Complicanze ostetriche e trattamento antitrombotico

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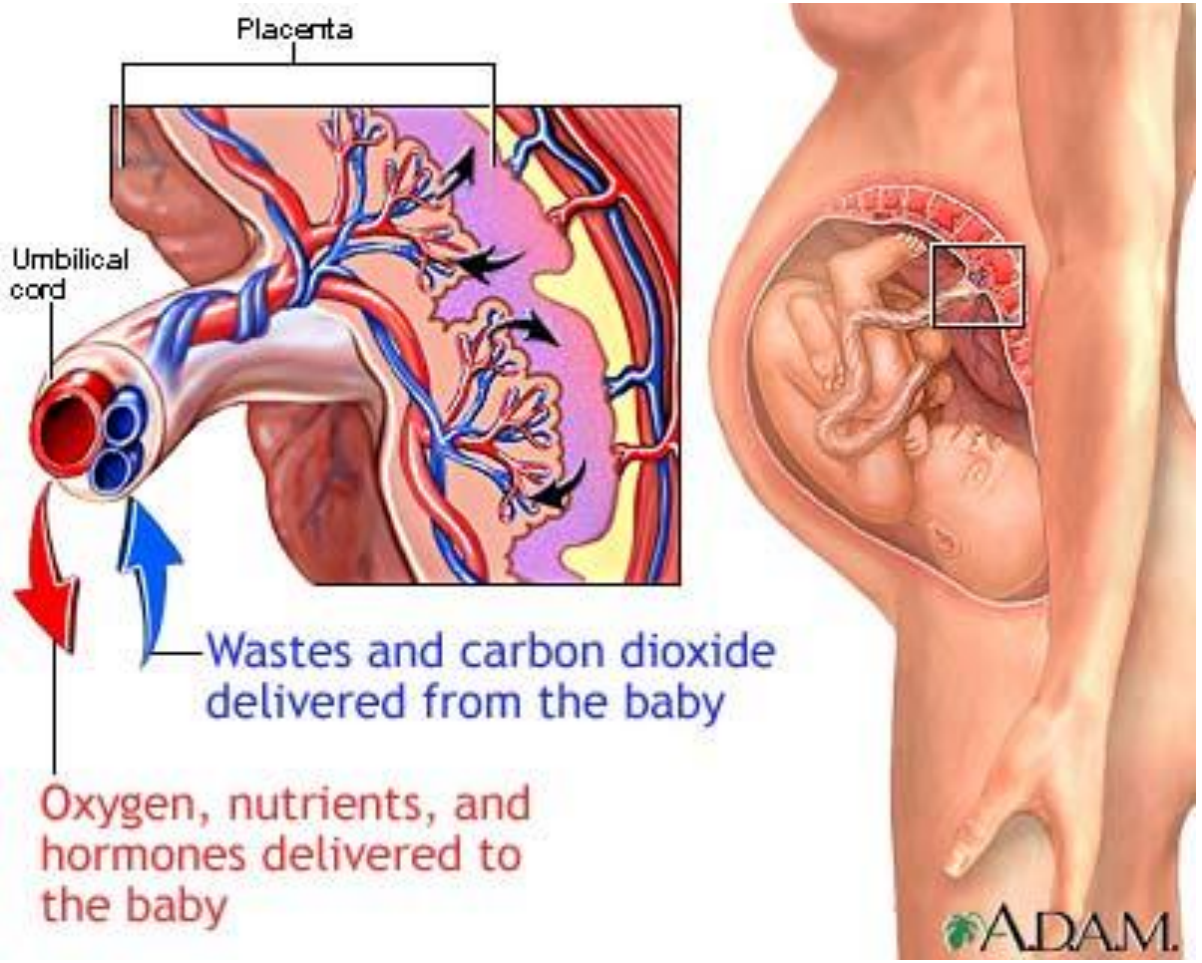
SISET
XXIV
CONGRESSO
NAZIONALE
Abano Terme, 9-12 novembre 2016


Placenta
Umbilical cord
Wastes and carbon dioxide delivered from the baby
Oxygen, nutrients, and hormones delivered to the baby
A.D.A.M.

Obstetrical complications

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

PLACENTA MEDIATED

Antiphospholipid antibodies

Recurrent miscarriage

Late obstetrical complications

Thrombosis
Autoimmunity
Inflammation/complement
Inhibition throphoblast proliferation

LMWH + ASA
Grade 2B - ACCP 2012

The association between antiphospholipid antibodies 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

Inherited thrombophilia

Recurrent miscarriage

Late obstetrical complications

?

