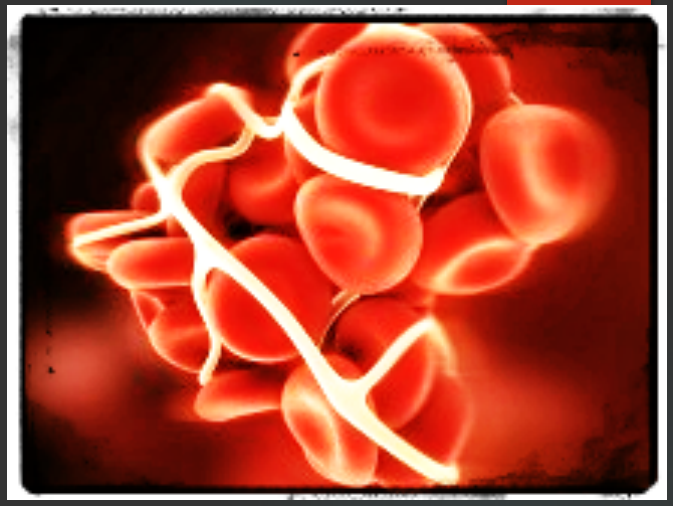
Toistuvat keskenmenot ja trombofilia



12.4.2018
RISTO KAAJA,
OBSTETRINEN SISÄTAUTILÄÄKÄRI
SISÄTAUTIOPIN PROFESSORI
TURUN YLIOPISTO

Sidonnaisuuksia

- Esitelmiä: Pfizer, Sanofi Aventis, Leo Pharma

Määritelmiä: Toistuva keskenmeno

- Kaksi tai useampi keskenmeno, raskaus todettu uä-tutkimuksin tai histologisesti: 2-5%
- Kolme tai useampi peräkkäinen keskenmeno: 0,4-1%

- Primaarinen: ei aikaisempia synnytyksiä
- Sekundaarinen: aikaisempi synnytys

Riskit ja syitä toistuville keskenmenoille

- Riski keskenmenolle:
  - Ensimmäinen raskaus: 11-13%
  - Yksi keskenmeno: 14-21%
  - Kaksi keskenmenoa: 22-29%
  - Kolme keskenmenoa: 31-33%
- Syitä keskenmenoille: 50% löytyy
  - Anatomiset: uterusanomalia, myoma, polyyppi
  - Immunologiset
  - Geneettiset syyt
  - Endokriiniset
  - TROMBOFILIA

Trombofiliat

- Perinnölliset:
  - V Leiden G1691A,
  - factor II or prothrombin G20210A,
  - Proteiini S ja proteiini C ja Antithrombiinin
  - F VIII
- Hankinnaiset:
  - Fosfolipidivasta-aineet: LAK, B2Gp1va ja kardiolipiiniva

Thromboprophylaxis for recurrentmiscarriage in women with or without thrombophilia. HABENOX: a randomized multicentre trial.

- Thromb Haemost 2011.

VISSER J, ULANDER V-M, HELMERHORST FM, LAMPINEN K, MORIN-PAPUNEN L, BLOEMENKAMP KWM, KAAJA RJ

HABENOX

- A randomised double-blind (for aspirin) multicentre trial
- Women
  - with three or more consecutive first trimester (<13 weeks) miscarriages
  - two or more second trimester (13-24 weeks) miscarriages or
  - one third trimester fetal loss combined with one first trimester miscarriage.
- Women were analysed for thrombophilia before pregnancy
  - factor V Leiden mutation, prothrombin gene mutation, protein C deficiency (<0.73 IU/ml), protein S deficiency (< 0.57 IU/ml), high factor VIII (≥ 1.5 IU/ml), anticardiolipin antibodies (8-40GPL) or beta-2 glycoprotein (>20 U/ml). Beta-2 glycoprotein was only tested in Finland (116 women).

HABENOX

- Women were randomly allocated before seven weeks' gestation to either
  - enoxaparin 40mg and placebo (n=68)
  - enoxaparin 40mg and aspirin 100mg (n=63)
  - aspirin 100mg (n=76).

