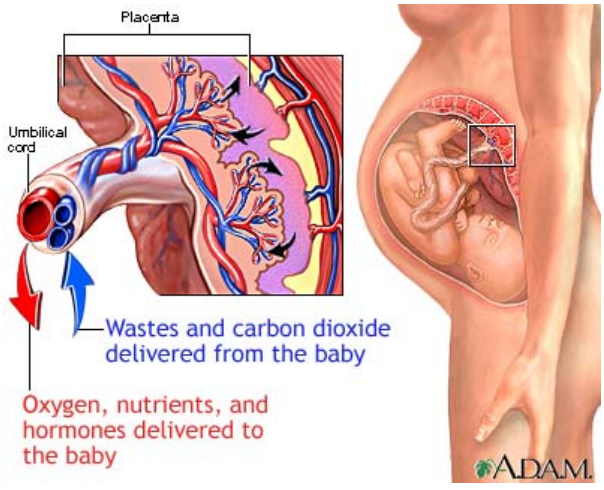




Obstetrical complications

- ✓ **Embryo/Fetal death:**
  - **- early → miscarriage**
  - **- late → stillbirth**
- ✓ **Preeclampsia / eclampsia / HELLP syndrome**
- ✓ **Intra-uterine growth restriction (IUGR)**
- ✓ **Placental abruption**

PLACENTA MEDIATED

Recurrent miscarriage

- ✓ HISTORYCAL 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

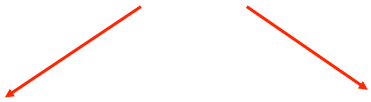
↓

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

Questions

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

Antiphospholipid antibodies



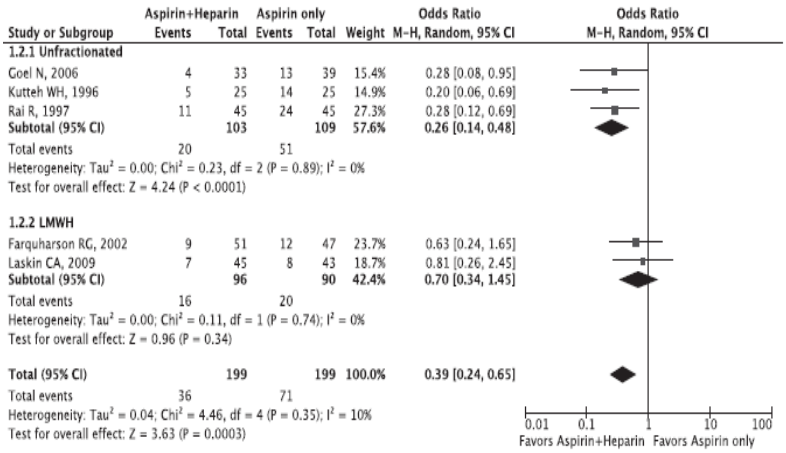
Recurrent miscarriage

Late obstetrical complications

Thrombosis
Autoimmunity
Inflammation/complement
Inhibition throphoblast proliferation

Prevention of miscarriage in women with APS and RPL

Ziakas PD et al, Obstet Gynecol 2010



ASA + LMWH

Grade 2B - ACCP 2012

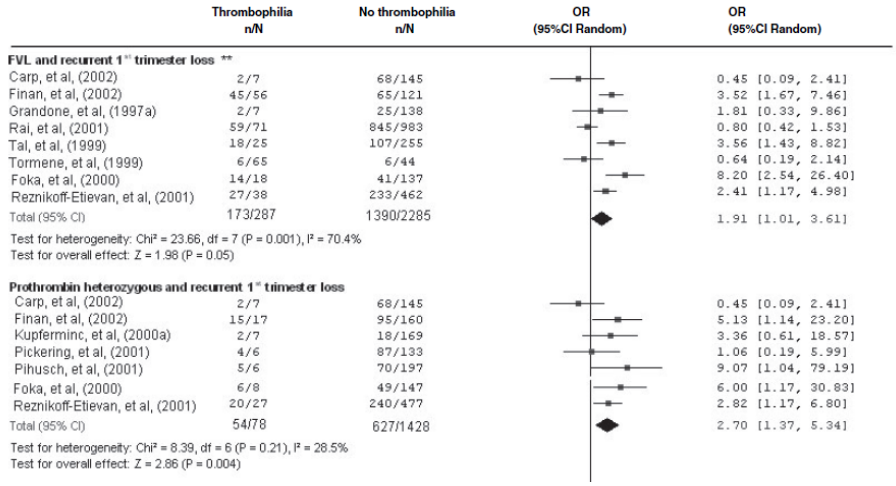
Association between APS and placenta mediated complications: meta-analysis of 28 studies.