Thrombophilia abnormalities

	general population	↑ risk of VTE
antiphospholipid antibodies	1-2 %	>10
antithrombin deficiency	0.02-0.2 %	5-50
protein C deficiency	0.1-0.5 %	7-15
protein S deficiency	?	6-10
factor V Leiden	3-7 %	5-8
G20210A prothrombin	2-5 %	2-4

Questions

- Is inherited thrombophilia associated with 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 obstetrical complications in women with or without inherited thrombophilia?

The easiest way…

- ✓ case-control studies
- ✓ retrospective cohort studies
- ✓ prospective cohort studies
- ✓ population cohort studies
- ✓ systematic reviews and meta-analysis

Thrombophilia in pregnancy. A systematic review.

	miscarriage 1° or 2° trim	miscarriage 1 at 2° trim	miscarriage rec. 1° trim	stillbirth 3° trim
FVL homoz.	2.7 (1.3-5.6)	-	-	2.0 (0.4-9.7)
FVL heteroz.	1.7 (1.1-2.6)	4.1 (1.9-8.8)	1.9 (1.0-3.6)	2.1 (1.1-3.9)
PT heteroz.	2.5 (1.2-5.0)	8.6 (2.2-34.0)	2.7 (1.4-5.3)	2.7 (1.3-5.5)
AT deficiency	0.9 (0.2-4.5)	-	-	7.6 (0.3-196)
PC deficiency	2.3 (0.2-26.4)	-	-	3.1 (0.2-38.5)
PS deficiency	3.6 (0.4-35.7)	-	-	20.1 (3.7-109)

Robertson L et al, Br J Haematol 2006

The association of FVL and prothrombin G20210A and placenta-mediated pregnancy complications: a systematic review and meta-analysis of 10 prospective cohort studies.

	late FL	PE	SGA	abruptio pl.
FVL	1.5 (1.1-2.2)	1.2 (0.9-1.7)	1.0 (0.8-1.3)	1.9 (0.9-3.7)
PTG20210A	1.1 (0.6-2.0)	1.3 (0.8-2.0)	1.3 (0.9-1.7)	2.0 (0.8-5.0)

Rodger MA et al, PloS Med 2010

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

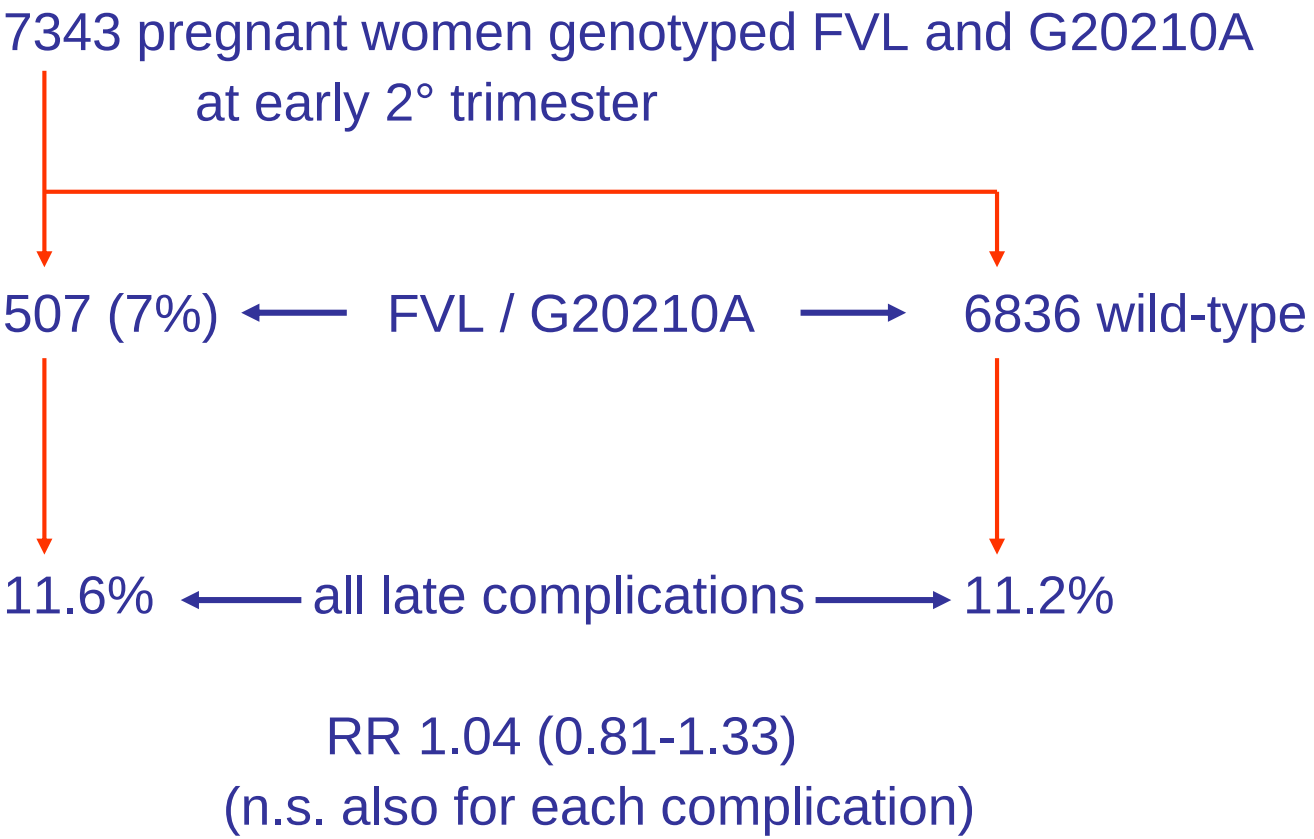
50% of all Danish pregnant women in 5 years (1997-2002) participated to the study, with 101042 pregnancies to 91661 women.