HABENOX

- The primary outcome was live birth rate: live birth after 24 weeks´ gestation
- The secondary outcomes: pre-eclampsia, abruptio placentae, premature delivery, IUGR, adverse effects
- The trial was ended prematurely because of slow recruitment.

: Demographic and baseline characteristics

Characteristic	enoxaparin and placebo (n=68)	enoxaparin and aspirin (n=63)	aspirin (n=76)
Thrombophilia	17 (25.0)	15 (23.8)	19 (25.0)
Factor V Leiden	4	9	4
Prothrombin gene mutation	3	1	1
Protein C deficiency	1	0	2
Protein S deficiency	1	0	0
High factor VIII	1	1	2
Anticardiolipin antibodies	4	2	5
Beta-2 glycoprotein	3	2	5

Primary outcome: live birth rate

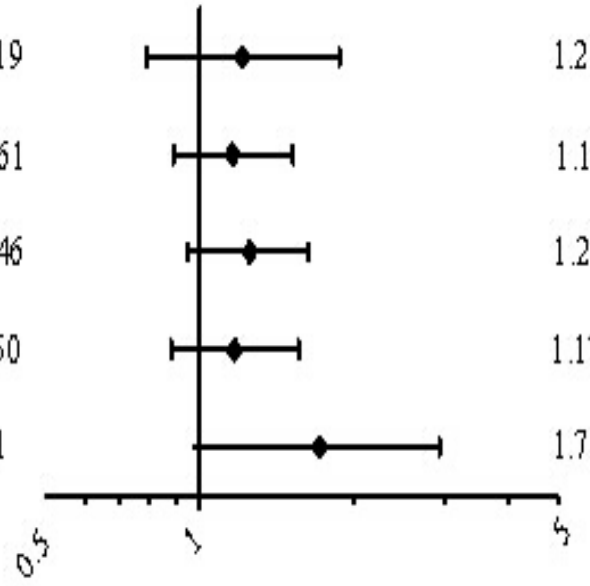
	aspirin (n=76)	enoxaparin and aspirin (n=63)	enoxaparin and placebo (n=68)	P
Live birth no. (%)	46 (61)	41(65)	48(71)	0.45
Relative Risk (95% CI)	1.00	1.08(0.83-1.39)	1.17(0.92-1.48)	

Live birth rate: impact of thrombophilia

	Aspirin (n=76)	enoxaparin and aspirin (n=63)	enoxaparin and placebo (n=68)
Thrombophilia	63%	60%	76%
RR (95 % CI)		0.95 (0.56-1.63)	1.21 (0.79-1.87)