		ca-co (n=20)	cohort (n=8)
LAC	PE	2.3 (1.2-4.6)	-
	IUGR	4.7 (1.3-16.7)	-
	PA	-	-
	LFL	4.7 (1.1-20.8)	10.6 (1.9-59.9)
ACA	PE	1.5 (1.1-2.2)	-
	IUGR	-	-
	PA	-	-
	LFL	4.3 (1.3-13.7)	8.9 (1.8-42.5)
antiβ2GP1	PE	-	19.1 (6.3-57.8)
	IUGR	-	20.0 (4.6-87.4)
	PA	-	-
	LFL	-	23.5 (1.2-455.0)

Abou-Nassar K et al, Thromb Res 2011

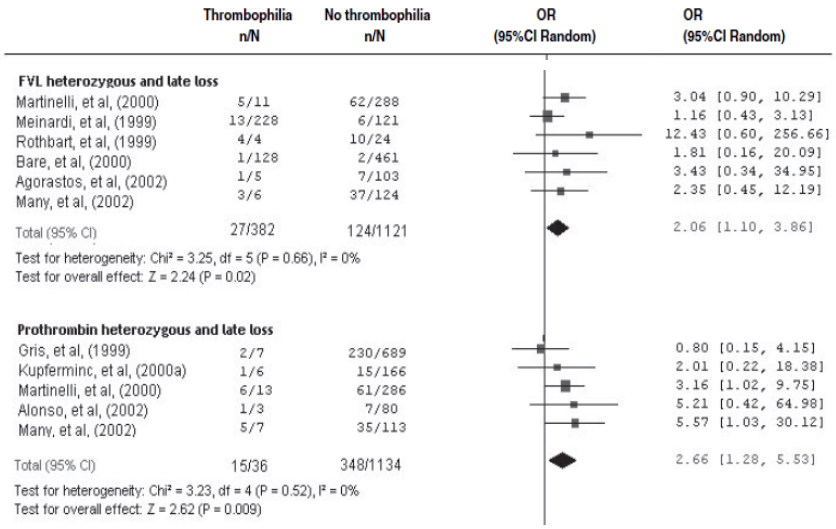
Thrombophilia and RPL

Robertson L et al, Br J Haematol 2006



Thrombophilia and late pregnancy loss

Robertson L et al, Br J Haematol 2006



Thrombophilia and adverse pregnancy outcomes: results from the Danish National Birth Cohort.

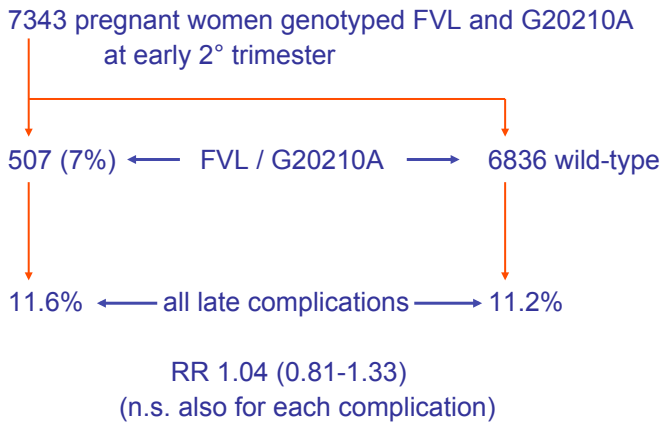
50% of all Danish pregnant women in 5 years (1997-2002) participated to the study, with 101042 pregnancies to 91661 women.