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 inherited thrombophilia associated with obstetrical complications? **Yes, with miscarriage. FVL may be also with late obsterical complications.**
- 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 obstetrical complications in women with or without inherited thrombophilia?

Pregnancy outcome in thrombophilic women with one previous pregnancy loss > 10th week

Gris JC et al, Blood 2004

	No. (%) live birth
40 mg/day enoxaparin (n=80)	69 (86%)
100 mg/day aspirin (n=80)	23 (29%)

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

2009-2014

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

**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	alla late OCs	289	LMWH 5000	2.6% (-6.4-11.6)

**control group receiveing oral placebo*

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TIPPS	**alla late OCs**	**289**	**LMWH 5000**	**2.6% (-6.4-11.6)**

#prematurely interrupted

Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT.

- ✓ 2000 - 2009: 139 pregnant women with previous delivery <34w with early-onset pre-eclamspia/eclampsia/HELLP and/or SGA
- ✓ PC (5%) or PS (17%) deficiency, APCR (3%), hetero factor V Leiden (60%) or G20210A (22%), hyperhomocysteinemia (12%)
- ✓ < 12w: ASA 80 mg (Holland), 100 mg (Australia), 75 mg (Sweden) ± dalteparin 2500 IU < 50 kg, 5000 IU 50-80 kg, 7500 IU > 80 kg
- ✓ Primary outcome: reduction of the above (50% reduction from a 35% recurrence).
- ✓ Risk difference:

  LMWH+ASA vs. ASA: 8.7% (95%CI 1.9 - 15.5) – NNT 12

De Vries JIP et al, JTH 2012

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial.

- ✓ 2000 - 2012: 289 pregnant women with thrombophilia (~ 60% factor V Leiden and ~ 20% G20210A) AND

- all late OCs or ≥3 < 10w, ≥2 10-16 or	~ 60%
- previous provoked proximal VTE or	~ 7%
- previous calf DVT or	~ 6%
- superficial vein thrombosis or	~ 5%
- positive family history in 1st degree	~ 30%

- ✓ < 21w: dalteparin 5000 IU od until 20w, then 5000 IU bid until at least 37w versus no dalteparin.

- ✓ Primary outcome: late obstetrical complications (including SGA and excluding AP) and VTE

- ✓ Risk difference:
  ITT: -1.8% (95%CI -10.6 to 7.1)
  on-treatment: 2.6% (-6.4 to 11.6)

Rodger MA et al, Lancet 2014

RCTs – consider limitations!

- pooled OC
- definition of type of OC
- LMWH/ASA starting gestational week
- dose of LMWH/ASA
- ASA allowed or not
- calculation of sample size
- complete enrollment
- monocenter/multicenter
- thrombophilia present/absent
- definition of thrombophilia
- etc. etc.

Today.

Where are we now?

IPDMA

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)

Added value of this study

The results of our individual patient data meta-analysis showed that only women with previous placental abruption might benefit from antepartum low-molecular-weight heparin, and suggest strongly that antepartum low-molecular-weight heparin is of no benefit in women with previous pre-eclampsia, previous birth of a small-for-gestational-age neonate, or previous late pregnancy loss.

This finding stems from a monocentric study and must be replicated in future multicenter trials

Questions

- Is inherited thrombophilia associated with obstetrical complications? **Yes, with miscarriage. FVL also with late obsterical complications.**

- 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 obstetrical complications in women with or without inherited thrombophilia? **Likely not.**

Take home message (1)

- ✓ **ASA and/or LMWH in pregnant women with previous unexplained recurrent early miscarriages does not improve the live-birth rate and therefore should NOT be given.**

- ✓ **LMWH in pregnant women with previous placenta-mediated obstetrical complications does not seem to reduce the risk of recurrence, regardless of thrombophilia, except (perhaps) in a small subgroup of women with prevous placental abruptio**

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 !