SUBGROUP ANALYSIS

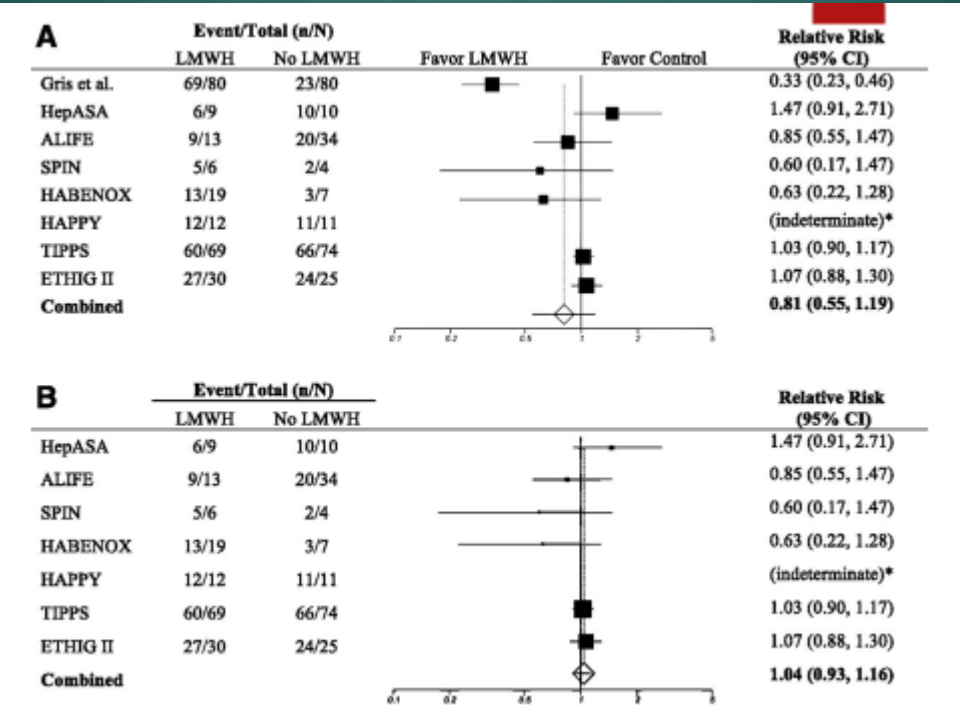
Subgroups	Enoxaparin and placebo n/N	Aspirin n/N	Relative Risk (95% CI)
thrombophilia	13/17	12/19	1.21(0.79-1.87)
history of early miscarriage	36/51	37/61	1.16(0.89-1.52)
history of primary miscarriage	26/32	30/46	1.25(0.95-1.63)
age<35 years	32/44	31/50	1.17(0.88-1.56)
4 or more miscarriages	22/30	9/21	1.71(1.00-2.93)



Recent RCT's

	patients no.	miscarriages no. (%)	start medication	treatment	live birth	P
ALIFE	364 itt* 299 pregnant	2 (40.1) ≥3 (59.9)	<6 weeks	1. LMWH+ aspirin 2. Aspirin 3. Placebo	69% 62% 67%	0.63
HABENOX	207	2 (1.0) ≥3 (99.0)	<7 weeks	1. LMWH+ aspirin 2. Aspirin 3. LMWH	65% 61% 71%	0.45
SPIN	294	2 (57.1) ≥3 (42.9)	<7 weeks	1. LMWH+ aspirin 2. Placebo	78% 80%	0.85

Blood. 2016 **A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia.** Skeith L[1], Carrier M[2], Kaaja R[3], Martinelli I[4], Petroff D[5], Schleußner E[6], Laskin CA[7], Rodger MA[8].



Fosfolipidivasta-aine syndrooma

Clinical criteria

1. Vascular thrombosis: ≥1 arterial, venous, or small vessel thrombosis.
2. Pregnancy morbidity
    a. ≥1 fetal death (at or beyond the 10th week of gestation)
    b. ≥1 premature birth before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency
    c. ≥3 consecutive (pre) embryonic losses (before the 10th week of gestation)

Laboratory criteria

1. Lupus anticoagulant positivity on ≥2 occasions at least 12 weeks apart.
2. Anticardiolipin antibody (IgG and/or IgM) in medium or high titer (i.e., >40, or above the 99th percentile), on two or more occasions at least 12 weeks apart.
3. Anti-β2-glycoprotein-I antibody (IgG and/or IgM) in medium or high titer (i.e., above the 99th percentile) on two or more occasions at least 12 weeks apart.

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met

Sydney 2006/Sapporo revised,

Epidemiologiaa

Väestössä: 1-5%
Sukupuoli: naiset/miehet: 5:1
SLE-potilailla: 30-40 %
FLVAS osallisena

- -14% aivoinfarkteissa
- -11% sydäninfarkteissa
- -10%: SLT
- -12%:PAH (SLE)
- -6% raskauskomplikaatioissa
- -9-15% toistuvissa keskenmenoissa

1000 naisella, joilla toistuvia keskenmenoja

- ACA+: 16% (kontr. 6.7%)
- Lupus-ak+: 3.5% (kontr. 0.5%)
  - Jaslow ym Fertil Steril 2010