Nested ca-co study (ca 1771 - co 1856) for genotyping:

	severe PE/HELLP n=236	fetal growth restriction (<3%) n=1227	placental abruptio n=308
FVL	1.6 (1.1-2.4)	1.4 (1.1-1.8)	1.7 (1.2-2.4)
PTG20210A	0.8 (0.3-2.3)	0.8 (0.5-1.4)	1.7 (0.8-3.5)

Lykke JA et al, JTH 2012

Prospective Canadian cohort study on thrombophilia and placenta-mediated pregnancy complications.



Rodger MA et al, JTH 2014

Questions

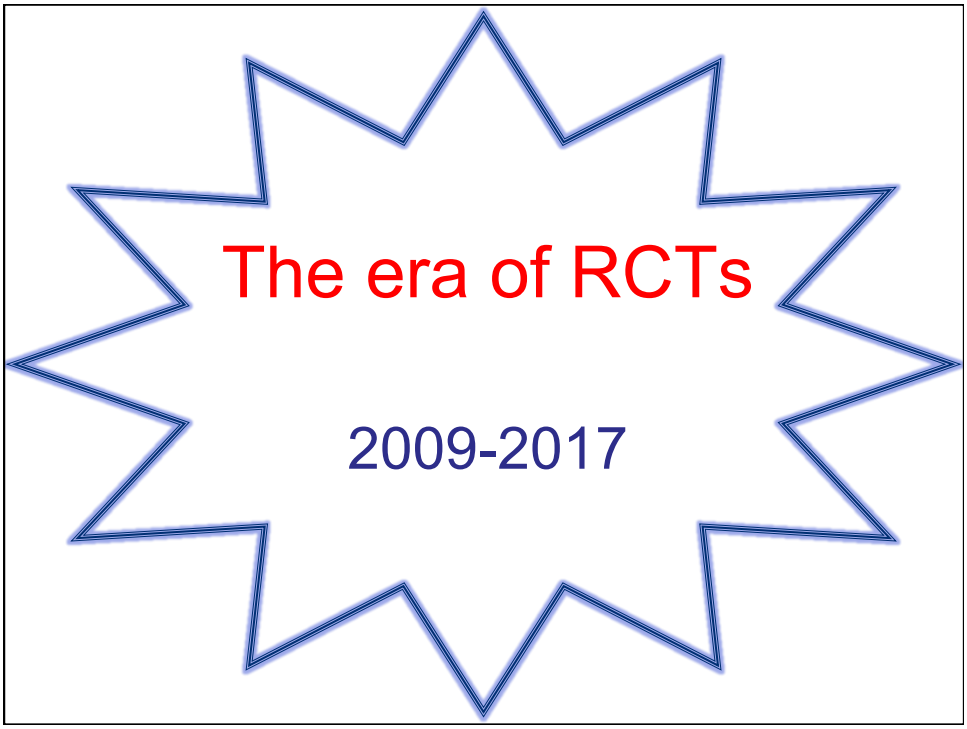
- Is thrombophilia associated with RPL and late obstetrical complications? **Controversial.**
- If yes, what is the strenght of the association and the magnitude of the risk? **The association is weak.**
- Is antithrombotic prophylaxis with LMWH ± ASA useful to prevent RPL or late obstetrical complications in women with or without thrombophilia?

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."



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
Egypt	2017	-	≥3 misc	2011-2014

**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)
-	≥3 misc	300	LMWH 4500	p=.002

**only non-thrombophilic women; §only thrombophilic women ; #control group receiveing oral placebo*

RCT in non thrombophilic women with RPL

Pasquier et al, Blood 2015

PREFIX study

258 non trombophilic 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.