Tukosvaara naisilla, joilla puhdas obstetrinen FLVAS

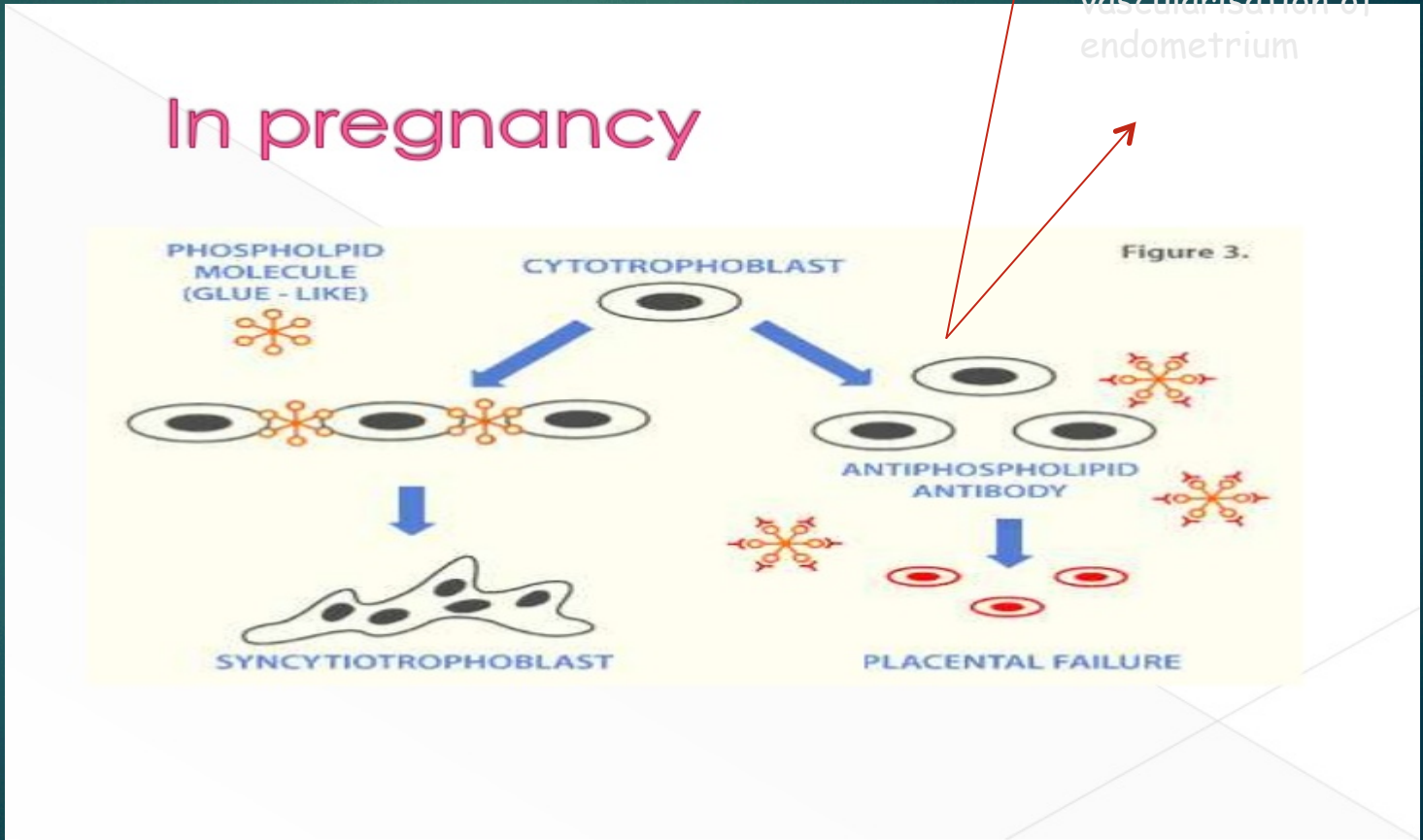
25% kehittää tukoksen 15 vuoden aikana (Gris ym 2012)

Obstetriset mekanismit

Obstetric APS (Kutteh 2014)

AP and trophoblastic cells: inhibition of proliferation, migration cell differentiation and apoptosis

AP decreases vascularisation of endometrium



Obstetrinen FLVAS: hoito

- Keskenmeno: pienmolekyylinen hepariini, profylaksia/korotettu profylaksia-annos vähintään 4 viikkoa post-abortum
- Varhainen IUGR/pre-eklampsia: pienmolekyylinen hepariini, korotettu profylaksia-annos +ASA loppuraskauden ajan ja vähintään 6 viikkoa postpartum
- Uusi raskaus: ASA+ pienmolekyylinen hepariini (korotettu profylaksiannos tai hoitoannos) koko raskauden ajan ja 6 kk postpartum

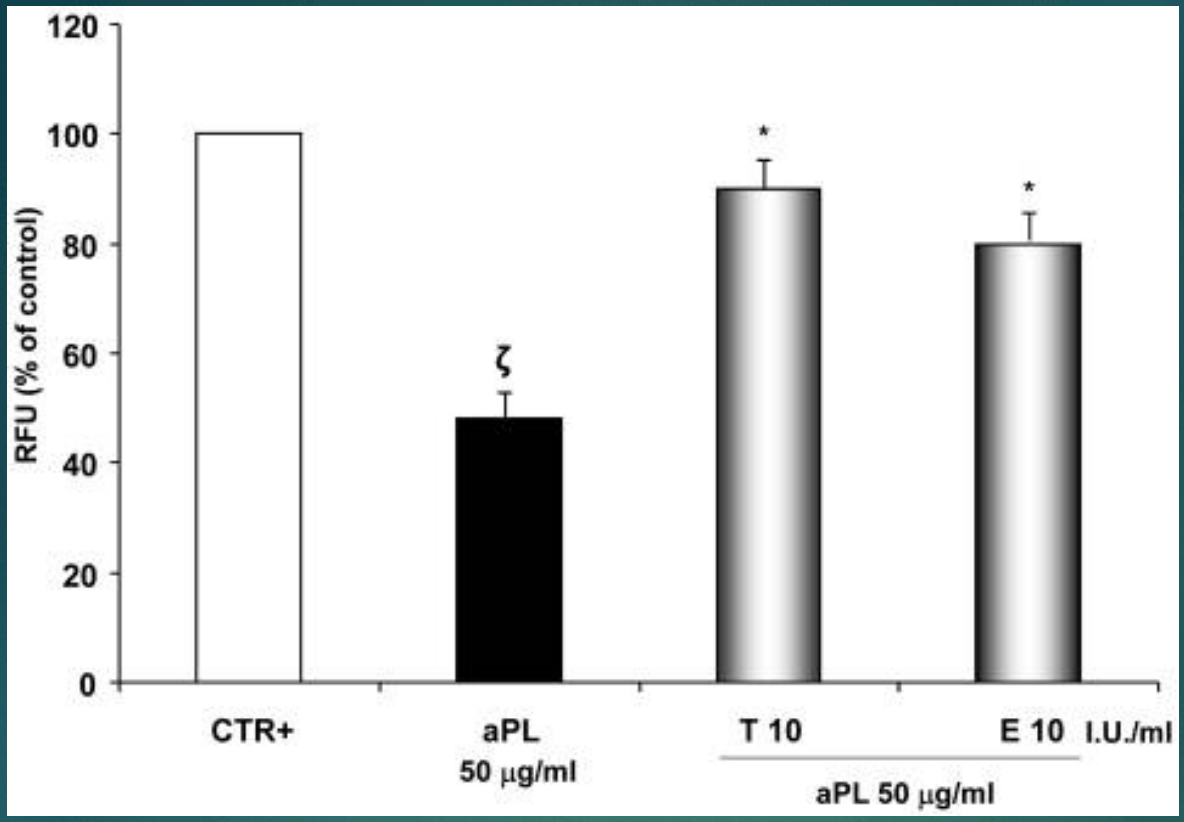
Hepariinin Uusia Tuulia

-Palauttaa fosfolipidien "liimavaikutuksen" sytotrofoblastosolukkoon

-Estää komplementtiaktivaation

-Vähentää fosfolipidivasta-aineiden negatiivista vaikutusta endometriumin angiogeneesiin (VEGF)

D´ Ippolito ym 2012



D'Ippolito S, et al 2012

Effects of aPL with or without LMWHs on angiogenesis process *in vivo*. Endothelial cells in the angioreactors. The analysis demonstrated reduced fluorescence (45%) in angioreactors containing aPL (50 μg/ml) compared with the positive controls. Tinzaparin or enoxaparin were able to completely reverse this angiogenesis inhibition.