RCTs in women with thrombophilia

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pilot study*	all late OCs	116#	LMWH 4/5/6000	0.15 (0.03-0.7)
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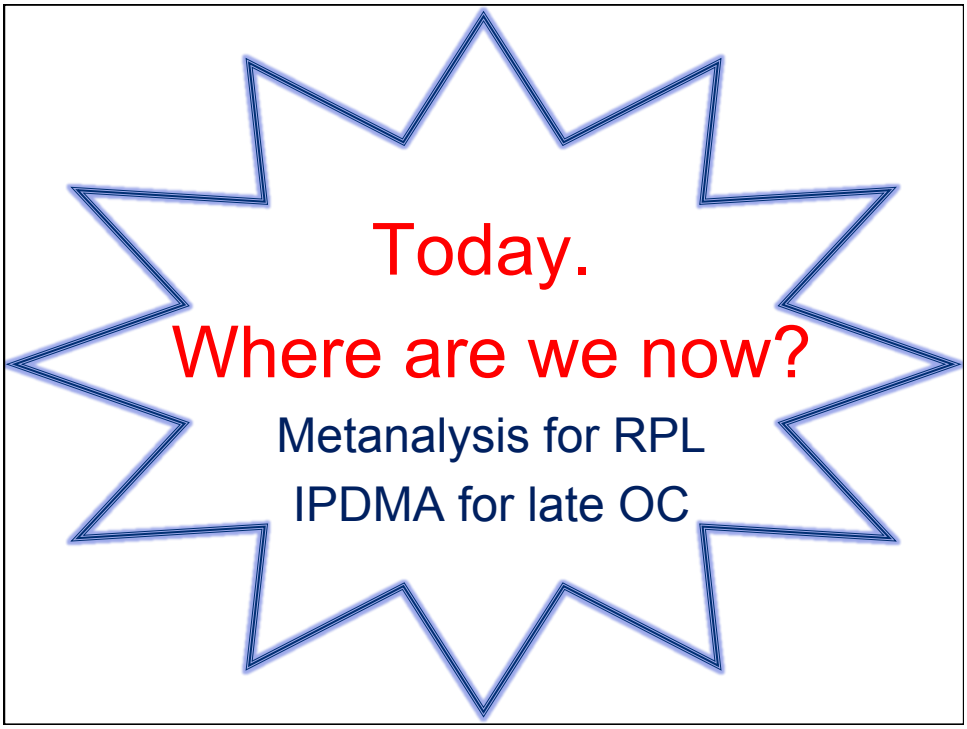

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia.

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

Low-molecular weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials

Rodger MA, Gris JC, de Vries JI, Martinelli I, Rey É, Schleussner E et al, for the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group.

Lancet. 2016 Oct 6. pii: S0140-6736(16)31139-4. doi: 10.1016/ S0140-6736(16)31139-4.

✓ 8 RCTs, 963 pregnant women of whom 480 LMWH + and 483 LMWH -

✓ recurrent placenta-mediated complications: 14% *vs* 22%
relative risk: 0.64 (0.36-1.11)

Questions

- Is thrombophilia associated with RPL and late obstetrical complications? **Controversial.**
- If yes, what is the strenght of the association and the magnitude of the risk? **The association is weak.**
- Is antithrombotic prophylaxis with LMWH ± ASA useful to prevent RPL or late obstetrical complications in women with or without thrombophilia?

No. **Uncertain.** **Likely not.**

Take home message (1)

- ✓ Owing the weak grade of recommendation, pregnant women with APS and RPL or late obstetrical complications should receive ASA + LMWH
- ✓ Although inherited thrombophilia is weakly associated with RPL, ASA and/or LMWH do not improve the live-birth rate and therefore should NOT be given.
- ✓ LMWH in pregnant women with previous late obstetrical complications does not seem to reduce the risk of recurrence, except (perhaps) in a small subgroup of women with prevous placental abruptio. Doubious effectiveness in women with thrombophilia.

Take home message (2)

- ✓ To date, the use of LMWH in women with previous obstetrical complications remains NOT evidence based.
- ✓ Before prescribing LMWH to pregnant women in order to improve the actual pregnancy outcome, 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 !