Desperado-tapauksia: possible last help from IVG

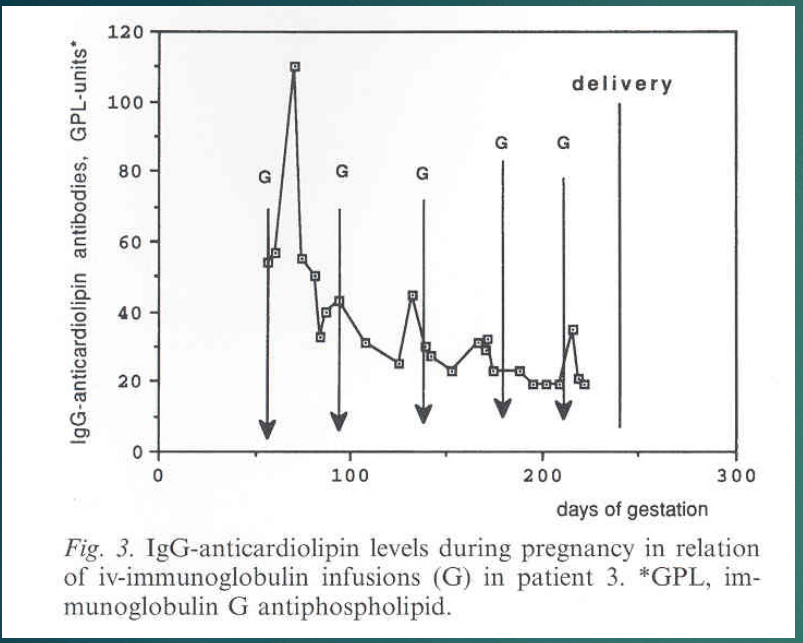


Fig. 3. IgG-anticardiolipin levels during pregnancy in relation of iv-immunoglobulin infusions (G) in patient 3. *GPL, immunoglobulin G antiphospholipid.

3 naista, joilla oli ollut
- 2 keuhkoemboliaa liittyneenä raskauteen ja E-pillereihin
- 13 keskenmenoa
- vain yksi elävänä syntynyt lapsi (varhainen vaikea pre-eklampsia)
- LMWH-profylaksiasta ja ASA:sta huolimatta

Seuraavien 4 raskauden aikana:
75 mg ASA, LMWH ja iv-immunoglobulin (1 g/kg) joka 5. viikko

Miten kävi: 3 tervettä last, ei IUGR (rv 36-38)
1 ennenaikainen synnytys (34 rv)

Kaaja et al Acta Obstet Gynecol Scand 1993

As a result


Happy
mothers


I'm not antisocial.
I just
Angry chief doctor
don't like humans.

Live birth rates in women with antiphospholipid syndrome and recurrent pregnancy loss treated with low-molecular-weight heparin plus low-dose aspirin compared with those treated with low-dose aspirin alone

.

Study	Number of patients	Medication commencement in gestational weeks	Treatment for each group	Live birth rate %	*P* value
Empson *et al.* (2005)43	119	7	1. LMWH + LDA	73	<0.05
			2. LDA	34	
Mak *et al.* (2010)44	334	6	1. LMWH + LDA	74.27	<0.05
			2. LDA	55.83	
Cohn *et al.* (2010)45	176	6	1. LMWH + LDA	79	<0.05
			2. LDA	62	
Al Abri *et al.* (2000) 46	88	7	1. LMWH + LDA	75	<0.05
			2. LDA	54	

Lancet. 2016

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

Rodger MA[1], Gris JC[2], de Vries JIP[3], Martinelli I[4], Rey É[5], Schleussner E[6], Middeldorp S[7], Kaaja R[8], Langlois NJ

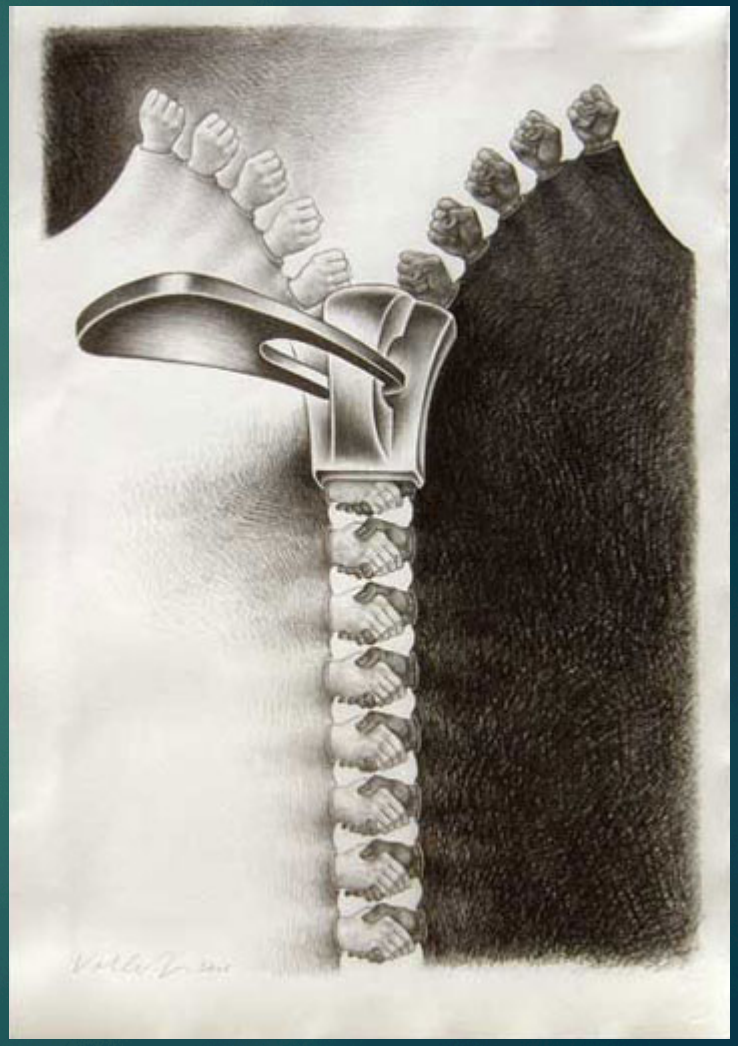
- low-molecular-weight heparin did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (low-molecular-weight heparin 62/444 [14%] versus no low-molecular-weight heparin 95/443 (22
- **INTERPRETATION:**
- Low-molecular-weight heparin does not seem to reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women. However, some decreases in event rates might have been too small for the power of our study to explore.

Milloin epäillä trombofiliaa (erityisesti FLVAS) toistuvissa keskenmenoissa

Keskenmenojen lkm	1	2	3	>3
1. trimestre	-	+	++	+++
2. trimestre	+	++	+++	+++
3. trimestre	++	+++	+++	+++
+ vähän, ++keskim. +++paljon				

Kotiinvietävää

- Hereditäärisellä trombofilialla (ja LMWH:lla) vähän vaikutusta toistuviin keskenmenoihin
- Mutta puuttuu kunnon RCT-tutkimus: homogeeninen populaatio, varhain (<rv 7) aloitettu profylaksia, >2 km
- FLVAS:lla parempi korrelaatio toistuviin keskenmenoihin



Kiitos !

VM Ulander,
Katja Lindberg
L Morin-Papunen
J Visser
K Bloemenkamp